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THESIS TITLE: COVID-19: WHAT EPIDEMIOLOGY CAN TELL ABOUT THE RELATIONSHIP WITH MULTIMORBIDITY AND ADDICTIONS

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1. INTRODUCTION

1.1 A general overview of the SARS-CoV-2 Pandemic

The Coronavirus Disease (COVID-19) is a viral respiratory disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a kind of Sarbecovirus belonging to the Betacoronavirus genus of the coronavirus family (1). In particular, SARS-CoV-2, initially named 2019-novel coronavirus (2019-nCoV), is a single-stranded RNA virus with a genome of approximately 30,000 nucleotides. Its genome encodes 4 structural (spike, membrane, envelope, and nucleocapsid) and 16 non-structural (nsp1-16) proteins, other than 9 accessory proteins (3a, 3b, 6, 7a, 7b, 8b, 9a, 9b, and orf10) (2–4). Among such proteins, two have great significance: the spike protein, because it is responsible for the viral entry into host cells, and the nsp12, also known as RNA-dependent RNA polymerase (RdRp), because it is crucial for viral replication (5,6).

The origins of COVID-19 can be traced back to Wuhan, China, where the first cases were officially reported to the World Health Organization (WHO) on December 31, 2019 (7). In particular, the first cases were linked to the Huanan market, a seafood wholesale market in Wuhan, Hubei Province, China, where live wild animals were also sold, raising early hypotheses about a zoonotic origin (4). The virus quickly spread within Wuhan and, subsequently, to other parts of China. Beyond China, the virus made its way to other countries, marking the beginning of the global pandemic. The first case outside of China was reported in Thailand on January 13, 2020, involving an individual who had traveled from Wuhan (7). Soon after, cases were identified in various countries worldwide, prompting concerted efforts to control the spread of the virus and understand its characteristics. In Europe, the first cases of COVID-19 were detected starting from January 24, 2020. The initial case was reported in France, followed by Germany on January 27, and then Italy and Spain on January 31 (7,8).

Since the first case was detected, the severity of this disease has been evident. According to a study conducted by Liu et al. (9), in the first quarter of 2020, 580,819 deaths were observed in the Wuhan region, indicating substantial excess mortality compared to the expected for all causes (1147.2 vs 734.7 per 100,000; Rate Ratio (RR): 1.56; 95% Confidence Interval (CI): 1.33-1.87) and specific causes, especially pneumonia (275.2 vs 33.1 per 100,000; RR: 8.32; 95% CI: 5.19-17.02). Similar results were also observed worldwide, including in Europe and the United States (9–12). Notably, the peak of excess mortality occurred locally in Bergamo, Italy, in the north of the country, where the excess mortality rate exceeded 800% (13). However, COVID-19 has not only affected mortality, but also national healthcare systems. The impact of the SARS-CoV-2 on hospitals and other healthcare structures was profound, with many healthcare systems worldwide facing unprecedented challenges. In the initial stages of the outbreak, hospitals, particularly in hotspot regions, experienced significant strain as they grappled with a surge in patients requiring intensive medical care (14). Overwhelmed emergency rooms, shortages of critical medical supplies, and strained healthcare personnel became common concerns, having several huge consequences, including poorer patient outcomes and the inability of staff to adhere to guideline-recommended treatment (15). The need for increased hospital capacity, ventilators, and personal protective equipment highlighted the urgency of the situation. This scenario prompted rapid adaptations in hospital protocols, with some facilities converting non-traditional spaces into makeshift treatment areas to accommodate the escalating number of COVID-19 cases.

Given the severity and effects of the COVID-19 outbreak, on March 11, 2020, the WHO declared COVID-19 a global pandemic (16). This pandemic lasted about 3 years: in fact, WHO declared the end of the pandemic on May 5, 2023 (17). To date, globally, WHO has identified 772,138,818 confirmed cases of COVID-19, and 6,985,964 deaths have been recorded. The geographical area where the largest number of cases have been identified is Europe (277,210,883 confirmed cases), while the 10 countries with the highest number of infections, in order, are the United States, China, India, France, Germany, Brazil, South Korea, Japan, Italy, and the United Kingdom. Regarding the deaths, instead, they occurred most in the Americas (2,975,163 confirmed deaths), while the countries with the highest number of deaths are the United States, Brazil, and India (18).

In response to the challenges posed by the COVID-19 pandemic, governments worldwide implemented different policies to mitigate the spread of the SARS-CoV-2. One of the earliest and widely adopted measures was the imposition of lockdowns or stay-at-home orders, restricting non-essential movement and gatherings (19,20). For example, educational institutions and some non-essential businesses adopted remote work and online learning solutions to minimize in-person interactions. In addition, social distancing guidelines were introduced, encouraging individuals to maintain a physical distance from others, and the widespread use of face masks became a rule not only for symptomatic individuals but also as a preventive measure in different public contexts. Quarantine measures were enforced for those exposed to the virus, and isolation protocols were established for confirmed cases. Also, testing and contact tracing played pivotal roles in identifying and isolating cases promptly. Finally, travel restrictions and border controls were implemented to limit the international spread of the virus.

Due to the severity of the disease and the government responses to the pandemic, COVID-19 has had a great impact on people's lives and habits, especially in economic, social, psychological, and clinical aspects.

From an economic point of view, SARS-CoV-2 had a great negative impact. The pandemic had severe adverse effects on employees, customers, supply chains, the insurance industry, and financial markets, especially in sectors such as travel, hospitality, and entertainment that experienced severe contractions (21–23). Lockdowns and social distancing measures led to business closures, layoffs, and disruptions in supply chains, resulting in economic contractions and rising unemployment rates (24). Governments tried to implement fiscal measures to mitigate the economic fallout, including stimulus packages and financial support for businesses and individuals. However, notwithstanding, small businesses faced heightened vulnerabilities, and disparities in economic impact became evident, disproportionately affecting marginalized and vulnerable communities (24,25).

In addition to its economic implications, the effects of COVID-19 have also impacted social dynamics. Measures such as increased isolation, prolonged periods spent at home, disruptions in traditional social activities, and heightened mental health concerns have played a significant role in influencing relationships among people and altering how individuals perceive empathy towards others (26). Furthermore, this period has been characterized by a higher prevalence of psychological issues. Several studies and reviews highlighted the effects on mental health of COVID-19 pandemic, revealing a significant increase in the prevalence of depression, anxiety, and stress symptoms across the general population, adolescents, as well as among the most vulnerable populations (27–29).

Finally, different clinical consequences were observed during the COVID-19 pandemic. In fact, beyond the excess mortality and hospital overload above discussed, many medical services have been drastically reduced due to the pandemic. Essential treatments such as biopsy, mastectomy, chemotherapy, physiotherapy, and other specialistic visits or medical care have experienced significant reduction (30–34). Additionally, the fear of SARS-CoV-2 infection has led to several subjects, being apprehensive about entering hospitals, developing worse clinical conditions, or dying from different comorbidities, such as cardiovascular disease, as they delayed or attempted to avoid hospitalization (35,36).

In addition, several preventive health measures have also experienced changes. For example, especially during the first phase of the pandemic, traditional screening programs faced disruptions due to the strain on healthcare resources and the need to prioritize COVID-19-related services. Therefore, screenings for conditions such as cancer, diabetes, and cardiovascular diseases experienced delays and reductions (37–39). According to a study conducted in the United States, statistically significant reductions in screening for breast, colon, prostate, and lung cancers were observed in 2020 compared to the previous year. In particular, the most significant decrease was observed in April for mammograms (−85%), lung (−75%), colon (−74%), and prostate (−56%) screenings (30).

1.2 The evolution of SARS-CoV-2 over time

Similar to other viruses that have caused pandemics in the past, the evolution of SARS-CoV-2 over time has been marked by the emergence of various variants (40), presenting an ongoing challenge in the battle against COVID-19. In fact, as the virus replicated, genetic mutations occurred, giving rise to distinct strains. Although the majority of alterations have minimal impact on the virus's characteristics, certain changes can influence its properties, including transmission ease, disease severity, and the effectiveness of vaccines, therapeutic drugs, diagnostic tools, and other public health or social interventions. Overall, scientists have identified several variants and mutations, with five specific variants having a more significant impact on populations.

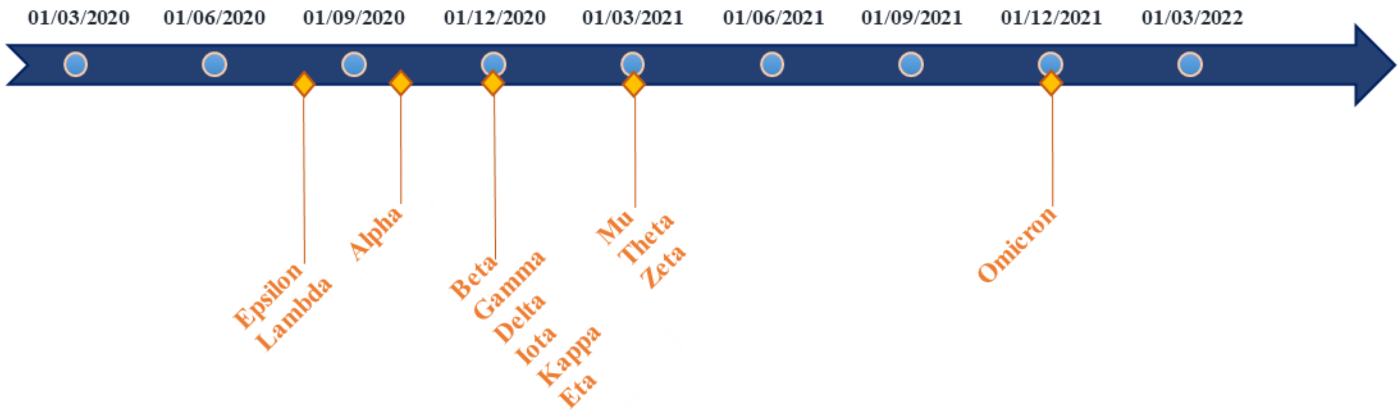
The first major variant detected was the Alpha variant (lineage B.1.1.7), identified in October 2020 for the first in the United Kingdom. The main peculiarity of this lineage was a significantly increased transmissibility: according to some studies, transmissibility was higher and peaked at up to 90% compared with previous lineages (41). On the contrary, it is unclear whether this variant led to more severe outcomes: some authors found no substantial differences in severity and lethality (42), while others identified an increased risk of a worse prognosis (43).

Another important variant was Beta (lineage B.1.351). It was first detected in December 2020, in South Africa, almost a year after the first cases of COVID-19 occurred in Wuhan. Several research identified an increased risk of infection and a more severe prognosis, including hospitalization and death, among individuals infected with the Beta lineage, compared to both the Alpha variants and earlier mutations (44,45). In addition, it emerged that the Beta variant exhibited the ability to reduce the effects of vaccines (46).

During the same period, two different significant lineages emerged. The first was the Gamma variant (lineage P.1), initially identified in Manaus, the largest city in the Amazonas State, Brazil (47). This variant exhibited high transmissibility, severity, and lethality. However, its most notable characteristic was its remarkable ability to evade up to 60% of immunity from previous SARS-CoV-2 lineages present in the territory, increasing the risk of reinfection even after recovery (47). The second variant was the Delta variant (lineage B.1.617.2), initially identified in the state of Maharashtra, India, in late 2020 (48). However, the first cases of this lineage outside India were detected in February 2021 in Europe and the United States. Numerous studies have indicated that the Delta variant exhibits higher transmissibility (between 40% and 60% compared to the Alpha variant (49)), and a greater severity (50). Additionally, findings suggest that various protective measures, including treatments and vaccines, might be less effective against infections by this lineage (49). Nevertheless, these interventions continued to demonstrate efficacy in preventing severe hospitalization and death. According to Lopez Bernal et al., two doses of the vaccine had an effectiveness of 88.0% (95% Confidence Interval (CI): 85.3%-90.1%) against the Delta variant, lower when compared to the efficacy against previous variants, such as Alpha (Effectiveness: 93.7%; 95% CI: 91.6%-95.3%) (51). Over time, Delta became a dominant variant globally, leading to a surge of cases in various regions of the world. To date, it is considered the most severe variant.

The most recent variant that significantly impacted global healthcare systems is Omicron (lineage B.1.1.529). Initially detected in South Africa and Botswana in November 2021, Omicron quickly spread worldwide, reaching almost every country by December 2021. In fact, the major peculiarity of this lineage was the very high transmissibility and diffusion, having the ability to spread much faster and infect more people than previous variants (52). Studies indicated that Omicron could infect three to six times more individuals compared to the Delta variant (53). However, although it was observed a higher probability of reinfection, Omicron appeared to be comparable to earlier coronavirus strains or potentially less severe than the Delta variant (52,54). A summary of the first time SARS-CoV-2 variants were detected is shown in Figure 1.

Figure 1. Summary of when SARS-CoV-2 variants were first detected



1.3 Factors associated with COVID-19-related outcomes

Since the first cases of COVID-19 were identified, researchers worldwide have started investigating all possible potential risk factors of SARS-CoV-2-related outcomes, including positivity, hospitalization, and mortality. Several demographics, socioeconomic, and clinical characteristics other than lifestyle behaviors were identified.

From a demographic point of view, age and gender were the first two factors found associated with COVID-19-related outcomes.

Regarding age, researchers found that older subjects faced a higher risk of severe illness, hospitalization, and mortality. According to a systematic review and meta-analysis published in 2021, an increased age-related risk of SARS-CoV-2 mortality (in-hospital and general) and hospitalization of 5.7%, 7.4%, and 3.4% per age year, respectively, was estimated (55). However, the risk was found particularly high for subjects over 60-65 years old, likely due to a diminished efficiency in their immune system (56).

Another important factor was gender. Although both males and females could develop COVID-19, some studies indicate that males might face a slightly higher risk of severe outcomes (57). However, other researchers have identified that there is no gender difference in outcomes related to COVID-19 (58). Therefore, even today, the direction of these associations remains unclear.

In addition to these two factors, ethnicity also played a significant role. Many authors observed that ethnic minorities had a higher likelihood of contracting SARS-CoV-2 and developing more severe illness (59). This could be due to several interconnected factors: worse job positions that exposed ethnic minorities to higher risks of infection, lower average socioeconomic condition, health disparities and unequal access to healthcare services, and cultural practices and behavioral patterns, such as communal living arrangements and close-knit social interactions (60). Moreover, as delineated in a report disseminated by the English National Health Service (NHS) (61), subjects belonging to ethnic minorities, particularly those of Black and Asian ethnic groups, also experienced a higher mortality rate compared to the White population. This observation assumes paramount importance, given the antithetical trajectory witnessed in antecedent years. The pre-existing inequalities across a wide array of sectors, including healthcare, employment, access to universal credit, housing, and the policy of non-recourse to public funds, have rendered the impact of the pandemic significantly more severe compared to their white counterparts (62).

Socioeconomic characteristics also had a strong impact on SARS-CoV-2-related outcomes, whether analyzed individually or collectively.

From an individual point of view, the main socioeconomic factors were educational level, occupational status, and income. Usually, in the epidemiology field, these factors were used as a proxy to measure the Socioeconomic Position (SEP), an important indicator of the social and economic condition and well-being of the subjects.

In the literature, all these three factors were analyzed in relation to the infection due to SARS-CoV-2 and its severity.

Regarding educational level, many studies showed that a higher educational qualification or educational attainment, which measures the number of years of schooling, decreased the risk of developing worse disease outcomes or death (63,64). In fact, subjects with higher educational levels exhibited greater adherence to imposed rules, including mask usage or avoiding crowded spaces, and demonstrated a heightened interest and/or engagement in science communication, thereby reducing their risk through correct behaviors.

Related to the occupational condition, it was observed during the COVID-19 pandemic that individuals with high public contact, such as essential workers in transportation or healthcare, faced a higher risk of infection (65,66) and mortality (61). In fact, in according to the data, the three occupations with the highest increase in mortality rates during the early stages of the pandemic were caring personal services, elementary security occupations, and road transport drivers. However, when comparing non-essential workers, it emerged that white-collar workers had a lower risk than their non-white counterparts (66).

Regarding income, few studies investigated the association between individual income and outcomes related to SARS-CoV-2 infection. However, more studies explored the household income. From the literature, it emerged that families with higher household income levels tend to experience a reduced risk of severe outcomes associated with COVID-19 (67). Higher household income, in fact, might afford families with greater resources to navigate the challenges posed by the pandemic, including better access to healthcare services, the ability to implement effective preventive measures, and the flexibility to adapt to changing circumstances.

Focusing on socioeconomic factors at the aggregate level, some researchers identified that municipalities with higher average incomes had a lower risk of infection, hospitalizations, and deaths due to COVID-19 (68). Similar results emerged when analyzing the deprivation index, a statistical tool used to measure and quantify socioeconomic deprivation in a specific geographic area. According to several reports and studies, more deprived areas were at a higher risk of contracting SARS-CoV-2 infection (61,69) and developing worse outcomes (70,71). The reasons for these results are clear: On one hand, individuals residing in more deprived areas often work in occupations with higher exposure to infection and have closer proximity to areas where the infection is prevalent; on the other hand, areas marked by higher deprivation often exhibit significant socioeconomic disparities, leading to unequal access to healthcare, education, and employment opportunities. Such disparities could pose significant challenges for residents in accessing timely healthcare services.

Therefore, these findings suggest a complex interplay between socioeconomic factors and health outcomes.

Although demographic and socioeconomic characteristics were important risk factors for greater susceptibility to virus infection and adverse disease outcomes, it was evident that pre-existing clinical conditions played an even greater impact. For this reason, from the outbreak of the pandemic, the association between specific pathologies and COVID-19 outcomes and how pre-existing health conditions influenced the course of the disease became a central focus of research, as it allowed health professionals to focus more on certain categories of patients. Subjects with underlying health conditions, such as cardiovascular and cerebrovascular diseases, diabetes, respiratory disorders, kidney diseases, and cancers often face an increased risk of experiencing more severe outcomes.

Several studies and meta-analyses showed the significant role of cerebrovascular or cardiovascular diseases, including hypertension, heart failure, myocardial infarction, cardiomyopathy, and coronary artery disease, as substantial contributors to severe COVID-19 outcomes. These conditions were associated with increased risks of hospitalization, ICU admissions, prolonged hospital stays, or mortality, with some authors reporting a doubling or even tripling of the risk in certain cases (72,73). Furthermore, despite potential confounding factors such as age or gender, cardiovascular disease emerged as an independent risk factor for adverse COVID-19 outcomes (74). Similar results were identified by investigating cerebrovascular diseases (75).

Likewise, patients with diabetes faced elevated risks: in diabetic patients, the presence of diabetes-related complications might worsen the prognosis. In addition, hyperglycemia was found to be a strong risk factor for a severe course of COVID-19 (76).

Other important health conditions were respiratory diseases, such as chronic obstructive pulmonary disease (COPD) or interstitial lung disease. From the literature, it emerged that pre-existing respiratory conditions amplified the vulnerability to respiratory infections, including SARS-CoV-2 (77). The virus' impact on the respiratory system could be particularly detrimental in patients with these pre-existing lung conditions.

Oncological diseases emerged as another significant risk factor in the context of COVID-19. Patients with cancer, often in an immunocompromised state due to either the underlying health conditions or medical treatments, encounter challenges in mounting a robust immune response against the virus (78). This compromised immunity increased the risk of prolonged illness and severe COVID-19 outcomes.

In addition to oncological concerns, kidney pathologies were a focus of investigation. Several studies indicated that chronic kidney conditions not only increased susceptibility to SARS-CoV-2 infection but also amplified the risks of a critical course of COVID-19 or mortality (79).

While these heightened risks were observed across both younger and older populations, specific studies have delved into the association within different age groups. According to McConnell et al. (80), it was found that underlying health conditions had a more pronounced impact on patients aged between 40 and 64 years old compared to those in the younger (18-39) and older (65+) age groups. Therefore, age could be considered an effect modifier in the association between clinical conditions and COVID-19-related outcomes.

However, while several single diseases appeared to increase the risk of developing COVID-19 more severely, the presence of multimorbidity had an even more significant impact.

Multimorbidity was defined in various ways, lacking a single universally accepted definition beyond the presence of one or more concurrent, often chronic, pathologies. Consequently, numerous indices have been developed over the years to assess the burden of multimorbidity in patients based on the clinical conditions they are experiencing. Some notable indices used in the epidemiological or medical field include: the Cumulative Illness Rating Scale (81), created in 1968 by Bernard S. Linn, an index ranges between 0 and 56 that rates the severity of comorbid diseases across different organ systems, offering a comprehensive assessment; the Chronic Disease Score (82), developed in 1992 by Meschede Von Korff, a system based on pharmacy data which measures the burden of chronic diseases based on prescribed medications; the Elixhauser Comorbidity Index (83), created in 1998 by Anne Elixhauser, which assesses comorbidity considering thirty different diseases; the Functional Comorbidity Index (84), developed in 2005 by Dianne L Groll, which consists of 18-item list of diagnoses that may impact physical function.

Another very important way to assess the patient’s comorbidity burden is the Charlson Comorbidity Index (CCI), maybe the most important indicator of multimorbidity used in epidemiology. The Charlson Comorbidity Index, created by Mary E. Charlson in 1987, is an index that assigns a score to different comorbidities. Each condition is assigned a weight, based on the likelihood of 10-year survival, and the total score is calculated by summing the weights of individual comorbidities present in a patient. The higher the score, the greater the burden of multimorbidity (85).

The CCI is commonly used in clinical research, epidemiology, and healthcare settings to stratify patients based on their overall health status. In fact, it could help clinicians and researchers account for the impact of comorbidities when analyzing outcomes, making it a valuable tool for risk adjustment in various medical studies. For this reason, during the COVID-19 pandemic, CCI was widely investigated by several researchers to assess how it influenced the risk of infection or worse prognosis of COVID-19 for different values of this index. Many studies showed that as the CCI increased, the risk of being hospitalized, being admitted to ICU, or dying significantly increased (86,87). According to a meta-analysis that investigated the association between CCI and COVID-19-related outcomes, it emerged that individuals with a CCI score of 1 or 2 experienced a 90% increase in the risk of poor outcomes (OR: 1.90; 95% CI: 1.61-2.24), while for those with a CCI score of ≥ 3, the risk tripled (OR: 2.95; 95% CI: 2.39-3.65) (87).

Similar to multimorbidity, the severity of the clinical condition at the time of access to the Emergency Department (ED) was a strong factor associated with COVID-19 outcomes. Among the various methods available to assess the severity of the clinical condition, the National Early Warning Score (NEWS) and its modified version, NEWS2, are two of the most widely used and appropriate tools (88). NEWS2 is a system that evaluates several physiological measurements (respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness, and temperature), generating a score between 0 and 23 and resulting in a standardized assessment of acute illness severity (88).

NEWS2 was widely used during the pandemic by healthcare professionals to identify patients at a higher risk of deterioration and guide appropriate interventions (89). Studies showed that higher NEWS score upon admission to the Emergency Department was associated with worse outcomes in COVID-19 patients. Particularly, patients with elevated scores (often NEWS2 score ≥ 5) were more likely to experience severe respiratory distress, require intensive care, and face an increased risk of mortality (90,91).

Finally, also some unhealthy lifestyle behaviors, such as smoking, substance use, and alcohol consumption, were found to be factors associated with COVID-19-related outcomes. Many studies and reviews showed that smoking habit and substance use, such as opioids, increased the risk of severe COVID-19 and mortality (92–94). However, in investigating cannabis consumption, studies identified a protective role, probably due to the anti-inflammatory and anti-oxidative properties of some chemical elements, such as cannabidiol (94,95).

Regarding alcohol consumption, instead, the association is still not completely clear. In fact, although many studies found that higher alcohol consumption was associated with a greater risk of worse COVID-19-related outcomes (96,97), some authors found the opposite effect (94,98).

1.4 The effect of SARS-CoV-2 pandemic on addictions

As discussed in paragraph 1.1, COVID-19 had an enormous impact on subjects' habits and mental health, leading to a significant increase in anxiety, depression, and stress levels (27–29). Therefore, these challenging circumstances brought about by the pandemic created an environment that fostered the development and adoption of several unhealthy behaviors and various addictions, including substance use, alcohol consumption, and gambling.

Many studies present in the literature showed that, during the COVID-19 pandemic, there was a large increase in alcohol consumption and substance use, such as opioids or illicit drugs (99–101). This increment could be also attributed to the heightened challenges in accessing support systems, rehabilitation programs, and treatment facilities. Additionally, disruptions to regular attendance at support group meetings and the limited access to in-person counseling sessions, which are crucial components of addiction support programs, fostered difficulties for subjects with addictions.

Another notable addiction that underwent significant changes during the COVID-19 pandemic was gambling. The policies implemented to limit the spread of the virus led to two important consequences: firstly, numerous sporting events globally, including prestigious leagues and tournaments, including the Premier League and the Italian male soccer leagues, EURO soccer 2020, the ice hockey season in Sweden, the 2020 Summer Olympics scheduled in Tokyo, the major tennis tournaments, the volleyball championships, and the basketball leagues (102,103); secondly, the physical closure of certain business activities like land-based casinos and betting stores (104). These factors, combined with more time spent at home, prompted more subjects to engage in gambling or betting, particularly online (105–107). Studies also indicated a significant shift in the gambling landscape, with sports bettors and casino gamblers migrating to online platforms (108). This notable change in the gambling environment during COVID-19 was characterized by a transition from traditional and land-based venues to online platforms, allowing individuals to gamble at home using smartphones and tablet apps (109).

1.5 The SARS-CoV-2 pandemic in Italy

The COVID-19 pandemic had a profound impact on Italy, with the country experiencing a significant and challenging trajectory. At least initially, Italy was the country most affected by the virus outside China. The first case of SARS-CoV-2 in Italy was officially confirmed on January 31, 2020, in Rome. However, the first real outbreak started on February 20, 2020, when subjects tested positive for the virus in a small town in the Lombardy region (Codogno), in the North of Italy (7). The situation quickly escalated, leading to a surge in cases throughout the northern regions and the densely populated area around the Po River by the end of March.

The first deaths were recorded on 22 February 2020, in two small municipalities in the North of Italy: Vo' and Casalpusterlengo. They were only the first in a long series of deaths. Some studies showed that during the first wave of COVID-19, excess mortality was recorded, especially in northern regions, where few provinces experienced increments up to 800% in March (110,111).

Recognizing the severity of the crisis, the Italian government, under Prime Minister Giuseppe Conte, implemented its first set of restrictive measures. On March 9, 2020, the government issued the first Decree of the President of the Council of Ministers (DPCM), imposing a nationwide lockdown to contain the spread of the virus (112). This DPCM marked the beginning of a stringent lockdown that included restrictions on movement, closure of non-essential businesses, and the suspension of public gatherings. The healthcare system faced unprecedented challenges as hospitals became overwhelmed, particularly in Lombardy and Piedmont, leading to a tragic surge in COVID-19-related deaths. Italy's response evolved with subsequent DPCMs, adjusting measures based on the dynamics of the pandemic.

The state of emergency, in Italy, lasted until March 31, 2022. To date, Italy is the ninth country by number of confirmed cases (26,318,717 confirmed cases), and the eighth country by number of deaths (192,909 deaths) (18).

Similar to the experience in other European and worldwide countries, the course of the SARS-CoV-2 pandemic in Italy evolved across distinct waves, each with its unique characteristics. These waves occurred during the periods of March-May 2020, October-December 2020, March-May 2021, and January-March 2022. It is important to note that the trajectory and duration of these waves exhibited variations from region to region.

During the first wave, Italy faced an overwhelming surge in hospital demands, combined with a scarcity of healthcare resources and professionals, resulting in a staggering death toll and a significant excess of mortality. The limited knowledge about the virus and the most effective treatments, combined with a high number of severe symptomatic cases, placed an immense strain on the national healthcare system. Additionally, the restricted availability of tests (Polymerase Chain Reaction (PCR) Tests and Serological tests) for detecting the virus, characterized by prolonged processing times and limited laboratory capacity, meant that not all subjects with COVID-19 were identified, exacerbating the challenges faced by the national healthcare system.

In subsequent waves, although the situation remained critical, small improvements were observed.

During the second wave, the number of subjects who tested positive for SARS-CoV-2 detected was significantly higher. This increment could be attributed in part to the wider availability of molecular or serological tests and the integration of rapid antigenic tests for virus detection into the hospitals, and in part could be explained by the presence of the highly transmissible Alpha variant during the second (and later third) wave. However, many Italian researchers observed a reduction in mortality and severity, identifying a significant decrease in the percentage of infected subjects who were hospitalized or admitted to ICU (113,114). The factors contributing to this improvement included an enhanced understanding of the virus, albeit evolving, an increase in healthcare workers, hospital facilities, and ICU beds, and the establishment of Special Units for Continuing Care at Home, specialized local medical services providing home care to infected patients.

A similar trend emerged during the third wave, where an even more noticeable improvement was observed in terms of severity and lethality (115,116). In addition to ongoing enhancements in the national healthcare system, two new features were introduced in this period: the availability of rapid antigen tests outside the hospital and the beginning of the Italian vaccination campaign against SARS-CoV-2 infection, which started in the early months of 2021.

In Italy, due to the scarcity of vaccines during the initial period, to start the vaccination program certain priority categories for vaccination were identified. The first groups who received the vaccine were healthcare professionals, teachers, university staff, military personnel, and patients who were clinically more vulnerable. Subsequently, vaccines were extended to older individuals (60+ years), with a focus on those with comorbidities. Finally, younger subjects with comorbidities and the rest of the population were vaccinated (117).

Several studies assessed the effect of vaccination campaigns on COVID-19-related outcomes in Italy, identifying a strong positive impact (118,119). According to Sacco et al. (118), the vaccination prevented a huge number of severe COVID-19 outcomes, including hospitalizations, ICU admissions, and deaths, especially among high-risk and vulnerable categories.

Finally, the fourth wave was indeed less intense in terms of severity and lethality, even though the number of infections reached a peak during this period (120). In fact, although the Omicron variant, which recently emerged, was highly contagious, the vaccination cycle that was completed by the majority of the population played a significant protective role. This had an important consequence: notable differences in adverse COVID-19 outcomes emerged when comparing vaccinated and non-vaccinated subjects. In particular, those who did not adhere to the vaccination program faced a higher risk of severe outcomes or death due to the infection (121).

Although Italy was one of the most affected countries in Europe and globally by the COVID-19 pandemic, an aspect that must also be considered is the fact that the impact of the pandemic may have been accentuated by the peculiar age distribution of the Italian population. According to some research that estimated mortality rates adjusted for age and sex, it emerged that some countries, including Italy, were comparatively less impacted than others such as the United Kingdom or Belgium (122,123). Therefore, the demographic age structure in Italy contributed significantly to the effect that the SARS-CoV-2 had in Italy, especially during the early phases of the pandemic.

2 AIMS

The main purpose of this doctoral project was to evaluate and investigate deeply and innovatively the association between multimorbidity and several COVID-19-related-outcomes. This was achieved by setting several primary aims.

The first primary objective was to assess the association between health conditions, susceptibility, and the severity of SARS-CoV-2. To achieve this aim, using data from the Piedmont Longitudinal Study, an administrative-health cohort containing clinical and sociodemographic information on subjects assisted by practitioners in the Piedmont region, the association between some clinical conditions or multimorbidity and several COVID-19-related outcomes was evaluated. In particular, four different groups of disease (cardiovascular, cerebrovascular, respiratory, and oncological) and three specific clinical conditions (myocardial infarction, heart failure, and diabetes) were assessed, while the Charlson Comorbidity Index was used as a proxy of multimorbidity. About the SARS-CoV-2 outcomes, five different endpoints were analyzed: access to the COVID-19 swab on the entire Piedmont population, positivity to SARS-CoV-2 among those who performed at least a swab, and hospitalization, ICU admissions, and death within thirty days from the first infection, among those who resulted positive to the virus. In addition, the last four outcomes were assessed also on the entire Piedmont population. The analyses were conducted by focusing exclusively on the first wave (February-May 2020), and separately by sex and by two different age groups: patients with 45-59 years old and 60-74 years old.

Moreover, the second objective of the same sample was to investigate the probability of transition into various states based on the CCI. The transitions that were considered involved three different possible states: from positivity for SARS-CoV-2 to hospitalization, from positivity to death within thirty days from the first infection, and from hospitalization to 30-day mortality.

The second main aim of this project was to evaluate the association between multimorbidity and various COVID-19-related outcomes, thoroughly exploring the potential mediating role played by the severity of the clinical condition of the patients at the time of access to the ED. Once again, CCI was utilized as a proxy of multimorbidity. Concerning the severity of clinical conditions, instead, the National Early Warning Score 2 (NEWS2), introduced in section 1.3, was used. Four distinct outcomes were examined: non-discharge from the Emergency Department on the entire sample, death within thirty days from the first positive swab on the entire sample, ICU admission or death among those who were hospitalized, and the length of hospitalization among those who were hospitalized and not deceased in the follow-up period. To achieve this objective, data from EPIDEMIOLOGIA CLINICA (EPICLIN) (124), a web platform containing clinical and demographic information from the EDs and medical records of patients admitted to 439 different hospitals, were used. Specifically, patients who tested positive for SARS-CoV-2 after accessing the Emergency Department of San Luigi Gonzaga Hospital in Orbassano (TO) and Molinette Hospital in Turin during the period from 1 March to 30 June 2020 were included in this project. Similar to the previous case, two age groups were considered to evaluate potential age-related differences: patients under 65 years old and patients with 65+ years old.

The third primary objective was to identify similarities and differences in the SARS-CoV-2 epidemic's timeline during the first three waves of the pandemic, evaluating clinical conditions, sociodemographic characteristics, and COVID-19 endpoints. This was done in four different Piedmont populations: infected subjects, hospitalized patients, patients who were admitted to the ICU, and subjects who died within 30 days from the first positive swab. The characteristics that were assessed were: age, gender, socioeconomic position, CCI, and several previous clinical conditions, including chronic obstructive pulmonary disease, cardiovascular disease, heart failure, coronary artery disease, cardiomyopathy, diabetes, kidney disease, cerebrovascular disease, dementia, neoplasia, hematologic disease, and immunodeficiency. About the COVID-19 outcomes, hospitalization, ICU admission, and death within thirty days from the first infection were analyzed. Moreover, this project aimed also to evaluate the severity of cases and the burden on Piedmont Hospital resources, assessing possible differences, among the waves, in the need for an Intensive Care Unit (ICU) and some respiratory supports (oxygen, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), intubation, invasive ventilation, and tracheotomy), and the length of hospitalization. Finally, the impact of the specific waves on the severity of COVID-19 was assessed, after eliminating all possible confounding. As for the first primary aim, data were obtained from the Piedmont Longitudinal Study.

Another main purpose of this doctoral project was to explore the impact of the COVID-19 pandemic and the related restrictive measures imposed by local governments on subjects' certain addictions and habits. In fact, this research identified the profound disruption inflicted by the pandemic on different aspects of individuals' lives, encompassing their habits, daily routines, and behaviors, irrespective of their demographic characteristics such as age, occupation, or health status. These disruptions transcended mere physical health repercussions, significantly affecting mental well-being, interpersonal relationships, and occupational landscapes. From abrupt transitions to remote work and virtual learning to heightened levels of stress and hurdles in accessing healthcare services, the pandemic fundamentally altered the day-to-day existence of millions worldwide, accentuating the intricate interplay between health outcomes and broader societal dynamics. For this reason, in this thesis the effect of the SARS-CoV-2 pandemic on gambling habits, one of the major addictions affecting many individuals, was investigated. Two different populations and three different outcomes were assessed: the general population, which involved both people who used to gamble before the pandemic and people who had never gambled in the pre-pandemic period, and the population consisted of gamblers or bettors who had gambling habits before the outbreak of pandemic. Regarding the outcomes, gambling frequency, gambling expenditure, and transitions among different types of gambling were investigated. To achieve this aim, a systematic review including 408 reports at the initial stage was conducted.

3 RESULTS

This section included PDFs of published or submitted articles that are the subject of this doctoral thesis. They are:

Article n° 1: Catalano A, Dansero L, Gilcrease W, Macciotta A, Saugo C, Manfredi L, Gnavi R, Strippoli E, Zengarini N, Caramello V, Costa G, Sacerdote C, Ricceri F. (2022) Multimorbidity and SARS-CoV-2- Related Outcomes: Analysis of a Cohort of Italian Patients. JMIR Public Health and Surveillance. Feb 9;9:e41404. doi: 10.2196/41404. PMID: 36626821; PMCID: PMC9951075. (IF: 8.5; n° citations: 4)

Article n° 2: Catalano A, Sacerdote C, Alvich M, Macciotta A, ..., Giraudo MT, Ciccone G, Pagano E, Boccuzzi A, Caramello V, Ricceri F. (2024). Multimorbidity and COVID-19 outcomes in Emergency Department: is the association mediated by the severity condition at admission? Western Journal of Emergency Medicine. (In review) (IF: 3.988)

Article n° 3: Caramello V, **Catalano A*,** Macciotta A, Dansero L, Sacerdote C, Costa G, Aprà F, Tua A, Boccuzzi A, Ricceri F. (2023). Improvements throughout the Three Waves of COVID-19 Pandemic: Results from 4 Million Inhabitants of North-West Italy. Journal of Clinical Medicine. Jul 25;11(15):4304. doi: 10.3390/jcm11154304. PMID: 35893395; PMCID: PMC9332615. (IF: 4.964; n° citations: 10)
***co-first author**

Article n° 4: Catalano A, Milani L, Franco M, Buscema F, Giommarini I, Gilcrease W, Mondo L, Marra M, Di Girolamo C, Bena A, Ricceri F. (2024). The impact of COVID-19 pandemic on gambling: A systematic review. Addictive Behaviors Journal. (Under Second Review) (IF: 4.4)

In the first part of this section, I present the results concerning the association between specific diseases or multimorbidity, as measured by the Charlson Comorbidity Index, and five distinct outcomes related to COVID-19: access to swab, SARS-CoV-2 positivity, hospitalization, admission to the ICU, and death within 30 days from the first infection. These outcomes, pertaining to the first wave of the pandemic, were derived from data collected in the Piedmont Longitudinal Study.
In the second part, also referring to the first wave of the COVID-19 pandemic, the results related to the association between the Charlson Comorbidity Index and four different COVID-19 outcomes (non-discharge from the emergency department, death within 30 days, ICU admission or death, and length of hospital stay) are shown, by assessing whether the NEWS2 Score, serving as a proxy for the severity of clinical conditions upon emergency department admission, acted as a mediator in these associations. Data

from San Luigi Gonzaga (Orbassano - TO) and Molinette (Turin) hospitals, available through the EPICLIN platform, were utilized for these analyses.

The third part comprises an investigation of the similarities and differences observed across the first three waves of COVID-19 in Piedmont. We focused on sociodemographic and clinical characteristics, as well as various COVID-19 outcomes including hospitalization, ICU admission, and death within 30 days. The analyses focused on four distinct Piedmont populations: individuals testing positive for SARS-CoV-2, hospitalized patients, patients who were admitted to the ICU, and subjects who succumbed within 30 days from the first infection. Again, the data were sourced from the Piedmont Longitudinal Study.

Lastly, the concluding segment of this section presents the findings of a systematic review that concentrated on the impact of COVID-19 and the ensuing restrictive measures on gambling habits. This review focused on two distinct populations (the general population and subjects with a history of gambling prior to the SARS-CoV-2 pandemic) and evaluated three endpoints: gambling frequency, expenditure on gambling activities, and transitions among different types of gambling.

Original Paper

3.1 Multimorbidity and SARS-CoV-2–Related Outcomes: Analysis of a Cohort of Italian Patients

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Abstract

Background: Since the outbreak of the COVID-19 pandemic, identifying the main risk factors has been imperative to properly manage the public health challenges that the pandemic exposes, such as organizing effective vaccination campaigns. In addition to gender and age, multimorbidity seems to be 1 of the predisposing factors coming out of many studies investigating the possible causes of increased susceptibility to SARS-CoV-2 infection and adverse outcomes. However, only a few studies conducted have used large samples.

Objective: The objective is to evaluate the association between multimorbidity, the probability to be tested, susceptibility, and the severity of SARS-CoV-2 infection in the Piedmont population (Northern Italy, about 4 million inhabitants). For this purpose, we considered 5 main outcomes: access to the swab, positivity to SARS-CoV-2, hospitalization, intensive care unit (ICU) admission, and death within 30 days from the first positive swab.

Methods: Data were obtained from different Piedmont health administrative databases. Subjects aged from 45 to 74 years and infections diagnosed from February to May 2020 were considered. Multimorbidity was defined both with the Charlson Comorbidity Index (CCI) and by identifying patients with previous comorbidities, such as diabetes and oncological, cardiovascular, and respiratory diseases. Multivariable logistic regression models (adjusted for age and month of infection and stratified by gender) were performed for each outcome. Analyses were also conducted by separating 2 age groups (45-59 and 60-74 years).

Results: Of 1,918,549 subjects, 85,348 (4.4%) performed at least 1 swab, of whom 12,793 (14.9%) tested positive for SARS-CoV-2. Of these 12,793 subjects, 4644 (36.3%) were hospitalized, 1508 (11.8%) were admitted to the ICU, and 749 (5.9%) died within 30 days from the first positive swab. Individuals with a higher CCI had a higher probability of being swabbed but a lower probability of testing positive. We observed the same results when analyzing subjects with previous oncological and cardiovascular diseases. Moreover, especially in the youngest group, we identified a greater risk of being hospitalized and dying. Among comorbidities considered in the study, respiratory diseases seemed to be the most likely to increase the risk of having a positive swab and worse disease outcomes.

Conclusions: Our study shows that patients with multimorbidity, although swabbed more frequently, are less likely to get infected with SARS-CoV-2, probably due to greater attention on protective methods. Moreover, a history of respiratory diseases is a risk factor for a worse prognosis of COVID-19. Nonetheless, whatever comorbidities affect the patients, a strong dose-response effect was observed between an increased CCI score and COVID-19 hospitalization, ICU admission, and death. These results are important in terms of public health because they help in identifying a group of subjects who are more prone to worse SARS-CoV-2 outcomes. This information is important for promoting targeted prevention and developing policies for the prioritization of public health interventions.

(JMIR Public Health Surveill 2023;9:e41404) doi: 10.2196/41404

KEYWORDS

multimorbidity; SARS-CoV-2; mortality; intensive care unit; epidemiology; COVID-19; pandemic; severity; cardiovascular; respiratory; disease; risk; public health; intervention

Introduction

Background

Since the outbreak of the COVID-19 pandemic in Italy and the world, identifying the risk factors for the development of a severe prognosis in patients with SARS-CoV-2 infection has been imperative to properly manage public health challenges that the pandemic exposes. For instance, organizing effective vaccination campaigns when just a limited number of vaccines were available was essential, and it is still important at the moment to decide on the prioritization of new campaigns for subsequent vaccine doses [1,2]. Moreover, the availability of accurate information about the possible evolution of the disease in the presence of risk factors can support the population in the choice of prudent behaviors aimed at preventing the spread of the contagion chain, with particular regard to the most vulnerable individuals.

Many studies in the literature have focused on the sociodemographic and clinical characteristics that are most associated with the development of a severe prognosis. Age and gender play an important role in determining the prognosis of patients with SARS-CoV-2. The elderly are especially at higher risk of becoming severely ill [3-5], and males are also a greater risk of a severe prognosis [5,6]. Among the several mechanisms proposed to explain the severity of COVID-19 in older adults, the increased burden of multimorbidity is 1 of the most relevant [7]. Moreover, several studies also have shown that multimorbidity affects COVID-19 severity in a way that is age independent, underscoring the need for an extensive study of the relationship between multimorbidity and SARS-CoV-2 outcomes [7].

Available evidence related to the identification of comorbidities that can negatively impact the prognosis in patients with SARS-CoV-2 refers essentially to observational, cross-sectional, retrospective cohort studies or case-control studies. There is general agreement on the role of hypertension, cardiovascular disease, and diabetes in increasing the risk of severe disease [5,6,8-10]. Therefore, comorbidities that affect the vascular system may play a key role in the worsening of clinical conditions in people affected by COVID-19. Moreover, there is some consensus on the role that obesity, cancer, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and immunodepression could play in aggravating the prognosis [4-6,9]. However, these associations have been highlighted in a more sporadic and less uniform way.

In an initial phase, the correlation between the presence and the number of comorbidities with a more unfavorable outcome was pointed out to evaluate the prognosis of patients with SARS-CoV-2 [9]. This tool has been nevertheless effective and useful in individuating the key feature of the population at risk, which was crucial during the first phase of the pandemic.
It was in fact observed that subjects with some comorbidities (measured as a Charlson Comorbidity Index [CCI] [11]) equal to or greater than 1 are at higher risk of severe COVID-19 outcomes compared to subjects with no comorbidity [12,13]. Moreover, an innovative approach to the SARS-CoV-2 pandemic (the so-called “syndemic approach”) suggests that both bio-bio and biosocial interactions can act as complex drivers that increase subjects’ susceptibility to worsen COVID-19 outcomes [14-17].

Consequently, it is crucial to identify multifactorial profiles, including social determinants of health, and multimorbidity patterns associated with COVID-19 outcomes in order to recognize a broader syndemic health burden in specific subgroups of subjects with those characteristics [18,19].

Study Design and Aim

This large population-based region-wide study based on administrative health databases aims to evaluate the association between multimorbidity and the susceptibility and severity of SARS-CoV-2 infection in the Piedmont population (Northern Italy, about 4 million inhabitants) aged from 45 to 74 years, considering COVID-19 infections diagnosed from February to May 2020.

Specifically, 5 different main outcomes were considered: access to the swab, positivity to SARS-CoV-2, hospitalization, admission to the intensive care unit (ICU), and death within 30 days from the first positive swab.

Methods

Study Population

For the analyses, data were obtained from the Piedmont Longitudinal Study (PLS), an administrative cohort based on the anonymous record linkage at the individual level of different social, health, and administrative databases. This study includes 2011 census data, hospital discharges, a mortality register, an outpatients register, an exemption register (in Italy, subjects with at least 1 chronic disease are exempt from paying for examinations related to their disease), and a drug prescriptions database. In addition, starting from February 2020, this study was enriched by the regional platform about COVID-19, in which infection data about subjects who had at least 1 contact with the regional health system related to SARS-CoV-2 are collected.

The study population comprised all assisted and domiciled subjects in Piedmont aged from 45 to 74 years. These 2 age classes were chosen in order to exclude young and elderly subjects, as they could have influenced the results. Furthermore, this choice made it possible to exclude the majority of patients residing in nursing homes in order to avoid any bias. With regard to SARS-CoV-2 infection, we considered those patients who developed the infection in Piedmont from February 22, 2020 (when the first case of SARS-CoV-2 was recorded in Italy), to May 31, 2020.

Variables' Definitions

Multimorbidity was defined using the CCI [11] retrieved by the record linkage with data of the hospital discharges and the drug prescription register between 2015 and 2019. In Multimedia Appendix 1, Table S1a, we present the algorithm's definition.

The presence of prevalent oncological, cardiovascular, and respiratory diseases was also retrieved, as well as prevalent previous myocardial infarctions, heart failures, cerebrovascular diseases, and diabetes (algorithms presented in Multimedia Appendix 1, Table S1b).

Five different outcomes were considered: access to a SARS-CoV-2 test (nasal swab in almost all cases), positivity to the test, hospitalization, admission to the ICU, and mortality within 30 days after testing positive for SARS-CoV-2 infection. The 4 latter outcomes were compared to both the general population and to the total tested subjects or the subjects positive for SARS-CoV-2, as appropriate.

Statistical Analysis

All the variables were described using absolute frequencies and percentages. For each outcome and exposure, we fitted a multivariable logistic regression model, in which the odds ratio (OR) estimates, together with their 95% Cls, were adjusted for age (used as a continuous variable) and for the month of infection or the first negative swab, where appropriate.

Moreover, to assess the probability of transition into various states on the basis of the CCI, multistate models were implemented. The possible transitions that were considered in the study involved 3 different states: from positivity to COVID-19 to hospitalization, from positivity to death within 30 days of the initial positive swab, and from hospitalization to 30-day mortality (Multimedia Appendix 1, Figure S1). In 1 case, the multistate models were stratified by the CCI score and adjusted for age and the month of infection; in the second case, the multistate models were adjusted for age, the month of infection, and the CCI.

All analyses were stratified by gender and 2 different age groups, 45-59 and 60-74 years, because we observed the differences between gender and age as effect modifiers.

Analyses were performed using SAS (V9.4) and R (V4.2.1).

Ethical Considerations

All analyses were conducted according to the World Medical Association's Declaration of Helsinki. In fact, the study is included in the National Statistical Plan and did not need approvals or permits from the ethics committee. For privacy purposes, the data used for analysis were anonymized.

Results

Study Population

Of 1,918,549 assisted and domiciled subjects in Piedmont aged from 45 to 74 years, 85,348 (4.4%) performed at least 1 swab during the observation period, of whom 12,793 (14.9%) tested positive for SARS-CoV-2. Of these 12,793 patients, 4644 (36.3%) were hospitalized due to COVID-19, 1508 (11.8%) were admitted to the ICU, and 749 (5.9%) died within 30 days from the first positive swab.

The descriptive statistics related to the exposures and variables used in the study are shown in Table 1. Among other results, the most interesting was related to gender. Overall, despite more women testing positive for SARS-CoV-2 (n=6832, 53.4%), higher percentages of men were hospitalized (3074/4644, 66.2%), were admitted to the ICU (1118/1508, 74.1%), and died (558/749, 74.5%). The same trend was observed when considering age: although more subjects aged 45-59 years tested positive for SARS-CoV-2 (n=7324, 57.2%), more individuals aged 60-74 years were hospitalized (2927/4644, 63%), were admitted to the ICU (1005/1508, 66.6%), and died (629/749, 84%).

Descriptive analyses also showed that multimorbidity (measured as CCI>1) increased the probability of being swabbed, hospitalized, admitted to the ICU, and dying from COVID-19.

Table 2 shows the OR estimates, together with their 95% Cls, related to accessing swabs for the entire population. The results showed that as the CCI increased, the likelihood of undergoing swab testing increased for both the male and the female population. In addition, other estimates indicated that being affected by 1 of the diseases considered in the study increased the likelihood of undergoing at least 1 swab test, especially in the case of heart failure, respiratory diseases, and cerebrovascular diseases (males aged 45-59 years: OR 2.60, 95% CI 2.30-2.94; males aged 60-74 years: OR 2.71, 95% CI 2.53-2.90; females aged 45-59 years: OR 1.63, 95% CI 1.45-1.85; females aged 60-74 years: OR 3.31, 95% CI 3.04-3.60).

The relationship between multimorbidity and SARS-CoV-2 positivity among those who performed at least 1 swab is shown in Table 3. The OR estimates indicated an inverse trend: the likelihood of testing positive for SARS-CoV-2 infection decreased as the CCI value increased. Moreover, those who were affected by oncological diseases had a significantly lower likelihood of testing positive for SARS-CoV-2, especially men (45-59 years old: OR 0.72, 95% CI 0.55-0.95; 60-74 years old: OR 0.63, 95% CI 0.53-0.73). Other specific diseases were less associated with the results of the SARS-CoV-2 infection test. On the contrary, when compared to the general population, multimorbid patients had an increased likelihood of testing positive (Multimedia Appendix 1, Table S2).

Table 4 shows the results related to the subjects who were admitted to the hospital from among those who tested positive for SARS-CoV-2. The results indicated that particularly for men from the ages of 45 to 59 years, the probability of hospital admission rose significantly as the CCI score increased (CCI=1: OR 1.50, 95% CI 1.20-1.88; CCI=2-3: OR 2.14, 95% CI 1.51-3.01; CCI=4+: OR 4.77, 95% CI 2.28-9.99). This also included females aged 60-74 years (CCI=1: OR 1.22, 95% CI 0.98-1,52; CCI=2-3: OR 2.28, 95% CI 1.74-2.99; CCI=4+: OR 4.22, 95% CI 2.56-6.97). Regarding the specific diseases considered in the study, the estimates suggested that except in the case of cerebrovascular diseases, patients affected by comorbidities had a significantly higher risk of being hospitalized. The results were similar when considering the entire population (Multimedia Appendix 1, Table S3).

The results related to admission to the ICU among those who tested positive with at least 1 swab are shown in Table 5. Unexpectedly, the association with multimorbidity was weak except for older women, while only a few associations were found with the specific diseases investigated. In contrast, compared to the general population, it emerged that patients with comorbidities and a higher CCI value had a higher risk of being admitted to intensive care for SARS-CoV-2 infection, especially in the case of respiratory diseases (Multimedia Appendix 1, Table S4).

Table 6 shows the OR estimates related to death within 30 days from the first positive swab among those who tested positive for SARS-CoV-2. Results suggested that as the CCI value increased, the risk of dying from COVID-19 significantly increased. When analyzing specific comorbidities, the estimates showed that the risk is significantly higher, especially among the younger population (eg, oncological diseases: OR 6.03, 95% CI 3.00-12.12 for males and OR 11.03, 95% CI 3.93-30.96 for females). Results were confirmed, considering the comparison with the general population (Multimedia Appendix 1, Table S5).

Table 7 and Multimedia Appendix 1, Figure S2, illustrate the outcomes of the multistate models. The probability of being hospitalized after testing positive for SARS-CoV-2 increased as the CCI increased, notably in the younger population, according to the hazard ratio (HR) estimates shown in the table. Furthermore, it appears that multimorbidity increased the risk of dying within 30 days of the first infection both without being hospitalized and after being hospitalized, with the exception of a small number of cases where some estimates were not statistically significant due to the low number of cases transiting among states.

Finally, stratifying the multistate models for the CCI revealed that both in the younger and the older population, the likelihood of COVID-19 severe outcomes considerably increased as the CCI score increased.

Table 1. Descriptive statistics related to the demographic and clinical characteristics of patients.

Variable and category	Entire population (N=1,918,549), n (%)	Access to the swab (n=85,348), n (%)	Positivity to SARS-Cov-2 (n=12,793), n (%)	Hospitalization (n=4644), n (%)	Admitted to the ICU[a] (n=1508), n (%)	Death within 30 days (n=749), n (%)
Gender						
Male	938,610 (48.9)	32,129 (37.6)	5961 (46.6)	3075 (66.2)	1118 (74.1)	558 (74.5)
Female	979,939 (51.1)	53,219 (62.4)	6832 (53.4)	1569 (33.8)	390 (25.9)	191 (25.5)
Age (years)						
45-59	1,062,861 (55.4)	54,672 (64.1)	7324 (57.2)	1717 (37.0)	503 (33.4)	120 (16.0)
60-74	855,688 (44.6)	30,676 (35.9)	5469 (42.8)	2927 (63.0)	1005 (66.6)	629 (84.0)
Month of first swab						
February-March	N/A[b]	14,134 (16.6)	5364 (41.9)	3088 (66.5)	1079 (71.5)	502 (67.0)
April-May	N/A	71,214 (83.4)	7429 (58.1)	1556 (33.5)	429 (28.5)	247 (33.0)
CCI[c]						
0	1,442,666 (75.2)	58,775 (68.8)	8,620 (67.4)	2,599 (56.0)	837 (55.5)	280 (37.4)
1	335,685 (17.5)	16,180 (19.0)	2540 (19.8)	1091 (23.5)	361 (23.9)	175 (23.3)
2-3	121,723 (6.3)	8099 (9.5)	1277 (10.0)	710 (15.3)	233 (15.5)	199 (26.6)
4+	18,475 (1.0)	2294 (2.7)	356 (2.8)	244 (5.2)	77 (5.1)	95 (12.7)
Oncological disease	58,742 (3.1)	3993 (4.7)	525 (4.1)	303 (6.5)	83 (5.5)	82 (11.0)
Cardiovascular disease	136,335 (7.1)	9239 (10.8)	1480 (11.6)	797 (17.2)	252 (16.7)	217 (29.0)
Respiratory disease	50,328 (2.6)	4792 (5.6)	751 (5.9)	426 (9.2)	124 (8.2)	129 (17.2)
Myocardial infarction	40,288 (2.1)	2416 (2.8)	420 (3.3)	278 (6.0)	99 (6.6)	78 (10.4)
Heart failure	7,817 (0.4)	762 (0.9)	117 (0.9)	79 (1.7)	22 (1.5)	28 (3.7)
Cerebrovascular disease	23,753 (1.2)	2197 (2.6)	378 (2.9)	186 (4.0)	53 (3.5)	72 (9.6)
Diabetes	157,214 (8.2)	8335 (9.8)	1547 (12.1)	896 (19.3)	352 (23.3)	239 (31.9)

[a]ICU: intensive care unit.

[b]N/A: not applicable.

[c]CCI: Charlson Comorbidity Index.

Table 2. OR[a] estimates related to access to the swab for the entire population (N=85,348), stratified by gender and age group (1 model for each variable).

Variable and category	Male		Female	
	Age 45-59 years (n=16,978, 19.9%), OR (95% CI)[b]	Age 60-74 years (n=15,151, 17.8%), OR (95% CI)[b]	Age 45-59 years (n=37,694, 44.2%), OR (95% CI)[b]	Age 60-74 years (n=15,525, 18.1%), OR (95% CI)[b]
CCI[c]				
0	Reference	Reference	Reference	Reference
1	1.37 (1.32-1.43)	1.31 (1.26-1.37)	1.22 (1.19-1.26)	1.39 (1.34-1.45)
2-3	2.41 (2.26-2.56)	2.31 (2.21-2.42)	1.37 (1.31-1.45)	2.19 (2.09-2.30)
4+	4.41 (3.93-4.95)	4.93 (4.62-5.26)	2.22 (1.91-2.57)	5.18 (4.73-5.68)
Oncological disease	2.31 (2.10-2.53)	2.04 (1.93-2.15)	1.18 (1.10-1.27)	1.80 (1.69-1.92)
Cardiovascular disease	1.94 (1.84-2.05)	2.11 (2.03-2.19)	1.45 (1.37-1.52)	2.19 (2.09-2.29)
Respiratory disease	2.41 (2.24-2.59)	3.20 (3.03-3.37)	1.68 (1.57-1.79)	3.34 (3.13-3.55)
Myocardial infarction	1.57 (1.42-1.74)	1.71 (1.62-1.81)	1.53 (1.32-1.77)	1.94 (1.76-2.14)
Heart failure	2.45 (2.00-3.00)	3.07 (2.78-3.40)	1.71 (1.27-2.29)	3.28 (2.81-3.83)
Cerebrovascular disease	2.60 (2.30-2.94)	2.71 (2.53-2.90)	1.63 (1.45-1.85)	3.31 (3.04-3.60)
Diabetes	1.46 (1.37-1.55)	1.46 (1.40-1.52)	1.21 (1.15-1.27)	1.60 (1.52-1.67)

[a]OR: odds ratio.

[b]Estimates adjusted for age. All estimates (95% confidence level) were significant.

[c]CCI: Charlson Comorbidity Index.

Table 3. OR[a] estimates related to positivity to SARS-CoV-2 among those who performed at least 1 swab (N=12,793), stratified by gender and age group (1 model for each variable).

Variable and category	Male		Female	
	Age 45-59 years (n=2847, 22.3%), OR (95% CI)[b]	Age 60-74 years (n=3114, 24.3%), OR (95% CI)[b]	Age 45-59 years (n=4477, 35.0%), OR (95% CI)[b]	Age 60-74 years (n=2355, 18.4%), OR (95% CI)[b]
CCI[c]				
0	Reference	Reference	Reference	Reference
1	0.97 (0.87-1.10)	1.07 (0.96-1.19)	1.01 (0.93-1.10)	1.05 (0.94-1.17)
2-3	0.79 (0.66-0.95)[d]	0.86 (0.77-0.97)[d]	0.98 (0.84-1.14)	0.93 (0.81-1.07)
4+	0.60 (0.42-0.86)[d]	0.79 (0.67-0.95)[d]	0.67 (0.41-1.09)	0.91 (0.71-1.17)
Oncological disease	0.72 (0.55-0.95)[d]	0.63 (0.53-0.73)[d]	0.82 (0.66-1.02)	0.70 (0.57-0.87)[d]
Cardiovascular disease	0.80 (0.68-0.94)[d]	0.91 (0.82-1.01)	0.89 (0.77-1.04)	1.02 (0.89-1.16)
Respiratory disease	0.89 (0.73-1.09)	0.88 (0.76-1.01)	0.82 (0.67-1.02)	1.05 (0.89-1.25)
Myocardial infarction	0.83 (0.62-1.12)	0.84 (0.72-0.98)	0.58 (0.34-0.99)[d]	1.10 (0.84-1.43)
Heart failure	0.46 (0.22-0.98)[d]	0.78 (0.59-1.04)	0.84 (0.33-2.14)	1.10 (0.74-1.65)
Cerebrovascular disease	0.95 (0.67-1.35)	1.18 (0.99-1.41)	0.83 (0.56-1.22)	1.12 (0.90-1.41)
Diabetes	1.02 (0.86-1.20)	1.25 (1.13-1.39)[d]	1.16 (1.01-1.34)[d]	1.11 (0.98-1.27)

[a]OR: odds ratio.

[b]Estimates adjusted for age and the month of the first swab.

[c]CCI: Charlson Comorbidity Index.

[d]Significant estimates (95% confidence level).

Table 4. OR[a] estimates related to admission to the hospital among those who tested positive for SARS-CoV-2 (N=4644), stratified by gender and age group (1 model for each variable).

Variable and category	Male		Female	
	Age 45-59 years (n=1101, 23.7%), OR (95% CI)[b]	Age 60-74 years (n=1974, 42.5%), OR (95% CI)[b]	Age 45-59 years (n=616, 13.3%), OR (95% CI)[b]	Age 60-74 years (n=953, 20.5%), OR (95% CI)[b]
CCI[c]				
0	Reference	Reference	Reference	Reference
1	1.50 (1.20-1.88)[d]	1.51 (1.23-1.84)[d]	1.50 (1.20-1.88)[d]	1.22 (0.98-1.52)
2-3	2.14 (1.51-3.01)[d]	1.40 (1.12-1.75)[d]	2.49 (1.77-3.50)[d]	2.28 (1.74-2.99)[d]
4+	4.77 (2.28-9.99)[d]	1.98 (1.41-2.78)[d]	2.45 (0.86-6.94)	4.22 (2.56-6.97)[d]
Oncological disease	2.62 (1.52-4.51)[d]	1.27 (0.93-1.73)	2.26 (1.39-3.68)[d]	1.97 (1.34-2.92)[d]
Cardiovascular disease	1.53 (1.13-2.08)[d]	1.30 (1.01-1.49)[d]	1.69 (1.17-2.44)[d]	1.52 (1.19-1.95)[d]
Respiratory disease	2.17 (1.48-3.19)[d]	1.47 (1.12-1.92)[d]	2.13 (1.31-3.45)[d]	2.16 (1.57-2.96)[d]
Myocardial infarction	1.84 (1.03-3.30)[d]	1.47 (1.09-1.97)[d]	2.05 (0.61-6.94)	2.36 (1.44-3.89)[d]
Heart failure	7.90 (1.53-40.70)[d]	2.18 (1.23-3.86)[d]	1.25 (0.12-12.56)	1.88 (0.90-3.93)
Cerebrovascular disease	1.39 (0.69-2.81)	0.92 (0.68-1.26)	1.30 (0.47-3.63)	1.11 (0.73-1.71)
Diabetes	1.65 (1.20-2.28)[d]	1.61 (1.31-1.96)[d]	1.89 (1.35-2.63)[d]	2.10 (1.64-2.69)[d]

[a]OR: odds ratio.

[b]Estimates adjusted for age and the month of the first swab.

[c]CCI: Charlson Comorbidity Index.

[d]Significant estimates (95% confidence level).

Table 5. OR[a] estimates related to admission to the ICU[b] among those who tested positive for SARS-CoV-2 (N=1508), stratified by gender and age group (1 model for each variable).

Variable and category	Male		Female	
	Age 45-59 years (n=370, 24.5%), OR (95% CI)[c]	Age 60-74 years (n=748, 49.6%), OR (95% CI)[c]	Age 45-59 years (n=133, 8.8%), OR (95% CI)[c]	Age 60-74 years (n=257, 17.1%), OR (95% CI)[c]
CCI[d]				
0	Reference	Reference	Reference	Reference
1	1.39 (1.04-1.86)[e]	1.15 (0.94-1.42)	1.06 (0.66-1.70)	1.25 (0.91-1.73)
2-3	1.32 (0.85-2.05)	1.04 (0.82-1.32)	2.46 (1.39-4.36)[e]	1.89 (1.32-2.71)[e]
4+	1.91 (0.83-4.39)	1.09 (0.77-1.54)	1.33 (0.17-10.35)	2.35 (1.32-4.19)[e]
Oncological disease	1.44 (0.74-2.80)	0.86 (0.62-1.20)	0.91 (0.28-2.94)	0.97 (0.55-1.71)
Cardiovascular disease	1.58 (1.09-2.30)[e]	0.84 (0.68-1.03)	2.02 (1.08-3.76)[e]	1.23 (0.87-1.75)
Respiratory disease	1.53 (0.96-2.45)	0.84 (0.63-1.14)	1.92 (0.81-4.51)	1.53 (1.01-2.32)[e]
Myocardial infarction	2.05 (1.08-3.86)[e]	1.04 (0.77-1.40)	2.00 (0.25-15.85)	1.75 (0.95-3.22)
Heart failure	N/A[f]	1.16 (0.66-2.06)	N/A	1.39 (0.52-3.69)
Cerebrovascular disease	1.39 (0.55-3.50)	0.74 (0.50-1.08)	1.08 (0.14-8.21)	0.94 (0.49-1.80)
Diabetes	1.43 (0.98-2.11)	1.58 (1.31-1.92)[e]	2.58 (1.51-4.42)[e]	2.14 (1.57-2.92)[e]

[a]OR: odds ratio.
[b]ICU: intensive care unit.
[c]Estimates adjusted for age and the month of the first swab.
[d]CCI: Charlson Comorbidity Index.
[e]Significant estimates (95% confidence level).
[f]N/A: not applicable.

Table 6. OR[a] estimates related to death within 30 days from the first positive swab among those who tested positive to SARS-CoV-2 (N=749), stratified by gender and age group (1 model for each variable).

Variable and category	Male		Female	
	Age 45-59 years (n=370, 24.5%), OR (95% CI)[b]	Age 60-74 years (n=748, 49.6%), OR (95% CI)[b]	Age 45-59 years (n=133, 8.8%), OR (95% CI)[b]	Age 60-74 years (n=257, 17.1%), OR (95% CI)[b]
CCI[c]				
0	Reference	Reference	Reference	Reference
1	1.56 (0.89-2.75)	1.33 (1.02-1.74)[d]	2.26 (0.68-7.56)	1.50 (0.99-2.27)
2-3	5.33 (3.06-9.27)[d]	2.24 (1.72-2.91)[d]	16.80 (6.35-44.45)[d]	2.43 (1.58-3.73)[d]
4+	17.32 (7.91-37.90)[d]	3.26 (2.29-4.64)[d]	31.88 (5.96-170.43)[d]	5.90 (3.31-10.52)[d]
Oncological disease	6.03 (3.00-12.12)[d]	1.46 (1.04-2.05)[d]	11.03 (3.93-30.96)[d]	1.38 (0.77-2.47)
Cardiovascular disease	3.52 (2.12-5.86)[d]	1.56 (1.24-1.95)[d]	2.81 (0.82-9.62)	2.04(1.41-2.94)[d]
Respiratory disease	3.89 (2.16-7.02)[d]	2.07 (1.54-2.78)[d]	5.88 (1.70-20.39)[d]	2.92 (1.91-4.45)[d]
Myocardial infarction	2.80 (1.15-6.81)[d]	1.50 (1.09-2.06)[d]	N/A[e]	2.16 (1.41-2.94)[d]
Heart failure	8.42 (1.66-42.77)[d]	1.79 (0.99-3.23)	N/A	6.04 (2.70-13.53)[d]
Cerebrovascular disease	5.68 (2.24-14.36)[d]	1.96 (1.38-2.79)[d]	N/A	2.06 (1.17-3.65)[d]
Diabetes	2.36 (1.34-4.15)[d]	1.79 (1.43-2.23)[d]	5.72 (2.21-14.79)[d]	2.35 (1.64-3.35)[d]

[a]OR: odds ratio.
[b]Estimates adjusted for age and the month of the first swab.
[c]CCI: Charlson Comorbidity Index.
[d]Significant estimates (95% confidence level).
[e]N/A: not applicable.

Table 7. HR[a] estimates related to multistate models for each possible transition, stratified by gender and age group.

CCI[b]	Male (age 45-59 years), HR (95% CI)[c]	Male (age 60-74 years), HR (95% CI)[c]	Female (age 45-59 years), HR (95% CI)[c]	Female (age 60-74 years), HR (95% CI)[c]
Positive --> hospitalization				
0	Reference	Reference	Reference	Reference
1	1.34 (1.15-1.56)	1.19 (1.06-1.33)	1.43 (1.17-1.75)	1.19 (1.01-1.39)
2-3	1.48 (1.18-1.86)	1.09 (0.96-1.23)	2.49 (1.90-3.26)	1.61 (1.34-1.93)
4+	2.71 (1.85-3.97)	1.25 (1.04-1.49)	2.42 (1.09.5.33)	2.39 (1.81-3.16)
Positive --> death within 30 days from first infection				
0	Reference	Reference	Reference	Reference
1	3.87 (0.01-infinity)	0.73 (0.29-1.87)	N/A[d]	2.67 (1.05-6.80)
2-3	1.20 (0.01-infinity)	2.10 (1.03-4.28)	22.57 (2.32-219.69)	4.13 (1.53-11.12)
4+	220750.22 (0.01-infinity)	3.33 (1.37-8.11)	N/A	7.69 (2.00-29.52)
Hospitalization --> death within 30 days from first infection				
0	Reference	Reference	Reference	Reference
1	1.42 (0.30-6.61)	1.22 (0.94-1.59)	8.29 (2.81-24.38)	1.40 (0.89-2.21)
2-3	5.10 (1.34-19.44)	1.92 (1.49-2.49)	0.03 (0.01-37674.39)	1.61 (0.99-2.61)
4+	728.13 (355.06-1493.24)	2.38 (1.71-3.31)	0.41 (0.01-93403.78)	3.46 (1.98-6.04)

[a]HR: hazard ratio.

[b]CCI: Charlson Comorbidity Index.

[c]Estimated adjusted for age and the month of the first swab.

[d]N/A: not applicable.

Discussion

Principal Findings

In this study, we analyzed the association between multimorbidity and SARS-CoV-2 outcomes in the population of the large Italian region of Piedmont. It emerged that multimorbidity is a strong risk factor for a worse prognosis of COVID-19, especially in the younger population. In addition, results highlighted that although subjects with previous diseases were more likely to be swabbed, they had a general lower risk of being infected.

Regarding access to the swab during the first wave of the COVID-19 pandemic, the estimates showed that the likelihood of being swabbed was greater for patients with previous diseases, regardless of the kind of disease, and this risk increased with the increase in multimorbidity (measured as the CCI). This is consistent with what was observed during the outbreak of the COVID-19 pandemic in early 2020, when only few laboratories were equipped for performing the SARS-CoV-2 test from nasal swabs and the Italian government published strict clinical and epidemiological criteria for accessing the tests (among those, subjects with a chronic disease are considered at higher risk), which were also limited in availability [20]. In addition, from April 2020, patients with chronic diseases were swabbed to access outpatient services, such as dialysis or cancer treatments.

Focusing on positivity to SARS-CoV-2, when considering the entire population, it emerged that the risk of infection is higher for subjects with previous comorbidities, in line with other studies [21,22]. This occurs because subjects affected by comorbidities, due to poor clinical conditions, generally perform more swabs compared to healthy subjects; thus, their probability of testing positive for COVID-19 is higher. In contrast, when investigating the likelihood of testing positive only among those who performed at least 1 swab, we identified that patients with comorbidities are less likely to test positive for SARS-CoV-2. This result could be due to the fact that subjects with poorer clinical conditions pay more attention to protective methods, such as social distancing, wearing masks, handwashing, and avoiding overcrowded places, which significantly reduce the risk of SARS-CoV-2 infection [23].

In our investigation of hospitalization, we also found that multimorbidity, which in our study was measured through the CCI, is a strong risk factor for a worse prognosis of COVID-19. This is consistent with a number of studies conducted on the topic [12,13,24]. Among all possible comorbidities, Chudasama et al [24] identified in their study that pre-existing hypertension is the most prevalent condition in subjects affected by severe SARS-CoV-2 infection, and it mainly coexists with other previous comorbidities: stroke, diabetes, and chronic kidney disease. However, the risk of severe COVID-19 is highest in patients affected by both previous diabetes and pre-existing chronic kidney disease.

One of the possible reasons patients with multiple comorbidities have an increased risk of developing severe SARS-CoV-2 is that they generally use inhibitors of the renin-angiotensin system (RAS) to limit the effect of their comorbidities. These inhibitors cause the overexpression of angiotensin-converting enzyme 2 (ACE2), which in turn facilitates the entry of SARS-CoV-2 into human target cells. In addition, high levels of some biomarkers, such as C-reactive protein, D-dimer, procalcitonin, and ferritin, in individuals with multiple comorbidities may lead or contribute to a worse prognosis of COVID-19 [13]. In fact, it has been found that these biomarkers are often elevated in subjects who contract severe infection.

In our study, we also identified that the risk of being admitted to the ICU among those who tested positive to the virus was not significantly higher for subjects affected by multimorbidity, except in a few cases, such as cardiovascular diseases and diabetes. Given the findings that emerged from our research in relation to hospital admissions and death, this result would seem to be counterintuitive. This finding may be attributable to the decisions made by health care professionals during the first pandemic wave about which patients to admit to intensive care and which not to admit. In fact, health care professionals had to choose which subjects to admit to the ICU on the basis of their clinical conditions, the number and severity of comorbidities, age, and possible benefits of admission, also due in the peak weeks of the pandemic to the limited number of beds available. Only subjects with the highest clinical outcomes and potential benefits were therefore admitted to the ICU. The mortality data support this explanation; in fact, as expected, the probability of dying from COVID-19 increased dramatically as the CCI value increased.

Considering specific comorbidities, we found that subjects with almost all previous comorbidities have a greater risk of developing a worse prognosis of COVID-19, considering both the general population and only patients with SARS-CoV-2. This is in line with other studies that have highlighted this topic. According to some research that investigated the relationship between oncological diseases and SARS-CoV-2–related outcomes [25-27], people with cancer have a greater risk of developing a worse prognosis of COVID-19. This finding could be due to the fact that patients with cancer are particularly susceptible to the immunosuppressive state caused by antitumor therapies received, such as radiotherapy and chemotherapy [26]. In addition, the risk of COVID-19 severity has been found to be higher for individuals who received their last chemotherapy within 14 days of admission [28].

Further studies that have investigated the association between cardiovascular or cerebrovascular diseases and COVID-19 outcomes found that the risk of severe SARS-CoV-2 is significantly higher for subjects affected by these comorbidities [8,29]. Furthermore, according to a meta-analysis conducted on 56 studies [30], it was shown that the risk of developing severe COVID-19 is greater, considering patients with SARS-CoV-2 and any pre-existing cardiovascular diseases and also when considering specific cardiovascular comorbidities separately, such as acute cardiac injury or heart failure, as shown in our study. This association could be due to the fact that drugs used to limit cardiovascular and cerebrovascular risk, such as ACE inhibitors and angiotensin II receptor blockers (ARBs), have numerous effects that could influence the susceptibility to or the severity of COVID-19. In fact, it was demonstrated that ACE inhibitors and ARBs increase the expression of ACE2, which is the viral receptor for SARS-COV-2 and facilitates the virus entry into pneumocytes [29,31].

In relation to diabetes, several studies have also shown that it is a risk factor for the mortality and severity of COVID-19. In fact, according to different studies and meta-analyses [32-35], the risk of contracting severe SARS-CoV-2 or dying from the virus infection has been found to be significantly higher for patients with diabetes. One possible reason for this is that subjects with diabetes have a higher risk of uncontrolled inflammatory response, higher levels of tissue injury–related enzymes, a higher hypercoagulable state, and higher serum levels of inflammatory biomarkers, such as C-reactive protein, D-dimer, interleukin-6 (IL-6), serum ferritin, and coagulation index. This greater susceptibility to an inflammatory status could lead to a worse prognosis of COVID-19, especially in patients with poor glycemic control, since hyperglycemia is a powerful antagonist of the immune response [32,36]. In addition, these subjects also have an immune system downregulated by impairing the function of innate immunity, such as chemotaxis and the activity of neutrophils and macrophages, that could lead to severe COVID-19 outcomes or mortality [35].

Other studies have instead found a relationship between pre-existing respiratory comorbidities and the risk of developing a worse prognosis of COVID-19, especially in the case of COPD, asthma, and obstructive sleep apnea (OSA) [37-39]. This association, on the one hand, is due to the fact that previous respiratory diseases could worsen lung function, could make the airways hypersensitive, and could cause immune alteration in the patients, possibly leading to subjects contracting more severe SARS-CoV-2 [38]. On the other hand, especially in the case of pre-existing OSA, hypercapnia and hypoxemia, surges of sympathetic activation, and increased inflammatory markers may contribute to contracting more severe SARS-CoV-2 [39].

Although in our study, we only investigated diabetes and oncological, cardiovascular, cerebrovascular, and respiratory diseases, previous research has shown that other comorbidities, such as chronic liver and chronic kidney diseases, are also associated with a more severe prognosis of COVID-19 [40,41].

Strengths and Limitations

This study represents an advance on what is already present in the literature. In fact, compared to what has been investigated on this topic to date, in this research, (1) a population study was conducted instead of a clinical study, which made it possible both to have a much larger number of people available and to investigate what happened in an entire region and not only in hospitals or health care institutions, whose studies are generally conducted in more advanced facilities (eg, university hospitals); (2) the period analyzed in the study (ie, the first wave of the COVID-19 pandemic) made it possible to obtain results that are not influenced by the various organized prevention/vaccination strategies implemented subsequently;

and (3) the assessment of the probability to be tested could be a bias in susceptibility evaluation.

The main limitation of this study is that data derived from record linkage of health administrative databases, where information bias (although not differential) is present, and depth of information were limited. A further limitation is that data were based only on the first wave of the pandemic. Moreover, the administrative nature of the sample was not able to capture the social elements that could be used to fully conceive a syndemic approach; however, the obtained results identified a disease-disease interaction that could be the basis for further research in this framework.

Conclusion

In a sample of nearly 2 million subjects, our study is 1 of the first to assess the association between multimorbidity and all SARS-CoV-2–related outcomes. Our findings show that during the first wave of the pandemic, patients with multimorbidity were closely monitored, as proven by a high frequency of tests for SARS-CoV-2. However, although swabbed more frequently, they appeared to be less likely to become infected with SARS-CoV-2, probably due to greater attention paid to protective methods. However, a history of respiratory diseases is a risk factor for a worse prognosis of COVID-19. Nonetheless, whatever comorbidities affect the patients, a strong dose-response effect was observed between an increased CCI score and COVID-19 hospitalization, ICU admission, and death.

These results are critical to public health policy and planning as they help in identifying a group of subjects who are more prone to worse SARS-CoV-2 outcomes. This information is particularly important for the current pandemic scenario, where the emergency has given way to the SARS-CoV-2 pandemic's embeddedness into daily life. In fact, these results suggest that future clinical and public health interventions (eg, vaccination prioritization, early monoclonal antibody treatment, prevention measurement and campaigns) should be centered on the multimorbid patient category because they are more likely to need to be protected from COVID-19 severe outcomes. Furthermore, the early response to the COVID-19 pandemic provided a framework for our observations that might be applicable to future health challenges. It will be crucial for future research to investigate the biosocial relationship in this context.

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Contributors AC and FR conceptualized the study, were responsible for data curation and investigation, and conducted the formal data analysis. AC, WG, RG, GC, CS, and FR oversaw the project. AC, LD, AM, LM, RG, ES, NZ, and FR accessed and verified the data. AC, WG, CS, and FR wrote the initial draft of the manuscript. LD, AM, LM, RG, ES, NZ, VC, GC, and CS reviewed and edited the manuscript. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

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Data Availability

Raw data cannot be made freely available because of restrictions imposed by the ethical committees, which do not allow open/public sharing of data on individuals. However, aggregated data are available for other researchers upon request to the corresponding author.

Conflicts of Interest

The authors have no financial or nonfinancial interests to disclose. The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Multimedia Appendix 1

Supplementary material.
[DOCX File, 259 KB-Multimedia Appendix 1]

References

1. Williams J, Degeling C, McVernon J, Dawson A. How should we conduct pandemic vaccination? Vaccine 2021 Mar 05;39(6):994-999 [FREE Full text] [doi: 10.1016/j.vaccine.2020.12.059] [Medline: 33423839]
2. Forman R, Shah S, Jeurissen P, Jit M, Mossialos E. COVID-19 vaccine challenges: what have we learned so far and what remains to be done? Health Policy 2021 May;125(5):553-567 [FREE Full text] [doi: 10.1016/j.healthpol.2021.03.013] [Medline: 33820678]
3. Chilimuri S, Sun H, Alemam A, Mantri N, Shehi E, Tejada J, et al. Predictors of mortality in adults admitted with covid-19: retrospective cohort study from New York City. West J Emerg Med 2020 Jul 08;21(4):779-784 [FREE Full text] [doi: 10.5811/westjem.2020.6.47919] [Medline: 32726241]

4. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020 Jun 06;395(10239):1763-1770 [FREE Full text] [doi: 10.1016/S0140-6736(20)31189-2] [Medline: 32442528]
5. España PP, Bilbao A, García-Gutiérrez S, Lafuente I, Anton-Ladislao A, Villanueva A, COVID-19-Osakidetza Working Group. Predictors of mortality of COVID-19 in the general population and nursing homes. Intern Emerg Med 2021 Oct 05;16(6):1487-1496 [FREE Full text] [doi: 10.1007/s11739-020-02594-8] [Medline: 33400164]
6. Ng WH, Tipih T, Makoah NA, Vermeulen J, Goedhals D, Sempa JB, et al. Comorbidities in SARS-CoV-2 patients: a systematic review and meta-analysis. mBio 2021 Mar 09;12(1):e03647-20 [FREE Full text] [doi: 10.1128/mBio.03647-20] [Medline: 33563817]
7. Gallo A, Pero E, Pellegrino S, Macerola N, Murace CA, Ibba F, et al. How can biology of aging explain the severity of covid-19 in older adults. Clin Geriatr Med 2022 Aug;38(3):461-472 [FREE Full text] [doi: 10.1016/j.cger.2022.04.002] [Medline: 35868666]
8. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020 May;109(5):531-538 [FREE Full text] [doi: 10.1007/s00392-020-01626-9] [Medline: 32161990]
9. Guan W, Liang W, Zhao Y, Liang H, Chen Z, Li Y, China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020 May;55(5):2000547 [FREE Full text] [doi: 10.1183/13993003.00547-2020] [Medline: 32217650]
10. Scheen A, Marre M, Thivolet C. Prognostic factors in patients with diabetes hospitalized for COVID-19: findings from the CORONADO study and other recent reports. Diabetes Metab 2020 Oct;46(4):265-271 [FREE Full text] [doi: 10.1016/j.diabet.2020.05.008] [Medline: 32447101]
11. Charlson ME, Pompei P, Ales KL, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987 Jan;40(5):373-383. [doi: 10.1016/0021-9681(87)90171-8]
12. Christensen DM, Strange JE, Gislason G, Torp-Pedersen C, Gerds T, Fosbøl E, et al. Charlson Comorbidity Index score and risk of severe outcome and death in Danish covid-19 patients. J Gen Intern Med 2020 Oct;35(9):2801-2803 [FREE Full text] [doi: 10.1007/s11606-020-05991-z] [Medline: 32583345]
13. Tuty Kuswardhani RA, Henrina J, Pranata R, Anthonius Lim M, Lawrensia S, Suastika K. Charlson Comorbidity Index and a composite of poor outcomes in COVID-19 patients: a systematic review and meta-analysis. Diabetes Metab Syndr 2020;14(6):2103-2109 [FREE Full text] [doi: 10.1016/j.dsx.2020.10.022] [Medline: 33161221]
14. Horton R. Offline: COVID-19 is not a pandemic. Lancet 2020 Sep 26;396(10255):874 [FREE Full text] [doi: 10.1016/S0140-6736(20)32000-6] [Medline: 32979964]
15. Rod MH, Hulvej Rod N. Towards a syndemic public health response to COVID-19. Scand J Public Health 2021 Mar;49(1):14-16. [doi: 10.1177/1403494820982862] [Medline: 33407002]
16. Jakovljevic M, Samarzija M, Milicic D, Reiner Z, Sartorius N. Comorbidities and syndemics in the covid-19 age: challenges and opportunities for bringing separated branches of medicine closer to each other. Psychiatr Danub 2021;33(Suppl 4):402-413 [FREE Full text] [Medline: 34718258]
17. Courtin E, Vineis P. COVID-19 as a syndemic. Front Public Health 2021;9:763830 [FREE Full text] [doi: 10.3389/fpubh.2021.763830] [Medline: 34568273]
18. Fronteira I, Sidat M, Magalhães JP, de Barros FPC, Delgado AP, Correia T, et al. The SARS-CoV-2 pandemic: a syndemic perspective. One Health 2021 Jul;12:100228 [FREE Full text] [doi: 10.1016/j.onehlt.2021.100228] [Medline: 33614885]
19. Gravlee CC. Systemic racism, chronic health inequities, and COVID-19: a syndemic in the making? Am J Hum Biol 2020 Oct;32(5):e23482 [FREE Full text] [doi: 10.1002/ajhb.23482] [Medline: 32754945]
20. Trevisan C, Pedone C, Maggi S, Noale M, Di Bari M, Sojic A, Epicovid Working Group. Accessibility to SARS-CoV-2 swab test during the covid-19 pandemic: did age make the difference? Health Policy 2021 Dec;125(12):1580-1586 [FREE Full text] [doi: 10.1016/j.healthpol.2021.10.002] [Medline: 34649753]
21. McQueenie R, Foster HME, Jani BD, Katikireddi SV, Sattar N, Pell JP, et al. Multimorbidity, polypharmacy, and COVID-19 infection within the UK Biobank cohort. PLoS One 2020;15(8):e0238091 [FREE Full text] [doi: 10.1371/journal.pone.0238091] [Medline: 32817712]
22. de Lusignan S, Dorward J, Correa A, Jones N, Akinyemi O, Amirthalingam G, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. Lancet Infect Dis 2020 Sep;20(9):1034-1042 [FREE Full text] [doi: 10.1016/S1473-3099(20)30371-6] [Medline: 32422204]
23. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet 2020 Jun 01;395(10242):1973-1987 [FREE Full text] [doi: 10.1016/S0140-6736(20)31142-9] [Medline: 32497510]
24. Chudasama YV, Zaccardi F, Gillies CL, Razieh C, Yates T, Kloecker DE, et al. Patterns of multimorbidity and risk of severe SARS-CoV-2 infection: an observational study in the U.K. BMC Infect Dis 2021 Oct 04;21(1):908 [FREE Full text] [doi: 10.1186/s12879-021-06600-y] [Medline: 34481456]

25. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020 Mar;21(3):335-337 [FREE Full text] [doi: 10.1016/S1470-2045(20)30096-6] [Medline: 32066541]
26. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020 Jul;31(7):894-901 [FREE Full text] [doi: 10.1016/j.annonc.2020.03.296] [Medline: 32224151]
27. Roel E, Pistillo A, Recalde M, Fernández-Bertolín S, Aragón M, Soerjomataram I, et al. Cancer and the risk of coronavirus disease 2019 diagnosis, hospitalisation and death: a population-based multistate cohort study including 4 618 377 adults in Catalonia, Spain. Int J Cancer 2022 Mar 01;150(5):782-794 [FREE Full text] [doi: 10.1002/ijc.33846] [Medline: 34655476]
28. Tian J, Yuan X, Xiao J, Zhong Q, Yang C, Liu B, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol 2020 Jul;21(7):893-903 [FREE Full text] [doi: 10.1016/S1470-2045(20)30309-0] [Medline: 32479790]
29. Pranata R, Huang I, Lim MA, Wahjoepramono EJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19-systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis 2020 Aug;29(8):104949. [doi: 10.1016/j.jstrokecerebrovasdis.2020.104949] [Medline: 32927523]
30. Hessami A, Shamshirian A, Heydari K, Pourali F, Alizadeh-Navaei R, Moosazadeh M, et al. Cardiovascular diseases burden in COVID-19: systematic review and meta-analysis. Am J Emerg Med 2021 Aug;46:382-391 [FREE Full text] [doi: 10.1016/j.ajem.2020.10.022] [Medline: 33268238]
31. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol 2020 Oct;17(9):543-558 [FREE Full text] [doi: 10.1038/s41569-020-0413-9] [Medline: 32690910]
32. Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabetes Metab Syndr 2020;14(4):535-545 [FREE Full text] [doi: 10.1016/j.dsx.2020.04.044] [Medline: 32408118]
33. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020 Mar 31;36(7):e3319 [FREE Full text] [doi: 10.1002/dmrr.3319] [Medline: 32233013]
34. Hartmann-Boyce J, Rees K, Perring JC, Kerneis SA, Morris EM, Goyder C, et al. Risks of and from SARS-CoV-2 infection and covid-19 in people with diabetes: a systematic review of reviews. Diabetes Care 2021 Dec;44(12):2790-2811 [FREE Full text] [doi: 10.2337/dc21-0930] [Medline: 34711637]
35. Wu J, Zhang J, Sun X, Wang L, Xu Y, Zhang Y, et al. Influence of diabetes mellitus on the severity and fatality of SARS-CoV-2 (COVID-19) infection. Diabetes Obes Metab 2020 Oct;22(10):1907-1914 [FREE Full text] [doi: 10.1111/dom.14105] [Medline: 32496012]
36. Giorda CB, Picariello R, Tartaglino B, Nada E, Doglio M, Romeo F, et al. From swab testing to health outcomes within the T2DM population: impact of diabetes background on COVID19 progression. Diabetes Res Clin Pract 2021 Oct;180:109021 [FREE Full text] [doi: 10.1016/j.diabres.2021.109021] [Medline: 34437941]
37. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, ISARIC4C Investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020 May 22;369:m1985 [FREE Full text] [doi: 10.1136/bmj.m1985] [Medline: 32444460]
38. Huang BZ, Chen Z, Sidell MA, Eckel SP, Martinez MP, Lurmann F, et al. Asthma disease status, COPD, and covid-19 severity in a large multiethnic population. J Allergy Clin Immunol Pract 2021 Oct;9(10):3621-3628.e2 [FREE Full text] [doi: 10.1016/j.jaip.2021.07.030] [Medline: 34389242]
39. Lohia P, Sreeram K, Nguyen P, Choudhary A, Khicher S, Yarandi H, et al. Preexisting respiratory diseases and clinical outcomes in COVID-19: a multihospital cohort study on predominantly African American population. Respir Res 2021 Mar 05;22(1):37 [FREE Full text] [doi: 10.1186/s12931-021-01647-6] [Medline: 33546658]
40. Gao Y, Ding M, Dong X, Zhang J, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: a review. Allergy 2021 Mar;76(2):428-455. [doi: 10.1111/all.14657] [Medline: 33185910]
41. Oyelade T, Alqahtani J, Canciani G. Prognosis of COVID-19 in patients with liver and kidney diseases: an early systematic review and meta-analysis. Trop Med Infect Dis 2020 May 15;5(2):E80 [FREE Full text] [doi: 10.3390/tropicalmed5020080] [Medline: 32429038]

Abbreviations

ACE: angiotensin-converting enzyme
ARB: angiotensin II receptor blocker
CCI: Charlson Comorbidity Index
COPD: chronic obstructive pulmonary disease
HR: hazard ratio
ICU: intensive care unit

OR: odds ratio
OSA: obstructive sleep apnea

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Table S1.

a) Algorithm related to the Charlson Comorbidity Index (CCI) definition

Disease	Weight	Hospital Discharges Codes[a]	Drug prescriptions Codes[b]	Disease exemptions Codes
Charlson Comorbidity Index (CCI)				
Diabetes	1	250	A10	013
Myocardial infarction	1	410-414	-	-
Peripheral hearth disease	1	440-448	-	-
Congestive heart failure	1	398.91[c], 402[c], 404.01[c], 404.03[c], 404.11[c], 404.13[c], 404.91[c], 404.93[c], 425.4-425.5[c], 425.9[c], 428[c], 785.50-785.51[c]	-	-
Cerebrovascular disease	1	430-434, 436-438	-	0B02
Dementia	1	046, 290-292, 294, 331	-	N06D
Mild liver disease	1	070	-	016
Hemiplegia	2	342, 436	-	-
Oncological disease	2	140-208	-	-
Ulcer	1	531-534	-	-
Severe liver disease	3	571	-	008
Connective tissue disease	1	696.0, 710.0, 714.0, 720.0	-	006, 028, 030, 045, 054,
Moderate or severe kidney disease	2	250.4, 403-404, 582-583, 585-588, 590.0, 753.1, V42.0, V56; 38.95[d], 39.27[d], 39.42[d], 39.43[d], 39.95[d], 54.93[d], 54.98[d], 55.23[d], 55.6[d]	B03XA01, B03XA02, B03XA03, V03AE01, V03AE02, V03AE03, V03AE05	023
Chronic pulmonary disease	1	518.81[c], 518.84[c], 786.0[c], 786.2[c], 786.4[c]; 490-494, 496	R03A, R03CC02, R03CC03, R03CC04, R03CK, R03BB01, R03BB02, R03BB04, R03DA01, R03DA04, R03DA05, R03DA08, RO3DA11, R03DA49	024

[a] International Classification of Diseases – IX
[b] Anatomical Therapeutic Chemical 7 Classification
[c] Only main diagnosis
[d] Intervention procedures

b) Algorithm related to the definition of the specific diseases considered in the study

Disease	Hospital Discharges Codes[a]	Drug prescriptions Codes[b]	Disease exemptions Codes
Specific Disease			
Oncological disease	140-208	-	-
Cardiovascular disease	390-459	-	-
Respiratory disease	460-519	-	-
Cerebrovascular disease	430-434, 436-438	-	0B02
Diabetes	250	A10	013
Myocardial infarction	410-414	-	-
Congestive heart failure	398.91[c], 402[c], 404.01[c], 404.03[c], 404.11[c], 404.13[c], 404.91[c], 404.93[c], 425.4-425.5[c], 425.9[c], 428[c], 785.50-785.51[c]	-	-

[a] International Classification of Diseases – IX
[b] Anatomical Therapeutic Chemical 7 Classification
[c] Only main diagnosis

Table S2. Odds ratio (OR) estimates related to positivity to SARS-CoV-2 on entire population, stratified by gender and age group (one model for each variable)

		Male		Female	
Variable	**Category**	*(N=2,847)* **45-59** OR (95% CI)[a]	*(N=3,114)* **60-74** OR (95% CI)[a]	*(N=4,477)* **45-59** OR (95% CI)[a]	*(N=2,355)* **60-74** OR (95% CI)[a]
Charlson Comorbidity Index	0	Ref	Ref	Ref	Ref
	1	**1.28 (1.16-1.42)**	**1.32 (1.21-1.44)**	**1.21 (1.11-1.30)**	**1.43 (1.30-1.58)**
	2-3	**1.93 (1.64-2.25)**	**1.95 (1.77-2.15)**	**1.32 (1.15-1.52)**	**2.09 (1.85-2.36)**
	4+	**2.56 (1.85-3.53)**	**3.68 (3.18-4.26)**	1.48 (0.93-2.36)	**4.63 (3.72-5.77)**
Oncological disease	-	**1.80 (1.41-2.29)**	**1.39 (1.22-1.59)**	0.97 (0.79-1.20)	**1.36 (1.14-1.63)**
Cardiovascular disease	-	**1.53 (1.33-1.76)**	**1.83 (1.68-1.99)**	**1.30 (1.13-1.50)**	**2.15 (1.92-2.41)**
Respiratory disease	-	**2.12 (1.79-2.53)**	**2.56 (2.27-2.87)**	**1.37 (1.12-1.68)**	**3.38 (2.92-3.91)**
Myocardial infarction	-	1.26 (0.97-1.64)	**1.56 (1.38-1.77)**	0.90 (0.54-1.50)	**2.14 (1.71-2.69)**
Heart failure	-	1.20 (0.62-2.32)	**2.23 (1.75-2.83)**	1.35 (0.56-3.27)	**3.46 (2.45-4.90)**
Cerebrovascular disease	-	**1.99 (1.45-2.74)**	**2.53 (2.19-2.92)**	1.31 (0.91-1.90)	**3.23 (2.66-3.94)**
Diabetes	-	**1.43 (1.23-1.65)**	**1.63 (1.50-1.77)**	**1.36 (1.19-1.55)**	**1.70 (1.52-1.90)**

[a] Estimates adjusted for age
Significant estimates (95% confidence level) are shown in bold type

Table S3. Odds ratio (OR) estimates related to admission to hospital on entire population, stratified by gender and age group (one model for each variable)

Variable	Category	Male		Female	
		(N=1,101) 45-59	*(N=1,974)* 60-74	*(N=616)* 45-59	*(N=953)* 60-74
		OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]
Charlson Comorbidity Index	0	Ref	Ref	Ref	Ref
	1	**1.58 (1.36-1.84)**	**1.50 (1.34-1.67)**	**1.68 (1.38-2.05)**	**1.64 (1.40-1.92)**
	2-3	**2.71 (2.18-3.38)**	**2.11 (1.87-2.39)**	**2.75 (2.08-3.63)**	**3.20 (2.70-3.80)**
	4+	**4.55 (3.07-6.75)**	**4.25 (3.57-5.06)**	**3.73 (1.66-8.37)**	**8.35 (6.36-10.95)**
Oncological disease	-	**2.55 (1.85-3.51)**	**1.48 (1.26-1.74)**	**1.94 (1.31-2.87)**	**1.91 (1.51-2.42)**
Cardiovascular disease	-	**1.84 (1.50-2.25)**	**1.86 (1.68-2.07)**	**2.04 (1.50-2.79)**	**2.60 (2.21-3.06)**
Respiratory disease	-	**3.03 (2.39-3.83)**	**2.64 (2.28-3.05)**	**2.61 (1.76-3.87)**	**4.70 (3.86-5.71)**
Myocardial infarction	-	**1.69 (1.19-2.41)**	**1.74 (1.50-2.03)**	1.57 (0.59-4.21)	**3.03 (2.26-4.05)**
Heart failure	-	**2.27 (1.07-4.78)**	**2.54 (1.92-3.35)**	1.77 (0.25-12.59)	**4.37 (2.76-6.89)**
Cerebrovascular disease	-	**1.97 (1.20-3.23)**	**2.20 (1.82-2.65)**	1.54 (0.64-3.72)	**3.22 (2.39-4.32)**
Diabetes	-	**1.87 (1.53-2.29)**	**1.85 (1.67-2.05)**	**2.32 (1.75-3.07)**	**2.35 (2.01-2.74)**

[a] Estimates adjusted for age
Significant estimates (95% confidence level) are shown in bold type

Table S4. Odds ratio (OR) estimates related to admission to intensive care unit (ICU) on entire population, stratified by gender and age group (one model for each variable)

		Male		Female	
Variable	**Category**	*(N=370)* **45-59** **OR (95% CI)[a]**	*(N=748)* **60-74** **OR (95% CI)[a]**	*(N=133)* **45-59** **OR (95% CI)[a]**	*(N=257)* **60-74** **OR (95% CI)[a]**
Charlson Comorbidity Index	0	Ref	Ref	Ref	Ref
	1	**1.69 (1.31-2.18)**	**1.45 (1.22-1.73)**	1.29 (0.81-2.05)	**1.80 (1.33-2.43)**
	2-3	**2.35 (1.58-3.47)**	**1.92 (1.58-2.35)**	**3.24 (1.88-5.60)**	**3.73 (2.70-5.15)**
	4+	**3.95 (1.95-8.01)**	**3.58 (2.66-4.81)**	**2.71 (0.38-19.47)**	**9.36 (5.61-15.61)**
Oncological disease	-	**2.20 (1.24-3.92)**	1.25 (0.94-1.65)	1.00 (0.32-3.13)	1.39 (0.82-2.34)
Cardiovascular disease	-	**2.15 (1.56-2.97)**	**1.50 (1.25-1.80)**	**2.66 (1.47-4.83)**	**2.53 (1.84-3.47)**
Respiratory disease	-	**3.00 (2.00-4.50)**	**1.97 (1.52-2.56)**	**2.77 (1.22-6.30)**	**4.69 (3.22-6.83)**
Myocardial infarction	-	**2.25 (1.34-3.78)**	**1.62 (1.26-2.08)**	1.76 (0.25-12.63)	**3.30 (1.92-5.67)**
Heart failure	-	-	**2.16 (1.33-3.50)**	-	**4.28 (1.76-10.39)**
Cerebrovascular disease	-	2.09 (0.93-4.70)	**1.68 (1.20-2.36)**	1.40 (0.19-10.01)	**2.78 (1.52-5.10)**
Diabetes	-	**1.99 (1.42-2.78)**	**2.19 (1.87-2.56)**	**3.51 (2.11-5.84)**	**3.19 (2.42-4.21)**

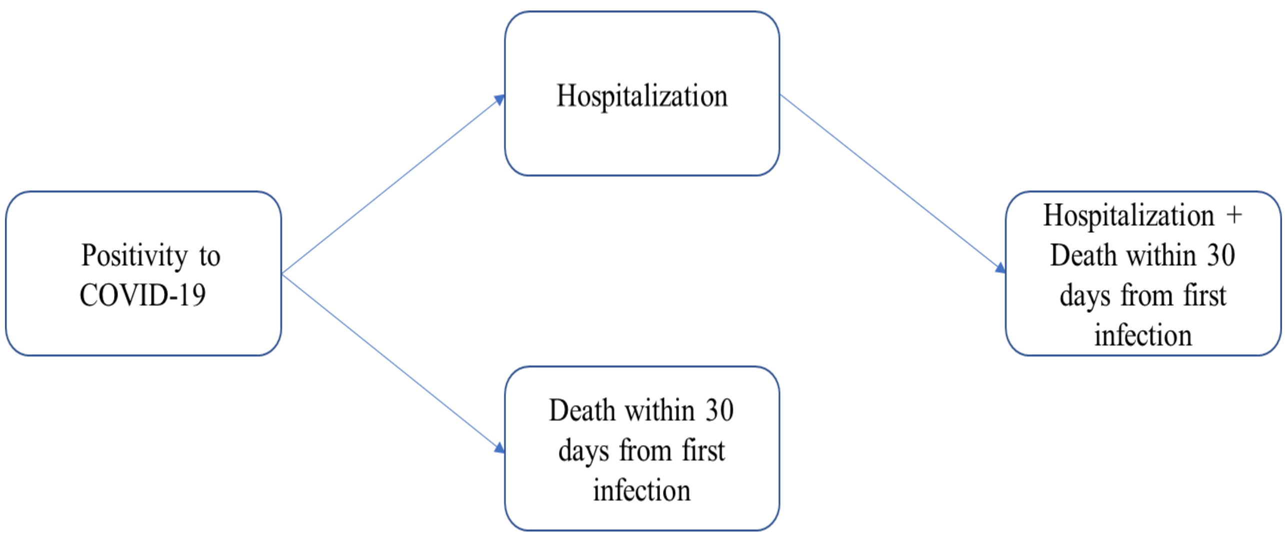
[a] Estimates adjusted for age
Significant estimates (95% confidence level) are shown in bold type

Table S5. Odds ratio (OR) estimates related to death within 30 days from the first positive swab on entire population, stratified by gender and age group (one model for each variable)

		Male		Female	
Variable	**Category**	*(N=97)* **45-59**	*(N=461)* **60-74**	*(N=23)* **45-59**	*(N=168)* **60-74**
		OR (95% CI)[a]	**OR (95% CI)[a]**	**OR (95% CI)[a]**	**OR (95% CI)[a]**
Charlson Comorbidity Index	0	Ref	Ref	Ref	Ref
	1	**2.00 (1.15-3.47)**	**1.67 (1.31-2.13)**	2.72 (0.82-9.05)	**2.23 (1.51-3.29)**
	2-3	**8.92 (5.27-15.11)**	**3.59 (2.84-4.54)**	**22.01 (8.45-57.33)**	**5.12 (3.44-7.61)**
	4+	**28.98 (14.96-65.14)**	**8.19 (6.07-11.15)**	**59.56 (12.54 -272.78)**	**20.09 (12.25-32.96)**
Oncological disease	-	**8.32 (4.42-15.66)**	**1.83 (1.36-2.45)**	**11.41 (4.22-30.81)**	**2.02 (1.19-3.43)**
Cardiovascular disease	-	**4.89 (3.03-7.89)**	**2.45 (2.00-2.99)**	**3.79 (1.12-12.80)**	**4.00 (2.87-5.59)**
Respiratory disease	-	**7.53 (4.34-13.06)**	**3.95 (3.08-5.06)**	**8.53 (2.53-28.75)**	**8.42 (5.81-12.19)**
Myocardial infarction	-	**3.43 (1.50-7.88)**	**2.16 (1.64-2.84)**	-	**4.07 (2.31-7.18)**
Heart failure	-	**6.98 (1.71-28.37)**	**3.03 (1.83-4.99)**	-	**11.06 (5.81-21.04)**
Cerebrovascular disease	-	**8.25 (3.60-18.92)**	**3.67 (2.72-4.94)**	-	**5.93 (3.58-9.82)**
Diabetes	-	**3.28 (1.91-5.64)**	**2.50 (2.06-3.04)**	**8.12 (3.20-20.65)**	**3.58 (2.59-4.94)**

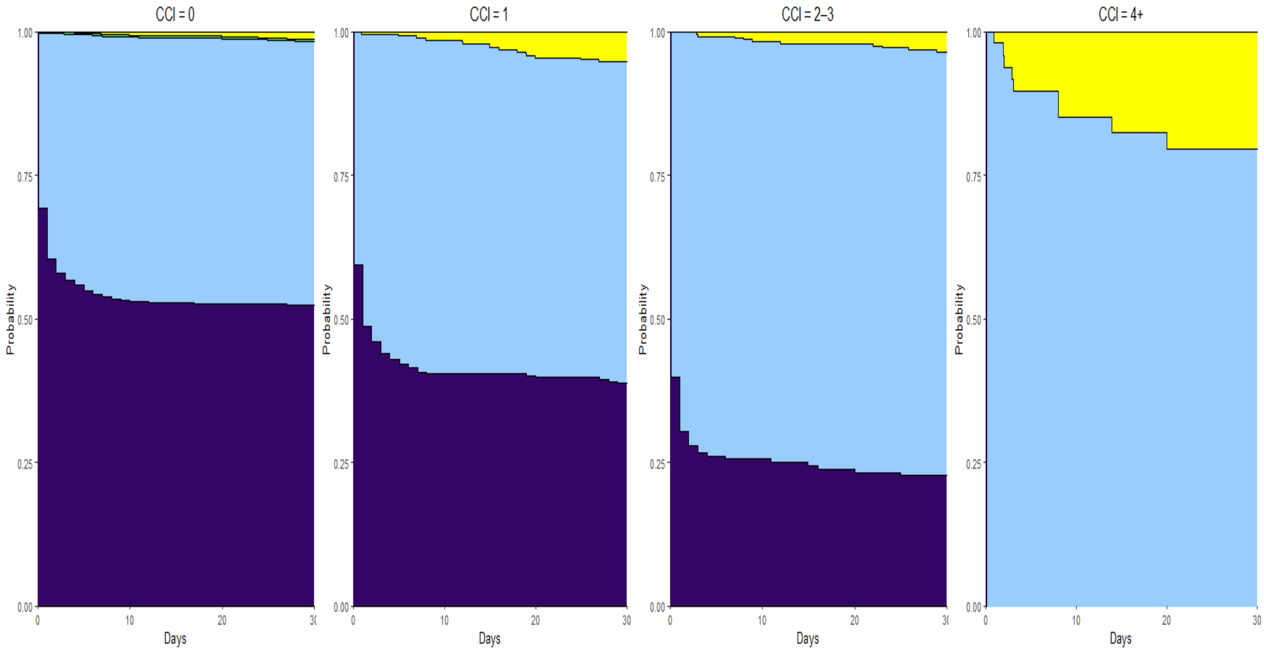
[a] Estimates adjusted for age
Significant estimates (95% confidence level) are shown in bold type

Supplementary Figure 1. Diagram of possible transitions among states

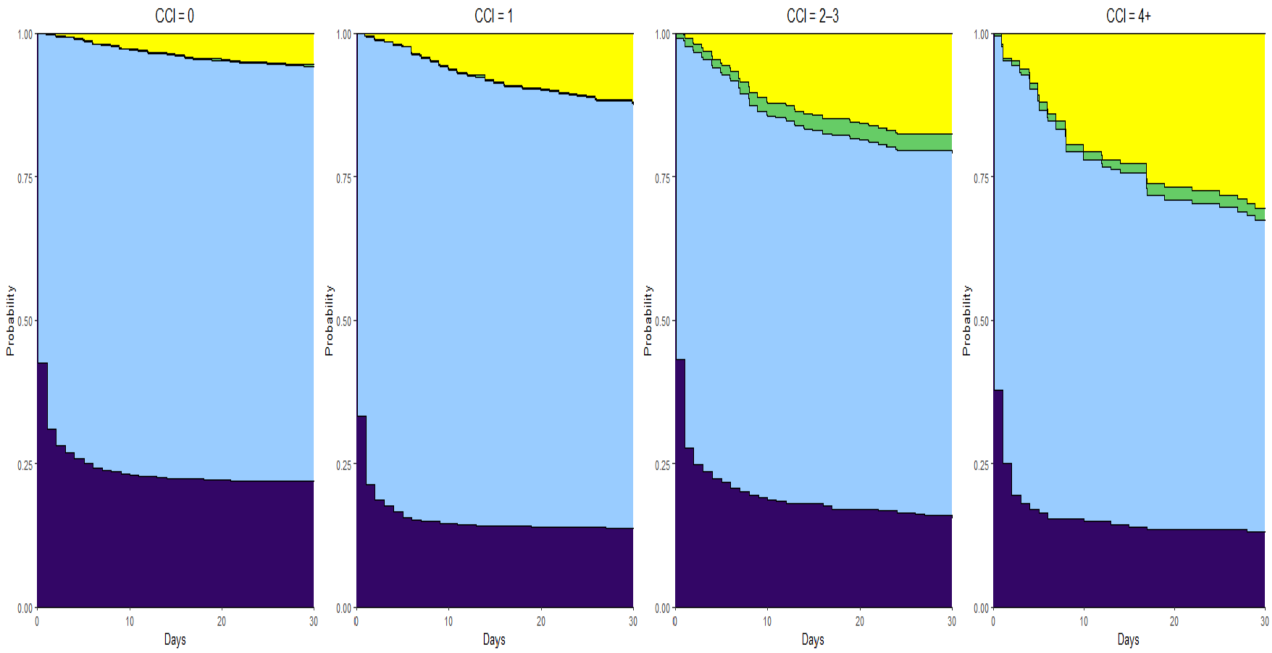


Supplementary Figure 2. Probability of transitions among states related to multistate models adjusted for age and month of infection, stratifying by Charlson Comorbidity Index (CCI), gender, and age group

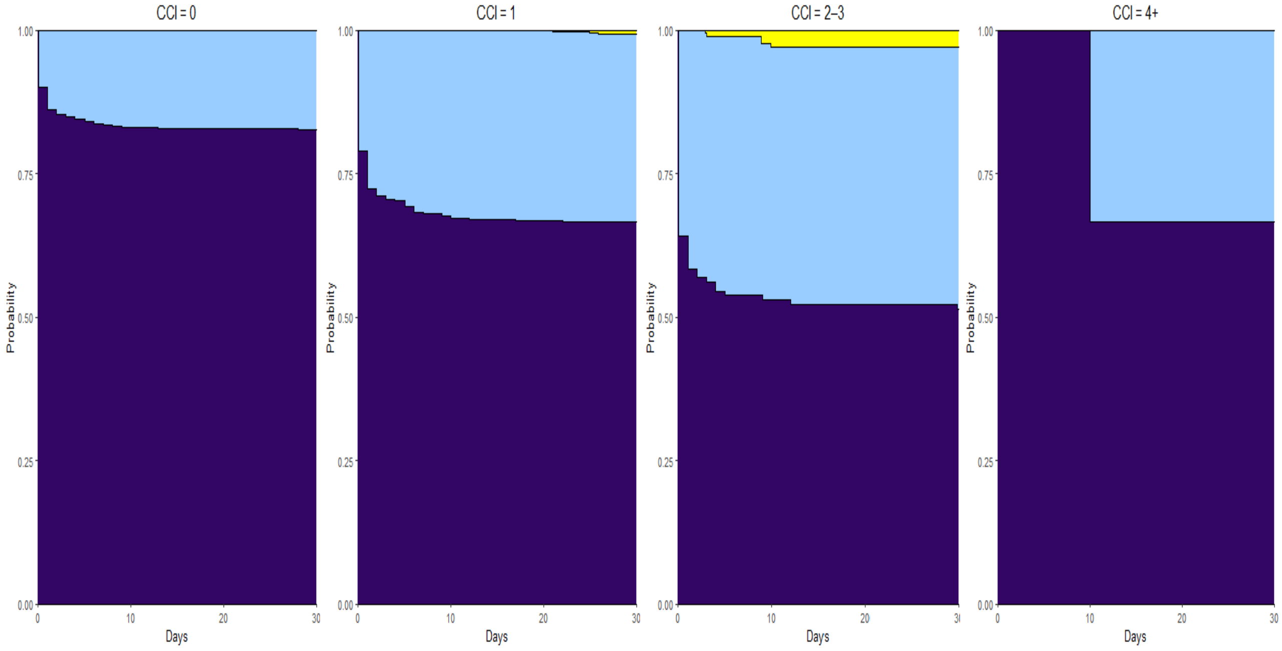
a) Males, 45-59 years old



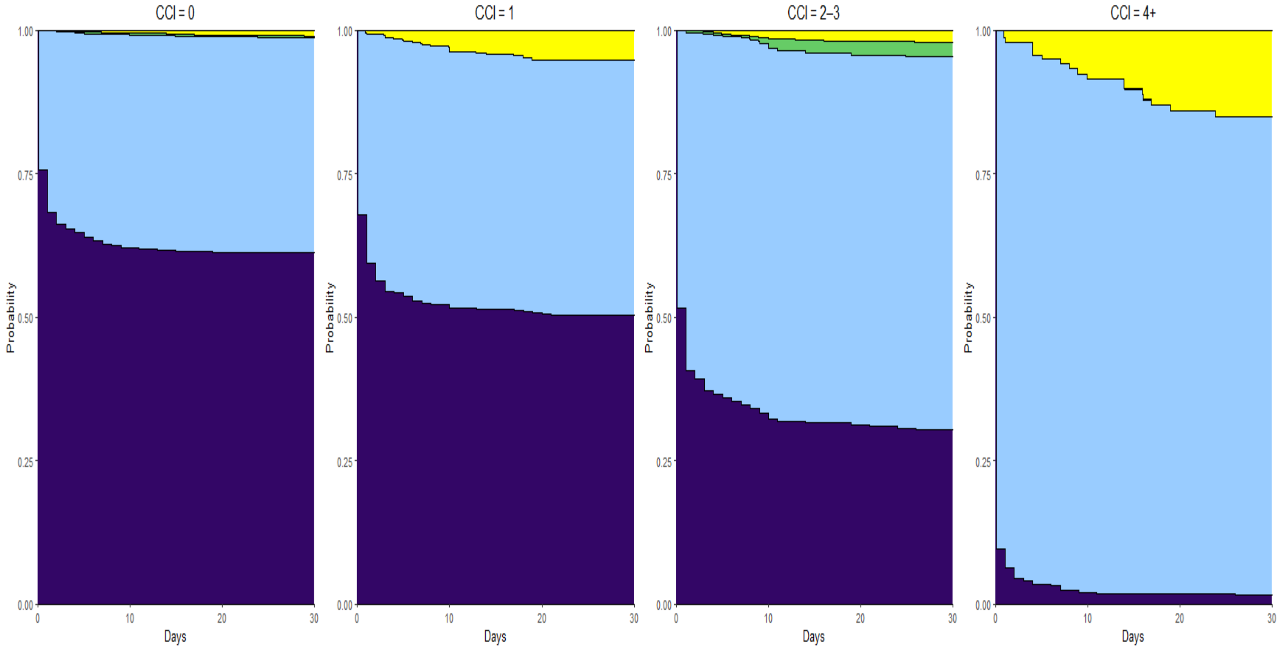
b) Males, 60-74 years old

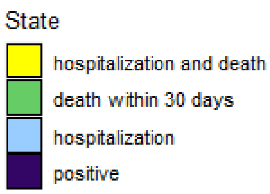


c) Females, 45-59 years old



d) Females, 60-74 years old





3.2 Multimorbidity and COVID-19 outcomes in Emergency Department: is the association mediated by the severity condition at admission?

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ABSTRACT

Introduction

Since the COVID-19 pandemic broke out, several studies explored what caused a worse prognosis of the virus. Charlson Comorbidity Index (CCI) was recognized as one of the most risk factors for COVID-19-related outcomes. At the same time, the patient's clinical condition was found to be associated with SARS-CoV-2 outcomes. This study aimed to analyze the association between multimorbidity and COVID-19-related outcomes, and to evaluate whether the National Early Warning Score 2 (NEWS2), which is a proxy for clinical severity at hospital access, played a mediating role in this association.

Methods

Data were obtained through the platform EPICLIN and the Piedmont Longitudinal Study. We considered all patients who tested positive for COVID-19 after accessing the Emergency Department (ED) of San Luigi Gonzaga and Molinette hospitals from 1 March to 30 June 2020. Four different outcomes were assessed: non-discharge from ED, death within 30 days from infection, ICU admission/death among hospitalized patients, and length of hospitalization among hospitalized and surviving patients. Two distinct subgroups of patients, those <65 years old and 65+ years old, were considered when multivariable logistic regression, Cox models, and mediation analyses were conducted.

Results

Among those who were younger and had a CCI score ≥ 2, there was a greater risk of not being discharged (OR: 3.14; 95% CI: 1.49-6.59) or dying (OR: 4.45; 95% CI: 1.01-19.71). Moreover, the higher the CCI score, the longer the length of hospitalization. Considering older subjects, a greater comorbidity burden was associated with a higher risk of death. Regarding the mediation analyses, multimorbidity in the younger population had a considerable direct impact on duration of hospitalization and not being discharged. Moreover, in the older population, the NEWS2 Score played a mediation role both in the association between CCI and not being discharged as well as ICU admissions and death.

Conclusion

This research showed that multimorbidity is a strong risk factor for a worse prognosis of COVID-19. Moreover, there was a strong direct effect of CCI on not being discharged, and the NEWS2 Score was found to act as a mediator in the association between multimorbidity and COVID-19-related outcomes.

Keywords

COVID-19; Charlson Comorbidity Index; multimorbidity; Intensive Care Unit; National Early Warning Score

INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared that Coronavirus Disease (COVID-19), a viral respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), also known as the novel coronavirus, could be characterized as a pandemic[1]. Up until the WHO declared the end of the COVID-19 pandemic, COVID-19 has now resulted in over 765 million cases and around 6.9 million deaths[2,3].

In literature, numerous authors have thoroughly explored the correlation between COVID-19 and multiple comorbidities. Strong associations between severe and fatal SARS-CoV-2 disease with chronic comorbidities such as kidney injury, diabetes, hypertension, cardiovascular diseases, cancer, chronic obstructive pulmonary disease (COPD), and obesity were found in studies, meta-analyses, and systematic reviews[4,5].

In the epidemiological field, comorbidity is defined in a variety of ways, but there isn't a single, accepted definition beyond the presence of one or more concurrent, often chronic, pathologies. One useful way to establish the weight of multiple comorbidities is through the use of the Charlson Comorbidity Index (CCI)[6]. The CCI is an assessment tool designed specifically to predict long-term mortality. It provides a valid description of the patient's clinical situation, and can also demarcate major diagnostic and prognostic differences among subgroups of patients sharing the same medical diagnosis[7]. The CCI has been proven useful in risk stratifications of hospitalized COVID-19 patients, as it is a reliable indicator of the clinical impact of multiple associated comorbidities. It has been observed that the per-point increase of the CCI matched an increment in mortality risk and was associated with disease severity[8–10]. Prognostic stratification of COVID-19 patients is not only associated with predisposing risk factors of the affected patient but also related to the severity of the disease itself, depending on the viral characteristics (e.g., strain-specific virulence)[11], the viral load (e.g., quantification of viral replication)[12], and the organ involvement (e.g., the presence of pneumonia, myocarditis, encephalitis, etc).

In addition to these elements, it is important to consider the severity of the clinical conditions at the time of access at the Emergency Department (ED) and whether or not it may influence the effect of multimorbidity on COVID-19 outcomes, given the impact of the presence of comorbidities on the patient's clinical condition[13]. One of the most common ways used is the National Early Warning Score (NEWS) and its modified version NEWS2, which evaluates changes in physiological measurements (respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness, temperature) and results in a standardized assessment of acute illness severity[14]. This is commonly adopted to stratify the risk of clinical deterioration.

During the SARS-CoV-2 pandemic, the NEWS was widely used for assessing the severity and monitoring of COVID-19 patients in healthcare settings. It was applied to patient care due to its effectiveness in identifying patients at risk of deterioration, for both accessing the healthcare facilities[15] and being hospitalized[16].

A combination of multimorbidity and severity was worth investigating, even if it may be debatable which factor has the most impact on the patient.

Our study's clinical cohort of patients admitted to the ED included the following objectives: 1) analyzing the relationship between the CCI, used as a proxy of multimorbidity, and SARS-CoV-2- related outcomes; 2) assessing the mediation role of the NEWS2 Score for this association, to disentangle the effect of the multimorbidity on COVID-19-related outcomes into two different effects: the direct effect of CCI on the SARS-CoV-2 related outcomes and the effect of CCI mediated by the NEWS2 Score on the same outcomes. Since some studies have shown that the association between clinical conditions and COVID-19 outcomes varies depending on age groups[17], the analyses were conducted in two different populations: patients <65 years old and 65+ years old.

METHODS

Study population

To investigate the association between multimorbidity and COVID-19-related outcomes and to assess the mediation role of the NEWS2 Score, we collected data from all patients who tested positive for SARS-CoV-2 through nasal and/or pharyngeal PCR molecular swab or bronchoalveolar lavage after accessing the ED of San Luigi Gonzaga Hospital in Orbassano or Molinette Hospital in Turin (Northwest Italy) during the period from 1 March to 30 June 2020. A description of the data collection was presented elsewhere [18–20].

Variables

Using ED and medical records, we collected clinical and demographic information on the study population. Specifically, in addition to gender and age, we obtained information on COVID-19 disease progression (including the presence of symptoms and whether the patients were admitted to the intensive care unit or died due to the disease), obesity, hypertension, smoking habit, NEWS2 Score, and Charlson Comorbidity Index (CCI)[6], which was used as a proxy of multimorbidity.

For the purpose of the analyses, we considered four different outcomes:

1) Non-discharge from ED (i.e., hospitalized, transferred to other hospitals, or died) on the entire sample;
2) Death within 30 days from the first positive swab on the entire sample;
3) ICU admission and/or death among patients who were hospitalized;
4) Length of hospitalization among patients who did not die while in the hospital. This choice was because deaths among hospitalized individuals would have greatly influenced estimates of this

association.

Statistical Analyses

After checking the normality distribution of quantitative variables through the Kolmogorov-Smirnov test, the sample was described through frequencies and percentages or medians and Interquartile Ranges (IQRs), for qualitative and quantitative data, respectively.

We employed Cox Proportional Hazards and multivariable logistic regression models, when applicable, to investigate the relationship between multimorbidity and COVID-19-related outcomes. The estimates were adjusted for gender, age, smoking, obesity, hypertension, and hospital stay to control for any possible confounding.

For the two outcomes on the entire population (non-discharge from ED and death within 30 days from the first positive swab) estimates were also adjusted for SARS-CoV-2 symptomatology as binary variables (yes vs no). The symptoms considered included fever, cough, and dyspnea. This was not possible for hospitalized patients, as all are symptomatic for COVID-19.

Later, to assess the mediation role played by the NEWS2 Score in the association between multimorbidity and COVID-19-related outcomes, mediation analyses were conducted. The mediation analysis is a statistical technique that is useful to explore the underlying mechanisms or pathways by which the exposure affects the outcome. Assessing whether the effect of the exposure on the outcome is partially or fully explained by one or more intervening variables, known as mediators, is the main purpose of the mediation analysis.

Among the different possible approaches, we implemented the counterfactual technique of VanderWeele for the first three binary outcomes[21]. For the last outcome, instead, an innovative approach based on the counterfactual technique of VanderWeele was applied[22]. These highly advanced statistical methods allowed us to disentangle the Total Effect (TE) of the multimorbidity on COVID-19 related outcomes into two different effects: the Pure Direct Effect (PDE), which represents the effect of the exposure on the outcome that is not mediated by the mediator(s), and the Total Indirect Effect (TIE), which expresses the effect of exposure on the same outcome that operates through the mediator(s) and quantifies the portion of the total effect that is transmitted through the mediator(s) in the causal pathway. Confidence Intervals (CIs) were obtained as 95% bootstrap CIs by using the percentile method.

Before applying this technique, the assumptions underlying the method were verified. In particular, using multivariable logistic, multinomial, and Cox Proportional Hazards regression models, preliminary analyses were conducted to evaluate the associations between exposure-mediator and mediator-outcomes.

The analyses were conducted on two different subgroups: subjects aged <65 years and 65+ years old.

Subjects with missing values for the variables of interest were not considered for analysis.

The study was performed using SAS (V 9.4) and R (V 4.2.1).

RESULTS

Out of 844 subjects who accessed the ED of San Luigi or Molinette hospitals in Turin, 458 (54.2%) were <65 years old and 386 (45.8%) were ≥ 65 years old. Of these, 564 (66.8%) were not immediately discharged from the ED, 144 (17.1%) died within 30 days from the diagnosis, and 499 (59.1%) were admitted to one of the hospital's wards, of which 222 (44.4%) died or were admitted to the ICU. In particular, 91 hospitalized patients (41.0%) died, 86 (38.7%) were admitted to the ICU, and 45 (20.3%) were admitted to the ICU and died. The clinical and demographic characteristics of the sample are shown in Table 1, Supplementary Table 1, and Supplementary Table 2.

Subjects with missing values for the variables of interests who were not considered were 233 patients.

Table 1. Demographic and clinical characteristics related to the entire sample, stratified by age

Variable	<65 (*N*= *458*) N[a](%)	65+ (*N* = *386*) N (%)
Age		
Median (IQR[a])	50.0 (41.0-56.8)	78.0 (73.0-85.0)
Gender		
Male	258 (56.3%)	212 (54.9%)
Female	200 (43.7%)	174 (45.1%)
Smoking		
No	382 (83.4%)	311 (80.6%)
Yes	76 (16.6%)	75 (19.4%)
Hospital		
San Luigi	144 (31.4%)	135 (35.0%)
Molinette	314 (68.6%)	251 (65.0%)
Obesity		
No	429 (93.7%)	360 (93.3%)
Yes	29 (6.3%)	26 (6.7%)
Hypertension		
No	297 (64.8%)	97 (25.1%)
Yes	161 (35.2%)	289 (74.9%)
COVID-19 symptoms		
No	16 (3.5%)	8 (2.1%)
Yes	442 (96.5%)	378 (97.9%)
Charlson Comorbidity Index		
0	353 (77.0%)	116 (30.0%)
1	58 (12.7%)	98 (25.4%)
2-3[b]	47 (10.3%)	94 (24.4%)
4+	-	78 (20.2%)
National Early Warning Score 2		
0	382 (83.4%)	173 (44.8%)
1	29 (6.3%)	52 (13.5%)
2+	47 (10.3%)	161 (41.7%)
Discharge		
Yes	254 (55.5%)	26 (6.7%)
No	204 (44.5%)	360 (93.3%)
Death within 30 days		
No	446 (97.4%)	254 (65.8%)
Si	12 (2.6%)	132 (34.2%)

[a] IQR: Interquartile Range;

[b] In the case of subjects under 65, the category refers to the value "2+".

Regarding the association between CCI and SARS-CoV-2-related outcomes detected through classical models, the OR and HR estimates are shown in Table 2. From the results, it emerged that among those who were younger (<65 years old) and had a CCI score ≥ 2, there was a greater risk of not being discharged from the ED (OR: 3.14; 95% CI: 1.49-6.59) or dying within 30 days (OR: 4.45; 95% CI: 1.01-19.71). In addition, we found that the higher the CCI score, the longer the length of hospitalization.

When considering the subgroup of older subjects (65+ years old), estimates showed that those with a greater comorbidity burden had a higher risk of death within 30 days from the first diagnosis of COVID-19.

Table 2. Odds ratio (OR) and Hazard Ratio (HR) estimates related to each outcome, stratifying by age

Charlson Comorbidity Index	Non-discharge OR[a] (95% CI[b])	Intensive Care Unit admission or death OR[a] (95% CI[b])	Death within 30 days OR[a] (95% CI[b])	Length of hospitalization HR[c] (95% CI[b])
<65				
0	Ref	Ref	Ref	Ref
1	1.27 (0.66-2.43)	1.81 (0.68-4.76)	2.83 (0.58-13.77)	0.55 (0.33-0.91)
2+	3.14 (1.49-6.59)	1.43 (0.58-3.55)	4.45 (1.01-19.71)	0.49 (0.32-0.76)
65+				
0	Ref	Ref	Ref	Ref
1	1.49 (0.48-4.54)	1.31 (0.70-2.45)	1.97 (1.02-3.82)	0.77 (0.52-1.15)
2-3[d]	2.52 (0.72-7.69)	1.55 (0.81-2.95)	2.14 (1.11-4.11)	0.66 (0.44-1.00)
4+	-	1.38 (0.69-2.75)	2.16 (1.06-4.39)	0.83 (0.54-1.28)

[a] OR: Odds Ratio; [b] CI: Confidence Interval; [c] HR: Hazard Ratio;

[d] In the case of non-discharge, the category refers to the value "2+".

Finally, the results related to the mediation analyses are summarized in Table 3, Figure 1, and Figure 2. The analysis of the association necessary to perform appropriate mediation analyses are presented in Supplementary Table 3. Based on the PDE estimates, we found a strong direct effect of multimorbidity on not being discharged from the ED in the younger population (CCI = 1: PDE: 1.17, 95% CI: 0.66-2.14; CCI = 2+: PDE: 2.13, 95% CI: 1.13-4.59). Therefore, there seems to be a direct association between multimorbidity and non-discharge. Furthermore, it emerged from TIE estimations that among older patients that the NEWS2 Score played a key mediation role both in the association between CCI and not being discharged from the ED (CCI = 1: TIE: 1.27, 95% CI: 0.84- 1.89; CCI = 2+: TIE: 1.51, 95% CI: 1.04-2.37) and in the relationship between CCI and the combined outcome “ICU admissions and/or death” (CCI = 1: TIE: 1.28, 95% CI: 1.02-1.70; CCI = 2-3: TIE: 1.27, 95% CI: 1.01-1.67; CCI = 4+: TIE: 1.15, 95% CI: 0.88-1.54). As we expected, the total effects show that in almost all cases the results are very similar to those estimated through the classical methods. Hence, the choice of mediation analysis for this study is justified by the identification of a statistically significant direct and indirect effect.

Table 3. Results related to mediation analyses for each outcome, stratifying by age

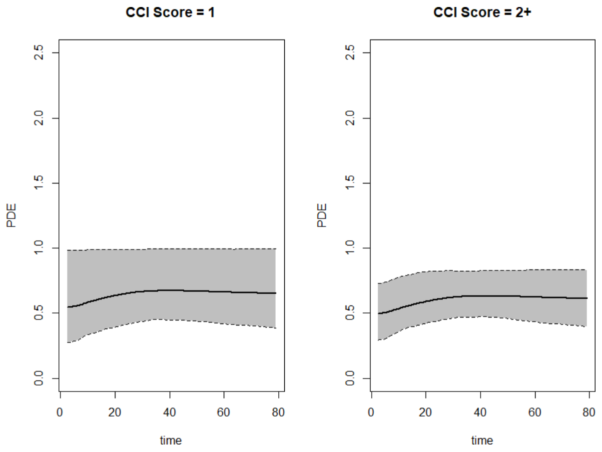
Charlson Comorbidity Index	Effect	Non-discharge OR[a] (95% CI[b])	Intensive Care Unit admission or death OR[a] (95% CI[b])	Death within 30 days OR[a] (95% CI[b])	Length of hospitalization HR[c] (95% CI[b])
<65					
0	Pure Direct Effect	Ref	Ref	Ref	Ref
1		1.17 (0.66-2.14)	1.62 (0.49-4.31)	1.90 (0.01-13.12)	0.66 (0.41-0.99)
2+		2.13 (1.13-4.59)	1.15 (0.42-2.52)	2.14 (0.22-11.05)	0.62 (0.43-0.83)
0	Total Indirect Effect	Ref	Ref	Ref	Ref
1		1.13 (0.88-1.63)	1.08 (0.58-1.77)	1.48 (0.31-3.72)	0.90 (0.67-1.32)
2+		1.54 (0.89-3.19)	1.17 (0.63-1.13)	2.65 (0.67-7.29)	1.05 (0.82-1.45)
0	Total Effect	Ref	Ref	Ref	Ref
1		1.32 (0.69-2.73)	1.75 (0.51-4.96)	2.80 (0.01-15.42)	0.59 (0.36-1.07)
2+		3.27 (1.48-8.22)	1.35 (0.38-3.75)	5.67 (0.57-26.82)	0.67 (0.41-1.06)
65+					
0	Pure Direct Effect	Ref	Ref	Ref	Ref
1		1.23 (0.47-4.60)	1.08 (0.58-2.07)	1.48 (0.86-2.73)	0.81 (0.52-1.25)
2-3*		1.67 (0.56-7.94)	1.29 (0.67-2.51)	1.59 (0.90-3.00)	0.70 (0.46-1.02)
4+		-	1.25 (0.60-2.53)	1.68 (0.94-3.17)	0.85 (0.56-1.30)
0	Total Indirect Effect	Ref	Ref	Ref	Ref
1		1.27 (0.84-1.89)	1.28 (1.02-1.70)	1.23 (0.97-1.56)	0.96 (0.84-1.07)
2-3*		1.51 (1.04-2.37)	1.27 (1.01-1.67)	1.17 (0.90-1.52)	1.00 (0.88-1.14)
4+		-	1.15 (0.88-1.54)	1.15 (0.83-1.52)	1.00 (0.80-1.20)
0	Total Effect	Ref	Ref	Ref	Ref
1		1.56 (0.56-6.36)	1.38 (0.72-2.67)	1.82 (1.06-3.39)	0.77 (0.51-1.19)
2-3*		2.52 (0.82-11.34)	1.64 (0.84-3.21)	1.87 (0.99-3.59)	0.70 (0.45-1.05)
4+		-	1.43 (0.67-2.94)	1.93 (0.99-3.82)	0.85 (0.53-1.34)

[a] OR: Odds Ratio; [b] CI: Confidence Interval; [c] HR: Hazard Ratio;

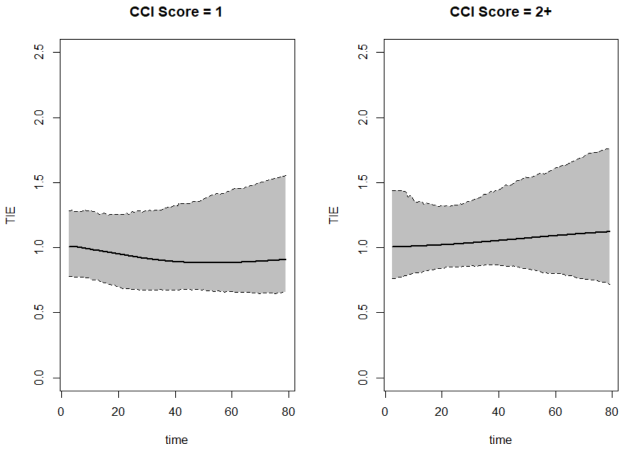
[d] In the case of non-discharge, the category refers to the value "2+".

Figure 1. Pure Direct Effect (PDE), Total Indirect Effect (TIE), and Total Effect (TE) over time related to the length of hospitalization for the younger population (<65 years), stratified by Charlson Comorbidity index.

a) Pure Direct Effect (PDE)



b) Total Indirect Effect (TIE)



c) Total Effect (TE)

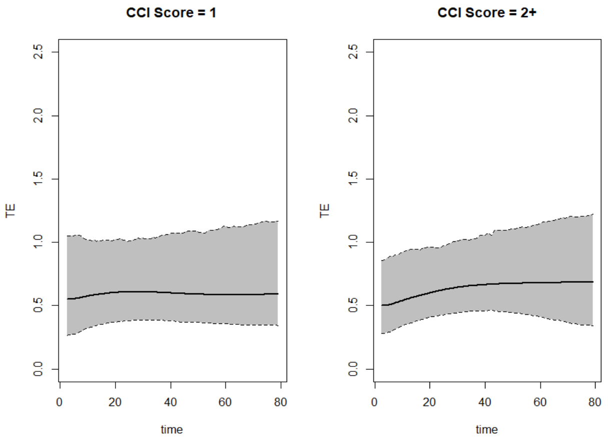
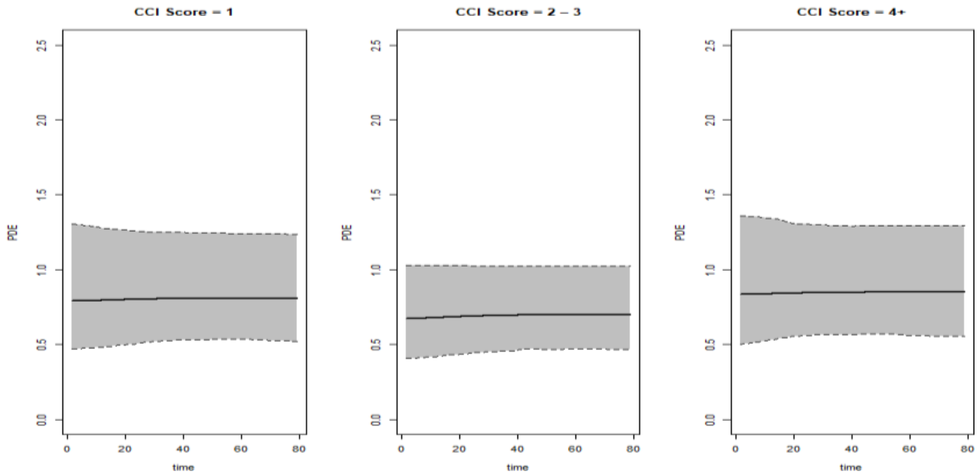
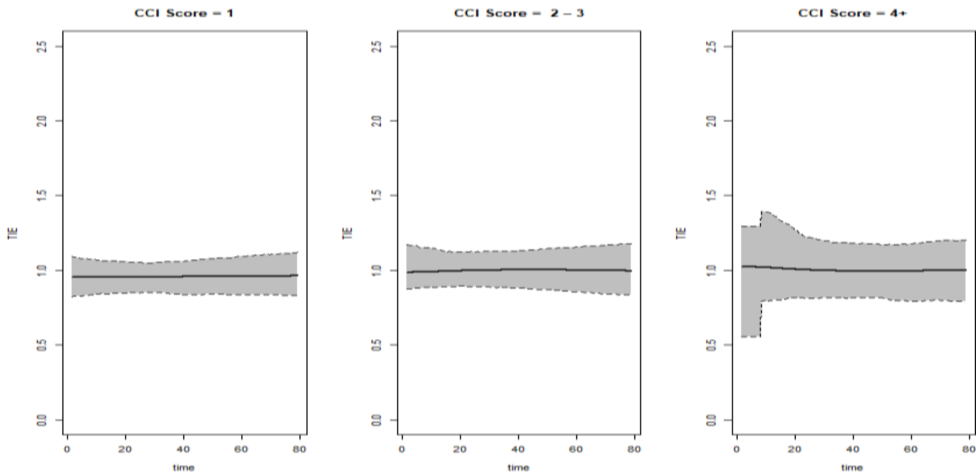


Figure 2. Pure Direct Effect (PDE), Total Indirect Effect (TIE), and Total Effect (TE) over time related to the length of hospitalization for the elderly population (65+ years), stratified by Charlson Comorbidity index.

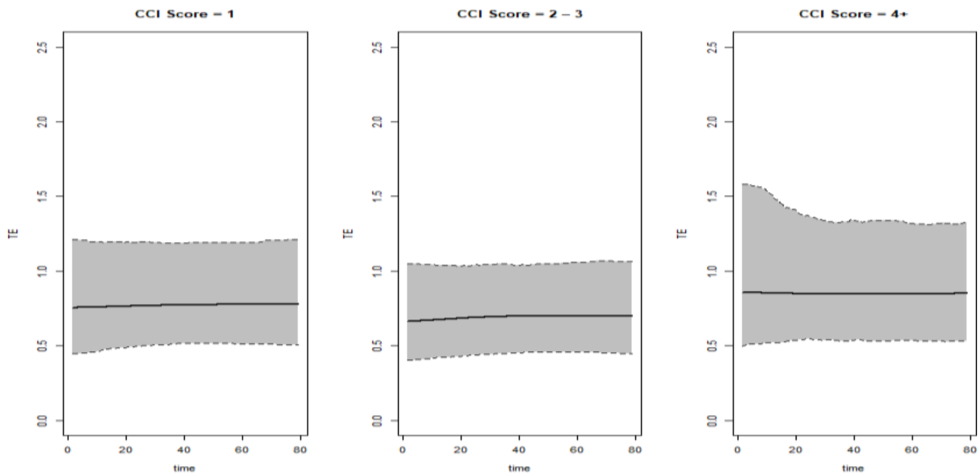
a) Pure Direct Effect (PDE)



b) Total Indirect Effect (TIE)



c) Total Effect (TE)



DISCUSSION

Through the use of the mediation analysis, this study aimed to better acknowledge the importance of COVID-19 severity at arrival in the ED, as measured by the National Early Warning Score2 (NEWS2), compared with the effect of multimorbidity, weighted with the CCI, in determining hospital outcomes. In particular, the objective of the mediation analysis was to gain a deeper understanding of the correlation between COVID-19, multimorbidity, and various outcomes. Additionally, this study aimed to determine any potential impact or influence that the NEWS2 may have on this relationship. Determining which factor has the most influence on the outcome may result in the improvement of early prediction of hospitalization necessity and resource management. Furthermore, a better stratification of the patients considering the combination of CCI and NEWS2 is useful in determining the best course of action for patient care.

Age was identified as the first prognostic determinant for COVID-19 since it has been proven that being older than 65 is a major risk factor for a more severe development of SARS-CoV-2 and worse outcome[23,24]. A similar trend was shown in our study, where patients older than 65 showed significant lower rates of discharge from the ED, and higher mortality in the first 30 days and checked into the ED with more severe conditions (Table 1).

It has been reported that a high CCI is associated with a higher risk of hospitalization, ICU admission, and death in both age subgroups. However, the NEWS has been observed as playing a key mediation role regarding the older population, strongly influencing the relationship between CCI and the outcomes of needing hospitalization and/or being admitted to the intensive care unit, whether or not a death occurs. Also, in regard to the young group of patients, we found that a high CCI is associated with a higher risk of long hospitalization while we didn't find a correlation between the NEWS2 and the length of hospital stay. In the younger subgroup, individuals with a high CCI also exhibited a higher risk of being hospitalized. This is observed as a strong direct effect, as demonstrated by the mediation test of multimorbidity on this specific outcome. It suggests that the presence of a comorbid condition may be a primary factor influencing the decision of ED physicians to admit the patient to the hospital. Taking into account the resources used during a hospital stay, this component may be rather relevant. According to the mediation effect study, it has been observed that the NEWS2 has a stronger impact on the relationship between CCI and outcomes for the older subgroup, potentially leading to a much more accurate prediction of the patient's progress.

The NEWS2 does not have the same weight on the younger subgroup. One reason among many to determine this may belong specifically to the higher homeostatic reserve of the younger patients.

The homeostatic reserve can be defined as the measure of the ability to function and the preservation of a specific body district, as well as the entire organism, specifically in relation to conditions that alter and lower the physiological functions. It has been described in recent literature how much the severe loss of reserve can impact the overall health of a person, specifically on frailty, which is a multidimensional geriatric syndrome[25]. Furthermore, homeostatic reserve can indeed be defined as a state of vulnerability to poor resolution of homeostasis following a stress, and is a consequence of cumulative decline in multiple physiological systems over a lifespan[26]. It is also described as an extreme vulnerability of the organism to endogenous and exogenous stressors, a syndrome that exposes the individual at higher risk of negative health-related outcomes as well as a transition phase between successful aging and disability[27].

Given that aging is widely recognized as one of the primary factors for the decline in organ reserve, research has shown that this reserve is sustained by excess in metabolic capacity, which, once impaired or exhausted, reduces the ability of the cell to cope with stress[28]. Therefore, a hypothesis can be made to explain why the course of the SARS-CoV-2 in the younger group has, in the worst cases, been found to abruptly worsen when the patient circumstances were relatively stable.

In this scenario, the NEWS2 has little impact on the outcome prediction in the younger group as the physiological reserve limits the organ disfunction during the first stages of the disease, causing NEWS2 to deteriorate only in the later phases of COVID-19 illness. In contrast, the elderly population's low physiological reserve is reduced earlier, thus the NEWS2 is predictive at arrival through the mediation test.

The process of loss of reserve that may culminate in the frailty syndrome is characterized by aging and multiple factors associated with it that alone are responsible for a worse condition of the elderly and a much more difficult recovery of stable physiological functions. In particular, the development of a mild pro-inflammatory state[29], commonly known as inflammageing, and the dysregulation it produces in the organism[30], are impactful in combination with multimorbidity. This is well- documented in literature[31–34], and can explain how the severity of the conditions at the time of access at the ED, hence the NEWS2, hold a key role in the association between CCI and the negative outcomes evaluated in our study.

STRENGTHS AND LIMITATIONS

This study presents several strengths. Firstly, the analyses are based on clinical data extracted from individual medical records, ensuring high quality, reliability, and accuracy of the data investigated. Secondly, beyond achieving high estimate accuracy, the use of advanced statistical methods, particularly mediation analyses, enabled a consistent examination of the roles played by the variables under investigation.

This study, however, also has some limitations. Firstly, the data comes from only two hospitals in Turin instead of from the entire Piedmont region, therefore, the results could not be representative of the entire region. Moreover, the study focused only on the first wave of the pandemic, limiting the generalizability of the results to the entire COVID-19 pandemic, especially given the different characteristics of the subsequent waves. Another limitation is the assessment of the patient's clinical condition upon arrival at the ED, which is based on the NEWS2 and serves as a proxy for clinical severity but may deviate from the actual patient's clinical condition in some cases.

CONCLUSION

This study showed that multimorbidity is a strong risk factor for a worse prognosis of COVID-19 in both in the younger and older populations. Additionally, the results of the mediation analyses found that the Charlson Comorbidity Index had a strong direct effect on not being discharged from the emergency department (ED) and the length of hospitalization. Furthermore, the NEWS2 Score, used as a proxy for the severity of the patient's clinical condition on arrival in the ED, was found to play the role of mediator in the association between multimorbidity and COVID-19-related outcomes, especially non-discharge and the combined outcome ICU admission and death. As a result, healthcare professionals must consider not only the comorbidity burden of the patients but also their clinical condition upon arrival at the ED. This consideration is crucial as it can significantly influence the outcomes of SARS-CoV-2 infection and help determine the most appropriate path for patient care.

Ethical Considerations

The study was conducted according to the World Medical Association's Declaration of Helsinki. Due to the retrospective nature of data collection and the relevance of the research, the Ethics Committee allowed the anonymous collection of data without informed consent.

Data Availability

Raw data cannot be openly shared due to ethical committee restrictions, which prohibit the public dissemination of individual-level data. Nonetheless, researchers can obtain aggregated data by reaching out to the corresponding author upon request.

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Conflict of interests

The authors declare no conflict of interest.

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REFERENCES

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Accessed November 28, 2023. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on- covid-19 ---------------11-march-2020

2. World Health Organization. WHO Director-General's opening remarks at the media briefing – 5 May 2023. Accessed November 28, 2023. https://www.who.int/director- general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing 5-may-2023

3. World Health Organization. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. Accessed November 28, 2023. https://covid19.who.int/

4. Li J, Huang DQ, Zou B, et al. Epidemiology of COVID-19: A systematic review and meta- analysis of clinical characteristics, risk factors, and outcomes. *J Med Virol*. 2021;93(3):1449- 1458. doi:10.1002/jmv.26424

5. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta- analysis of 42 studies and 423,117 patients. *BMC Infect Dis*. 2021;21(1):855. doi:10.1186/s12879-021-06536-3

6. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8

7. Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson Comorbidity Index: A Critical Review of Clinimetric Properties. *Psychother Psychosom*. 2022;91(1):8-35. doi:10.1159/000521288

8. Tuty Kuswardhani RA, Henrina J, Pranata R, Anthonius Lim M, Lawrensia S, Suastika K. Charlson comorbidity index and a composite of poor outcomes in COVID-19 patients: A systematic review and meta-analysis. *Diabetes Metab Syndr*. 2020;14(6):2103-2109. doi:10.1016/j.dsx.2020.10.022

9. Comoglu S, Kant A. Does the Charlson comorbidity index help predict the risk of death in COVID-19 patients? *North Clin Istanb*. 2022;9(2):117-121. doi:10.14744/nci.2022.33349

10. Catalano A, Dansero L, Gilcrease W, et al. Multimorbidity and SARS-CoV-2-Related Outcomes: Analysis of a Cohort of Italian Patients. *JMIR Public Health Surveill*. 2023;9:e41404. doi:10.2196/41404

11. Forchette L, Sebastian W, Liu T. A Comprehensive Review of COVID-19 Virology, Vaccines, Variants, and Therapeutics. *Curr Med Sci*. 2021;41(6):1037-1051. doi:10.1007/s11596-021- 2395-1

12. Shenoy S. SARS-CoV-2 (COVID-19), viral load and clinical outcomes; lessons learned one year into the pandemic: A systematic review. *World J Crit Care Med*. 2021;10(4):132-150. doi:10.5492/wjccm.v10.i4.132

13. Negewo NA, Gibson PG, McDonald VM. COPD and its comorbidities: Impact, measurement and mechanisms. *Respirol Carlton Vic*. 2015;20(8):1160-1171. doi:10.1111/resp.12642

14. Royal College of Physicians. National Early Warning Score (NEWS) 2. RCP London. Published December 19, 2017. Accessed November 28, 2023. https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2

15. Kostakis I, Smith GB, Prytherch D, et al. The performance of the National Early Warning Score and National Early Warning Score 2 in hospitalised patients infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Resuscitation*. 2021;159:150-157. doi:10.1016/j.resuscitation.2020.10.039

16. Pokeerbux MR, Yelnik CM, Faure E, et al. National early warning score to predict intensive care unit transfer and mortality in COVID-19 in a French cohort. *Int J Clin Pract*. 2021;75(6):e14121. doi:10.1111/ijcp.14121

17. McConnell KH, Hajat A, Sack C, Mooney SJ, Khosropour CM. Association between any underlying health condition and COVID-19-associated hospitalization by age group, Washington State, 2020-2021: a retrospective cohort study. *BMC Infect Dis*. 2023;23(1):193. doi:10.1186/s12879-023-08146-7

18. Caramello V, Maciotta A, De Salve AV, et al. Clinical characteristics and management of COVID-19 patients accessing the emergency department in a hospital in Northern Italy in March and April 2020. *Epidemiol Prev*. 2020;44(5-6 Suppl 2):208-215. doi:10.19191/EP20.5-6.S2.120

19. Sacerdote C, Milani L, Castiglione A, et al. Risk of Intensive Care Unit admission or mortality in patients hospitalised for COVID-19 during the first two waves: An Italian cohort study. *J Infect*. 2022;85(4):436-480. doi:10.1016/j.jinf.2022.06.023

20. EPICLIN. Il progetto EPICLIN. Accessed November 28, 2023. https://new.epiclin.it/

21. Vanderweele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *Am J Epidemiol*. 2010;172(12):1339-1348. doi:10.1093/aje/kwq332

22. Fasanelli F, Giraudo MT, Ricceri F, Valeri L, Zugna D. Marginal Time-Dependent Causal Effects in Mediation Analysis With Survival Data. *Am J Epidemiol*. 2019;188(5):967-974. doi:10.1093/aje/kwz016

23. Sundaram SS, Melquist S, Kalgotra P, et al. Impact of age, sex, race, and regionality on major clinical outcomes of COVID-19 in hospitalized patients in the United States. *BMC Infect Dis*. 2022;22(1):659. doi:10.1186/s12879-022-07611-z

24. O'Hare AM, Berry K, Fan VS, et al. Age differences in the association of comorbid burden with adverse outcomes in SARS-CoV-2. *BMC Geriatr*. 2021;21(1):415. doi:10.1186/s12877-021- 02340-5

25. Mendiratta P, Schoo C, Latif R. Clinical Frailty Scale. In: *StatPearls*. StatPearls Publishing; 2023. Accessed November 28, 2023. http://www.ncbi.nlm.nih.gov/books/NBK559009/

26. Cesari M, Calvani R, Marzetti E. Frailty in Older Persons. *Clin Geriatr Med*. 2017;33(3):293-303. doi:10.1016/j.cger.2017.02.002

27. Tabue-Teguo M, Simo N, Gonzalez-Colaço Harmand M, et al. Frailty in elderly: a brief review. *Geriatr Psychol Neuropsychiatr Vieil*. 2017;15(2):127-137. doi:10.1684/pnv.2017.0670

28. Atamna H, Tenore A, Lui F, Dhahbi JM. Organ reserve, excess metabolic capacity, and aging. *Biogerontology*. 2018;19(2):171-184. doi:10.1007/s10522-018-9746-8

29. Morrisette-Thomas V, Cohen AA, Fülöp T, et al. Inflamm-aging does not simply reflect increases in pro-inflammatory markers. *Mech Ageing Dev*. 2014;139:49-57. doi:10.1016/j.mad.2014.06.005

30. Bektas A, Schurman SH, Sen R, Ferrucci L. Aging, inflammation and the environment. *Exp Gerontol*.

2018;105:10-18. doi:10.1016/j.exger.2017.12.015

31. Teissier T, Boulanger E, Cox LS. Interconnections between Inflammageing and Immunosenescence during Ageing. *Cells*. 2022;11(3):359. doi:10.3390/cells11030359

32. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol*. 2018;15(9):505-522. doi:10.1038/s41569-018-0064-2

33. Friedman EM, Mroczek DK, Christ SL. Multimorbidity, inflammation, and disability: a longitudinal mediational analysis. *Ther Adv Chronic Dis*. 2019;10:2040622318806848. doi:10.1177/2040622318806848

34. Friedman EM, Christ SL, Mroczek DK. Inflammation Partially Mediates the Association of Multimorbidity and Functional Limitations in a National Sample of Middle-Aged and Older Adults: The MIDUS Study. *J Aging Health*. 2015;27(5):843-863. doi:10.1177/0898264315569453

Supplementary Table 1. Demographic and clinical characteristics related to hospitalized patients, stratifying by age

Variable	<65 (*N= 180*) N (%)	65+ (*N = 319*) N (%)
Age		
Median (IQR[a])	53.0 (47.0-58.0)	79.0 (73.0-85.0)
Gender		
Male	123 (68.3%)	173 (54.2%)
Female	57 (31.7%)	146 (45.8%)
Smoking		
No	144 (80.0%)	254 (79.6%)
Yes	36 (20.0%)	65 (20.4%)
Hospital		
San Luigi	68 (36.7%)	125 (39.2%)
Molinette	114 (63.3%)	194 (60.8%)
Obesity		
No	159 (88.3%)	297 (93.1%)
Yes	21 (11.7%)	22 (7.9%)
Hypertension		
No	96 (53.3%)	74 (23.2%)
Yes	84 (46.7%)	245 (76.8%)
Charlson Comorbidity Index		
0	119 (66.1%)	87 (27.3)
1	29 (16.1%)	89 (27.9%)
2-3[b]	32 (17.8%)	76 (23.8%)
4+	-	67 (21.0%)
National Early Warning Score 2		
0	118 (65.5%)	140 (43.9%)
1	21 (11.7%)	46 (14.4%)
2+	41 (22.8%)	133 (41.7%)
Intensive Care Unit admission or death		
No	119 (66.1%)	158 (49.5%)
Yes	61 (33.9%)	161 (50.5%)

[a] IQR: Interquartile Range;

[b]In the case of subjects under 65, the category refers to the value "2+".

Supplementary Table 2. Demographic and clinical characteristics related to hospitalized patients who didn't die in the follow-up period

Variable	<65 (*N= 164*) N (%)	65+ (*N = 191*) N (%)
Age		
Median (IQR[a])	53.0 (47.0-58.0)	76.0 (71.0-84.0)
Gender		
Male	112 (68.3%)	101 (52.9%)
Female	52 (31.7%)	90 (47.1%)
Smoking		
No	132 (80.5%)	153 (80.1%)
Yes	32 (19.5%)	38 (19.9%)
Hospital		
San Luigi	56 (34.1%)	71 (37.2%)
Molinette	108 (65.9%)	120 (62.8%)
Obesity		
No	147 (89.6%)	176 (92.1%)
Yes	17 (10.4%)	15 (7.9%)
Hypertension		
No	91 (55.5%)	41 (21.5%)
Yes	73 (44.5%)	150 (78.5%)
Charlson Comorbidity Index		
0	113 (68.9%)	59 (30.9%)
1	24 (14.6%)	54 (28.3%)
2-3[b]	27 (16.5%)	41 (21.4%)
4+	-	37 (19.4%)
National Early Warning Score 2		
0	115 (70.1%)	100 (52.4%)
1	19 (11.6%)	38 (19.9%)
2+	30 (18.3%)	53 (27.7%)
Length of hospitalization		
Median (IQR[a])	9.0 (6.0-18.0)	16.0 (9.0-25.0)

[a] IQR: Interquartile Range;

[b] In the case of subjects under 65, the category refers to the value "2+"

Supplementary Table 3. Association between mediator-exposure and outcome-mediator, conducted through multivariable logistic regression, multinomial regression, and Cox Proportional Hazards Models

Outcome	Dependent variable	Independent variable	<65 OR[a] (95% CI[b])	65+ OR[a] (95% CI[b])
Mediator-Exposure				
Non-discharge	NEWS2 Score = 1	CCI[c] = 1	1.43 (0.48-4.29)	0.74 (0.31-1.81)
		CCI[c] = 2+	1.48 (0.47-4.68)	1.12 (0.53-2.36)
	NEWS2 Score = 2+	CCI[c] = 1	1.29 (0.50-3.30)	1.79 (0.96-3.36)
		CCI[c] = 2+	2.60 (1.10-6.14)	2.13 (1.21-3.76)
Intensive Care Unit admission or death	NEWS2 Score = 1	CCI[c] = 1	1.58 (0.39-6.34)	0.69 (0.27-1.81)
		CCI[c] = 2-3	1.65 (0.45-6.01)	0.83 (0.32-2.15)
		CCI[c] = 4+	-	1.30 (0.50-3.35)
	NEWS2 Score = 2+	CCI[c] = 1	1.28 (0.43-3.82)	1.79 (0.90-3.57)
		CCI[c] = 2-3	2.09 (0.80-5.46)	1.77 (0.88-3.59)
		CCI[c] = 4+	-	1.54 (0.72-3.31)
Death within 30 days	NEWS2 Score = 1	CCI[c] = 1	1.43 (0.48-4.29)	0.75 (0.31-1.83)
		CCI[c] = 2-3	1.48 (0.47-4.68)	0.98 (0.41-2.34)
		CCI[c] = 4+	-	1.33 (0.53-3.35)
	NEWS2 Score = 2+	CCI[c] = 1	1.29 (0.50-3.30)	1.79 (0.96-3.36)
		CCI[c] = 2-3	2.60 (1.10-6.14)	2.10 (1.11-3.94)
		CCI[c] = 4+	-	2.18 (1.08-4.41)
Length of hospitalization	NEWS2 Score = 1	CCI[c] = 1	2.22 (0.53-9.23)	0.98 (0.34-2.82)
		CCI[c] = 2-3	1.22 (0.29-5.06)	0.85 (0.28-2.58)
		CCI[c] = 4+	-	1.61 (0.53-4.89)
	NEWS2 Score = 2+	CCI[c] = 1	0.70 (0.17-2.85)	1.94 (0.75-5.01)
		CCI[c] = 2-3	1.27 (0.41-4.00)	1.22 (0.44-3.39)
		CCI[c] = 4+	-	1.57 (0.52-4.69)
Outcome-Mediator				
Non-discharge		NEWS2 Score = 0	Ref	Ref
		NEWS2 Score = 1	4.50 (1.70-11.87)	2.31 (0.61-8.68)
		NEWS2 Score = 2+	29.71 (6.94-127.30)	17.39 (2.25-134.48)
Intensive Care Unit admission or death		NEWS2 Score = 0	Ref	Ref
		NEWS2 Score = 1	1.89 (0.63-5.58)	1.00 (0.49-2.01)
		NEWS2 Score = 2+	4.98 (2.15-11.55)	3.88 (2.26-6.64)
Death within 30 days		NEWS2 Score = 0	Ref	Ref
		NEWS2 Score = 1	12.01 (0.67-216.53)	0.50 (0.20-1.25)
		NEWS2 Score = 2+	117.86 (13.34-1041.47)	3.90 (2.30-6.58)
Length of hospitalization		NEWS2 Score = 0	Ref	Ref
		NEWS2 Score = 1	0.77 (0.46-1.29)	0.96 (0.65-1.44)
		NEWS2 Score = 2+	0.68 (0.44-1.04)	0.82 (0.58-1.17)

[a] OR: Odds Ratio; [b] CI: Confidence Interval; [c] CCI: Charlson Comorbidity Index

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Article

3.3 Improvements throughout the Three Waves of COVID-19 Pandemic: Results from 4 Million Inhabitants of North-West Italy

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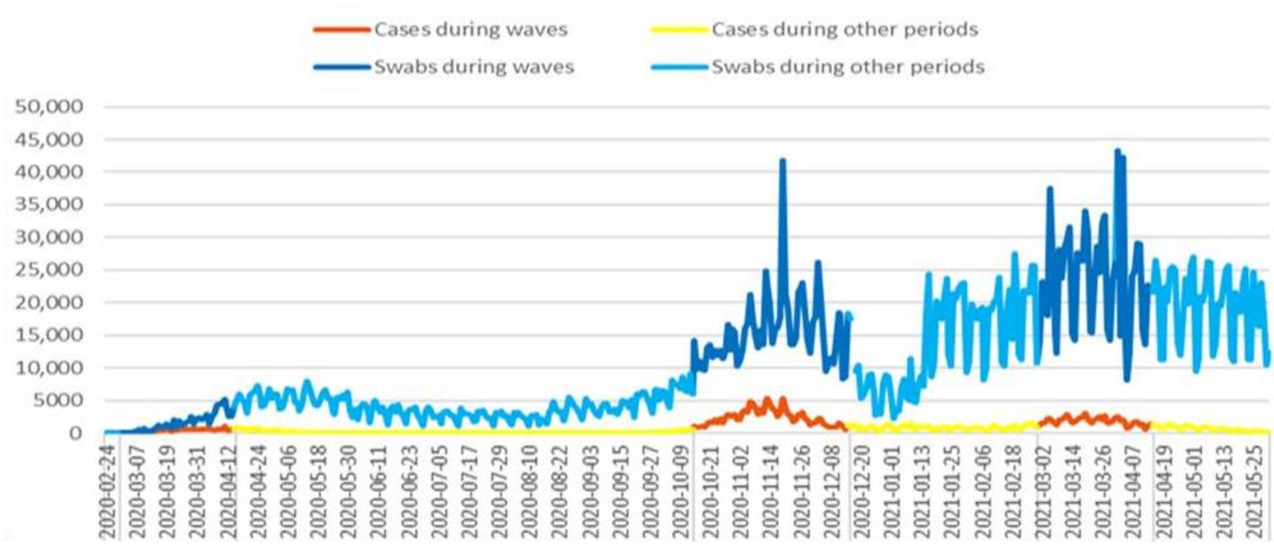
Abstract: At the very beginning of the European spread of SARS-CoV-2, Piedmont was one of the most affected regions in Italy, with a strong impact on healthcare organizations. In this study, we evaluated the characteristics and outcomes of the COVID-19 patients in an entire region during the first three pandemic waves, identifying similarities and differences in the SARS-CoV-2 epidemic's timeline. We collected the health-administrative data of all the Piedmont COVID-19 patients infected during the first three pandemic waves (1 March 2020–15 April 2020; 15 October 2020–15 December 2020; 1 March 2021–15 April 2021, respectively). We compared differences among the waves in subjects positive for SARS-CoV-2 and in patients admitted to ICU. Overall, 18.621 subjects tested positive during the first wave (405 patients/day), 144.350 (2366.4 patients/day) in the second, and 81.823 (1778.8 patients/day) in the third. In the second and third waves, we observed a reduction in median age, comorbidity burden, mortality in outpatients, inpatients, and patients admitted to ICU, in intubation, invasive ventilation and tracheostomy, and a parallel increase in the use of CPAP. Our study confirmed a trend towards younger and healthier patients over time but also showed an independent effect of the period on mortality and ICU admission. The appearance of new viral variants, the starting of vaccination, and organizational improvements in tracking, outpatients and inpatients management could have influenced these trends.

Keywords: SARS-CoV-2; mortality; intensive care units; patients; comorbidity; epidemiology

1. Introduction

Since the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was declared a pandemic in March 2020 [1], Italy was the first country outside China and the first European country to be strongly impacted by the COVID-19 pandemic, which resulted in a significant health burden. Since the first case was reported in Lombardy on the 20th of February, the infection spread very quickly in the Northern regions and the densely populated area around the Po River by the end of March, with an observed increase in 29.5% from the expected mortality. In Italy, Piedmont (Figure S1) was the second affected region during the first wave and suffered from hospital overload, shortage of healthcare resources and professionals, as well as a massive death toll [1]. A structural reorganization and improvements in resource allocation were needed to cope with the emergency, both at the hospital level and in primary care, managed by the regional Crisis Unit. The emergency lasted many months, with three following waves in the first 16 months. These waves (1 March 2020–15 April 2020; 15 October 2020–15 December 2020; 1 March 2021–15 April 2021) were defined by a rising number of cases (405 cases/day; 2366.4 cases/day; 1778.8 cases/day, respectively) [1] with a corresponding increase in hospitalizations and deaths related to Coronavirus disease (COVID-19) and by the parallel restriction policies issued by the government [2] (Figure 1 and Figure S2). A summary of the main interventions is presented in Figure 1. As time passed, a better knowledge of COVID-19 physiopathology, clinical staging, and therapeutic possibilities was achieved, followed by an attenuation in the excess mortality [1,3,4] European Countries and, especially, Italy recorded an extremely high fatality rate (with a case fatality ratio up to 11%) [5,6] compared to China (Hubei region case fatality ratio of 4.7%) [7], which was the country where the pandemic started [3,4,8]. This is likely due to an underestimation of infection rates, the overload of ICUs, and the older age of infected patients during the first wave [4,8–10]. Many Italian authors observed a reduction in mortality, hospitalization, and ICU admission in the following second and third waves [9,10]. Others do not agree, especially when evaluating regions that were relatively spared or lightly affected during the first waves [8].



	First wave	**Second wave**	**Third wave**[a]
Containment measures (politics)	First national lockdown Closure of school and all non-essential activities Non-essential workers at home Restricted travel and movements	Second national lockdown More activities considered "essentials" More workers allowed to work Closure of secondary school, except for the first years of each cycle Wear of mask mandatory Restricted travel and movements	Third national lockdown More activities considered "essentials" More workers allowed to work Closure of school Wear of mask mandatory Restricted travel and movements
Organization of local health services	Only two laboratories for SARS-CoV-2 tests (increased during the first wave) Special COVID-19 recruitment of staff for Public health services	Availability of many laboratories for SARS-CoV-2 tests Implementation of "USCA" (special territorial medical service for infected patients) Regional department in charge of pandemic response (DIRMEI) Special COVID-19 recruitment of staff for Public health services	Many laboratories for SARS-CoV-2 tests Availability of "USCA" (special territorial medical service for infected patients) Availability of antigenic tests outside hospitals Deployment of staff for vaccination
Hospital organization	Local crisis unit Special COVID-19 recruitment of health professionals Increase of COVID-19 wards with the increase of number of cases	Hospital crisis unit Special COVID-19 recruitment of health professionals Increase of COVID-19 wards by steps Increase of ICUs Increase of HDUs	Use of CPAP in normal wards Increase of ICUs Increase of HDUs
Available therapies	Hydroxychloroquine Antiviral drugs Tocilizumab	Steroids Remdesivir Tocilizumab	Steroids Remdesivir Tocilizumab Monoclonal antibodies

Figure 1. Number of swabs performed, number of new SARS-CoV-2 positive cases registered in Piedmont during the COVID-19 pandemic, and main interventions issued by the Italian Government and the health care system. (Data source: GitHub—pcm-dpc/COVID-19: COVID-19 Italia—Monitoraggio situazione). [a] Spread of Delta variant.

To the best of our knowledge, despite the worldwide spread of the disease, only a few studies have thoroughly compared the disease severity and the demographic and clinical characteristics of infected patients in subsequent waves [11–13]: these studies are monocentric [11,14,15] or on a regional [9,10,15–17] or national level [12,13,18] or concern specific populations [19].

Currently, the role of demographic and lifestyle factors and comorbid conditions on the risk of progression to severe COVID-19 is well defined; however, it is still controversial how different patient characteristics and the improvements in treatment and health care organization could contribute to morbidity and mortality. Moreover, public health institutions worldwide imposed different lockdown restrictions, tracing and control measures aiming, on one side, to reduce the number of cases and to protect the health system from overload or, on the other side, to achieve herd immunity. The systematic interpretation at a global level is challenging because of the enormous heterogeneity in sampling and methodology: many reports are based on mathematical modeling only [20], others are derived from different healthcare systems or are limited to a single medical center [9,10,14,15,19].

Study Design and Aims

The aim of this large population-based region-wide study based on health administrative databases is to evaluate the characteristics and outcomes of the COVID-19 patients of the Piedmont Region during the three pandemic waves in an attempt to identify similarities and differences in the SARS-CoV-2 epidemic's timeline during the first year of the Pandemic.

Secondarily, in the subgroup of COVID-19 inpatients, we aimed to evaluate the differences in the need for respiratory support, for Intensive Care Unit (ICU), and the hospital length of stay to assess the severity of cases and the burden on Piedmont Hospitals resources.

2. Materials and Methods

2.1. Study Population

To assess the characteristics of patients affected by COVID-19 for the first time during the three COVID-19 pandemic waves, data were obtained through record-linkage of regional health administrative data, as explained in Figure 2.

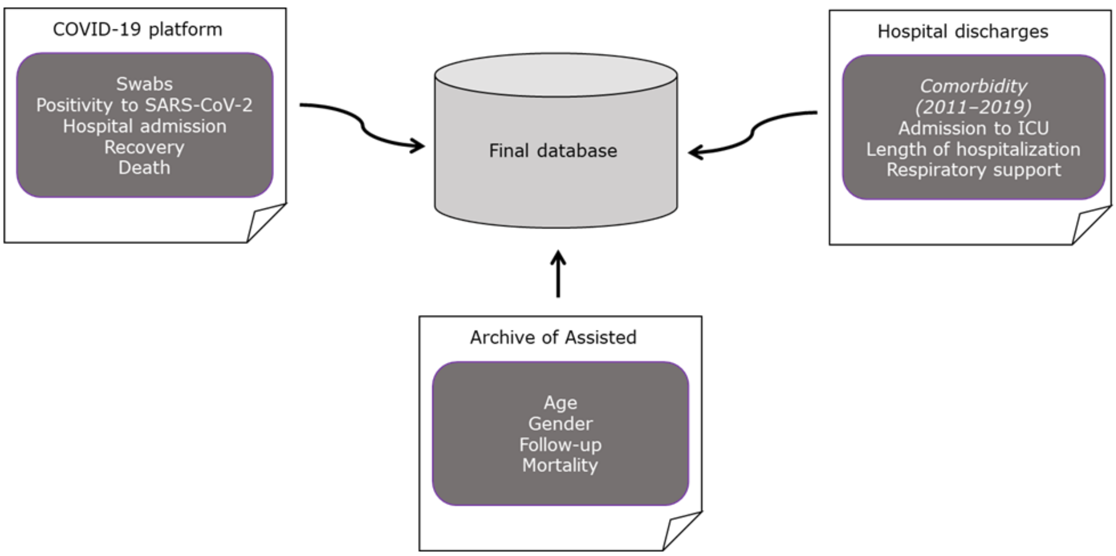


Figure 2. Flow chart on data collection process by record linkage of three different regional-health administrative archives.

The sources included were:

The regional platform "COVID-19", in which data on subjects who had contact with the Piedmont health system related to SARS-CoV-2 (tested, quarantined, infected, sick, hospital admitted, dead or recovered) are collected;

The regional archive of Hospital Discharge Forms, which contains information on each patient from Piedmont discharged from public and private hospitalization institutions;

The Regional Unitary Archive of Assisted, which provides information on all those who applied for a general practitioner in the region and information on deaths.

The three COVID-19 pandemic waves were defined based on the number of cases (Figure 1) and on the restrictions implemented by the Italian Government, as follows:

First wave: 1 March 2020–15 April 2020;

Second wave: 15 October 2020–15 December 2020;

Third wave: 1 March 2021–15 April 2021.

2.2. Variables

Using data from the regional Archive of Hospital Discharge Forms related to a five-year period of 2015–2019, patients with previous neoplasia, diabetes, dementia, immunodeficiency, cardiomyopathy, heart failure and cardiovascular, coronary artery, cerebrovascular, haematologic, kidney, and chronic obstructive pulmonary diseases (COPD) have been identified. Moreover, for each subject, the value of the Charlson Comorbidity Index (CCI) [21] was calculated, and, only for hospitalized subjects, other information, such as the duration of hospitalization due to SARS-CoV-2 infection and the intervention procedures implemented were retrieved (oxygen, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), intubation, invasive ventilation, and tracheotomy).

The outcome variables were defined as: hospitalization, hospitalization in ICU (both data were retrieved from the archives of hospital discharge forms), and mortality (retrieved by the combination of all the sources available).

2.3. Statistical Analysis

The data were described using the median, mean, interquartile range, and standard deviation or standardized frequencies, expressed as the average number of cases per day (due to the difference in length of the different waves) and percentages for quantitative and qualitative data, respectively. Moreover, for each clinical and sociodemographic variable, we tested possible significant differences between the three waves by using the Chi-square or Fisher test and ANOVA or Kruskal–Wallis test, both by considering all infected individuals and only the subjects admitted to the hospital for COVID-19, admitted to an intensive care unit (ICU) and who died within 30 days from the first positive swab.

To control for possible confounding factors, we evaluated the impact of the waves on the severity of COVID-19 using a logistic regression model for the combined outcome of ICU admission or mortality adjusted by age, gender, and comorbidity index.

Analyses were performed using SAS (V9.4), SAS Institute Inc., Cary, NC, USA, and R (V4.1.2), R foundation for statistical computing, Vienna, Austria.

3. Results

Among a population of about 4.3 million inhabitants, 357.436 tested positive for SARS-CoV-2 during the observed pandemic period (from 22 February 2020 to 31 May 2021). In the first wave, 18.621 subjects tested positive, which corresponds to a daily number of cases of about 405. During the second wave, the number of positive subjects increased to 144.350, corresponding to a daily number of 2366.4 cases. In the third wave, the number of positive decreased to 81.823, corresponding to a daily number of cases of 1778.8.

The descriptive data about the positive patients are presented in Table 1 and in Figure 3. In the first wave, the positive patients were older (I: 48.4% more than 65 years old; II: 24.1%; 21.5%, respectively), with more comorbidities (I: 41.0% with at least one comorbidity; II: 27.1%; III: 24.5%), and with more severe disease compared to the two following waves (higher percentage of hospitalizations, ICU admissions, and deaths). As expected, the daily number of cases of all categories considerably increased in the second waves and slightly decreased in the third waves; this is likely due to patients with no or mild symptoms, who were probably under-tested during the first wave. Indeed, outpatients in the second and third waves were, respectively, about 9 times and 6.5 times higher than in the first wave, and the increase in hospitalized patients was notably lower, being 1.3 and 1.1 times for the second and third waves. Interestingly, in the third wave, it was possible to observe a substantial decrease both in number and in the percentage of positive older subjects (>85 years old) (I: 15.8%; II: 6.3%; III: 2.9%), subjects with dementia (I: 3.8%; II: 1.1%; III: 0.3%), and dead patients (I: 17.9%; II: 3.9%; III: 2.6%), even if we compare the data with the first wave.

Table 1. Demographic characteristics, comorbid conditions, hospitalization, intensive care unit (ICU) admission, and death from COVID-19 of subjects tested positive for SARS-CoV-2, stratifying by waves.

	First Wave (1 March–15 April 2020) N/Day [a] (%)	**Second Wave (15 October–15 December 2020) N/Day [a] (%)**	**Third Wave (1 March–15 April 2021) N/Day [a] (%)**	***p*-Value [b]**
Age group				
≤65	209.0 (51.6%)	1797.3 (75.9%)	1397.0 (78.5%)	<0.001
66–75	55.3 13.7%)	216.4 (9.2%)	196.4 (11.1%)	
76–85	76.6 (18.9%)	204.1 (8.6%)	133.2 (7.5%)	
86+	63.8 (15.8%)	148.5 (6.3%)	52.2 (2.9%)	
Gender				
F	221.6 (54.7%)	1275.8 (53.9%)	900.3 (50.6%)	<0.001
M	183.2 (45.3%)	1090.6 (46.1%)	878.5 (49.4%)	
Charlson Comorbidity Index				
0	238.7 (59.0%)	1725.8 (72.9%)	1343.5 (75.5%)	<0.001
1	89.5 (22.1%)	436.1 (18.4%)	317.3 (17.8%)	
2–3	57.8 (14.3%)	165.3 (7.0%)	98.8 (5.6%)	
4+	18.7 (4.6%)	39.2 (1.7%)	19.2 (1.1%)	
Chronic Obstructive Pulmonary Disease (COPD)				
No	328.4 (81.1%)	2019.2 (85.3%)	1529.7 (86.0%)	<0.001
Yes	76.4 (18.9%)	347.1 (14.7%)	249.1 (14.0%)	
Cardiovascular disease				
No	327.9 (81.0%)	2151.7 (90.9%)	1655.8 (93.1%)	<0.001
Yes	76.9 (19.0%)	214.7 (9.1%)	123.0 (6.9%)	
Heart failure				
No	393.9 (97.3%)	2344.1 (99.1%)	1768.9 (99.5%)	<0.001
Yes	10.9 (2.7%)	22.3 (0.9%)	9.8 (0.5%)	
Coronary artery disease				
No	385.5 (95.2%)	2314.8 (97.8%)	1747.1 (98.2%)	<0.001
Yes	19.3 (4.8%)	51.6 (2.2%)	31.6 (1.8%)	
Cardiomyopathy				
No	385.9 (95.3%)	2328.7 (98.4%)	1761.8 (99.0%)	<0.001
Yes	18.9 (4.7%)	37.7 (1.6%)	17.0 (1.0%)	
Diabetes				
No	340.4 (84.1%)	2161.8 (91.3%)	1647.6 (92.6%)	<0.001

Yes	64.4 (15.9%)	294.6 (8.7%)	131.1 (7.4%)	
Kidney disease				
No	388.5 (96.0%)	2330.7 (98.5%)	1761.0 (99.0%)	<0.001
Yes	16.3 (4.0%)	35.7 (1.5%)	17.8 (1.0%)	
Cerebrovascular disease				
No	379.8 (93.8%)	2311.3 (97.7%)	1755.5 (98.7%)	<0.001
Yes	25.0 (6.2%)	55.1 (2.3%)	23.3 (1.3%)	
Dementia				
No	378.3 (96.2%)	2340.1 (98.9%)	1773.1 (99.7%)	<0.001
Yes	15.5 (3.8%)	26.3 (1.1%)	5.7 (0.3%)	
Neoplasia				
No	384.2 (94.9%)	2303.1 (97.3%)	1735.5 (97.6%)	<0.001
Yes	20.6 (5.1%)	63.3 (2.7%)	43.3 (2.4%)	
Haematologic disease				
No	402.3 (99.4%)	2359.7 (99.7%)	1774.8 (99.8%)	<0.001
Yes	2.5 (0.6%)	6.7 (0.3%)	3.9 (0.2%)	
Immunodeficiency				
No	404.6 (99.9%)	2365.7 (99.9%)	1778.3 (99.9%)	0.55
Yes	0.2 (0.1%)	0.7 (0.1%)	0.5 (0.1%)	
Hospitalization				
No	240.1 (59.3%)	2147.8 (90.8%)	1596.8 (89.8%)	<0.001
Yes	164.7 (40.7%)	218.6 (9.2%)	182.0 (10.2%)	
Intensive care unit (ICU) admission				
No	359.9 (88.9%)	2312.7 (97.7%)	1734.7 (97.5%)	<0.001
Yes	44.9 (11.1%)	53.7 (2.3%)	44.1 (2.5%)	
Death				
No	332.3 (82.1%)	2275.1 (96.1%)	1732.1 (97.4%)	<0.001
Yes	72.5 (17.9%)	91.3 (3.9%)	46.6 (2.6%)	

[a] N/day average number of cases per day; [b] Comparisons among the three waves tested by Chi-square or Fisher test.

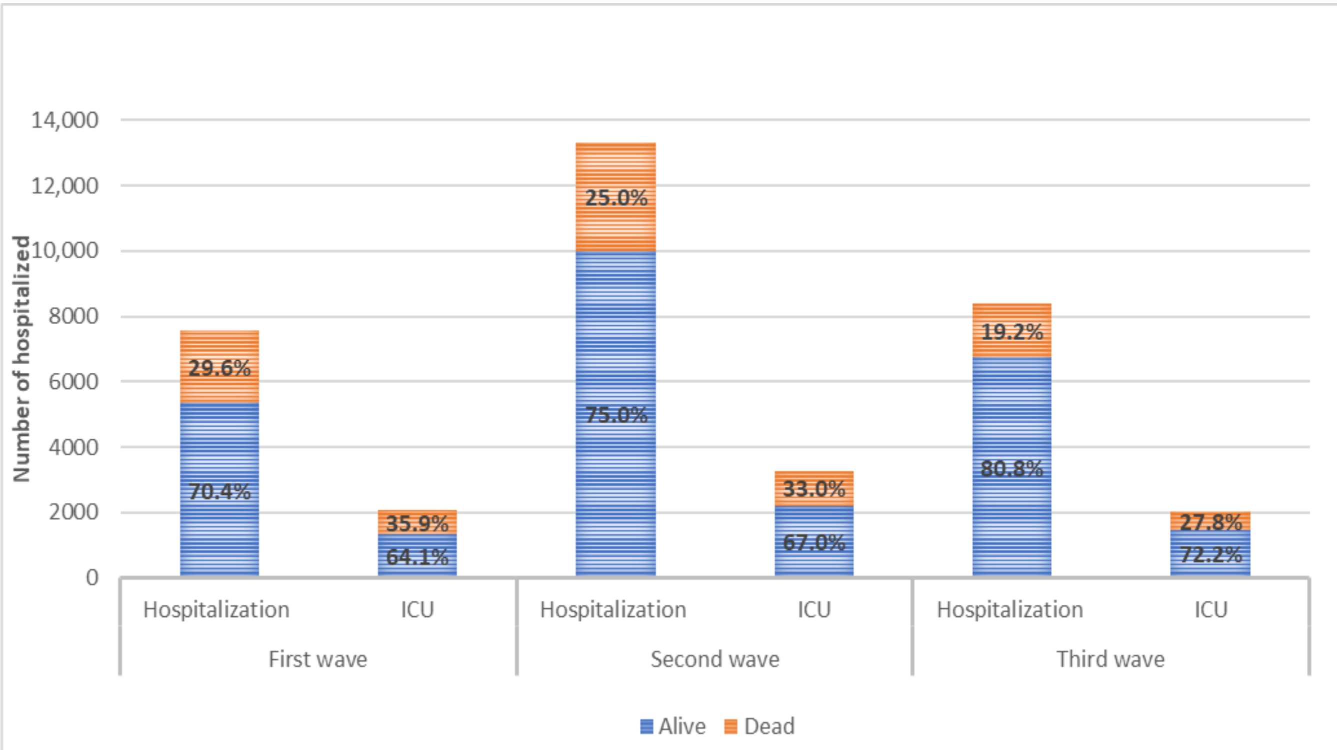


Figure 3. Mortality within 30 days from the first positive swab in hospitalized patients and in the subgroup of patients admitted to intensive care unit (ICU) in the three waves.

Patients who needed hospitalization (Table 2 and Table S1) in all the three waves were significantly older (I: patients admitted 65 + 64.4% vs. patients not admitted 65 + 37.4%; II: 70.0% vs. 19.4%; III: 64.1% vs. 16.6%)., of male gender (I: admitted 59.9% vs. not admitted 35.2%; II: 59.1% vs. 44.8%; III: 58.0% vs. 48.4%), and with more comorbidities (I: admitted with at least one comorbidity 51.6% vs. not admitted with at least one comorbidity 33.8%; II: 53.4% vs. 24.4%; III: 47.3% vs. 21.9%), but fewer differences could have been identified in hospitalized patients among the waves.

Table 2. Demographic characteristics, comorbid conditions, intensive care unit (ICU) admission, and death from COVID-19 of subjects tested positive for SARS-CoV-2, stratifying by hospitalization and waves.

	First Wave (1 March–15 April 2020)		**Second Wave (15 October–15 December 2020)**		**Third Wave (1 March–15 April 2021)**		
	No Admission N/Day [a] (%)	**Admission N/Day [a] (%)**	**No Admission N/Day [a] (%)**	**Admission N/Day [a] (%)**	**No Admission N/Day [a] (%)**	**Admission N/Day [a] (%)**	***p*-Value [b]**
Age group							
≤65	150.4 (62.6%)	58.7 (35.6%) ***,c	1731.8 (80.6%)	65.6 (30.0%) ***,d	1331.7 (83.4%)	65.3 (35.9%) ***,e	<0.001
66–75	19.5 (8.1%)	35.8 (21.8%)	168.4 (7.9%)	48.0 (22.0%)	148.7 (9.3%)	47.7 (26.2%)	
76–85	30.8 (12.9%)	45.8 (27.8%)	137.2 (6.4%)	66.9 (30.6%)	85.4 (5.3%)	47.8 (26.3%)	
86+	39.4 (16.4%)	24.4 (14.8%)	110.4 (5.1%)	38.1 (17.4%)	31.0 (2.0%)	21.1 (11.6%)	
Gender							
F	155.5 (64.8%)	66.0 (40.1%) ***,c	1196.5 (55.2%)	89.3 (40.9%) ***,d	823.8 (51.6%)	76.5 (42.0%) ***,e	0.04
M	84.6 (35.2%)	98.7 (59.9%)	961.4 (44.8%)	128.2 (59.1%)	773.0 (48.4%)	105.5 (58.0%)	
Charlson Comorbidity Index							
0	159.0 (66.2%)	79.6 (48.4%) ***,c	1624.0 (75.6%)	101.8 (46.6%) ***,d	1247.6 (78.1%)	96.9 (52.7%) ***,e	<0.001
1	45.4 (18.9%)	44.1 (25.8%)	374.5 (17.4%)	61.6 (28.2%)	268.6 (16.8%)	48.7 (26.7%)	
2–3	27.5 (11.5%)	30.3 (18.4%)	123.9 (5.8%)	41.3 (18.9%)	69.4 (4.4%)	29.4 (16.2%)	
4+	8.1 (3.4%)	10.6 (6.4%)	25.4 (1.2%)	13.8 (6.3%)	11.2 (0.7%)	8.0 (4.4%)	
ICU admission							
No	..	119.8(72.8%) ***,c	..	164.9 (75.5%) ***,d	..	137.9 (75.8%) ***,e	<0.001
Yes	..	44.9 (27.2%)	..	53.7 (24.6%)	..	44.1 (24.2%)	
Death							
No	216.3 (90.1%)	116.0 (70.5%) ***,c	2111.1 (98.3%)	164.0 (75.0%) ***,d	1585.1 (99.3%)	147.0 (80.8%) ***,e	<0.001
Yes	23.8 (9.9%)	48.7 (29.5%)	36.7 (1.7%)	54.6 (25.0%)	11.7 (0.7%)	35.0 (19.2%)	

[a] N/day average number of cases per day; [b] Comparisons of hospital admitted patients among the three waves tested by Chi-square or Fisher test; [c] Comparison between hospitalized and not hospitalized subjects during the first wave tested by Chi-square or Fisher test; [d] Comparison between hospitalized and not hospitalized subjects during the second wave tested by Chi-square or Fisher test; [e] Comparison between hospitalized and not hospitalized subjects during the third wave tested by Chi-square or Fisher test; *** $p < 0.001$.

Differences among the three waves were less evident, both in absolute numbers and in percentages, considering patients hospitalized in ICU (Table 3 and Table S2). However, it is interesting to notice that in the third wave, a reduction in deaths was recorded both in the ICU and in the other wards.

Table 3. Demographic characteristics, comorbid conditions, and death from COVID-19 of patients hospitalized for SARS-CoV-2, stratifying by admission to intensive care unit (ICU) and waves.

	First Wave (1 March–15 April 2020)		Second Wave (15 October–15 December 2020)		Third Wave (1 March–15 April 2021)		
	No ICU N/Day [a] (%)	ICU N/Day [a] (%)	No ICU N/Day [a] (%)	ICU N/Day [a] (%)	No ICU N/Day [a] (%)	ICU N/Day [a] (%)	p-Value [b]
Age group							
≤65	38.3 (32.8%)	19.4 (43.2%) ***,c	47.8 (29.0%)	17.8 (33.2%) ***,d	47.2 (34.2%)	18.2 (41.2%) ***,e	<0.001
66–75	22.5 (18.8%)	13.3 (29.7%)	31.2 (18.9%)	16.8 (31.2%)	32.5 (23.6%)	15.2 (34.5%)	
76–85	36.0 (30.0%)	9.8 (21.9%)	51.9 (31.5%)	15.0 (27.9%)	39.0 (28.3%)	8.8 (20.0%)	
86+	22.1 (18.4%)	2.3 (5.2%)	33.9 (20.6%)	4.1 (7.7%)	19.2 (13.9%)	1.9 (4.3%)	
Gender							
F	52.9 (44.1%)	13.2 (29.4%) ***,c	72.4 (43.9%)	17.0 (31.6%) ***,d	60.7 (44.0%)	15.8 (35.9%) ***,e	<0.001
M	67.0 (55.9%)	31.7 (70.6%)	92.5 (56.1%)	36.7 (68.4%)	77.2 (56.0%)	28.3 (64.1%)	
Charlson Comorbidity Index							
0	56.6 (47.2%)	23.1 (51.4%) **,c	76.9 (46.6%)	25.0 (46.5%) *,d	71.9 (52.1%)	24.0 (54.5%) **,e	<0.001
1	32.1 (26.8%)	12.0 (26.7%)	45.7 (27.7%)	16.0 (29.8%)	36.5 (26.5%)	12.2 (27.6%)	
2–3	23.0 (19.2%)	7.4 (16.4%)	31.6 (19.2%)	9.7 (18.1%)	23.1 (16.8%)	6.3 (14.2%)	
4+	8.2 (6.8%)	2.5 (2.5%)	10.7 (6.5%)	3.0 (5.6%)	6.4 (4.6%)	1.6 (3.7%)	
Death							
No	87.3 (72.8%)	28.7 (64.0%) ***,c	128.0 (77.6%)	36.0 (67.0%) ***,d	115.2 (83.5%)	31.8 (72.2%) ***,e	<0.001
Yes	32.5 (27.2%)	16.1 (36.0%)	36.9 (22.4%)	17.7 (33.0%)	22.7 (16.5%)	12.3 (27.8%)	

[a] N/day average number of cases per day; [b] Comparisons of patients admitted to ICU among the three waves tested by Chi-square or Fisher test; [c] Comparison between patients admitted in ICU and in other wards (No ICU) during the first wave tested by Chi-square or Fisher test; [d] Comparison between patients admitted in ICU and in other wards (No ICU) during the second wave tested by Chi-square or Fisher test; [e] Comparison between patients admitted in ICU and in other wards (No ICU) during the third wave tested by Chi-square or Fisher test; *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

Table 4 presents data regarding the therapeutic interventions received by patients once they were hospitalized, both in ICU and not in ICU. As expected, the length of hospitalization was longer in patients who were admitted to ICU, even if it seems that in the second wave, the length of hospitalization was shorter for those patients. About two out of three patients needed oxygen support during their hospitalization, provided both in ICU and in other wards. The need for CPAP significantly increased during the three waves (21.8%, in the first wave, 22.8% in the second wave, and 32.7% in the third wave), also because of a large increase in patients admitted out of the ICU. In the second and third waves, patients in ICUs underwent less intubation, invasive ventilation, and tracheostomy.

Table 4. Length of hospital stay and therapeutic interventions performed in patients hospitalized for SARS-CoV-2, in intensive care unit (ICU), and other wards (No ICU), stratifying by waves.

	First Wave (1 March–15 April 2020)			Second Wave (15 October–15 December 2020)			Third Wave (1 March–15 April 2021)			
	Admitted (%)	**No ICU N/Day [a] (%)**	**ICU N/Day [a] (%)**	**Admitted (%)**	**No ICU N/Day [a] (%)**	**ICU N/Day [a] (%)**	**Admitted (%)**	**No ICU N/Day [a] (%)**	**ICU N/Day [a] (%)**	***p*-Value [b]**
Length of hospital stay										
Mean (SD)	21.3 (23.9)	18.8 (19.5)	28.0 (32.0) ***,[c]	18.5 (19.8)	17.0 (17.5)	23.0 (25.1) ***,[d]	18.4 (17.4)	16.4 (15.0)	24.8 (22.4) ***,[e]	<0.001
Median (IQR)	14.0 (7.0–28.0)	12.0 (6.0–25.0)	19.0 (9.0–35.0) ***,[c]	13.0 (7.0–22.0)	12.0 (7.0–21.0)	16.0 (9.0–26.0) ***,[d]	14.0 (8.0–23.0)	12.0 (7.0–21.0)	18.0 (11.0–30.0) ***,[e]	<0.001
Oxygen										
No	57.9 (35.2%)	35.9 (30.0%)	22.0 (49.0%) ***,[c]	78.0 (35.7%)	55.5 (33.7%)	22.5 (41.9%) ***,[d]	67.8 (37.3%)	46.4 (33.7%)	21.4 (48.5%) ***,[e]	<0.001
Yes	106.8 (64.8%)	83.9 (70.0%)	22.9 (51.0%)	140.5 (64.3%)	109.3 (66.3%)	31.2 (58.1%)	114.2 (62.7%)	91.5 (66.3%)	22.7 (51.5%)	
CPAP										
No	128.8 (78.2%)	106.2 (88.6%)	22.6 (50.3%) ***,[c]	168.6 (77.2%)	140.9 (85.5%)	27.7 (51.6%) ***,[d]	122.5 (67.3%)	103.8 (75.3%)	18.7 (42.4%) ***,[e]	<0.001
Yes	35.9 (21.8%)	13.7 (11.4%)	22.3 (49.7%)	49.9 (22.8%)	24.0 (14.5%)	26.0 (48.4%)	59.4 (32.7%)	34.1 (24.7%)	25.4 (57.6%)	
NIV										
No	162.5 (98.7%)	119.3 (99.5%)	43.2 (96.4%) ***,[c]	214.7 (98.2%)	163.3 (99.0%)	51.4 (95.8%) ***,[d]	177.2 (97.4%)	135.6 (98.3%)	41.7 (94.5%) ***,[e]	0.01
Yes	2.2 (1.3%)	0.5 (0.5%)	1.6 (3.6%)	3.8 (1.8%)	1.6 (1.0%)	2.2 (4.2%)	4.8 (2.6%)	2.3 (1.7%)	2.4 (5.5%)	
Intubation										
No	155.9 (94.6%)	..	36.2 (80.7%) ***,[c]	212.8 (97.3%)	..	48.0 (89.5%) ***,[d]	175.3 (96.3%)	..	37.6 (85.4%) ***,[e]	<0.001
Yes	8.8 (5.4%)	..	8.7 (19.3%)	5.8 (2.7%)	..	5.6 (10.5%)	6.7 (3.7%)	..	6.4 (14.6%)	
Invasive ventilation										
No	146.4 (88.9%)	118.8 (99.2%)	27.6 (61.5%) ***,[c]	203.9 (93.3%)	164.3 (99.6%)	39.6 (73.8%) ***,[d]	167.5 (92.0%)	137.3 (99.6%)	30.2 (68.5%) ***,[e]	<0.001
Yes	18.3 (11.1%)	1.0 (0.8%)	17.3 (38.5%)	14.7 (6.7%)	0.6 (0.4%)	14.1 (26.2%)	14.5 (8.0%)	0.6 (0.4%)	13.9 (31.5%)	
Tracheotomy										
No	158.7 (96.3%)	..	38.9 (86.6%) ***,[c]	214.3 (98.0%)	..	49.4 (92.1%) ***,[d]	177.8 (97.7%)	..	40.0 (90.7%) ***,[e]	<0.001
Yes	6.0 (3.7%)	..	6.0 (13.4%)	4.3 (2.0%)	..	4.2 (7.9%)	4.2 (2.3%)	..	4.1 (9.3%)	

[a] N/day average number of patients who underwent an intervention per day; [b] Comparisons of patients admitted to ICU among the three waves tested by Chi-square or Fisher test and Kruskal–Wallis or *t*-test; [c] Comparison between patients admitted in ICU and in other wards (No ICU) during the first wave tested by Chi-square or Fisher test and Kruskal–Wallis or *t*-test; [d] Comparison between patients admitted in ICU and in other wards (No ICU) during the second wave tested by Chi-square or Fisher test and Kruskal–Wallis or *t*-test; [e] Comparison between patients admitted in ICU and in other wards (No ICU) during the third wave tested by Chi-square or Fisher test and Kruskal–Wallis or *t*-test; *** $p < 0.001$.

As expected, the patients who died were significantly older and with more comorbidities in all three waves (Tables 5 and S3–S5). Considering the confounding by age, gender, and comorbidity, patients in the second and third waves showed a reduction in severe outcomes (ICU hospitalization or death) compared with patients in the first wave (OR: 0.75, 95% CI: 0.71–0.79; OR: 0.67, 95% CI: 0.63–0.72, respectively) (Figure 4).

Table 5. Demographic characteristics, comorbid conditions, and intensive care unit (ICU) admission of hospitalized for SARS-CoV-2, stratifying by death within 30 days from the first positive swab and waves.

	First Wave (1 March–15 April 2020)		Second Wave (15 October–15 December 2020)		Third Wave (1 March–15 April 2021)		
	No Death N/Day [a] (%)	Death N/Day [a] (%)	No Death N/Day [a] (%)	Death N/Day [a] (%)	No Death N/Day [a] (%)	Death N/Day [a] (%)	*p*-Value [b]
Age group							
≤65	54.2 (46.7%)	4.4 (9.1%) ***,c	61.3 (37.4%)	4.2 (7.8%) ***,d	61.5 (41.9%)	3.8 (10.8%) ***,e	<0.001
66–75	26.6 (22.9%)	9.3 (19.1%)	39.2 (23.9%)	8.8 (16.2%)	39.6 (26.9%)	8.1 (23.2%)	
76–85	25.3 (21.9%)	20.5 (42.0%)	44.2 (26.9%)	22.8 (41.7%)	34.2 (23.3%)	13.6 (38.8%)	
86+	9.9 (8.5%)	14.5 (29.8%)	19.3 (11.8%)	18.8 (34.3%)	11.6 (7.9%)	9.5 (27.2%)	
Gender							
F	47.8 (41.2%)	18.3 (37.6%) **,c	68.1 (41.5%)	21.2 (38.8%) **,d	62.7 (42.7%)	13.8 (39.3%) *,e	0.49
M	68.3 (58.8%)	30.4 (62.4%)	95.8 (58.5%)	33.4 (61.2%)	84.3 (57.3%)	21.2 (60.7%)	
Charlson Comorbidity Index							
0	63.2 (54.5%)	16.4 (33.7%) ***,c	82.9 (50.5%)	19.0 (34.7%) ***,d	82.1 (55.8%)	13.8 (39.4%) ***,e	0.006
1	29.6 (25.5%)	14.5 (29.8%)	45.9 (28.0%)	15.7 (28.8%)	38.6 (26.3%)	10.0 (28.7%)	
2–3	17.9 (15.4%)	12.4 (25.6%)	27.3 (16.7%)	14.0 (25.7%)	21.4 (14.6%)	8.0 (22.9%)	
4+	5.3 (4.6%)	5.3 (10.9%)	7.9 (4.8%)	5.9 (10.8%)	4.9 (3.3%)	3.1 (8.9%)	
ICU admission							
No	87.3 (75.2%)	32.5 (66.9%) ***,c	128.0 (78.0%)	36.9 (67.6%) ***,d	115.2 (78.4%)	22.7 (65.0%) ***,e	0.18
Yes	28.7 (24.8%)	16.1 (33.1%)	36.0 (22.0%)	17.7 (32.4%)	31.8 (21.6%)	12.3 (35.0%)	

[a] N/day average number of cases per day; [b] Comparisons of dead patients among the three waves tested by Chi-square or Fisher test; [c] Comparison between alive and dead patients during the first wave tested by Chi-square or Fisher test; [d] Comparison between alive and dead patients during the second wave tested by Chi-square or Fisher test; [e] Comparison between alive and dead patients during the third wave tested by Chi-square or Fisher test; *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

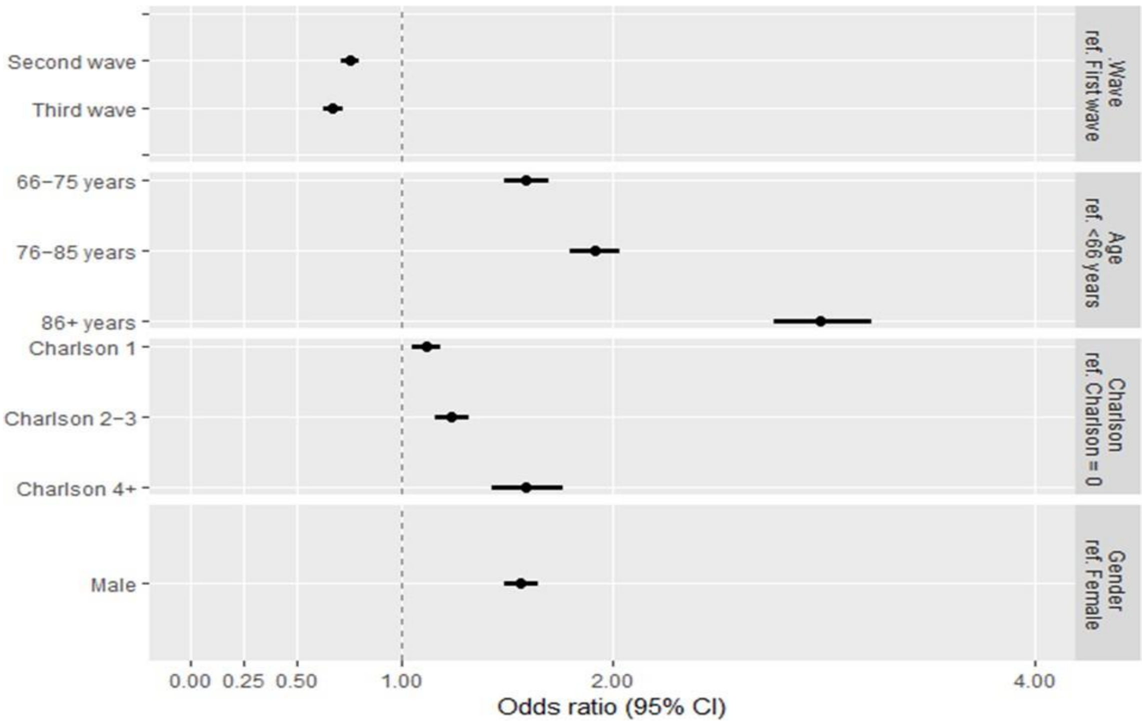


Figure 4. Odds ratio (OR) and 95% confidence interval (CI) estimates showing the effect of being infected in different waves on the combined outcome mortality and ICU admission, adjusting by age, gender, and comorbidity burden.

3. Discussion

Many authors described the pandemic trends in editorials or opinion papers [18,22,23], and registries have collected data from different COVID-19 waves in 2020 [12,13,24,25], but this is the first observational study that collected clinical data on a region-wide cohort in Italy, evaluating about 245,000 SARS-CoV-2 infected subjects in the first three waves since the beginning of the pandemic. While in Italy, the first wave overwhelmed an unprepared health care system until strict restrictions were imposed at the national level [2], organizational improvement was achieved over time, and policies were targeted at the regional level throughout the following waves [26]. Moreover, as depicted in Figure 1, in the third wave, vaccination started to be implemented, and new therapies (e.g.,: monoclonal antibodies and antiviral drugs) were used.

Our study's first evidence is the higher number of cases in the second wave, which outnumbered by a five-factor the first one and was double that of the third one [8–10,26,27]. The first wave in Italy was affected by an underestimation of cases, which could have been six times lower than the true prevalence, as described by De Natale et al. [28]. The improvement in testing capacity was achieved by increasing the number of laboratories performing RT-PCR and the approval of the use of rapid antigenic testing in January 2021. Nevertheless, the strict lockdown strategy during the first wave could have played a role in reducing the prevalence and shortening the "peak period", as demonstrated by other authors [18,27], while in the second one, restrictive measures were milder.

Patients with COVID-19 were significantly younger in the second and third waves, reflecting a diffusion of the illness in the active working population, whereas cases in nursing-home residents prevailed at the end of the first wave. After several COVID-19 outbreaks in nursing homes, in April 2020, access for visitors was forbidden, and isolation and tracking protocols for staff and patients were implemented to reduce SARS-CoV-2 transmission.

The decrease in the median age of affected patients over time was described in France, Spain, and the USA [11,15,17] in contrast to Germany [29]. Nevertheless, over time we observed a similar need for hospitalization in people aged over 70 and a higher rates of comorbid conditions in admitted patients compared with outpatients, both associated with a poor prognosis [11–13,15,17,26].

Despite the absolute number of cases (RT-PCR positive patients) and the massive reorganization of the Piedmont hospitals [4,8,26], in the second and third waves, we observed only a slight increase in hospital admissions that, due to the dramatic increase in asymptomatic patients, resulted in a reduction in the percentage of admitted patients. A higher awareness of Emergency Department Physicians in diagnosing and staging COVID-19 disease and a better organization for out-of-hospital COVID care (with the creation of special units to treat COVID patients at home) are possible explanations [26].

We observed that the admission of patients with a Charlson index of more than 2 reduced over time because of the related observed reduction in comorbid burden in the whole cohort [11,15,17]. Nevertheless, in the third wave, we observed a reduced hospitalization of patients with many comorbid conditions in accordance with recent evidence that older patients could be treated safely at home or in nursing homes [30] but also for the possible effect of prioritizing vaccination to frail patients. Moreover, this latter effect is likely the cause of the strong reduction in SARS-CoV-2 infections observed in subjects more than 85 years old and in patients with dementia.

Similar to other authors [11,12,15], in the second and third waves, we observed a slight reduction in the percentage of patients hospitalized in ICUs in comparison with the first wave, with a parallel reduction in invasive mechanical ventilation and tracheostomy.

On the contrary, the group of patients treated with CPAP and non-invasive ventilation increased over time, both in ICUs and in high dependency units and low-intensity-of-care wards, in line with other observations [11,15]. This trend toward the increased use of CPAP out of the ICU described the massive implementation in resource availability, staff education, and better knowledge about ventilation and its weaning [31]. During the third wave, we observed a trend toward the greater use of CPAP in and out of the ICU setting and a moderate increase in intubation and invasive ventilation. Little data exist about the third wave, as many studies end in the year 2020 [11–13], in January 2021 [15,17,29], and others consider the second and third waves as a continuum [11–13,15,29]. The differences we observed in the third wave suggest that patients with COVID-19 diagnosed in the spring of 2021 were younger, severely ill, and treated for a more severe respiratory failure, possibly because they were infected by the delta variant or because of age-related differences in the immune response.

The length of hospital stay and in-hospital mortality, both in the ICU and in other hospital wards, reduced over time in our cohort as well as being observed elsewhere [11,12,15,17,29]. We hypothesize that this reduction is related to the effect of therapeutic improvements in-between these epidemic waves [11,15,27,31] and the effect of resource optimization due to a better understanding of COVID-19 illness. Organizational improvements (the availability of a higher number of hospital high dependency unit beds and the availability of low-intensity beds in external facilities) reduced the overload of ICUs and hospitals, patients were admitted at the right time during COVID-19's natural history, and in the right place, both clinical decisions and resource allocation were more efficient. The reduction in overall mortality in outpatients and inpatients reflects this process, which was also described in other countries [11,12,15]. Interestingly, we also observed a reduction in mortality also in more severe cases, such as those admitted to ICUs, whereas in other studies, ICU mortality was persistently higher [11] or not separately described [12,15,17].

Examining the subgroup of patients with a poor outcome (death), we observed an increase in mortality that occurs every ten years, with the median age for death always around 80 and a threefold higher risk of death for those over 85. In the third wave, patients who died tended to be younger and concurrently have fewer comorbidities.

Male gender and the presence of comorbid conditions are associated with death; nevertheless, patients infected in the second and third waves showed an independent reduction in the risk of death. Moreover, in the spring of 2021, the proportion of deceased patients with cardiovascular, renal, cerebrovascular diseases, and dementia significantly decreased, both in the inpatient group and in the overall population. This pattern could be the effect of the Italian government vaccination policy that chose to prioritize vaccination of elderly and frail patients and health care workers.

Our study has the strength of collecting a broad sample including all of the COVID-19 positive patients of the Piedmont region, allowing some considerations on the effect of organizational improvements that were decided at the regional level.

Moreover, we tried to observe trends in different subgroups (admitted patients vs. outpatients, admitted in ICU vs. regular wards) to understand differences in resource allocation and mortality in different intensities of care settings and patients with different illness severity.

Our study has limitations. Firstly, the first wave was affected by an underestimation of positive cases due to the novelty of the emergency, an overwhelmed health care system, and the challenge of tracking. The diagnosis happened more often in patients with severe disease, whereas mild cases with reduced symptoms were underdiagnosed. The analysis of the subgroup of hospitalized patients solved this bias.

Another limitation is the retrospective nature of this study, which resulted in a possible under-recording of therapeutic procedures on the chart collection system, especially in times of emergency. Nevertheless, this bias is probably equally distributed in the entire sample; we searched for many different codes to avoid missing or misclassifying a procedure. We chose to restrict our analysis to the strongest outcomes and to the procedures with the less possible misinterpretations, taking into account how our health care system of hospital retribution per patient (the ICD-9/DRG system) works [32].

4. Conclusions

Our study, the first that evaluated using a broad sample, the clinical characteristics of patients affected by COVID-19, confirmed a trend toward younger and healthier patients over time but also showed an independent effect of the period on mortality and ICU admission. The natural course of the pandemic, the appearance of new viral variants, the starting of vaccination, and the improvements in the tracking of new cases and patient management have influenced these trends. Our analysis of the interventions performed on inpatients allowed us to suggest a role also for organizational improvements (resource availability and more effective patient care) in reducing poor outcomes.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/article/10.3390/jcm11154304/s1, Figure S1: Map showing Italy and Piedmont region; Figure S2: Number of deaths from SARS-CoV-2 registered in Piedmont during the COVID-19 pandemic. (Data source: GitHub - pcm-dpc/COVID-19: COVID-19 Italia - Monitoraggio situazione). Table S1: Comorbid conditions of subjects tested positive for SARS-CoV-2, stratifying by hospital admission and waves; Table S2: Comorbid conditions of patients hospitalized for SARS-CoV-2, stratifying by admission to intensive care unit (ICU) and waves; Table S3: Comorbid conditions of patients hospitalized for SARS-CoV-2, stratifying by death within 30 days from the first positive swab and waves; Table S4: Demographic characteristics, comorbid conditions, hospitalization, and intensive care unit (ICU) admission of subjects tested positive for SARS-CoV-2, stratifying by death within 30 days from the first positive swab and waves; Table S5: Demographic characteristics and comorbid conditions of subjects admitted to the ICU, stratifying by death within 30 days from the first positive swab and waves.

Author Contributions: Contributors V.C., A.C., F.R., A.B., A.T. and F.A. conceptualised the study. V.C., A.C., F.R. and A.B. were responsible for data curation and investigation. A.C. and F.R. did the formal data analysis G.C., C.S., F.A., A.B. and F.R. oversaw the project. V.C., A.B., F.A., A.M., C.S. and F.R. accessed and verified the data. V.C., A.C., F.R. and A.B. wrote the initial draft of the manuscript. V.C., A.C., F.R., A.B., F.A., C.S. and L.D. reviewed and edited the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: All analyses were conducted according to the World Medical Association's Declaration of Helsinki. The study, included in the National Statistical Plan, does not need approval by the ethics committee.

Informed Consent Statement: Patient consent was waived because the study is included in the National Statistical Plan and subjects are treated anonymously.

Data Availability Statement: Raw data cannot be made freely available because of restrictions imposed by the Ethical Committees which do not allow open/public sharing of data on individuals. However aggregated data are available for other researchers, on request. Requests should be sent to the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Coronavirus disease (COVID-19) pandemic, WHO. Available online: https://www.who.int/Emergencies/Diseases/Novel-Coronavirus-2019 (accessed on 21 October 2021).
2. Government of Italy: Decree of the President of the Council of Ministers. Available online: https://www.gazzettaufficiale.it/eli/Id/2020 (accessed on 21 October 2021).
3. Balasco, N.; D'Alessandro, V.; Ferrara, P.; Smaldone, G.; Vitagliano, L. Analysis of the Time Evolution of COVID-19 Lethality during the First Epidemic Wave in Italy. *Acta Biomed.* **2021**, *92*, E2021171. https://doi.org/10.23750/Abm.V92i2.11149.

4. Mattiuzzi, C.; Lippi, G.; Henry, B.M. Healthcare Indicators Associated with COVID-19 Death Rates in the European Union. *Public Health* **2021**, *193*, 41–42. https://doi.org/10.1016/j.Puhe.2021.01.027.
5. Scortichini, M.; Schneider Dos Santos, R.; de' Donato, F.; de Sario, M.; Michelozzi, P., Davoli, M.; Masselot, P.; Sera, F.; Gasparrini, A. Excess Mortality during the COVID-19 Outbreak in Italy: A Two-Stage Interrupted Time-Series Analysis. *Int. J. Epidemiol*. **2021**, *49*, 1909–1917. https://doi.org/10.1093/Ije/Dyaa169.
6. De Natale, G.; Ricciardi, V.; de Luca, G.; de Natale, D.; di Meglio, G.; Ferragamo, A.; Marchitelli, V.; Piccolo, A.; Scala, A.; et al. The COVID-19 Infection in Italy: A Statistical Study of an Abnormally Severe Disease. *J. Clin. Med*. **2020**, *9*, 1564. https://doi.org/10.3390/Jcm9051564.
7. Wu, R.; Ai, S.; Cai, J.; Zhang, S.; Qian, Z.M.; Zhang, Y.; Wu, Y.; Chen, L.; Tian, F.; Li, H. Predictive Model and Risk Factors for Case Fatality of COVID-19: A Cohort of 21,392 Cases in Hubei, China. *Innovation* **2020**, *1*, 100022. https://doi.org/10.1016/j.Xinn.2020.100022.
8. Chirico, F.; Nucera, G.; Szarpak, L. COVID-19 Mortality in Italy: The First Wave Was More Severe and Deadly, but Only in Lombardy Region. *J. Infect.* **2021**, *83*, E16. https://doi.org/10.1016/j.Jinf.2021.05.006.
9. Borghesi, A.; Golemi, S.; Carapella, N.; Zigliani, A.; Farina, D.; Maroldi, R. Lombardy, Northern Italy: COVID-19 Second Wave Less Severe and Deadly than the First? A Preliminary Investigation. *Infect. Dis.* **2021**, *53*, 370–375. https://doi.org/10.1080/23744235.2021.1884745.
10. Bongiovanni, M.; Arienti, R.; Bini, F.; Bodini, B.D.; Corbetta, E.; Gianturco, L. Differences between the Waves in Northern Italy: How the Characteristics and the Outcome of COVID-19 Infected Patients Admitted to the Emergency Room Have Changed. *J. Infect.* **2021**, *83*, E32–E33. https://doi.org/10.1016/j.Jinf.2021.04.024.
11. Martinot, M.; Eyriey, M.; Gravier, S.; Kayser, D.; Ion, C.; Mohseni-Zadeh, M.; Ongagna, J.C.; Schieber, A.; Kempf, C.; et al. Evolution of Baseline Characteristics and Severe Outcomes in COVID-19 Inpatients during the First and Second Waves in Northeastern France. *Infect. Dis. Now* **2021**, *52*, 35–39. https://doi.org/10.1016/j.Idnow.2021.10.002.
12. Saito, S.; Asai, Y.; Matsunaga, N.; Hayakawa, K.; Terada, M.; Ohtsu, H.; Tsuzuki, S.; Ohmagari, N. First and Second COVID-19 Waves in Japan: A Comparison of Disease Severity and Characteristics. *J. Infect.* **2021**, *82*, 84–123. https://doi.org/10.1016/j.Jinf.2020.10.033.
13. Marcolino, M.S.; Ziegelmann, P.K.; Souza-Silva, M.V.R.; Nascimento, I.J.B.D.; Oliveira, L.M.; Monteiro, L.S.; Thaís L.S.Sales; Ruschel, K.B.; Martins, K.P.M.P.; Etges, A.P.B.S.; et al. COVID-19 Registry Investigators. Clinical Characteristics and Outcomes of Patients Hospitalized with COVID-19 in Brazil: Results from the Brazilian COVID-19 Registry. *Int. J. Infect. Dis*. **2021**, *107*, 300–310. https://doi.org/10.1016/j.Ijid.2021.01.019.
14. Contou, D.; Fraissé, M.; Pajot, O.; Tirolien, J.A.; Mentec, H.; Plantefève, G. Comparison between First and Second Wave among Critically Ill COVID-19 Patients Admitted to a French ICU: No Prognostic Improvement during the Second Wave? *Crit. Care* **2021**, *25*, 3. https://doi.org/10.1186/S13054-020-03449-6.
15. Iftimie, S.; Lopez-Azcona, A.F.; Vallverdu, I.; Hernández-Flix, S.; de Febrer, G.; Parra, S.; Hernández-Aguilera, A.; Riu, F.; Joven, J.; Andreychuk, N.; et al. First and Second Waves of Coronavirus Disease-19: A Comparative Study in Hospitalized Patients in Reus, Spain. *PLoS ONE* **2021**, *16*, E0248029. https://doi.org/10.1371/Journal.Pone.0248029.
16. Atkin, C.; Kamwa, V.; Reddy-Kolanu, V.; Parekh, D.; Evison, F.; Nightingale, P.; Gallier, S.; Ball, S.; Sapey, E. The Changing Characteristics of COVID-19 Presentations: A Regional Comparison of SARS- CoV-2 Hospitalised Patients during the First and Second Wave. *Acute Med.* **2021**, *20*, 92–100.
17. Hoogenboom, W.S.; Pham, A.; Anand, H.; Fleysher, R.; Buczek, A.; Soby, S.; Mirhaji, P.; Yee, J.; Duong, T.Q. Clinical Characteristics of the First and Second COVID-19 Waves in the Bronx, New York: A Retrospective Cohort Study. *Lancet Reg. Health Am*. **2021**, *3*, 100041. https://doi.org/10.1016/j.Lana.2021.100041.
18. Karako, K.; Song, P.; Chen, Y.; Tang, W.; Kokudo, N. Overview of the Characteristics of and Responses to the Three Waves of COVID-19 in Japan during 2020–2021. *Biosci. Trends* **2021**, *15*, 1–8. https://doi.org/10.5582/Bst.2021.01019.
19. Mariniello, A.; Bironzo, P.; Pisano, C.; de Filippis, M.; Persano, I.; Olmetto, E.; Caramello, V.; Boccuzzi, A.; Capelletto, E.; Passiglia, F.; et al. Descriptive Comparative Analysis of Patients With Cancer Referring to the Emergency Department of an Italian University Hospital Across the Severe Acute Respiratory Syndrome Coronavirus 2 Waves. *JCO Oncol. Pract.* **2021**, *17*, E1887–E1894. https://doi.org/10.1200/OP.21.00098.
20. Ferrante, P. The First Year of COVID-19 in Italy: Incidence, Lethality, and Health Policies. *J. Public Health Res.* **2022**, *online ahead of print*. https://doi.org/10.4081/Jphr.2021.2201.
21. Charlson, M.E.; Pompei, P.; Ales, K.L.; MacKenzie, C.R. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. *J. Chronic. Dis*. **1987**, *40*, 373–383. https://doi.org/10.1016/0021-9681(87)90171-8.
22. Wei, Y.; Guan, J.; Ning, X.; Li, Y.; Wei, L.; Shen, S.; Zhang, R.; Zhao, Y.; Shen, H.; Chen, F. Global COVID-19 Pandemic Waves: Limited Lessons Learned Worldwide over the Past Year. *Engineering* **2021**, *in press*. https://doi.org/10.1016/j.Eng.2021.07.015.
23. Graichen, H. What Is the Difference between the First and the Second/Third Wave of COVID-19?—German Perspective. *J. Orthop.* **2021**, *24*, A1–A3. https://doi.org/10.1016/j.Jor.2021.01.011.
24. Reilev, M.; Kristensen, K.B.; Pottegård, A.; Lund, L.C.; Hallas, J.; Ernst, M.T.; Christiansen, C.F.; Sørensen, H.T.; Johansen, N.B.; Brun, N.C.; et al. Characteristics and Predictors of Hospitalization and Death in the First 11 122 Cases with a Positive RT-PCR Test for SARS-CoV-2 in Denmark: A Nationwide Cohort. *Int. J. Epidemiol*. **2020**, *49*, 1468–1481. https://doi.org/10.1093/Ije/Dyaa140.
25. Salyer, S.J.; Maeda, J.; Sembuche, S.; Kebede, Y.; Tshangela, A.; Moussif, M.; Ihekweazu, C.; Mayet, N.; Abate, E.; Ouma, A.O. The First and Second Waves of the COVID-19 Pandemic in Africa: A Cross-Sectional Study. *Lancet* **2021**, *397*, 1265–1275. https://doi.org/10.1016/S0140-6736(21)00632-2.

26. Chirico, F.; Sacco, A.; Nucera, G.; Magnavita, N. "Coronavirus Disease 2019: The Second Wave in Italy". *J. Health Res*. **2021**, *35*, 359–363. https://doi.org/10.1108/JHR-10-2020-0514.
27. Vinceti, M.; Filippini, T.; Rothman, K.J.; di Federico, S.; Orsini, N. SARS-CoV-2 Infection Incidence during the First and Second COVID-19 Waves in Italy. *Environ. Res*. **2021**, *197*, 111097. https://doi.org/10.1016/j.Envres.2021.111097.
28. De Natale, G.; de Natale, L.; Troise, C.; Marchitelli, V.; Coviello, A.; Holmberg, K.G.; Somma, R. The Evolution of Covid-19 in Italy after the Spring of 2020: An Unpredicted Summer Respite Followed by a Second Wave. *Int. J. Environ. Res. Public Health* **2020**, *17*, 8708. https://doi.org/10.3390/Ijerph17238708.
29. Budweiser, S.; Baş, Ş.; Jörres, R.A.; Engelhardt, S.; Thilo, C.; von Delius, S.; Eckel, F.; Biller, U.; Lenherr, K.; Deerberg-Wittram, J. et al. Comparison of the First and Second Waves of Hospitalized Patients With SARS-CoV-2. *Dtsch. Arztebl. Int.* **2021**, *118*, 326–327. https://doi.org/10.3238/Arztebl.M2021.0215.
30. Costantino, G.; Solbiati, M.; Elli, S.; Paganuzzi, M.; Massabò, D.; Montano, N.; Mancarella, M.; Cortellaro, F.; Cataudella, E.; Bellone, A.; et al. Utility of Hospitalization for Elderly Individuals Affected by COVID-19. *PLoS ONE* **2021**, *16*, E0250730. https://doi.org/10.1371/Journal.Pone.0250730.
31. Chalmers, J.D.; Crichton, M.L.; Goeminne, P.C.; Cao, B.; Humbert, M.; Shteinberg, M.; Antoniou, K.M.; Ulrik, C.S.; Parks, H.; Wang, C.; et al. Management of Hospitalised Adults with Coronavirus Disease 2019 (COVID-19): A European Respiratory Society Living Guideline. *Eur. Respir. J.* **2021**, *57*, 2100048. https://doi.org/10.1183/13993003.00048-2021.
32. Ricoveri ospedalieri, Miistero della Salute. Available online: https://www.salute.gov.it/Portale/Temi/P2_6.Jsp?Id=1278&area=ricoveriOspedalieri&menu=classificazione (accessed 23 January 2022).

Figure S1. Map showing Italy and Piedmont Region

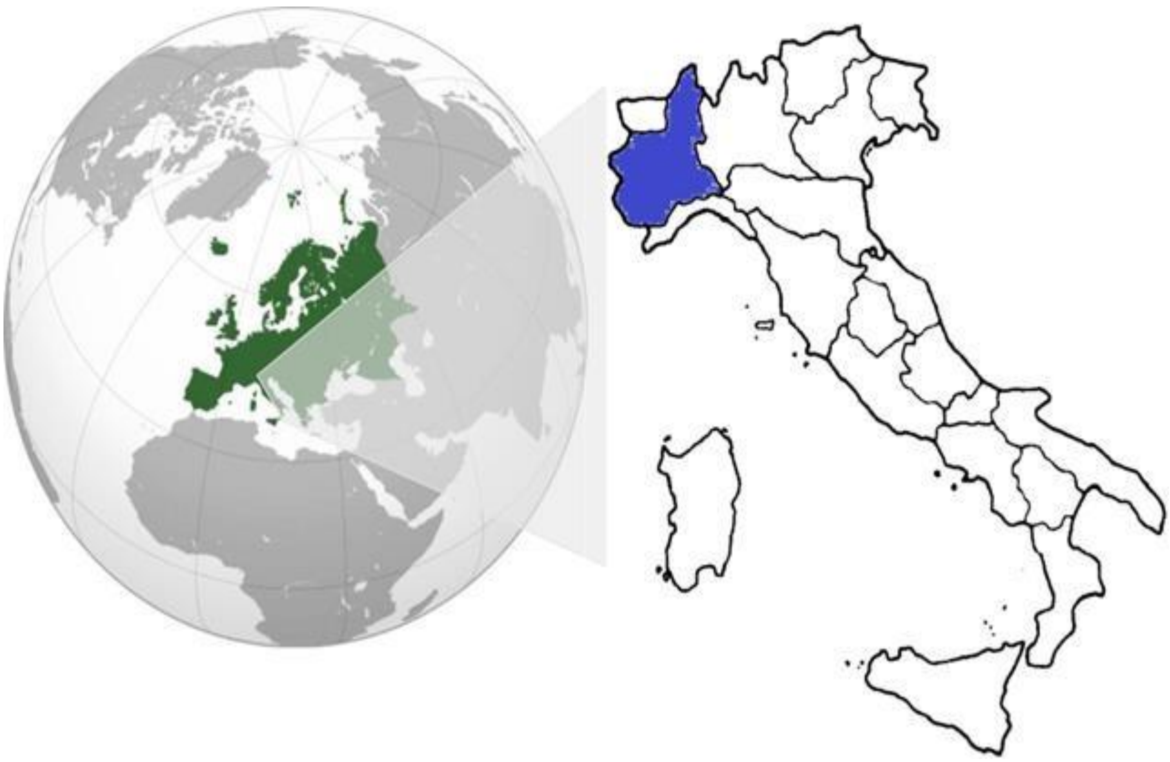

Figure S2. Number of deaths from SARS-CoV-2 registered in Piedmont during the COVID-19 pandemic. (Data source: GitHub - pcm- dpc/COVID-19: COVID-19 Italia - Monitoraggio situazione)

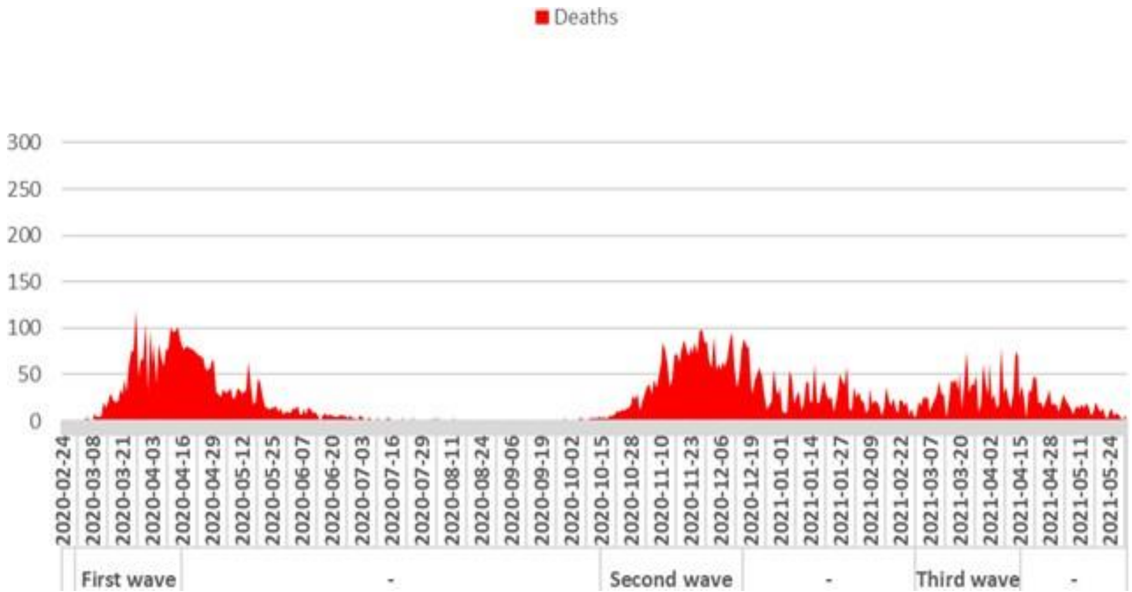

Table S1. Comorbid conditions of subjects tested positive for SARS-CoV-2, stratifying by hospital admission and waves

	1° Wave (01/03-15/04/20)		2° Wave (15/10-15/12/20)		3° Wave (01/03-15/04/21)		P-value[b]
	No Admission N/days[a] (%)	Admission N/days[a] (%)	No Admission N/days[a] (%)	Admission N/days[a] (%)	No Admission N/days[a] (%)	Admission N/days[a] (%)	
COPD							
No	201.3 (83.8%)	127.2 (77.2%)***[c]	1853.7 (86.3%)	165.6 (75.8%)***[d]	1387.4 (86.9%)	142.3 (78.2%)***[e]	<0.001
Yes	38.8 (16.2%)	37.5 (22.8%)	294.2 (13.7%)	53.0 (24.2%)	209.4 (13.1%)	39.7 (21.8%)	
Cardiovascular disease							
No	202.6 (84.4%)	125.4 (76.1%)***[c]	1985.7 (92.4%)	165.9 (75.9%)***[d]	1509.6 (94.5%)	146.2 (80.3%)***[e]	<0.001
Yes	37.5 (15.6%)	39.3 (23.9%)	162.1 (7.6%)	52.6 (24.1%)	87.2 (5.5%)	35.8 (19.7%)	
Heart failure							
No	234.7 (97.7%)	159.2 (96.6%)***[c]	2133.4 (99.3%)	210.7 (96.4%)***[d]	1591.3 (99.7%)	177.6 (97.6%)***[e]	<0.001
Yes	5.4 (2.3%)	5.5 (3.4%)	14.4 (0.7%)	7.9 (3.6%)	5.5 (0.3%)	4.3 (2.4%)	
Coronary artery disease							
No	232.4 (96.8%)	153.1 (92.9%)***[c]	2111.7 (98.3%)	203.0 (92.9%)***[d]	1575.1 (98.6%)	172.0 (94.5%)***[e]	<0.001
Yes	7.7 (3.2%)	11.6 (7.1%)	36.1 (1.7%)	15.5 (7.1%)	21.7 (1.4%)	10.0 (5.5%)	
Cardiomyopathy							
No	230.7 (96.1%)	155.1 (94.2%)***[c]	2122.8 (98.8%)	205.9 (94.2%)***[d]	1587.1 (99.4%)	174.7 (96.0%)***[e]	<0.001
Yes	9.4 (3.9%)	9.6 (5.8%)	25.0 (1.2%)	12.7 (5.8%)	9.7 (0.6%)	7.3 (4.0%)	
Diabetes							
No	211.9 (88.3%)	128.5 (78.0%)***[c]	1995.0 (92.9%)	166.8 (76.3%)***[d]	1503.0 (94.1%)	144.6 (79.5%)***[e]	<0.001
Yes	28.2 (11.7%)	36.2 (22.0%)	152.8 (7.1%)	51.8 (23.7%)	93.8 (5.9%)	37.3 (20.5%)	
Kidney disease							
No	233.2 (97.1%)	155.3 (94.3%)***[c]	2124.4 (98.9%)	206.2 (94.4%)***[d]	1586.8 (99.4%)	173.2 (95.7%)***[e]	<0.001
Yes	6.9 (2.9%)	9.4 (5.7%)	23.4 (1.1%)	12.3 (5.6%)	10.0 (0.6%)	7.8 (4.3%)	
Cerebrovascular disease							
No	227.0 (94.6%)	152.8 (92.8%)***[c]	2106.6 (98.1%)	204.7 (93.7%)***[d]	1581.6 (99.0%)	173.9 (95.6%)***[e]	<0.001
Yes	13.1 (5.4%)	11.9 (7.2%)	41.2 (1.9%)	13.8 (6.3%)	15.2 (1.0%)	8.1 (4.4%)	
Dementia							
No	230.1 (95.8%)	159.2 (96.6%)**[c]	2127.2 (99.0%)	212.9 (97.4%)***[d]	1593.2 (99.8%)	179.9 (98.8%)***[e]	<0.001
Yes	10.0 (4.2%)	5.5 (3.4%)	20.7 (1.0%)	5.6 (2.6%)	3.6 (0.2%)	2.1 (1.2%)	
Neoplasia							
No	231.2 (96.3%)	153.0 (92.9%)***[c]	2100.1 (97.8%)	203.0 (92.9%)***[d]	1565.5 (98.0%)	170.0 (93.4%)***[e]	0.31
Yes	8.9 (3.7%)	11.7 (7.1%)	47.8 (2.2%)	15.5 (7.1%)	31.2 (2.0%)	12.0 (6.6%)	
Haematologic disease							
No	239.3 (99.7%)	163.0 (99.0%)***[c]	2143.3 (99.8%)	216.3 (99.0%)***[d]	1594.3 (99.8%)	180.5 (99.2%)***[e]	0.18
Yes	0.8 (0.3%)	1.7 (1.0%)	4.5 (0.2%)	2.2 (1.0%)	2.5 (0.2%)	1.4 (0.8%)	
Immunodeficiency							
No	240.1 (99.9%)	164.6 (99.9%)°[c]	2147.3 (99.9%)	218.4 (99.9%)**[d]	1596.4 (99.9%)	181.9 (99.9%)°[e]	0.88
Yes	0.1 (0.1%)	0.1 (0.1%)	0.5 (0.1%)	0.2 (0.1%)	0.4 (0.1%)	0.1 (0.1%)	

[a] N/days average number of cases per day
[b] Comparisons of hospitalized patients among the three waves tested by Chi-square or Fisher test
[c] Comparison between hospitalized and not hospitalized subjects during the first wave tested by Chi-square or Fisher test
[d] Comparison between hospitalized and not hospitalized subjects during the second wave tested by Chi-square or Fisher test
[e] Comparison between hospitalized and not hospitalized subjects during the third wave tested by Chi-square or Fisher test
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; ° $p \geq 0.05$

Table S2. Comorbid conditions of patients hospitalized for SARS-CoV-2, stratifying by admission to intensive care unit (ICU) and waves

	1° Wave (01/03-15/04/20)		**2° Wave** (15/10-15/12/20)		**3° Wave** (01/03-15/04/21)		
	No ICU N/days[a] (%)	**ICU N/days[a] (%)**	**No ICU N/days[a] (%)**	**ICU N/days[a] (%)**	**No ICU N/days[a] (%)**	**ICU N/days[a] (%)**	**P-value[b]**
COPD							
No	91.3 (76.2%)	35.9 (80.0%)***[c]	124.4 (75.4%)	41.2 (76.7%°)[d]	108.1 (78.4%)	34.2 (77.6%)[e]	0.02
Yes	28.6 (23.8%)	9.0 (20.0%)	40.5 (24.6%)	12.5 (23.3%)	29.8 (21.6%)	9.8 (22.4%)	
Cardiovascular disease							
No	90.0 (75.1%)	35.3 (78.8%)**[c]	123.5 (74.9%)	42.4 (79.1%)***[d]	109.5 (79.4%)	36.7 (83.2%)***[e]	<0.001
Yes	29.8 (24.9%)	9.5 (21.2%)	41.4 (25.1%)	11.2 (20.9%)	28.4 (20.6%)	7.4 (16.8%)	
Heart failure							
No	115.4 (96.3%)	43.8 (97.6%)**[c]	158.4 (96.0%)	52.3 (97.5%)***[d]	134.5 (97.5%)	43.2 (98.0%)°[e]	0.51
Yes	4.5 (3.7%)	1.1 (2.4%)	6.5 (4.0%)	1.3 (2.5%)	3.4 (2.5%)	0.9 (2.0%)	
Coronary artery disease							
No	111.7 (93.2%)	41.4 (92.2%)°[c]	153.4 (93.0%)	49.7 (92.6%)°[d]	130.2 (94.4%)	41.8 (94.9%)°[e]	0.001
Yes	8.1 (6.8%)	3.5 (7.8%)	11.5 (7.0%)	4.0 (7.4%)	7.7 (5.6%)	2.3 (5.1%)	
Cardiomyopathy							
No	112.1 (93.6%)	43.0 (95.8%)***[c]	154.7 (93.8%)	41.2 (95.4%)**[d]	132.2 (95.9%)	42.5 (96.4%)°[e]	0.18
Yes	7.7 (6.4%)	1.9 (4.2%)	10.2 (6.2%)	2.5 (4.6%)	5.7 (4.1%)	1.6 (3.6%)	
Diabetes							
No	94.0 (78.5%)	34.4 (76.7%)°[c]	126.5 (76.7%)	40.2 (75.0%)*[d]	109.5 (79.4%)	35.1 (79.7%)°[e]	<0.001
Yes	25.8 (21.5%)	10.5 (23.3%)	38.4 (23.3%)	13.4 (25.0%)	28.4 (20.6%)	9.0 (20.3%)	
Kidney disease							
No	112.5 (93.9%)	42.8 (95.4%)**[c]	155.6 (94.4%)	50.6 (94.3%)°[d]	131.7 (95.5%)	42.5 (96.4%)°[e]	0.003
Yes	7.3 (6.1%)	2.0 (4.6%)	9.3 (5.6%)	3.0 (5.7%)	6.2 (4.5%)	1.6 (3.6%)	
Cerebrovascular disease							
No	110.1 (91.9%)	42.6 (95.1%)***[c]	153.4 (93.0%)	51.3 (95.6%)***[d]	131.2 (95.2%)	42.6 (96.8%)**[e]	0.02
Yes	9.7 (8.1%)	2.2 (4.9%)	11.5 (7.0%)	2.4 (4.4%)	6.7 (4.8%)	1.4 (3.2%)	
Dementia							
No	114.8 (95.8%)	44.3 (98.8%)***[c]	159.6 (96.8%)	53.3 (99.3%)***[d]	136.0 (98.6%)	43.9 (99.6%)**[e]	0.03
Yes	5.0 (4.2%)	0.5 (1.2%)	5.2 (3.2%)	0.4 (0.7%)	1.9 (1.4%)	0.2 (0.4%)	
Neoplasia							
No	110.9 (92.6%)	42.1 (93.7%)°[c]	153.4 (93.0%)	49.6 (92.4%)°[d]	127.9 (92.8%)	42.0 (95.4%)***[e]	<0.001
Yes	8.9 (7.4%)	2.8 (6.3%)	11.5 (7.0%)	4.1 (7.6%)	10.0 (7.2%)	2.0 (4.6%)	
Haematologic disease							
No	118.7 (99.1%)	44.3 (98.7%)°[c]	163.4 (99.1%)	52.9 (98.6%)*[d]	136.6 (99.1%)	43.9 (99.6%)*[e]	0.001
Yes	1.1 (0.9%)	0.6 (1.3%)	1.5 (0.9%)	0.8 (1.4%)	1.3 (0.9%)	0.2 (0.4%)	
Immunodeficiency							
No	119.7 (99.9%)	44.8 (99.9%)°[c]	164.7 (99.9%)	53.6 (99.9%)°[d]	137.8 (99.9%)	44.0 (99.9%)°[e]	0.86
Yes	0.1 (0.1%)	0.1 (0.1%)	0.1 (0.1%)	0.1 (0.1%)	0.1 (0.1%)	0.1 (0.1%)	

[a] N/days average number of cases per day
[b] Comparisons of patients admitted to ICU among the three waves tested by Chi-square or Fisher test
[c] Comparison between patients admitted in ICU and in other wards (No ICU) during the first wave tested by Chi-square or Fisher test
[d] Comparison between patients admitted in ICU and in other wards (No ICU) during the second wave tested by Chi-square or Fisher test
[e] Comparison between patients admitted in ICU and in other wards (No ICU) during the third wave tested by Chi-square or Fisher test
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; ° $p \geq 0.05$

Table S3. Comorbid conditions of patients hospitalized for SARS-CoV-2, stratifying by death within 30 days from the first positive swab and waves

	1° Wave (01/03-15/04/20)		2° Wave (15/10-15/12/20)		3° Wave (01/03-15/04/21)		P-value[b]
	No Death N/days[a] (%)	Death N/days[a] (%)	No Death N/days[a] (%)	Death N/days[a] (%)	No Death N/days[a] (%)	Death N/days[a] (%)	
COPD							
No	92.3 (79.5%)	34.9 (71.6%)***[c]	127.0 (77.5%)	38.5 (70.6%)***[d]	117.2 (79.7%)	25.1 (71.7%)***[e]	0.62
Yes	23.7 (20.5%)	13.8 (28.4%)	36.9 (22.5%)	16.0 (29.4%)	29.8 (20.3%)	9.9 (28.3%)	
Cardiovascular disease							
No	93.3 (80.4%)	32.0 (65.8%)***[c]	129.9 (79.2%)	36.0 (66.0%)***[d]	121.6 (82.7%)	24.6 (70.3%)***[e]	0.005
Yes	22.7 (19.6%)	16.6 (34.2%)	34.0 (20.8%)	18.6 (34.0%)	25.3 (17.3%)	10.4 (29.7%)	
Heart failure							
No	113.4 (97.8%)	45.7 (93.9%)***[c]	159.4 (97.2%)	51.3 (94.0%)***[d]	144.5 (98.3%)	33.2 (94.7%)***[e]	0.55
Yes	2.6 (2.2%)	3.0 (6.1%)	4.6 (2.8%)	3.2 (6.0%)	2.5 (1.7%)	1.8 (5.3%)	
Coronary artery disease							
No	109.5 (94.4%)	43.6 (89.6%)***[c]	153.9 (93.8%)	49.2 (90.1%)***[d]	140.1 (95.3%)	31.9 (91.1%)***[e]	0.29
Yes	6.5 (5.6%)	5.1 (10.4%)	10.1 (6.2%)	5.4 (9.9%)	6.9 (4.7%)	3.1 (8.9%)	
Cardiomyopathy							
No	111.6 (96.2%)	43.5 (89.5%)***[c]	156.9 (95.7%)	49.0 (89.8%)***[d]	142.7 (97.1%)	32.0 (91.3%)***[e]	0.14
Yes	4.4 (3.8%)	5.1 (10.5%)	7.1 (4.3%)	5.6 (10.2%)	4.3 (2.9%)	3.0 (8.7%)	
Diabetes							
No	94.1 (81.1%)	34.4 (70.6%)***[c]	128.0 (78.1%)	38.7 (70.9%)***[d]	119.3 (81.1%)	25.4 (72.5%)***[e]	0.40
Yes	21.9 (18.9%)	14.3 (29.4%)	35.9 (21.9%)	15.9 (29.1%)	27.7 (18.9%)	9.6 (27.5%)	
Kidney disease							
No	111.1 (95.8%)	44.2 (90.8%)***[c]	157.2 (95.9%)	49.0 (89.8%)***[d]	142.3 (96.8%)	31.9 (91.2%)***[e]	0.21
Yes	4.9 (4.2%)	4.5 (9.2%)	6.7 (4.1%)	5.6 (10.2%)	4.7 (3.2%)	3.1 (8.8%)	
Cerebrovascular disease							
No	109.9 (94.7%)	42.9 (88.2%)***[c]	155.9 (95.1%)	48.8 (89.4%)***[d]	141.4 (96.2%)	32.5 (92.7%)***[e]	<0.001
Yes	6.2 (5.3%)	5.7 (11.8%)	8.1 (4.9%)	5.8 (10.6%)	5.5 (3.8%)	2.5 (7.3%)	
Dementia							
No	113.6 (97.9%)	45.6 (93.7%)***[c]	161.4 (98.4%)	51.6 (94.5%)***[d]	145.6 (99.1%)	34.3 (97.9%)***[e]	<0.001
Yes	2.5 (2.1%)	3.1 (6.3%)	2.6 (1.6%)	3.0 (5.5%)	1.4 (0.9%)	0.7 (2.1%)	
Neoplasia							
No	109.2 (94.1%)	43.8 (90.0%)***[c]	153.6 (93.7%)	49.4 (90.5%)***[d]	138.0 (93.9%)	31.9 (91.2%)***[e]	0.49
Yes	6.8 (5.9%)	4.8 (10.0%)	10.3 (6.3%)	5.2 (9.5%)	8.9 (6.1%)	3.1 (8.8%)	
Haematologic disease							
No	115.1 (99.2%)	47.9 (98.5%)**[c]	162.5 (99.1%)	53.9 (98.7%)°[d]	146.0 (99.3%)	34.5 (98.7%)**[e]	0.75
Yes	1.0 (0.8%)	0.7 (1.5%)	1.5 (0.9%)	0.7 (1.3%)	1.0 (0.7%)	0.5 (1.3%)	
Immunodeficiency							
No	115.9 (99.9%)	48.7 (99.9%)°[c]	163.9 (99.9%)	54.5 (99.8%)°[d]	146.9 (99.9%)	35.0 (100%)°[e]	0.28
Yes	0.1 (0.1%)	0.1 (0.1%)	0.1 (0.1%)	0.1 (0.2%)	0.1 (0.1%)	0 (0%)	

[a] N/days average number of cases per day
[b] Comparisons of dead patients among the three waves tested by Chi-square or Fisher test
[c] Comparison between alive and dead patients during the first wave tested by Chi-square or Fisher test
[d] Comparison between alive and dead patients during the second wave tested by Chi-square or Fisher test
[e] Comparison between alive and dead patients during the third wave tested by Chi-square or Fisher test
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; ° $p \geq 0.05$

Table S4. Demographic characteristics, comorbid conditions, hospitalization, and intensive care unit (ICU) admission of subjects tested positive for SARS-CoV-2, stratifying by death within 30 days from the first positive swab and waves

	1° Wave (01/03-15/04/20)		2° Wave (15/10-15/12/20)		3° Wave (01/03-15/04/21)		
	No Death N/days[a] (%)	Death N/days[a] (%)	No Death N/days[a] (%)	Death N/days[a] (%)	No Death N/days[a] (%)	Death N/days[a] (%)	P-value[b]
Age group							
≤ 65	203.1 (61.1%)	5.9 (8.2%)***[c]	1791.7 (78.7%)	5.6 (6.2%)***[d]	1392.2 (80.4%)	4.7 (10.2%)***[e]	<0.001
66-75	42.9 (12.9%)	12.4 (17.1%)	204.3 (9.0%)	12.2 (13.3%)	186.6 (10.8%)	9.8 (21.0%)	
76-85	48.1 (14.5%)	28.5 (39.3%)	169.6 (7.5%)	34.6 (37.8%)	115.5 (6.6%)	17.8 (38.1%)	
86+	38.1 (11.5%)	25.6 (35.4%)	109.5 (4.8%)	39.0 (42.7%)	37.8 (2.2%)	14.3 (30.7%)	
Gender							
F	190.7 (57.4%)	39.8 (42.6%)***[c]	1232.7 (54.2%)	43.1 (47.2%)***[d]	881.6 (50.9%)	18.7 (40.0%)***[e]	<0.001
M	141.6 (42.6%)	41.6 (57.4%)	1042.4 (45.8)	48.2 (52.8%)	850.5 (49.1%)	28.0 (60.0%)	
Charlson Comorbidity Index							
0	213.8 (64.3%)	24.9 (34.3%)***[c]	1693.3 (74.4%)	32.5 (35.6%)***[d]	1324.8 (76.5%)	18.7 (40.0%)***[e]	<0.001
1	69.4 (20.9%)	20.2 (27.8%)	410.1 (18.0%)	26.0 (28.5%)	303.9 (17.5%)	13.4 (28.7%)	
2-3	38.6 (11.6%)	19.3 (26.6%)	142.2 (6.3%)	23.9 (25.2%)	88.3 (5.1%)	10.5 (22.5%)	
4+	10.5 (3.2%)	8.2 (11.3%)	29.5 (1.3%)	9.7 (10.7%)	15.1 (0.9%)	4.1 (8.8%)	
COPD							
No	276.6 (83.2%)	51.8 (71.5%)***[c]	1953.8 (85.9%)	65.4 (71.6%)***[d]	1496.2 (86.4%)	33.5 (71.7%)***[e]	0.99
Yes	55.7 (16.8%)	20.7 (28.5%)	321.2 (14.1%)	25.9 (28.4%)	235.9 (13.6%)	13.2 (28.3%)	
Cardiovascular disease							
No	280.9 (84.5%)	47.0 (64.9%)***[c]	2092.1 (92.0%)	59.5 (65.2%)***[d]	1623.1 (93.7%)	32.7 (70.1%)***[e]	<0.001
Yes	51.4 (15.5%)	25.5 (35.1%)	182.9 (8.0%)	31.8 (34.8%)	109.0 (6.3%)	13.9 (29.9%)	
Heart failure							
No	326.2 (98.2%)	67.7 (93.3%)***[c]	2258.5 (99.3%)	85.7 (93.8%)***[d]	1724.7 (99.6%)	44.2 (94.8%)***[e]	0.079
Yes	6.1 (1.8%)	4.8 (6.7%)	16.6 (0.7%)	5.7 (6.2%)	7.4 (0.4%)	2.4 (5.2%)	
Coronary artery disease							
No	320.2 (96.4%)	65.3 (90.0%)***[c]	2231.7 (98.1%)	83.1 (91.0%)***[d]	1704.5 (98.4%)	42.6 (91.4%)***[e]	0.19
Yes	12.1 (3.6%)	7.2 (10.0%)	43.4 (1.9%)	8.2 (9.0%)	27.6 (1.6%)	4.0 (8.6%)	
Cardiomyopathy							
No	321.5 (96.7%)	64.4 (88.8%)***[c]	2247.0 (98.8%)	81.7 (89.5%)***[d]	1719.1 (99.2%)	42.7 (91.4%)***[e]	0.006
Yes	10.8 (3.3%)	8.1 (11.2%)	28.1 (1.2%)	9.6 (10.5%)	13.0 (0.8%)	4.0 (8.6%)	
Diabetes							
No	288.6 (86.8%)	51.8 (71.4%)***[c]	2095.5 (92.1%)	66.3 (72.6%)***[d]	1613.5 (93.1%)	34.1 (73.1%)***[e]	0.34
Yes	43.7 (13.2%)	20.7 (28.6%)	179.6 (7.9%)	25.0 (27.4%)	118.6 (6.9%)	12.6 (26.9%)	
Kidney disease							
No	323.1 (97.2%)	65.4 (90.2%)***[c]	2248.0 (98.8%)	82.7 (90.5%)***[d]	1718.0 (99.2%)	43.0 (92.1%)***[e]	0.039
Yes	9.2 (2.8%)	7.1 (9.8%)	27.1 (1.2%)	8.7 (9.5%)	14.1 (0.8%)	3.7 (7.9%)	
Cerebrovascular disease							
No	316.5 (95.2%)	63.3 (87.4%)***[c]	2231.2 (98.1%)	80.2 (87.8%)***[d]	1712.4 (98.9%)	43.1 (92.4%)***[e]	<0.001
Yes	15.8 (4.8%)	9.2 (12.6%)	43.9 (1.9%)	11.2 (12.2%)	19.7 (1.1%)	3.6 (7.6%)	
Dementia							
No	322.5 (97.0%)	66.8 (92.1%)***[c]	2255.6 (99.1%)	84.5 (92.5%)***[d]	1727.7 (99.7%)	45.4 (97.3%)***[e]	<0.001

Yes	9.8 (3.0%)	5.7 (7.9%)	19.4 (0.9%)	6.9 (7.5%)	4.4 (0.3%)	1.2 (2.7%)	
Neoplasia							
No	318.9 (96.0%)	65.3 (90.1%)***[c]	2219.9 (97.6%)	83.2 (91.1%)***[d]	1693.0 (97.7%)	42.5 (91.2%)***[e]	0.22
Yes	13.4 (4.0%)	7.2 (9.9%)	55.2 (2.4%)	8.1 (8.9%)	39.2 (2.3%)	4.1 (8.8%)	
Haematologic disease							
No	330.8 (99.5%)	71.5 (98.6%)***[c]	2269.3 (99.7%)	90.4 (99.0%)***[d]	1728.8 (99.8%)	46.1 (98.8%)***[e]	0.37
Yes	1.5 (0.5%)	1.0 (1.4%)	5.8 (0.3%)	0.9 (1.0%)	3.3 (0.2%)	0.6 (1.2%)	
Immunodeficiency							
No	332.2 (99.9%)	72.5 (99.9%)°[c]	2274.5 (99.9%)	91.3 (99.9%)**[d]	1731.6 (99.9%)	46.7 (100%)°[e]	0.20
Yes	0.2 (0.1%)	0.1 (0.1%)	0.6 (0.1%)	0.1 (0.1%)	0.5 (0.1%)	0 (0%)	
Hospitalization							
No	216.3 (65.1%)	23.8 (32.9%)***[c]	2111.1 (92.8%)	36.7 (40.2%)***[d]	1585.1 (91.5%)	11.7 (25.0%)***[e]	<0.001
Yes	116.0 (34.9%)	48.7 (67.1%)	164.0 (7.2%)	54.6 (59.8%)	147.0 (8.5%)	35.0 (75.0%)	
Admission to ICU							
No	303.6 (91.3%)	56.4 (77.7%)***[c]	2239.1 (98.4%)	73.6 (80.6%)***[d]	1700.3 (98.2%)	34.4 (73.7%)***[e]	<0.001
Yes	28.7 (8.7%)	16.1 (22.3%)	36.0 (1.6%)	17.7 (19.4%)	31.8 (1.8%)	12.3 (26.3%)	

[a] N/days average number of cases per day
[b] Comparisons of dead subjects among the three waves tested by Chi-square or Fisher test
[c] Comparison between alive and dead subjects during the first wave tested by Chi-square or Fisher test
[d] Comparison between alive and dead subjects during the second wave tested by Chi-square or Fisher test
[e] Comparison between alive and dead subjects during the third wave tested by Chi-square or Fisher test
*** p < 0.001; ** p < 0.01; * p < 0.05; ° p ≥0.05

Table S5. Demographic characteristics and comorbid conditions of subjects admitted to the intensive care unit (ICU), stratifying by death within 30 days from the first positive swab and waves

	1° Wave (01/03-15/04/20)		2° Wave (15/10-15/12/20)		3° Wave (01/03-15/04/21)		P-value[b]
	No Death N/days[a] (%)	Death N/days[a] (%)	No Death N/days[a] (%)	Death N/days[a] (%)	No Death N/days[a] (%)	Death N/days[a] (%)	
Age group							
≤ 65	16.2 (56.5%)	3.1 (19.4%)***[c]	14.7 (40.9%)	3.1 (17.3%)***[d]	15.2 (47.6%)	3.0 (24.5%)***[e]	<0.001
66-75	7.8 (27.3%)	5.5 (34.0%)	11.3 (31.5%)	5.4 (30.7%)	9.8 (30.0%)	5.4 (43.8%)	
76-85	3.9 (13.5%)	6.0 (36.9%)	8.0 (22.1%)	7.0 (39.8%)	5.7 (17.8%)	3.2 (25.7%)	
86+	0.8 (2.7%)	1.6 (9.7%)	2.0 (5.5%)	2.2 (12.2%)	1.2 (3.7%)	0.7 (6.0%)	
Gender							
F	8.8 (30.7%)	4.3 (27.0%)°[c]	11.4 (31.6%)	5.6 (31.5%)°[d]	11.9 (37.5%)	3.9 (31.6%)*[e]	0.079
M	19.9 (69.3%)	11.8 (73.0%)	24.6 (68.4%)	12.1 (68.5%)	19.9 (62.5%)	8.4 (68.4%)	
Charlson Comorbidity Index							
0	16.7 (58.2%)	6.3 (39.4%)***[c]	18.6 (51.7%)	6.4 (36.0%)***[d]	18.7 (58.9%)	5.3 (43.1%)***[e]	0.040
1	7.2 (25.0%)	4.8 (29.8%)	10.3 (28.5%)	5.7 (32.3%)	8.2 (25.7%)	4.0 (32.5%)	
2-3	3.7 (12.7%)	3.7 (23.0%)	5.6 (15.4%)	4.1 (23.5%)	4.1 (12.9%)	2.2 (17.5%)	
4+	1.2 (4.1%)	1.3 (7.8%)	1.6 (4.4%)	1.5 (8.2%)	0.8 (2.5%)	0.8 (6.9%)	
COPD							
No	23.8 (82.9%)	12.1 (74.8%)***[c]	28.5 (79.2%)	12.7 (71.6%)***[d]	25.4 (80.0%)	8.8 (71.6%)***[e]	0.26
Yes	4.9 (17.1%)	4.1 (25.2%)	7.5 (20.8%)	5.0 (28.4%)	6.4 (20.0%)	3.5 (28.4%)	
Cardiovascular disease							
No	24.0 (83.5%)	11.3 (70.3%)***[c]	29.6 (82.2%)	12.9 (72.7%)***[d]	27.0 (84.9%)	9.7 (78.9%)***[e]	0.002
Yes	4.7 (16.5%)	4.8 (29.7%)	6.4 (17.8%)	4.8 (27.3%)	4.8 (15.1%)	2.6 (21.1%)	
Heart failure							
No	28.2 (98.1%)	15.6 (96.6%)*[c]	35.3 (98.0%)	17.0 (96.4%)**[d]	31.4 (98.6%)	11.8 (96.3%)**[e]	0.94
Yes	0.5 (1.9%)	0.5 (3.4%)	0.7 (2.0%)	0.6 (3.6%)	0.4 (1.4%)	0.5 (3.7%)	
Coronary artery disease							
No	27.0 (94.1%)	14.3 (88.8%)***[c]	33.6 (93.4%)	16.1 (90.8%)**[d]	30.5 (96.0%)	11.3 (92.0%)***[e]	0.13
Yes	1.7 (5.9%)	1.8 (11.2%)	2.4 (6.6%)	1.6 (9.2%)	1.3 (4.0%)	1.0 (8.0%)	
Cardiomyopathy							

No	27.9 (97.1%)	15.1 (93.5%)***[c]	34.7 (96.5%)	16.5 (93.1%)***[d]	31.0 (97.3%)	11.5 (94.0%)***[e]	0.81
Yes	0.8 (2.9%)	1.0 (6.5%)	1.3 (3.5%)	1.2 (6.9%)	0.8 (2.7%)	0.7 (6.0%)	
Diabetes							
No	23.0 (80.0%)	11.4 (70.7%)***[c]	27.7 (77.0%)	12.5 (70.9%)***[d]	26.1 (82.1%)	9.0 (73.4%)***[e]	0.50
Yes	5.7 (20.0%)	4.7 (29.3%)	8.3 (23.0%)	5.1 (29.1%)	5.7 (17.9%)	3.3 (26.6%)	
Kidney disease							
No	27.9 (97.0%)	15.0 (92.7%)***[c]	34.5 (95.9%)	16.1 (91.3%)***[d]	31.0 (97.3%)	11.5 (94.0%)***[e]	0.14
Yes	0.9 (3.0%)	1.2 (7.3%)	1.5 (4.1%)	1.5 (8.7%)	0.8 (2.7%)	0.7 (6.0%)	
Cerebrovascular disease							
No	27.5 (95.8%)	15.1 (93.8%)*[c]	34.6 (96.2%)	16.7 (94.2%)*[d]	30.8 (97.0%)	11.8 (96.3%)°[e]	0.12
Yes	1.2 (4.2%)	1.1 (6.2%)	1.4 (3.8%)	1.0 (5.8%)	1.0 (3.0%)	0.5 (3.7%)	
Dementia							
No	28.5 (99.2%)	15.8 (98.1%)*[c]	35.8 (99.5%)	17.5 (99.0%)°[d]	31.7 (99.7%)	12.2 (99.1%)°[e]	0.17
Yes	0.2 (0.8%)	0.3 (1.9%)	0.2 (0.5%)	0.2 (1.0%)	0.1 (0.3%)	0.1 (0.9%)	
Neoplasia							
No	27.3 (95.0%)	14.8 (91.5%)**[c]	33.7 (93.7%)	15.9 (89.8%)***[d]	30.4 (95.7%)	11.6 (94.7%)°[e]	0.004
Yes	1.4 (5.0%)	1.4 (8.5%)	2.3 (6.3%)	1.8 (10.2%)	1.4 (4.3%)	0.7 (5.3%)	
Haematologic disease							
No	28.4 (98.9%)	15.8 (98.2%)°[c]	35.5 (98.7%)	17.4 (98.3%)°[d]	31.7 (99.7%)	12.2 (99.5%)°[e]	0.12
Yes	0.3 (1.1%)	0.3 (1.8%)	0.5 (1.3%)	0.3 (1.7%)	0.1 (0.3%)	0.1 (0.5%)	
Immunodeficiency							
No	28.7 (99.8%)	16.1 (100%)°[c]	36.0 (100%)	17.7 (99.8%)°[d]	31.8 (99.9%)	12.3 (100%)°[e]	0.50
Yes	0.1 (0.2%)	0 (0%)	0 (0%)	0.1 (0.2%)	0.1 (0.1%)	0 (0%)	

[a] N/days average number of cases per day
[b] Comparisons of ICU admitted dead patients among the three waves tested by Chi-square or Fisher test
[c] Comparison between ICU admitted alive and dead patients during the first wave tested by Chi-square or Fisher test
[d] Comparison between ICU admitted alive and dead patients during the second wave tested by Chi-square or Fisher test
[e] Comparison between ICU admitted alive and dead patients during the third wave tested by Chi-square or Fisher test
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; ° $p \geq 0.0$

3.4 The impact of COVID-19 pandemic on gambling: A systematic review

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ABSTRACT

Background and Aims

Since the COVID-19 outbreak, people's habits changed radically. In fact, to limit the spread of SARS-CoV-2, governments implemented restrictive measures that influenced the lives of individuals. The aim of this systematic review is to analyze the impact of COVID-19 on gambling by examining three different outcomes: frequency, expenditure, and transitions among different types of gambling.

Methods

All studies assessing the impact of restrictive measures implemented to limit the spread of SARS-CoV-2 on gambling were included. For the search, two different databases were used: Pubmed and CINAHL. Moreover, two different populations were analyzed: the general population, and subjects who used to gamble before SARS-CoV-2 pandemic. All qualitative studies, reports not based on peer-review, and papers in which the statistical unit was not the subject but the gambling or wagering operators were excluded.

Results

From the search, 408 reports were identified. Of these, 28 were included in the systematic review. From the studies, a strong reduction in the frequency and expenditure of land-based gambling emerged, while the results about online gambling were different among the studies. However, a reduction was observed assessing sports betting, and an increase emerged considering online casino and skill games. Finally, a significant migration from land-based gambling to online platforms was identified. The main reasons for these findings were the physical closures of land-based gambling venues and the more time spent at home, the suspension or cancelation of sporting events on which subjects used to bet, and more mental health issues during this challenging period.

Conclusions

The COVID-19 pandemic greatly affected subjects' habits, including gambling, by reducing land-based gambling and sports betting, and increasing gambling on online platforms. This shift poses significant challenges, requiring a comprehensive approach to monitor and mitigate the negative consequences of this increase in online gambling caused by the pandemic.

Keywords

COVID-19; Restrictive measures; Gambling habits; Land-based gambling; Online gambling; Sports betting

1. INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared Coronavirus Disease (COVID-19) a global pandemic. The first cases of COVID-19 were detected in Wuhan, China, in December 2019, and subsequently in the rest of the world between January and February 2020 (World Health Organization, 2020.). Since the first case occurred, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has significantly altered the global landscape, with a huge number of deaths and an even higher number of hospitalizations or intensive care unit (ICU) admissions, leading even the most advanced national health care systems to collapse (Caramello et al., 2022). For this reason, in almost all countries, local governments implemented several policies to counteract the spread of COVID-19 and reduce its effects. Generally, such measures imposed a strict lockdown involving isolation, social and physical distancing, and taking preventive measures such as wearing mask and hand washing. Moreover, the restrictions imposed the closure of all non-essential activities, allowing only essential stores or services (e.g., food stores, supermarkets, pharmacies, hospitals, etc.) to remain open, and movement restrictions, including the prohibition of leaving the house without a necessary reason. In some countries such as Italy, which was the first country to face the emergency in Europe (Alessi et al., 2022; Saglietto et al., 2020), New Zealand (Rodda et al., 2022), Australia (Black et al., 2022), Denmark (Håkansson, 2021), Germany (Smith et al., 2023), Israel (Bonny-Noach & Gold, 2021), and the United Kingdom (Emond et al., 2022) these restrictions were strictly implemented through the se-called lockdown. In other countries, instead, the measures implemented were less restrictive. For example, in Sweden, the government only recommended limiting social contacts and maintaining physical distancing, prohibiting public gatherings of more than 500 people, and subsequently more than 50 people (Håkansson, 2020a; Månsson et al., 2021). In addition, the local authorities encouraged to work from home, without imposing it (Månsson et al., 2021).

The restrictions implemented during the COVID-19 pandemic had a great impact on several aspects, including gambling (Quinn et al., 2022) and other addictions such as problematic internet use and problematic social media (Gjoneska et al., 2022; Casale et al., 2023).

The word gambling concerns all types of games that involve wagering money on the outcome of a future event for which the outcome cannot be certain, with the primary intent of winning additional money or material goods. Common forms of gambling include casino games (such as slot machines, poker, blackjack, and roulette), sports betting, lottery games, scratch cards, and online gambling platforms. While some people engage in gambling for entertainment, others may develop problematic gambling behavior, leading to negative consequences such as financial losses, relationship issues, and psychological distress (Buchanan et al., 2020; Mathews & Volberg, 2013).

For these reasons and others related to religion and culture, some local governments chose to regulate gambling. The extent of regulation varies significantly among countries. In some nations, such as Saudi Arabia (Alshammari & Goto, 2022), North Korea, and Qatar (Mattar, 2020), gambling is strictly prohibited. In others, such as the United Kingdom (Atherton & Beynon, 2019; Thomas et al., 2023), Australia, Denmark, Sweden (Binde, 2013), and Italy (Bastiani et al., 2013), gambling is regulated under several legislation and regulations, to ensure transparency, consumer protection, and responsible gaming practices. Finally, there are some countries where gambling regulations are relatively lenient or non-existent, allowing for a more permissive or open approach. The most important examples of such countries include Singapore (Winslow et al., 2015) and the state of Nevada in the United States, particularly in the renowned gambling destination of Las Vegas (Tucker et al., 2021). The diffusion of gambling varies significantly across countries in terms of size, prevalence, and type of gambling. These differences depend in part on the presence or absence of public health interventions aimed at preventing and combating abuse, as well as treating pathological dependence, although their effectiveness differs from intervention to intervention (Velasco et al., 2021).

In addition to these factors, the complexity of restrictions due to the COVID-19 pandemic outbreak complicated the situation, because the differences among countries' restrictions above discussed may have had different impacts on gambling consumption patterns.

In general, the national lockdowns implemented in many countries not only imposed the physical closure of certain business activities such as land-based casinos and betting stores, allowing only the purchase of lottery tickets or scratch cards at essential stores (Fluharty et al., 2022), but they also led to the cancellation or suspension of most sporting events worldwide (Cataldo et al., 2022). Specifically, on March 9, 2020, Italian male soccer leagues were canceled, on 12 March United States Major League Baseball was suspended, on March 13 Premier League was halted, on March 15 there was the decision to suspend ice hockey season in Sweden, and on March 24 the 2020 Summer Olympics scheduled in Tokyo were postponed (Håkansson, 2020b). In addition, major tennis and the Six Nations rugby tournaments, volleyball championships, and basketball leagues were suspended or postponed due to the COVID-19 pandemic**.**

Therefore, it is possible that the imposed closures of many gambling venues, the cancellation of major sporting events many subjects traditionally bet on, the increased time spent at home, and the higher level of anxiety and depression experienced by gamblers, especially during a period in which anxiety and depression levels increased (Brodeur et al., 2021; Kessler et al., 2008; Rajkumar, 2020; Zhu et al., 2023), may have had a very strong impact on gambling habits.

Several studies have investigated the impact of the COVID-19 pandemic on gambling. However, to date, no systematic work has specifically examined and summarized this effect. Therefore, this systematic review aims to summarize the results of the studies present in the literature that assessed the effect of the restrictive measures implemented due to the COVID-19 pandemic on gambling, both land-based and online. The focus of this systematic review is on the gambling frequency, gambling expenditure, and transitions among different types of gambling.

2. METHODS

2.1 Design and Registration

The current systematic review was conducted using the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The PRISMA 2020 Checklist is shown in Supplementary Table 1. The protocol of this study was registered within the International Prospective Register of Systematic Reviews PROSPERO (registration number: CRD42023484007). In this systematic review, there is no deviation from the registered protocol.

2.2 Search Strategy and eligibility criteria

For the purpose of this systematic review, all studies assessing the impact that restrictive measures implemented to limit the spread of SARS-CoV-2 had on gambling were included, both considering land-based and online gambling. Specifically, the types of gambling considered included betting (on sports, racing, and eSports), casinos, card games (Poker, Blackjack, baccarat, etc.), lottery, bingo, Keno, slot machines or Electronic Gambling Machines (EGMs), and scratch cards.

Two different academic databases were used to search: PubMed and CINAHL. The search strings used in these databases are shown in Table 1. Only papers published 1 January 2020 and 9 October 2023 were checked.

Qualitative studies (including commentaries, editorials, text mining or sentiment analyses, protocols, and different types of reviews), and reports not based on peer review were excluded. In addition, all papers in which the statistical unit was not the subject but the gambling or wagering operators were not included in this systematic review. No restrictions on geographical area and on the type of quantitative study were considered.

Table 1. Search strategy implemented on PUBMED and CINAHL to conduct the systematic review.

N° Step	Search strategy
PUBMED	
S1	"COVID-19"[Mesh] OR COVID-19*[Title/Abstract] OR 2019-nCoV[Title/Abstract] OR COV-19*[Title/Abstract] OR "SARS-CoV-2"[Mesh] OR SARS-CoV-2*[Title/Abstract]
S2	"Pandemics"[Mesh] OR pandemic*[Title/Abstract]
S3	S1 OR S2
S4	"Gambling"[Mesh] OR gambl*[Title/Abstract] OR betting[Title/Abstract] OR "slot machine*"[Title/Abstract] OR slots[Title/Abstract] OR lotter*[Title/Abstract] OR roulette*[Title/Abstract] OR blackjack[Title/Abstract] OR baccarat[Title/Abstract] OR

	bingo[Title/Abstract] OR poker[Title/Abstract] OR casino*[Title/Abstract] OR "gaming machine*"[Title/Abstract] OR craps[Title/Abstract] OR lotto[Title/Abstract]
S5	S3 AND S4
S6	Limits to 2020-2023 and English language
CINAHL	
S1	MH "COVID-19+" OR TI "COVID-19*" OR AB "COVID-19*" OR TI "2019-nCoV" OR AB "2019-nCoV" OR TI "COV-19*" OR AB "COV-19*" OR MH "SARS-CoV-2" OR TI "SARS-CoV-2*" OR AB "SARS-CoV-2*"
S2	MH "COVID-19 Pandemic" OR TI pandemic* OR AB pandemic*
S3	S1 OR S2
S4	MH "Gambling" OR TI gambl* OR AB gambl* OR TI betting OR AB betting OR TI "slot machine*" OR AB "slot machine*" OR TI slots OR AB slots OR TI lotter* OR AB lotter* OR TI roulette* OR AB roulette* OR TI blackjack OR AB blackjack OR TI baccarat OR AB baccarat OR TI bingo OR AB bingo OR TI poker OR AB poker OR TI casino* OR AB casino* OR TI "gaming machine*" OR AB "gaming machine*" OR TI craps OR AB craps OR TI lotto OR AB lotto
S5	S3 AND S4
S6	Limits to 2020-2023 and English language

2.3 Outcomes

In this systematic review, three different outcomes were assessed. The change in (1) frequency and (2) expenditure in gambling between before and after the outbreak of the COVID-19 pandemic was analyzed. The third outcome concerned the change in the type of gambling used by the subjects due to the restrictive measures implemented to limit the spread of COVID-19. This outcome was investigated only considering gamblers or bettors.

Moreover, this review focused separately on two different populations:

1) the general population, which included both people who used to gamble before the pandemic and people who had never gambled;

2) the population composed of gamblers or bettors who had gambled at least once before the COVID-19 pandemic.

2.4 Study selection and data extraction

Study selection was performed in two different stages. First, after removal of duplicate records, a selection by titles and abstracts of all studies derived from the search string according to the eligibility criteria was performed. Second, the full texts of the studies selected in the first stage were reviewed for final eligibility. In both stages, two reviewers operated independently. Moreover, in instances where the two reviewers did not agree, a third reviewer was involved. Reference management, duplicate elimination and item selection was conducted through Zotero software (V. 6.0.30).

Data were extracted by both reviewers. The information retrieved from each study, reported in Table 1, include: the first author, year of publication, country, type of population, sample size, study design, types of gambling analyzed, outcomes assessed, and different possible predictors of changing gambling habits analyzed in the studies.

2.5 Risk of Bias

To assess the risk of bias of the selected studies, the Newcastle Ottawa Scale (NOS) was used (Wells et al, 2000). This scale is generally used for observational studies. There are three different versions for the assessment of observational studies: a version for cross-sectional studies (7 items), one for case-control studies (8 items), and one for prospective cohorts (8 items). In all three versions, the highest attainable score is 9, and a score below 5 corresponds to a high risk of bias (Luchini et al., 2017). In this systematic review, studies with a high risk of bias were excluded.

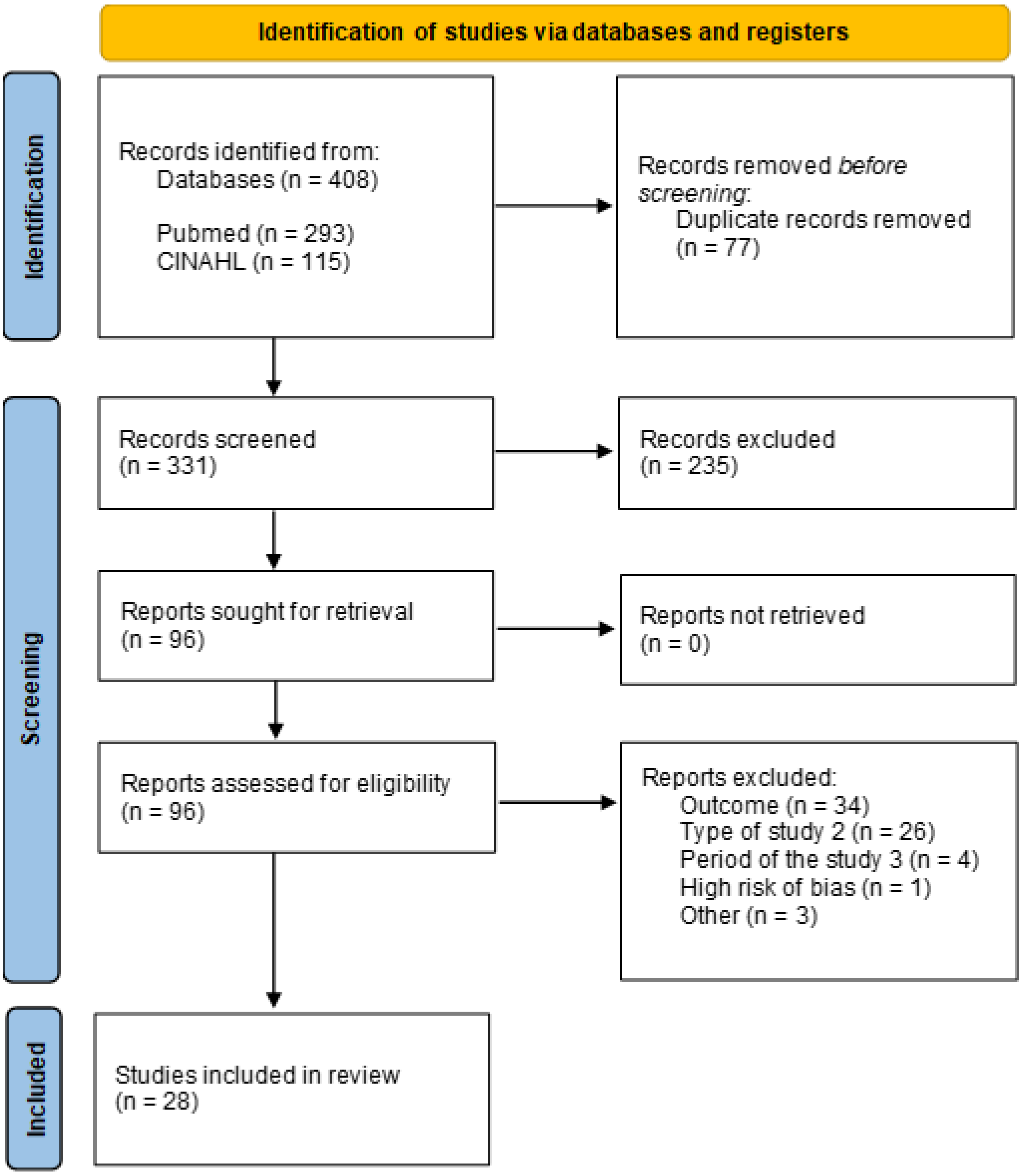
The risk of bias was assessed by two different co-authors, and in case of disagreement, the opinion of a third author was taken into consideration.

3. RESULTS

3.1 Selection Process

The above-mentioned search strategy identified a total of 408 reports: 293 were found in PubMed, and 115 in CINAHL. After excluding duplicate records (n = 77), in the first screening phase (for title and abstract), a total of 235 papers were excluded. Subsequently, out of the remaining 96 reports, 67 were removed after full texts‘ assessment. The primary reasons for exclusion were (1) assessing an outcome different from the one under investigation (n = 34) and (2) being qualitative studies or editorials (n = 26) (Supplementary Table 2). Of the final 29 studies, only a paper had a Newcastle-Ottawa Scale score below 5 and was therefore excluded from the systematic review. Therefore, overall, 28 different papers were included in this systematic review. The PRISMA Flow Chart (Page et al., 2021) representing the entire selection process is summarized in Figure 1.

Figure 1. PRISMA flow diagram representing the entire selection process



3.2 Characteristics of included studies

Of the 28 studies included in this systematic review, six analyzed only the general population, 14 focused attention on gamblers or bettors before the COVID-19 pandemic, and eight studied both populations. In addition, eighteen were cross-sectional studies and ten were longitudinal studies. The sample size ranged from a minimum of 70 to a maximum of 616,245 subjects.

From a geographic point of view, most studies were conducted in Sweden (n = 7), the United Kingdom (n = 4), and Italy (n = 4). The other countries involved were Australia (n = 2), Canada (n = 2), Czech Republic, Denmark, Germany, Greece, Israel, New Zealand, Spain, and Switzerland. Only one paper involved subjects from multiple countries (Germany, Finland, Norway, and Sweden). Regarding the outcomes, the impact of the COVID-19 pandemic on gambling frequency was assessed by 26 studies, the effects on gambling expenditure were investigated by 7 reports, and the influence on the changes in gambling types was analyzed in 6 papers. The characteristics of each study are summarized in Table 1.

Table 1. Main information about the studies included in the systematic review

First author and year of publication	Country	Population	Sample size	Study design	Outcomes assessed in the study	Type of gambling	Variables assessed in the study	Type of analysis conducted
MC. Alessi, 2022 (Alessi et al., 2022)	Italy	Gamblers before the pandemic period	153 gamblers	Cross-sectional	Frequency	Land-based Gambling Online gambling	None	Frequency Percentage
A. Amerio, 2022 (Amerio et al., 2022)	Italy	General population	6,003 subjects	Cross-sectional	Frequency	Overall gambling	None	Regression
M. Auer, 2022 (Auer & Griffiths, 2022)	Sweden	Gamblers before the pandemic period	133,286 gamblers	Longitudinal	Expenditure	Online gambling	Intensity of gambling	Percentage
M. Auer, 2023 (Auer et al., 2023)	Germany, Sweden, Finland, Norway	Gamblers before the pandemic period	5,396 gamblers	Longitudinal	Expenditure	Online gambling	None	Percentage
M. Balem, 2023 (Balem et al., 2023)	Sweden	Gamblers before the pandemic period	616,245 gamblers	Longitudinal	Frequency Expenditure	Online gambling	Gender	Regression
ME. Bellringer, 2021 (Bellringer & Garrett, 2021)	New Zealand	Gamblers before the pandemic period	301 gamblers	Longitudinal	Frequency	Online gambling	Gender Age Ethnicity Occupational status Education level Alcohol consumption Level of problematic gambling	Regression
N. Black, 2022 (Black et al., 2022)	Australia	Gamblers before the pandemic period	462 gamblers	Longitudinal	Frequency	Overall gambling	Level of problematic gambling	Regression
H. Bonny-Noach, 2021 (Bonny-Noach & Gold, 2021)	Isreal	General population	113 subjects	Cross-sectional	Frequency	Online gambling	Cannabis use Drugs use	Regression

E. Claesdotter-Knutsson, 2021 (Claesdotter-Knutsson & Håkansson, 2021)	Sweden	Gamblers before the pandemic period	1,064 gamblers	Cross-sectional	Frequency	Online gambling	Gender Age Occupational status Education level Income Time at home Alcohol consumption Level of problematic gambling Distress level	Regression
A. Emond, 2022 (Emond et al., 2022)	United Kingdom	General population Gamblers before the pandemic period	2,160 subjects 1,255 gamblers	Longitudinal	Frequency	Overall gambling Land-based gambling Online gambling	Intensity of gambling	Regression
M. Fluharty, 2022 (Fluharty et al., 2022)	United Kingdom	Gamblers before the pandemic period	7,026 gamblers	Longitudinal	Frequency	Overall gambling	Gender Age Ethnicity Education level Income Living with someone Alcohol consumption Smoking status Anxiety level Depression level Distress level	Regression
SM. Gainsbury, 2021 (Gainsbury et al., 2021)	Australia	Gamblers before the pandemic period	769 gamblers	Cross-sectional	Frequency	Overall gambling Land-based gambling Online gambling	Age Level of problematic gambling	Regression
A. Håkansson, 2020 (Håkansson, 2020a)	Sweden	General population Gamblers before the pandemic period	2,016 subjects 1,246 gamblers	Cross-sectional	Frequency Changes in type of gambling	Overall gambling Land-based gambling Online gambling	Age Gender Occupational status Living with children Time at home	Regression

							Alcohol consumption Level of problematic gambling Distress level	
A. Håkansson 2021 (Håkansson, 2021)	Denmark	General population Gamblers before the pandemic period	1,971 subjects 1,098 gamblers	Cross-sectional	Frequency	Overall gambling Land-based gambling Online gambling	Age Gender Occupational status Living with children Income Time at home Alcohol consumption Level of problematic gambling Distress level	Regression
A. Håkansson 2020 (Håkansson et al., 2020)	Sweden	General population Gamblers before the pandemic period	327 subjects 277 gamblers	Cross-sectional	Frequency Changes in type of gambling	Overall gambling Land-based gambling Online gambling	Age Gender Alcohol consumption Gambling intensity Depression level Anxiety level	Frequency Percentage
A. Håkansson 2021 (Håkansson & Widinghoff, 2021)	Sweden	General population Gamblers before the pandemic period	2,029 subjects 1,281 gamblers	Cross-sectional	Frequency	Land-based gambling Online gambling	Age Occupational status Income Time at home Alcohol consumption Level of problematic gambling Distress level	Regression
J. Kalke, 2022 (Kalke et al., 2022)	Germany	Gamblers before the pandemic period	612 gamblers	Cross-sectional	Frequency Changes in type of gambling	Land-based gambling Online gambling	Age Gender Migration background Gambling intensity Level of problematic gambling	Regression

S. Lischer, 2021 (Lischer et al., 2021)	Switzerland	Gamblers before the pandemic period	110 gamblers	Longitudinal	Frequency	Overall gambling Land-based gambling Online gambling	None	Frequency Percentage
A. Lugo, 2021 (Lugo et al., 2021)	Italy	General population Gamblers before the pandemic period	6,003 subjects 980 gamblers	Cross-sectional	Frequency	Land-based gambling Online gambling	Age Gender Educational level Alcohol consumption Smoking status Cannabis use Anxiety level Depression level Quality of life Sleep quality Sleep quantity	Regression
V. Månsson, 2021 (Månsson et al., 2021)	Sweden	General population	325 subjects	Longitudinal	Frequency Expenditure	Overall gambling Land-based gambling Online gambling	Age Gender Level of problematic gambling Mental health issues	Regression
V. Mravčík, 2021 (Mravčík & Chomynová, 2021)	Czech Republic	General population	3,000 subjects	Cross-sectional	Frequency	Online gambling	None	Frequency
E. Otis, 2022 (Otis et al., 2022)	Canada	Gamblers before the pandemic period	100 subjects	Cross-sectional	Frequency Expenditure	Overall gambling Land-based gambling	None	Regression
A. Pérez-Albéniz, 2022 (Pérez-Albéniz et al., 2022)	Spain	General population	540 subjects	Cross-sectional	Frequency	Overall gambling	None	Frequency Percentage
K. Rantis, 2022 (Rantis et al., 2022)	Greece	Gamblers before the pandemic period	70 gamblers	Cross-sectional	Frequency Changes in type of gambling	Overall gambling Land-based gambling	None	Frequency Percentage
L. Salerno, 2021 (Salerno & Pallanti, 2021)	Italy	General population	254 subjects	Cross-sectional	Frequency	Overall gambling	Gender Occupational status	Frequency Percentage

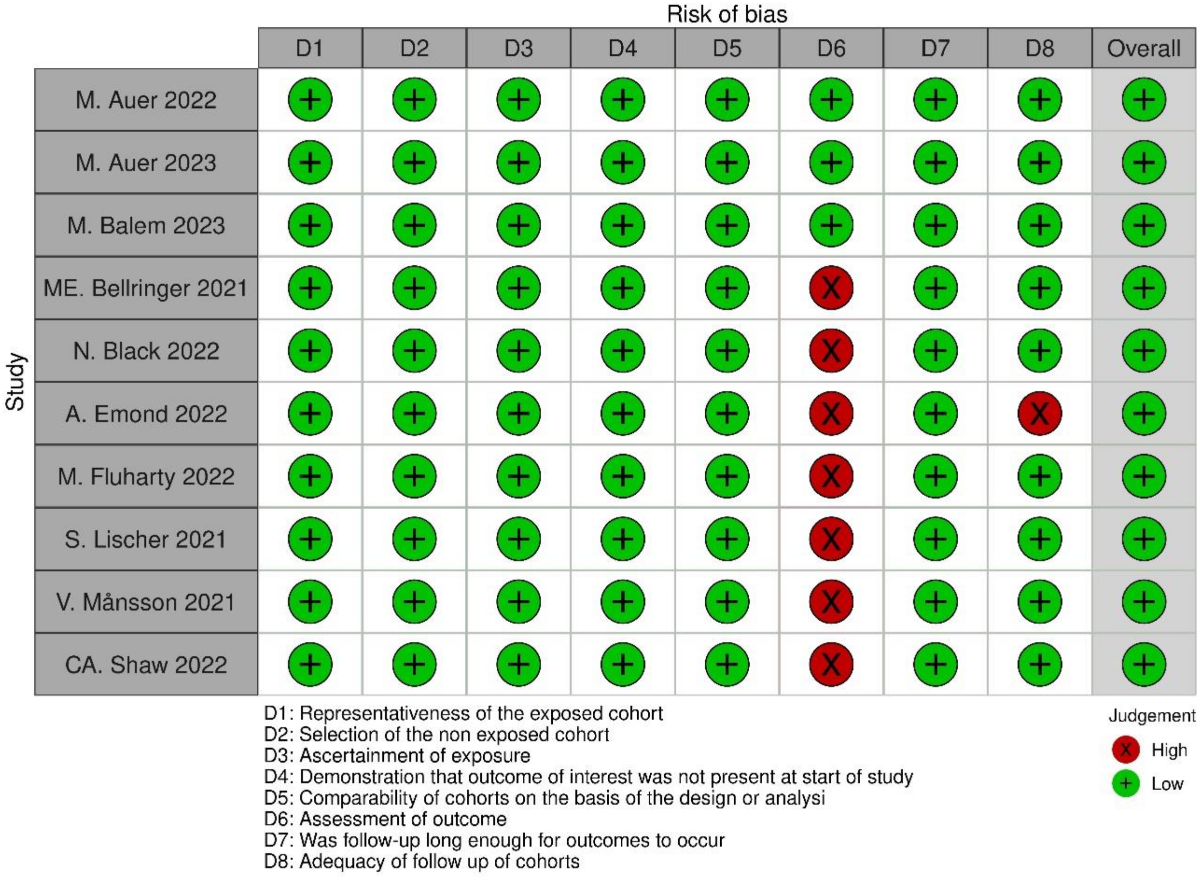
S. Sharman, 2022 (Sharman et al., 2022)	United Kingdom	General population Gamblers before the pandemic period	1,028 subjects 505 gamblers	Cross-sectional	Frequency Expenditure	Overall gambling	Changes in employment status	Frequency Percentage
CA. Shaw, 2022 (Shaw et al., 2022)	Canada	General population Gamblers before the pandemic period	3,449 subjects 2,394 gamblers	Longitudinal	Frequency Expenditure Changes in type of gambling	Overall gambling Online gambling Land-based gambling	Level of problematic gambling Number of types of gambling played	Regression
H. Wardle, 2021 (Wardle et al., 2021)	United Kingdom	Gamblers before the pandemic period	3,866 gamblers	Cross-sectional	Frequency Changes in type of gambling	Land-based gambling Online gambling	Gender	Regression

3.3 Risk of Bias assessment

The results related to the risk of bias assessment are shown in Figure 2 and Figure 3 (McGuinness & Higgins, 2021). Item-specific ratings for each study are shown in Supplementary Table 3 and Supplementary Table 4.

Of the 29 included studies, only one cross-sectional study was found to have a NOS score of less than 5, and therefore was excluded from the systematic review.

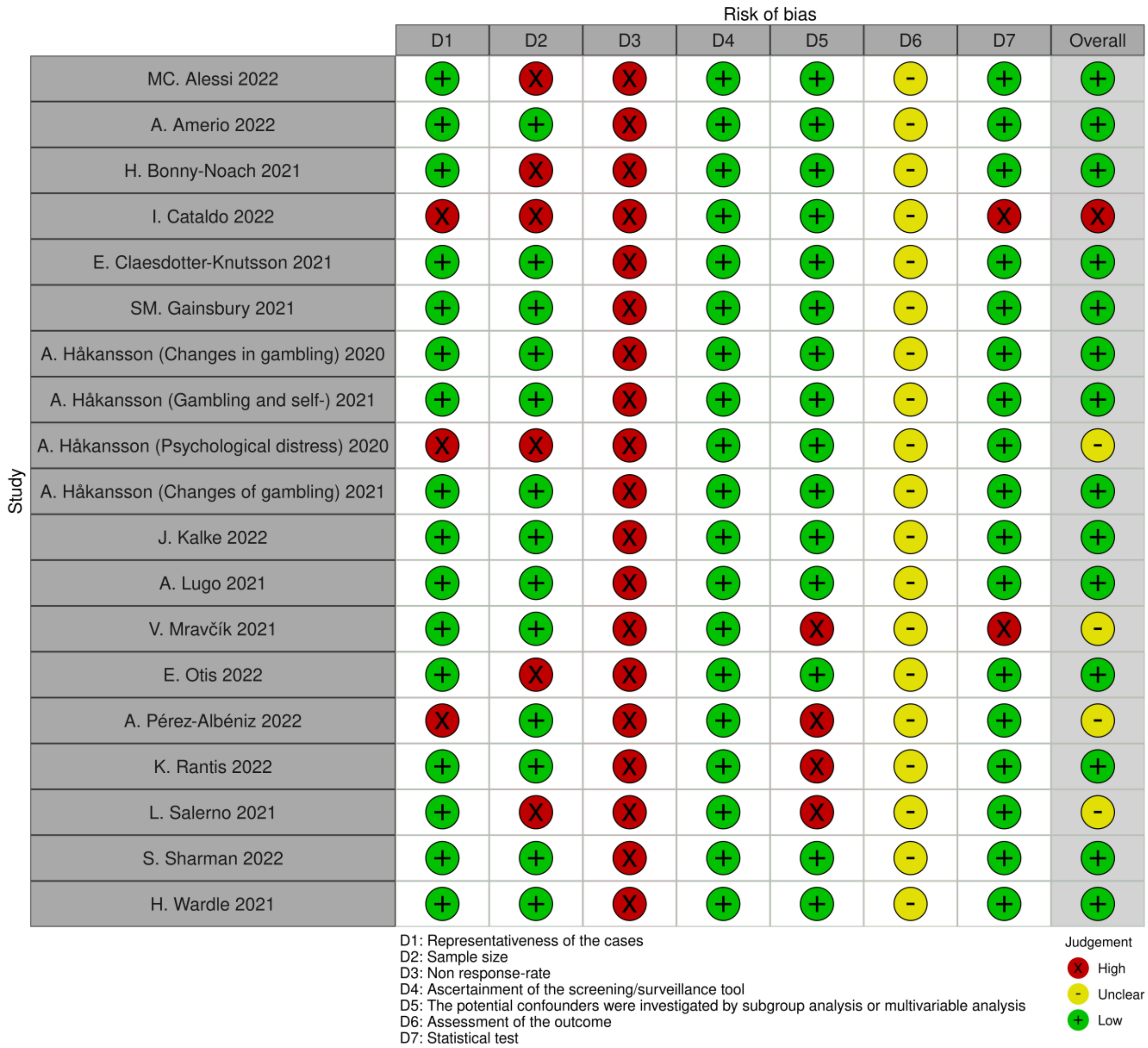
Figure 2. Risk of Bias for each longitudinal study which met inclusion and exclusion criteria, evaluated through Newcastle-Ottawa Scale



*D1: High = 1, Low = 0; D2: High = 1, Low = 0; D3: High = 1, Low = 0; D4: High = 1, Low = 0; D5: High = 2, Unclear = 1, Low = 0; D6: High = 1, Low = 0; D7: High = 1, Low = 0; D8: High = 1, Low = 0; Overall: High = 6-9, Unclear = 5, Low = 0-4.

** “Unclear” not present as there is no case among the assessed studies.

Figure 3. Risk of Bias for each cross-sectional study which met inclusion and exclusion criteria, evaluated through Newcastle-Ottawa Scale



*D1: High = 1, Low = 0; D2: High = 1, Low = 0; D3: High = 1, Low = 0; D4: High = 2, Unclear = 1; Low = 0; D5: High = 1, Low = 0; D6: High = 2, Unclear = 1, Low = 0; D7: High = 1, Low = 0; Overall: High = 6-9, Unclear = 5, Low = 0-4.

3.4 General Population

3.4.1 Frequency

Fourteen different studies assessed the impact of COVID-19 on gambling frequency.

Regarding overall gambling, studies showed mixed effects on gambling habits. Authors reported a decrease in overall gambling frequency (Amerio et al., 2022 (cross-sectional); Emond et al., 2022 (longitudinal); Håkansson, 2020a, 2021 (cross-sectional); Håkansson et al., 2020 (cross-sectional); Pérez-Albéniz et al., 2022 (cross-sectional); Sharman et al., 2022 (cross-sectional); Shaw et al., 2022 (longitudinal)), and indicated that a subset of individuals started (Amerio et al., 2022 (cross-sectional); Håkansson & Widinghoff, 2021 (cross-sectional); Salerno & Pallanti, 2021 (cross-sectional); Shaw et al., 2022 (longitudinal)) or increased their gambling habits (Amerio et al., 2022 (cross-sectional); Håkansson, 2020a, 2021 (cross-sectional); Håkansson et al., 2020 (cross-sectional); Håkansson & Widinghoff, 2021 (cross-sectional); Shaw et al., 2022 (longitudinal)). The percentage of those reporting more gambling varied across studies, ranging from about 4 to 16%.

However, it emerges that most people did not change their gambling habits during the period when the restrictive measures aimed at counteracting the COVID-19 pandemic were implemented, keeping their gambling frequency unchanged or never gambling either before or after the pandemic (Amerio et al., 2022 (cross-sectional); Håkansson, 2020a, 2021 (cross-sectional); Håkansson et al., 2020 (cross-sectional); Håkansson & Widinghoff, 2021 (cross-sectional); Salerno & Pallanti, 2021 (cross-sectional); Sharman et al., 2022 (cross-sectional); Shaw et al., 2022 (longitudinal)). Predictors of having increased overall gambling frequency identified by the authors were younger age (Håkansson, 2020a, 2021 (cross-sectional); Håkansson & Widinghoff, 2021 (cross-sectional)), higher gambling problem severity level (Håkansson, 2020a, 2021 (cross-sectional); Håkansson et al., 2020 (cross-sectional); Shaw et al., 2022 (longitudinal)), spending more time at home (Håkansson, 2020a, 2021 (cross-sectional); Håkansson & Widinghoff, 2021 (cross-sectional)), higher alcohol consumption (Håkansson, 2020a, 2021 (cross-sectional); Håkansson & Widinghoff, 2021 (cross-sectional)), psychological distress (Håkansson, 2020a, 2021 (cross-sectional); Håkansson & Widinghoff, 2021 (cross-sectional)), worry about mental health (Månsson et al., 2021 (longitudinal)), irregular occupation (Håkansson, 2021 (cross-sectional); Håkansson & Widinghoff, 2021 (cross-sectional)), job loss or reduced working hours (Sharman et al., 2022 (cross-sectional)), and playing in more types of gambling (Shaw et al., 2022 (longitudinal)). Starting gambling, instead, resulted positively and significantly associated with younger age and use of cannabis (Lugo et al., 2021 (cross-sectional)).

Focusing on land-based gambling, a strong decrease during the COVID-19 pandemic emerged, even considering different types (land-based casinos, poker, lotteries, EMGs, etc.) (Månsson et al., 2021 (longitudinal)). However, one study reported a very low percentage of subjects who increased their land-based gambling habits, although the decreases were larger (Håkansson, 2021 (cross-sectional)). Another study by the same author conducted in Sweden (where restrictive measures due to COVID-19 pandemic were more lenient) showed that a small percentage of people who started land-based gambling during the pandemic (1 to 3% considering different types of land-based gambling) (Håkansson & Widinghoff, 2021 (cross-sectional)).

Concerning the frequency of online gambling, again studies show different directions. A study shows a strong reduction in online gambling frequency (Mravčík & Chomynová, 2021 (cross-sectional)), although less strong than land-based gambling. Others, however, show a significant increase (Bonny-Noach & Gold, 2021 (cross-sectional)). In addition, a study (Månsson et al., 2021 (longitudinal)) observed a reduction in specific types of online gambling (online casino (table games), online sports betting, land-based horse betting, land-based bingo, online bingo, land-based scratch cards, and land-based number games), and an increase in other types (Online casino (slots), online horses betting, online scratch cards, and online number games). Finally, some studies reported also that a small minority of subjects started online gambling during COVID-19 pandemic (Håkansson, 2021 (cross-sectional); Håkansson & Widinghoff, 2021 (cross-sectional)).

3.4.2 Expenditure

Three studies investigated the impact of the COVID-19 pandemic on gambling expenditure in the general population. The majority of people reported either no changes or a reduction in the amount of money spent on gambling, while the percentage of those reporting an increase in gambling expenditure ranged between 16% and 32% (Månsson et al., 2021 (longitudinal); Shaw et al., 2022 (longitudinal)). Regarding different amounts of money gambled, subjects had a lower probability of weekly gambling in the range of 1-50£, while there were not significant differences when assessing larger amounts (51-200£) (Sharman et al., 2022 (cross-sectional)).

Concerning different types of gambling, higher expenditures were observed for online casino games (slots and table games), electronic gambling machines, online bingo, and land-based scratch cards. Conversely, lower or no changes in the amount of money spent were reported for online poker, land-based gambling, online horse betting, online scratch cards, land-based number games, and sports betting (Månsson et al., 2021 (longitudinal)). Predictors significantly associated with increasing gambling expenditures were greater frequency of overall gambling, online gambling, and lower Problem Gambling Severity Index scores (Shaw et al., 2022 (longitudinal)).

3.5 Gamblers

3.5.1 Frequency

Eighteen different studies assessed the impact of COVID-19 on gambling or identified the main predictors of increasing/decreasing gambling habits among those who gambled at least once before the COVID-19 pandemic.

Regarding overall gambling, the studies indicate that most subjects either maintained their gambling habits or decreased them, while only a minority of gamblers increased their frequency during the SARS-CoV-2 pandemic (Black et al., 2022 (longitudinal); Fluharty et al., 2022 (longitudinal); Gainsbury et al., 2021 (cross-sectional); Lischer et al., 2021 (longitudinal); Otis et al., 2022 (cross-sectional); Rantis et al., 2022 (cross-sectional); Sharman et al., 2022 (cross-sectional)). The percentage of subjects reporting an increase ranged from 7 to 13.6%.

The main predictors of increasing gambling habits identified by the authors were: younger age (Håkansson, 2020a, 2021 (cross-sectional); Lugo et al., 2021 (cross-sectional)), female gender (Håkansson, 2021 (cross-sectional)), high alcohol consumption (Fluharty et al., 2022 (longitudinal); Håkansson, 2020a, 2021 (cross-sectional); Håkansson & Widinghoff, 2021 (cross-sectional); Lugo et al., 2021 (cross-sectional)), cannabis use (Lugo et al., 2021 (cross-sectional)), higher gambling problem severity (Gainsbury et al., 2021 (cross-sectional); Håkansson, 2020a, 2021 (cross-sectional); Håkansson & Widinghoff, 2021 (cross-sectional)), psychological distress (Fluharty et al., 2022 (longitudinal); Håkansson, 2020a, 2021 (cross-sectional); Håkansson & Widinghoff, 2021 (cross-sectional)), anxiety and depression symptoms (Fluharty et al., 2022 (longitudinal); Lugo et al., 2021 (cross-sectional)), and more time spent at home (Håkansson, 2020a, 2021 (cross-sectional)). No clear relationship emerged, however, when considering smoking habit and occupation. Moreover, older age and being an EGM player were identified as predictors of stopping or decreasing gambling (Gainsbury et al., 2021 (cross-sectional); Lugo et al., 2021 (cross-sectional)).

Also focusing on land-based gambling, it was found that the majority of subjects either decreased their frequency or maintained the same pre-pandemic habits. Only a very small percentage of subjects increased the frequency of land-based gambling; nevertheless, these increases ranged from 1% to 6%, which is far below those identified by assessing overall gambling (Alessi et al., 2022 (cross-sectional); Gainsbury et al., 2021 (cross-sectional); Håkansson, 2020a (cross-sectional); Kalke et al., 2022 (cross-sectional); Lischer et al., 2021 (longitudinal); Otis et al., 2022 (cross-sectional); Rantis et al., 2022 (cross-sectional); Wardle et al., 2021 (cross-sectional)).

The characteristics associated with a significant increase in land-based gambling identified by the studies were higher problem severity and spending more time at home (Håkansson, 2020a (cross-sectional)). However, contrasting associations emerged considering younger age and female gender. In fact, according to (Håkansson, 2020a (cross-sectional)), younger age and female gender are predictors of increasing gambling, while for Kalke et al. (Kalke et al., 2022 (cross-sectional)), they are predictors of quitting land-based gambling.

Concerning online gambling, the results are not entirely consistent among the studies. According to some research, online gambling habits remained unchanged or decreased during the COVID-19 pandemic compared to pre-pandemic levels for the majority of subjects (Alessi et al., 2022 (cross-sectional); Bellringer & Garrett, 2021 (longitudinal); Claesdotter-Knutsson & Håkansson, 2021 (cross-sectional); Håkansson, 2020a (cross-sectional); Lischer et al., 2021 (longitudinal); Wardle et al., 2021 (cross-sectional)). However, the reported increase in online gambling in these studies reached as high as 27% in some cases, much higher than that recorded in the case of land-based gambling. On the contrary, according to other studies, an overall increase in online gambling was reported (Balem et al., 2023 (longitudinal);

Emond et al., 2022 (longitudinal)). However, when considering the different types of online gambling, only online betting did not show a significant increase (Emond et al., 2022 (longitudinal)).

The most important predictors of increasing online gambling were: higher level of education (Bellringer & Garrett, 2021 (longitudinal)), greater gambling severity problem (Claesdotter-Knutsson & Håkansson, 2021 (cross-sectional); Håkansson, 2020a (cross-sectional)), high alcohol consumption (Bellringer & Garrett, 2021 (longitudinal)), and higher stress level (Claesdotter-Knutsson & Håkansson, 2021 (cross-sectional)). No clear associations were found for age and gender. Finally, being a regular sports bettor seemed to decrease the risk of gambling online more (Gainsbury et al., 2021 (cross-sectional)).

3.5.2 Expenditure

Five different studies investigated the impact of COVID-19 on gambling expenditure among those who gambled in the pre-pandemic period.

The results showed that overall and land-based gambling expenditure decreased significantly during the SARS-CoV-2 pandemic (Otis et al., 2022 (cross-sectional); Sharman et al., 2022 (cross-sectional)), especially when assessing sports betting (Auer et al., 2023 (longitudinal); Balem et al., 2023 (longitudinal); Otis et al., 2022 (cross-sectional)). However, regarding online gambling expenditure, one study reported a significant increase, especially considering online casino, bingo, and poker (Balem et al., 2023 (longitudinal)), while two studies found a decrease in money wagered (Auer et al., 2023 (longitudinal); Auer & Griffiths, 2022 (longitudinal)). However, results changed considering gambling intensity: for low-intensity gamblers, the daily amount of money wagered was larger during the COVID-19 pandemic, while for high-intensity gamblers, there emerged a significant decrease in the daily bet (Auer & Griffiths, 2022 (longitudinal)).

Another characteristic for which gambling expenditure seemed to change was gender. According to Balem et al. (Balem et al., 2023 (longitudinal)), women wagered higher amounts of money in online casino and online bingo, while men wagered more in online poker.

3.5.3 Transitions among different types of gambling.

Six different studies assessed transitions among possible gambling types during the COVID-19 pandemic. Two authors focused on land-based-only gamblers. According to these studies (Kalke et al., 2022 (cross-sectional); Shaw et al., 2022 (longitudinal)), only a minority of subjects migrated to online gambling during COVID-19 (8% and 17.6%, respectively). Instead, most subjects preferred to either stop gambling or remain consistent with their previous habits. Among the different types of gamblers, especially sports bettors or casino gamblers switched to online gambling. The variables that were found to be associated with the transition to online gambling services were younger age, high gambling frequency, a history of problem gambling during the pre-pandemic period, and cognitive distortions (Kalke et al., 2022 (cross-sectional)).

Three studies, instead, assessed the transitions in gambling of sports bettors. The results showed that the majority of sports bettors either stopped participating or decreased their gambling habits due to the reduced sports betting market (Håkansson, 2020a (cross-sectional); Håkansson et al., 2020 (cross-sectional); Wardle et al., 2021 (cross-sectional)). However, small percentages of people switched to other types of gambling, in particular lotteries, online betting on virtual sports, online casinos, and horse betting. Finally, the last study assessing this outcome revealed a significant change in the place of gambling during COVID-19. Specifically, there was a transition from land-based venues to online, with individuals gambling at home or using smartphone and tablet apps (Rantis et al., 2022 (cross-sectional)).

4. DISCUSSION

The spread of COVID-19 has led to significant changes in people's behaviors in social, occupational, and lifestyle aspects, including a shift in gambling habits. This systematic review aimed to evaluate the impact of the COVID-19 pandemic on the diffusion and evolution of gambling, focusing on three different outcomes: frequency, expenditure, and transitions among different types of gambling.

The first important result of this systematic review was that a significant reduction in the frequency and expenditure of land-based gambling emerged ((Lischer et al., 2021; Lugo et al., 2021; Månsson et al., 2021; Rantis et al., 2022; Wardle et al., 2021). The main reason for the strong decline observed in land-based gambling is the physical closure of many land-based gambling business activities such as casinos and betting stores, and the resulting restrictions imposed on citizens, prohibiting them from leaving their homes except for strictly essential reasons (Ghaharian et al., 2021; Zhang et al., 2023).

However, the evidence concerning online gambling is more complex, with some studies reporting an increase (Bonny-Noach & Gold, 2021; Shaw et al., 2022), and other a clear and significant decrease in sports betting but a notable increase in online casino activities and skill games (Balem et al., 2023; Månsson et al., 2021; Wardle et al., 2021). The possible reasons leading to an increase in online gambling include the increased time spent at home during the more challenging phases of the pandemic (McQuade & Gill, 2020; Savolainen et al., 2020) and the worsened mental state of individuals, characterized by higher levels of anxiety, depression, and stress during this challenging period (Rossi et al., 2020; Santomauro et al., 2021). In fact, the implementation of lockdown measures caused a sudden disruption of daily routines, economic uncertainty, fears about personal and loved ones' health, and social isolation, particularly for those living alone or separated from their support networks. This had a great impact on health mental well-being of individuals. These exacerbating mental health issues during the pandemic contributed to risky behaviors, such as alcohol consumption, tobacco smoking, and also gambling (Barrault et al., 2017; Huțul & Karner-Huțuleac, 2022; Zhao et al., 2023). Focusing on sports betting, instead, the observed decline was mainly influenced by the massive cancellation or suspension of events during the first phase of the COVID-19 pandemic period (Lindner et al., 2020; Russell et al., 2023), which made it impossible to bet on major sporting events that individuals used to bet on before COVID-19, such as football, baseball, basketball, tennis, and volleyball.

Another important result is the apparent migration of people from land-based points to online platforms (Kalke et al., 2022; Rantis et al., 2022; Shaw et al., 2022). These migrated gamblers had no differences in gambling habits (i.e., those who were used to playing slot machines in land-based points moved to online slot machines, and those who were used to playing casino games in land-based points moved to online casino games), although a decrease in frequency and an increase in expenditure arose from studies (Månsson et al., 2021). One possible explanation for the failure to initiate new online gambling habits might be in the type of people: individuals who played video poker or sports betting tended to be younger, better educated, and more knowledgeable about the dynamics of these games (Gainsbury et al., 2014; Holmes, 2005).

In general, the studies included in this systematic review suggested that the most vulnerable segments of the population, including the unemployed or precarious workers, individuals with mental health issues, and those prone to alcohol (or other substances) consumption problems, were the most affected by the restrictions. The increase in free time resulting from stay-at-home measures exacerbated addictions and mental health problems (Breslau et al., 2021; Rolland et al., 2020; Rossi et al., 2020; Santomauro et al., 2021). Consequently, these groups experienced a worsening of their conditions during the pandemic, and individuals with a pathological addiction faced an elevated risk of relapse to due to the limitations imposed by stay-at-home measures and the resulting greater desire (Alessi et al., 2022). Within this context, these vulnerable groups of people were more prone to an increase in their gambling frequency.

Focusing on individuals accustomed to gambling before the outbreak, some studies of this review highlighted a surge in both the frequency and expenditure of online gambling activities, which is probably attributed to the increase in leisure time spent at home. Additionally, the review also emphasizes unchanged habits regarding the types of games played and an increase in the amount of money spent (Bonny-Noach & Gold, 2021).

Another significant aspect concerns the impact of the COVID-19 pandemic on younger populations. During the most severe phase of the pandemic, restrictions are known to have significantly impacted the mental and physical well-being of younger segments of the population. The closure of schools and universities along with restrictions on social gathering resulted in a substantial increase in the time spent at home by young people, leading to heightened levels of anxiety, depression, and frustration (Lee et al., 2021; Sundler et al., 2023; Volpe et al., 2022). In this context, adolescents' technological proficiency played a key role in maintaining distant social relationships with friends, through the use of social media and online games. However, this proficiency also led to negative implications and internet addiction. Gambling is one of these possible implications: accessibility to online gaming platforms, coupled with available free time and the attractiveness of possible monetary winnings, has contributed to an increase in gambling among young people. Nevertheless, it is important to note that the results are not entirely consistent across the studies included in this review (Claesdotter-Knutsson & Håkansson, 2021;

Gainsbury et al., 2021; Håkansson, 2020a; Håkansson & Widinghoff, 2021; Kalke et al., 2022; Lugo et al., 2021).

Finally, inconsistent results emerged considering gender: while some articles evidenced a decrease in gambling for both males and females, others evidenced an increase in expenditure for women. Otherwise, some differences in the type of games played arose: women seemed to be more prone to casino and bingo, while men spent more time on poker games.

As we move forward, potential future directions could involve conducting systematic research into not only the effect of COVID-19 on gambling behavior but also exploring its impacts on other addictions or problematic habits prevalent among individuals. This broader scope of investigation could offer valuable insights into the multifaceted impacts of the pandemic on various aspects of human behavior and mental health, ultimately aiding in the development of comprehensive strategies for intervention and support, especially to the most vulnerable subjects.

5. LIMITATIONS AND STRENGTHS

This systematic review has some limitations. Firstly, it was conducted across all countries, without considering possible differences in the restrictive measures implemented by local governments to limit the spread of COVID-19 and how gambling was regulated, both of which may differ from country to country. Another aspect is that this review did not assess studies that assessed illegal gambling and its evolution in the pandemic period. in the literature, there is a lack of information about this topic, and due to this fact, this systematic review gives no information about it. An additional limitation regarding, in this case, the studies included in this systematic review, pertains to the fact that a substantial portion of them had an insufficient sample size and did not provide information on the response rates. Moreover, several papers included might be subject to bias due to questionnaire completion. First of all, responses regarding the amount of time and money spent on gambling in the pre-pandemic period may be affected by recall bias. Secondly, many studies provided a reward (monetary or in the form of points convertible into money), potentially leading respondents to provide wrong answers in pursuit of compensation (information bias).

However, this systematic review has several strengths. The first lies in its systematic approach, following protocol registration, and adhering to all typical rules associated with such reviews. The second major strength is that it is the first comprehensive systematic review of the impact of the COVID-19 pandemic on gambling. It deepened various aspects, including frequency, expenditure, and the transition between different forms of gambling.

6. CONCLUSIONS

During the COVID-19 pandemic period, a significant reduction in land-based gambling emerged, due to physical closures imposed by local governments and the cancelation of most important sports events. Furthermore, this period seemed to cause a troubling escalation in the risks associated with online gambling, with frequent transitions from land-based to online gambling especially among those who gambled before the pandemic period, due to a confluence of factors, including more time spent at home and an increase in anxiety, stress, and depression levels. With less stigma attached to digital gambling activities, individuals were more inclined to explore these platforms as a source of entertainment and escape during periods of isolation. The dangerousness of this instrument was amplified by the easy accessibility and the allure of potential financial gains, making online gambling a precarious endeavor. Moreover, the association between online gambling and mental health concerns was more pronounced, as the stress and uncertainties of the pandemic drove individuals toward these potentially harmful outlets. The increased habit of online gambling contributed to reduced personal relationships, as individuals might become engrossed in virtual pursuits at the expense of real-world connections. This shift toward negative lifestyles poses significant challenges, requiring a thoughtful and comprehensive approach to monitor and mitigate the negative consequences of this increase in online gambling caused by the pandemic.

Therefore, this systematic review suggests the need for stricter regulation and enhanced monitoring of online gambling, especially during time of crisis like the COVID-19 pandemic. This is crucial to protect players and the most vulnerable subgroups and to mitigate issues associated with compulsive gambling.

Conflict of Interests

The authors declare no conflict of interests.

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Data availability

All tables and figures are original and were produced by the authors for this publication for the first time.

7. REFERENCES

Alessi, M. C., Martinotti, G., De Berardis, D., Sociali, A., Di Natale, C., Sepede, G., Cheffo, D. P. R., Monti, L., Casella, P., Pettorruso, M., Sensi, S., & Di Giannantonio, M. (2022). Craving variations in patients with substance use disorder and gambling during COVID-19 lockdown: The Italian experience. *World Journal of Clinical Cases*, *10*(3), 882–890. https://doi.org/10.12998/wjcc.v10.i3.882

Alshammari, S., & Goto, S. (2022). Are lottery-like stocks overvalued in markets that have no lotteries?–Evidence from Saudi Arabia. *Finance Research Letters*, *46*, 102460. https://doi.org/10.1016/j.frl.2021.102460

Amerio, A., Stival, C., Lugo, A., Fanucchi, T., Gorini, G., Pacifici, R., Odone, A., Serafini, G., & Gallus, S. (2022). COVID-19 lockdown: The relationship between trait impulsivity and addictive behaviors in a large representative sample of Italian adults. *Journal of Affective Disorders*, *302*, 424–427. https://doi.org/10.1016/j.jad.2022.01.094

Atherton, F., & Beynon, C. (2019). Is gambling an emerging public health issue for Wales, UK? *Journal of Public Health*, *41*(4), 858–863. https://doi.org/10.1093/pubmed/fdy164

Auer, M., & Griffiths, M. D. (2022). Gambling Before and During the COVID-19 Pandemic Among Online Casino Gamblers: An Empirical Study Using Behavioral Tracking Data. *International Journal of Mental Health and Addiction*, *20*(3), 1722–1732. https://doi.org/10.1007/s11469-020-00462-2

Auer, M., Malischnig, D., & Griffiths, M. D. (2023). Gambling Before and During the COVID-19 Pandemic Among European Regular Sports Bettors: An Empirical Study Using Behavioral Tracking Data. *International Journal of Mental Health and Addiction*, *21*(1), 20–27. https://doi.org/10.1007/s11469-020-00327-8

Balem, M., Karlsson, A., Widinghoff, C., Perrot, B., Challet-Bouju, G., & Håkansson, A. (2023). Gambling and COVID-19: Swedish national gambling data from a state-owned gambling sports and casino operator. *Journal of Behavioral Addictions*, *12*(1), 230–241. https://doi.org/10.1556/2006.2022.00089

Barrault, S., Bonnaire, C., & Herrmann, F. (2017). Anxiety, Depression and Emotion Regulation Among Regular Online Poker Players. *Journal of Gambling Studies*, *33*(4), 1039–1050. https://doi.org/10.1007/s10899-017-9669-3

Bastiani, L., Gori, M., Colasante, E., Siciliano, V., Capitanucci, D., Jarre, P., & Molinaro, S. (2013). Complex Factors and Behaviors in the Gambling Population of Italy. *Journal of Gambling Studies*, *29*(1), 1–13. https://doi.org/10.1007/s10899-011-9283-8

Bellringer, M. E., & Garrett, N. (2021). Risk Factors for Increased Online Gambling during COVID-19 Lockdowns in New Zealand: A Longitudinal Study. *International Journal of Environmental Research and Public Health*, *18*(24). https://doi.org/10.3390/ijerph182412946

Binde, P. (2013). *Gambling in Sweden: The cultural and socio-political context—Binde—2014—Addiction—Wiley Online Library*. *109*(2), 193–198. https://doi.org/10.1111/add.12103

Black, N., Swanton, T. B., Burgess, M. T., & Gainsbury, S. M. (2022). Impact of Gambling Supply Reduction During COVID-19 Shutdowns on Gambling Problems and Gambling Behaviour in Australia: A National Longitudinal Study. *Journal of Gambling Studies*, *38*(2), 353–365. https://doi.org/10.1007/s10899-021-10067-6

Bonny-Noach, H., & Gold, D. (2021). Addictive behaviors and craving during the COVID-19 pandemic of people who have recovered from substance use disorder. *Journal of Addictive Diseases*, *39*(2), 257–264. https://doi.org/10.1080/10550887.2020.1856298

Breslau, J., Finucane, M. L., Locker, A. R., Baird, M. D., Roth, E. A., & Collins, R. L. (2021). A longitudinal study of psychological distress in the United States before and during the COVID-19 pandemic. *Preventive Medicine*, *143*, 106362. https://doi.org/10.1016/j.ypmed.2020.106362

Brodeur, M., Audette-Chapdelaine, S., Savard, A.-C., & Kairouz, S. (2021). Gambling and the COVID-19 pandemic: A scoping review. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *111*, 110389. https://doi.org/10.1016/j.pnpbp.2021.110389

Buchanan, T. W., McMullin, S. D., Baxley, C., & Weinstock, J. (2020). Stress and gambling. *Current Opinion in Behavioral Sciences*, *31*, 8–12. https://doi.org/10.1016/j.cobeha.2019.09.004

Caramello, V., Catalano, A., Macciotta, A., Dansero, L., Sacerdote, C., Costa, G., Aprà, F., Tua, A., Boccuzzi, A., & Ricceri, F. (2022). Improvements throughout the Three Waves of COVID-19 Pandemic: Results from 4 Million Inhabitants of North-West Italy. *Journal of Clinical Medicine*, *11*(15), 4304. https://doi.org/10.3390/jcm11154304

Casale, S., Akbari, M., Seydavi, M., Bocci Benucci, S., Fioravanti, G. (2023). Has the prevalence of problematic social media use increased over the past seven years and since the start of the COVID-19 pandemic? A meta-analysis of the studies published since the development of the Bergen social media addiction scale. *Addictive Behaviors*. 147:107838. doi: 10.1016/j.addbeh.2023.107838.

Cataldo, I., Casonato, E., Levari, E., Negri, A., Simonato, P., Tomasi, G., Branz, G., Coppola, A., Gianfranceschi, P., Leoni, E., Mistretta, P., Stefani, M., Vanzetta, M., Franceschini, A., Esposito, G., & Corazza, O. (2022). Gambling at the time of COVID-19: Results from interviews in an Italian sample of gamblers. *Emerging Trends in Drugs, Addictions, and Health*, *2*, 100032. https://doi.org/10.1016/j.etdah.2022.100032

Claesdotter-Knutsson, E., & Håkansson, A. (2021). Changes in Self-Reported Web-Based Gambling Activity During the COVID-19 Pandemic: Cross-sectional Study. *JMIR Serious Games*, *9*(4), e30747. https://doi.org/10.2196/30747

Emond, A., Nairn, A., Collard, S., & Hollén, L. (2022). Gambling by Young Adults in the UK During COVID-19 Lockdown. *Journal of Gambling Studies*, *38*(1), 1–13. https://doi.org/10.1007/s10899-021-10029-y

Fluharty, M., Paul, E., & Fancourt, D. (2022). Predictors and patterns of gambling behaviour across the COVID-19 lockdown: Findings from a UK cohort study. *Journal of Affective Disorders*, *298*(Pt A), 1–8. https://doi.org/10.1016/j.jad.2021.10.117

Gainsbury, S. M., Russell, A., & Hing, N. (2014). An investigation of social casino gaming among land-based and Internet gamblers: A comparison of socio-demographic characteristics, gambling and co-morbidities. *Computers in Human Behavior*, *33*, 126–135. https://doi.org/10.1016/j.chb.2014.01.031

Gainsbury, S. M., Swanton, T. B., Burgess, M. T., & Blaszczynski, A. (2021). Impacts of the COVID-19 Shutdown on Gambling Patterns in Australia: Consideration of Problem Gambling and Psychological Distress. *Journal of Addiction Medicine*, *15*(6), 468–476. https://doi.org/10.1097/ADM.0000000000000793

Ghaharian, K., Abarbanel, B., Soligo, M., & Bernhard, B. (2021). Crisis management practices in the hospitality and gambling industry during COVID-19. *International Hospitality Review*, *35*(2), 171–194. https://doi.org/10.1108/IHR-08-2020-0037

Gjoneska, B., Potenza, M. N., Jones, J., Corazza, O., Hall, N., Sales, C. M. D., Grünblatt, E., Martinotti, G., Burkauskas, J., Werling, A. M., Walitza, S., Zohar, J., Menchón, J. M., Király, O., Chamberlain, S. R., Fineberg, N. A., & Demetrovics, Z. (2022). Problematic use of the internet during the COVID-19 pandemic: Good practices and mental health recommendations. *Comprehensive Psychiatry*, *112*, 152279. https://doi.org/10.1016/j.comppsych.2021.152279

Håkansson, A. (2020a). Changes in Gambling Behavior during the COVID-19 Pandemic-A Web Survey Study in Sweden. *International Journal of Environmental Research and Public Health*, *17*(11). https://doi.org/10.3390/ijerph17114013

Håkansson, A. (2020b). Effects on Gambling Activity From Coronavirus Disease 2019-An Analysis of Revenue-Based Taxation of Online- and Land-Based Gambling Operators During the Pandemic. *Frontiers in Psychiatry*, *11*, 611939. https://doi.org/10.3389/fpsyt.2020.611939

Håkansson, A. (2021). Gambling and self-reported changes in gambling during COVID-19 in web survey respondents in Denmark. *Heliyon*, *7*(7), e07506. https://doi.org/10.1016/j.heliyon.2021.e07506

Håkansson, A., Jönsson, C., & Kenttä, G. (2020). Psychological Distress and Problem Gambling in Elite Athletes during COVID-19 Restrictions-A Web Survey in Top Leagues of Three Sports during the Pandemic. *International Journal of Environmental Research and Public Health*, *17*(18). https://doi.org/10.3390/ijerph17186693

Håkansson, A., & Widinghoff, C. (2021). Changes of Gambling Patterns during COVID-19 in Sweden, and Potential for Preventive Policy Changes. A Second Look Nine Months into the Pandemic. *International Journal of Environmental Research and Public Health*, *18*(5). https://doi.org/10.3390/ijerph18052342

Holmes, N. (2005). Digital Technology, Age, and Gaming. *Computer*, *38*(11), 108–107. https://doi.org/10.1109/MC.2005.376

Huțul, T.-D., & Karner-Huțuleac, A. (2022). The Level of Gambling Prediction Using Depression and Anxiety in the Romanian Population. *Journal of Gambling Studies*, *38*(2), 653–662. https://doi.org/10.1007/s10899-021-10051-0

Kalke, J., Schütze, C., Lahusen, H., & Buth, S. (2022). Parameters for Change in Offline Gambling Behavior After the First COVID-19 Lockdown in Germany. *Frontiers in Psychology*, *13*, 857234. https://doi.org/10.3389/fpsyg.2022.857234

Kessler, R. C., Hwang, I., LaBrie, R., Petukhova, M., Sampson, N. A., Winters, K. C., & Shaffer, H. J. (2008). DSM-IV pathological gambling in the National Comorbidity Survey Replication. *Psychological Medicine*, *38*(9), 1351–1360. https://doi.org/10.1017/S0033291708002900

Lee, J., Solomon, M., Stead, T., Kwon, B., & Ganti, L. (2021). Impact of COVID-19 on the mental health of US college students. *BMC Psychology*, *9*(1), 95. https://doi.org/10.1186/s40359-021-00598-3

Lindner, P., Forsström, D., Jonsson, J., Berman, A. H., & Carlbring, P. (2020). Transitioning Between Online Gambling Modalities and Decrease in Total Gambling Activity, but No Indication of Increase in Problematic Online Gambling Intensity During the First Phase of the COVID-19 Outbreak in Sweden: A Time Series Forecast Study. *Frontiers in Public Health*, *8*, 554542. https://doi.org/10.3389/fpubh.2020.554542

Lischer, S., Steffen, A., Schwarz, J., & Mathys, J. (2021). The Influence of Lockdown on the Gambling Pattern of Swiss Casinos Players. *International Journal of Environmental Research and Public Health*, *18*(4). https://doi.org/10.3390/ijerph18041973

Luchini, C., Stubbs, B., Solmi, M., & Veronese, N. (2017). Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. *World Journal of Meta-Analysis*, *5*(4), 80–84. https://doi.org/10.13105/wjma.v5.i4.80

Lugo, A., Stival, C., Paroni, L., Amerio, A., Carreras, G., Gorini, G., Mastrobattista, L., Minutillo, A., Mortali, C., Odone, A., Pacifici, R., Tinghino, B., & Gallus, S. (2021). The impact of COVID-19 lockdown on gambling habit: A cross-sectional study from Italy. *Journal of Behavioral Addictions*, *10*(3), 711–721. https://doi.org/10.1556/2006.2021.00033

Månsson, V., Wall, H., Berman, A. H., Jayaram-Lindström, N., & Rosendahl, I. (2021). A Longitudinal Study of Gambling Behaviors During the COVID-19 Pandemic in Sweden. *Frontiers in Psychology*, *12*, 708037. https://doi.org/10.3389/fpsyg.2021.708037

Mathews, M., & Volberg, R. (2013). Impact of problem gambling on financial, emotional and social well-being of Singaporean families. *International Gambling Studies*, *13*(1), 127–140. https://doi.org/10.1080/14459795.2012.731422

Mattar, M. Y. (2020). A Code of Conduct for Tourists Visiting Qatar for the World Cup 2022. *International Review of Law*, *2019*(3), Article 3. https://doi.org/10.29117/irl.2019.0079

McGuinness, L. A., & Higgins, J. P. T. (2021). Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods*, *12*(1), 55–61. https://doi.org/10.1002/jrsm.1411

McQuade, A., & Gill, P. (2020). The role of loneliness and self-control in predicting problem gambling behaviour. *Gambling Research: Journal of the National Association for Gambling Studies (Australia)*, *24*(1), 18–30. https://doi.org/10.3316/informit.859155913483693

Mravčík, V., & Chomynová, P. (2021). Substance use and addictive behaviours during COVID-19 confinement measures increased in intensive users: Results of an online general population survey in the Czech Republic. *Epidemiologie, Mikrobiologie, Imunologie : Casopis Spolecnosti pro Epidemiologii a Mikrobiologii Ceske Lekarske Spolecnosti J.E. Purkyne*, *70*(2), 98–103.

Otis, E., Kim, A. J., Stewart, S. H., Sherry, S. B., & Yakovenko, I. (2022). Changes in sports gambling behavior during the COVID-19 pandemic in Canada. *Frontiers in Psychiatry*, *13*, 1018234. https://doi.org/10.3389/fpsyt.2022.1018234

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)*, *372*, n71. https://doi.org/10.1136/bmj.n71

Pérez-Albéniz, A., Nuez, C., Lucas-Molina, B., Ezquerra, M., & Fonseca-Pedrero, E. (2022). Impact of lockdown on the addictive behavior of university students in La Rioja. *Adicciones*, *0*(0), 1646. https://doi.org/10.20882/adicciones.1646

Quinn, A., Grant, JE., Chamberlain SR. (2022). COVID-19 and resultant restrictions on gambling behaviour. *Neuroscience & Biobehavioral Reviews.* 143:104932. doi: 0.1016/j.neubiorev.2022.104932.

Rajkumar, R. P. (2020). COVID-19 and mental health: A review of the existing literature. *Asian Journal of Psychiatry*, *52*, 102066. https://doi.org/10.1016/j.ajp.2020.102066

Rantis, K., Panagiotidis, P., Parlapani, E., Holeva, V., Tsapakis, E. M., & Diakogiannis, I. (2022). Substance use during the COVID-19 pandemic in Greece. *Journal of Substance Use*, *27*(3), 231–238. CINAHL Complete. https://doi.org/10.1080/14659891.2021.1941344

Rodda, S. N., Park, J. J., Wilkinson-Meyers, L., & King, D. L. (2022). The impact of COVID-19 on addiction treatment in New Zealand. *Addictive Behaviors*, *127*, 107230. https://doi.org/10.1016/j.addbeh.2021.107230

Rolland, B., Haesebaert, F., Zante, E., Benyamina, A., Haesebaert, J., & Franck, N. (2020). Global Changes and Factors of Increase in Caloric/Salty Food Intake, Screen Use, and Substance Use During the Early COVID-19 Containment Phase in the General Population in France: Survey Study. *JMIR Public Health and Surveillance*, *6*(3), e19630. https://doi.org/10.2196/19630

Rossi, R., Socci, V., Talevi, D., Mensi, S., Niolu, C., Pacitti, F., Di Marco, A., Rossi, A., Siracusano, A., & Di Lorenzo, G. (2020). COVID-19 Pandemic and Lockdown Measures Impact on Mental

Health Among the General Population in Italy. *Frontiers in Psychiatry*, *11*. https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00790

Russell, A. M. T., Hing, N., Bryden, G. M., Thorne, H., Rockloff, M. J., & Browne, M. (2023). Gambling advertising on Twitter before, during and after the initial Australian COVID-19 lockdown. *Journal of Behavioral Addictions*, *12*(2), 557–570. https://doi.org/10.1556/2006.2023.00020

Saglietto, A., D'Ascenzo, F., Zoccai, G. B., & De Ferrari, G. M. (2020). COVID-19 in Europe: The Italian lesson. *Lancet (London, England)*, *395*(10230), 1110–1111. https://doi.org/10.1016/S0140-6736(20)30690-5

Salerno, L., & Pallanti, S. (2021). COVID-19 Related Distress in Gambling Disorder. *Frontiers in Psychiatry*, *12*, 620661. https://doi.org/10.3389/fpsyt.2021.620661

Santomauro, D. F., Herrera, A. M. M., Shadid, J., Zheng, P., Ashbaugh, C., Pigott, D. M., Abbafati, C., Adolph, C., Amlag, J. O., Aravkin, A. Y., Bang-Jensen, B. L., Bertolacci, G. J., Bloom, S. S., Castellano, R., Castro, E., Chakrabarti, S., Chattopadhyay, J., Cogen, R. M., Collins, J. K., … Ferrari, A. J. (2021). Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *The Lancet*, *398*(10312), 1700–1712. https://doi.org/10.1016/S0140-6736(21)02143-7

Savolainen, I., Oksanen, A., Kaakinen, M., Sirola, A., & Paek, H.-J. (2020). The Role of Perceived Loneliness in Youth Addictive Behaviors: Cross-National Survey Study. *JMIR Mental Health*, *7*(1), e14035. https://doi.org/10.2196/14035

Sharman, S., Roberts, A., Bowden-Jones, H., & Strang, J. (2022). Gambling and COVID-19: Initial Findings from a UK Sample. *International Journal of Mental Health and Addiction*, *20*(5), 2743–2754. https://doi.org/10.1007/s11469-021-00545-8

Shaw, C. A., Hodgins, D. C., Williams, R. J., Belanger, Y. D., Christensen, D. R., El-Guebaly, N., McGrath, D. S., Nicoll, F., Smith, G. J., & Stevens, R. M. G. (2022). Gambling in Canada During the COVID Lockdown: Prospective National Survey. *Journal of Gambling Studies*, *38*(2), 371–396. https://doi.org/10.1007/s10899-021-10073-8

Smith, E., Michalski, S., Knauth, K. H. K., Kaspar, K., Reiter, N., & Peters, J. (2023). Large-Scale Web Scraping for Problem Gambling Research: A Case Study of COVID-19 Lockdown Effects in Germany. *Journal of Gambling Studies*, *39*(3), 1487–1504. CINAHL Complete. https://doi.org/10.1007/s10899-023-10187-1

Sundler, A. J., Bergnehr, D., Haffejee, S., Iqbal, H., Orellana, M. F., Vergara Del Solar, A., Angeles, S. L., Faircloth, C., Liu, L., Mwanda, A., Sepúlveda Galeas, M., Simelane, T., Twamley, K., & Darcy, L. (2023). Adolescents' and young people's experiences of social relationships and health concerns during COVID-19. *International Journal of Qualitative Studies on Health and Well-Being*, *18*(1), 2251236. https://doi.org/10.1080/17482631.2023.2251236

Thomas, S. L., McKee, M., & Daube, M. (2023). Gambling reform in the UK. *BMJ*, *381*, p1026. https://doi.org/10.1136/bmj.p1026

Tucker, W., Garn, J. V., & Yang, W. (2021). *Relationship between Adverse Childhood Experiences and Gambling i...: Ingenta Connect*. *45*(2), 246–255. https://doi.org/10.5993/AJHB.45.2.5

Velasco, V., Scattola, P., Gavazzeni, L., Marchesi, L., Nita, I. E., & Giudici, G. (2021). Prevention and Harm Reduction Interventions for Adult Gambling at the Local Level: An Umbrella Review of Empirical Evidence. *International Journal of Environmental Research and Public Health*, *18*(18), 9484. https://doi.org/10.3390/ijerph18189484

Volpe, U., Orsolini, L., Salvi, V., Albert, U., Carmassi, C., Carrà, G., Cirulli, F., Dell'Osso, B., Luciano, M., Menculini, G., Nanni, M. G., Pompili, M., Sani, G., Sampogna, G., Group, W., & Fiorillo, A. (2022). COVID-19-Related Social Isolation Predispose to Problematic Internet and Online Video Gaming Use in Italy. *International Journal of Environmental Research and Public Health*, *19*(3), Article 3. https://doi.org/10.3390/ijerph19031539

Wardle, H., Donnachie, C., Critchlow, N., Brown, A., Bunn, C., Dobbie, F., Gray, C., Mitchell, D., Purves, R., Reith, G., Stead, M., & Hunt, K. (2021). The impact of the initial Covid-19 lockdown upon regular sports bettors in Britain: Findings from a cross-sectional online study. *Addictive Behaviors*, *118*, N.PAG-N.PAG. CINAHL Complete. https://doi.org/10.1016/j.addbeh.2021.106876

Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P. (2000). *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Retrieved January 30, 2024, from https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Winslow, M., Cheok, C., & Subramaniam, M. (2015). Gambling in Singapore: An overview of history, research, treatment and policy. *Addiction*, *110*(9), 1383–1387. https://doi.org/10.1111/add.12931

World Health Organization. (2020). *Coronavirus disease (COVID-19) pandemic*. Retrieved January 30, 2024, from https://www.who.int/europe/emergencies/situations/covid-19

Zhang, T., Seet, P.-S., Redmond, J., & Sharafizad, J. (2023). Relieving the Gambling Itch Through Alcohol Consumption: The Impact of COVID-19 Restrictions on Australian Casino Patrons. *Journal of Gambling Studies*. https://doi.org/10.1007/s10899-023-10252-9

Zhao, Z., Li, L., & Sang, Y. (2023). The COVID-19 pandemic increased poor lifestyles and worsen mental health: A systematic review. *American Journal of Translational Research*, *15*(5), 3060–3066.

Zhu, C., Zhang, T., Li, Q., Chen, X., & Wang, K. (2023). Depression and Anxiety During the COVID-19 Pandemic: Epidemiology, Mechanism, and Treatment. *Neuroscience Bulletin*, *39*(4), 675–684. https://doi.org/10.1007/s12264-022-00970-2

Supplementary Table 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	pp. 3-4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	pp. 4-5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p. 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p. 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	pp. 4-5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	pp. 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	pp. 5-6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p. 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p. 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p. 5

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p. 5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p. 6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary Table 1
Study characteristics	17	Cite each included study and present its characteristics.	pp. 7-11
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	pp. 11-13
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	pp. 13-17
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	pp. 7-17
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	pp. 13-17
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	pp. 13-17
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	pp. 13-17
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	pp 13-17
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	pp. 17-19
	23b	Discuss any limitations of the evidence included in the review.	pp. 19-20
	23c	Discuss any limitations of the review processes used.	pp. 19-20
	23d	Discuss implications of the results for practice, policy, and future research.	pp. 19-20
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p. 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p. 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	p. 4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p. 20
Competing interests	26	Declare any competing interests of review authors.	p. 20
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	None

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary Table 2. Reasons for exclusion of reports excluded during text screening phase

First author	Title	Year of Publication	Reason for exclusion
L. Albertella (Albertella et al., 2021)	The Influence of Trait Compulsivity and Impulsivity on Addictive and Compulsive Behaviors During COVID-19.	2021	Outcome
Z. Alimoradi (Alimoradi et al., 2022)	Estimation of Behavioral Addiction Prevalence During COVID-19 Pandemic: A Systematic Review and Meta-analysis.	2022	Qualitative study
MJ. Andersson (Andersson et al., 2022)	An interrupted time series analysis of gambling behavior based on gambling operator revenue-based taxation during the COVID-19 pandemic in Sweden	2022	The statistical units are not the individuals
N. Avena (Avena et al., 2021)	Substance Use Disorders and Behavioral	2021	Qualitative study

	Addictions During the COVID-19 Pandemic and COVID-19-Related Restrictions.		
N. Azevedo (Azevedo et al., 2023)	Gambling Disorder among Porto's University Students.	2023	Outcome
E. Bouza (Bouza et al., 2023)	Impact of the COVID-19 pandemic on the mental health of the general population and health care workers.	2023	Qualitative study
M. Brodeur (Brodeur et al., 2021b)	Gambling and the COVID-19 pandemic in the province of Quebec (Canada): protocol for a mixed-methods study.	2021	Qualitative study
M. Brodeur (Brodeur et al., 2021a)	Gambling and the COVID-19 pandemic: A scoping review.	2021	Qualitative study
M. Brodeur (Brodeur et al., 2023)	Experience of LGBTQIA2S+ populations with gambling during the COVID-19	2023	Qualitative study

	pandemic: protocol for a mixed-methods study.		
I. Cataldo (Cataldo et al., 2022)	Gambling at the time of COVID-19: Results from interviews in an Italian sample of gamblers.	2022	High risk of bias
M. Chóliz (Chóliz, 2023a)	Crisis, What Crisis? The Effect of Economic Crises on Spending on Online and Offline Gambling in Spain: Implications for Preventing Gambling Disorder.	2023	Analyses in a period when restrictive measures due to pandemic were absent or limited
M. Chóliz (Chóliz, 2023b)	Is gambling like a virus?: A conceptual framework and proposals based on empirical data for the prevention of gambling addiction.	2023	Analyses in a period when restrictive measures due to pandemic were absent or limited
E. Claesdotter-Knutsson (Claesdotter-Knutsson et al., 2022)	Gaming Activity and Possible Changes in Gaming Behavior Among Young People During the COVID-19	2022	Outcome

	Pandemic: Cross-sectional Online Survey Study.		
W. DeCamp (DeCamp & Daly, 2023)	Loot box consumption by adolescents pre- and post-pandemic lockdown.	2023	Analyses in a period when restrictive measures due to pandemic were absent or limited
MA. Donati (Donati et al., 2021)	Being a Gambler during the COVID-19 Pandemic: A Study with Italian Patients and the Effects of Reduced Exposition.	2021	Outcome
Y. Efrati (Efrati & Spada, 2022)	Self-perceived substance and behavioral addictions among Jewish Israeli adolescents during the COVID-19 pandemic.	2022	Outcome
A. Englund (Englund et al., 2022)	Could COVID expand the future of addiction research? Long-term implications in the pandemic era	2021	Outcome

E. Fino (Fino et al., 2021)	Exploring the public's perception of gambling addiction on Twitter during the COVID-19 pandemic: Topic modelling and sentiment analysis	2021	Qualitative study
D. Forsström (Forsström et al., 2022)	Isolation and worry in relation to gambling and onset of gambling among psychiatry patients during the COVID-19 pandemic: A mediation study.	2022	Outcome
S. George (George, 2020)	Holidays in People Who Are Addicted to Lotteries: A Window of Treatment Opportunity Provided by the COVID-19 Lockdown.	2020	Qualitative study
B. Gjoneska (Gjoneska et al., 2022)	Problematic use of the internet during the COVID-19 pandemic: Good practices and mental health recommendations.	2022	Qualitative study

S. Griffiths (Griffiths et al., 2020)	Pandemics and epidemics: public health and gambling harms.	2020	Qualitative study
P. Haddad (Haddad et al., 2022)	Gambling problems among Lebanese adults: Arabic-Language version of the South Oaks Gambling Screen (SOGS) scale validation and correlates.	2022	Outcome
A. Håkansson (Håkansson et al., 2020)	Gambling During the COVID-19 Crisis -- A Cause for Concern.	2020	Qualitative study
A. Håkansson (Håkansson, 2020a)	Effects on Gambling Activity From Coronavirus Disease 2019-An Analysis of Revenue-Based Taxation of Online- and Land-Based Gambling Operators During the Pandemic.	2020	The statistical units are not the individuals
A. Håkansson (Håkansson, 2020b)	Impact of COVID-19 on Online Gambling - A General Population	2020	Outcome

	Survey During the Pandemic.		
A. Håkansson (Håkansson, Fernández-Aranda, et al., 2021)	Gambling-Like Day Trading During the COVID-19 Pandemic - Need for Research on a Pandemic-Related Risk of Indebtedness and Mental Health Impact.	2021	Outcome
A. Håkansson (Håkansson, Widinghoff, et al., 2021)	Self-Exclusion from Gambling-A Measure of COVID-19 Impact on Gambling in a Highly Online-Based Gambling Market?	2021	Outcome
LC. Hall(Hall et al., 2021)	Effects of self-isolation and quarantine on loot box spending and excessive gaming-results of a natural experiment.	2021	Outcome
D. Hodgins (Hodgins & Stevens, 2021)	The impact of COVID-19 on gambling and gambling disorder: emerging data.	2021	Qualitative study

C. Incerti (Incerti et al., 2021)	Covid-19 and addiction: A comparison between Substance Use Disorder patients and gamblers.	2021	Outcome
MDS. Islam (Islam et al., 2020)	Problematic internet use among young and adult population in Bangladesh: Correlates with lifestyle and online activities during the COVID-19 pandemic.	2020	Outcome
S. Jiménez-Murcia (Jiménez-Murcia & Fernández-Aranda, 2022)	COVID-19 and Behavioral Addictions: Worrying consequences?	2022	Qualitative study
H. Jouhki (Jouhki et al., 2022)	Escapism and Excessive Online Behaviors: A Three-Wave Longitudinal Study in Finland during the COVID-19 Pandemic.	2022	Outcome
SY. Kim (Kim et al., 2022)	Changes in the Mean of and Variance in Psychological Disease	2022	Outcome

	Incidences before and during the COVID-19 Pandemic in the Korean Adult Population.		
O. Király (Király et al., 2020)	Preventing problematic internet use during the COVID-19 pandemic: Consensus guidance.	2020	Qualitative study
M. Koós (Koós et al., 2022)	No Significant Changes in Addictive and Problematic Behaviors During the COVID-19 Pandemic and Related Lockdowns: A Three-Wave Longitudinal Study.	2022	Outcome
Z. Kovačić Petrović (Kovačić Petrović et al., 2022)	Internet use and internet-based addictive behaviours during coronavirus pandemic.	2022	Qualitative study
D. Li (Li et al., 2022)	Coping efficacy is associated with the domain specificity in risk-taking behaviors during the COVID-19 pandemic.	2022	Outcome

P. Lindner (Lindner et al., 2020)	Transitioning Between Online Gambling Modalities and Decrease in Total Gambling Activity, but No Indication of Increase in Problematic Online Gambling Intensity During the First Phase of the COVID-19 Outbreak in Sweden: A Time Series Forecast Study.	2020	The statistical units are not the individuals
A. Maraz (Maraz et al., 2021)	Potentially addictive behaviours increase during the first six months of the Covid-19 pandemic.	2021	Outcome
V. Marionneau (Marionneau & Järvinen-Tassopoulos, 2021)	From Habit-Forming to Habit-Breaking Availability: Experiences on Electronic Gambling Machine Closures During COVID-19.	2021	Qualitative study
V. Marionneau (Marionneau & Järvinen-Tassopoulos, 2022)	Treatment and help services for	2022	Outcome

	gambling during COVID-19: Experiences of gamblers and their concerned significant others.		
Marsden J. (Marsden et al., 2020)	Mitigating and learning from the impact of COVID-19 infection on addictive disorders.	2020	Qualitative study
J. Marsden (Marsden et al., 2022)	The impact of the COVID-19 pandemic on addictive disorders—an update.	2022	Qualitative study
N. Masaeli (Masaeli & Farhadi, 2021)	Prevalence of Internet-based addictive behaviors during COVID-19 pandemic: a systematic review.	2021	Qualitative study
MS. Mohamed (Mohamed et al., 2022)	Worsened Anxiety and Loneliness Influenced Gaming and Gambling during the COVID-19 Pandemic	2022	Analyses in a period when restrictive measures due to pandemic were absent or limited
N. Niba Rawlings (Niba Rawlings et al., 2022)	Perceived risks of COVID-19, attitudes towards preventive guidelines and impact	2022	Outcome

	of the lockdown on students in Uganda: A cross-sectional study.		
A. Price (Price, 2022a)	Health Inequities Among East and South Asian Gamblers During COVID-19: Key Risk Factors and Comorbidities.	2022	Outcome
A. Price (Price et al., 2022)	Mental Health Over Time and Financial Concerns Predict Change in Online Gambling During COVID-19.	2022	Outcome
A. Price (Price, 2022b)	Online Gambling in the Midst of COVID-19: A Nexus of Mental Health Concerns, Substance Use and Financial Stress.	2022	Outcome
C. Primi (Primi et al., 2022)	Loot boxes use, video gaming, and gambling in adolescents: Results from a path analysis before and during COVID-19-	2022	Outcome

	pandemic-related lockdown in Italy.		
A. Pritchard (Pritchard & Dymond, 2022)	Gambling problems and associated harms in United Kingdom Royal Air Force personnel.	2022	Outcome
A. Quinn (Quinn et al., 2022)	COVID-19 and resultant restrictions on gambling behaviour.	2022	Qualitative study
M. Renard (Renard et al., 2022)	Gamblers' Perceptions of the Impact of the COVID-19 Pandemic on Their Gambling Behaviours: Analysis of Free-Text Responses Collected through a Cross-Sectional Online Survey.	2022	Qualitative study
M. Renard (Renard, 2022)	Impacts of the COVID-19 pandemic on gamblers in Canada: qualitative analysis of responses to an open-ended question.	2022	Qualitative study

S. Rodda (Rodda et al., 2022)	The impact of COVID-19 on addiction treatment in New Zealand.	2022	Outcome
V. Sachdeva (Sachdeva et al., 2022)	Gambling behaviors during COVID-19: a narrative review.	2022	Qualitative study
I. **Savolainen (Savolainen et al., 2022)**	Gambling and gaming during COVID-19: The role of mental health and social motives in gambling and gaming problems.	2022	Outcome
F. Scafuto (Scafuto et al., 2023)	COVID-19 Pandemic and Internet Addiction in Young Adults: A Pilot Study on Positive and Negative Psychosocial Correlates.	2023	Outcome
S. Sharman (Sharman et al., 2021)	Gambling in COVID-19 Lockdown in the UK: Depression, Stress, and Anxiety.	2021	Outcome
A. Sirola (Sirola et al., 2023)	Psychosocial Perspective on Problem Gambling: The role of Social Relationshi	2023	Outcome

	ps, Resilience, and COVID-19 Worry.		
E. Smith (E. Smith et al., 2023)	Large-Scale Web Scraping for Problem Gambling Research: A Case Study of COVID-19 Lockdown Effects in Germany.	2023	Outcome
N. Smith (N. D. L. Smith et al., 2022)	Telehealth treatment for gambling disorder in the COVID-19 era: seismic shifts and silver linings.	2022	Qualitative study
NL. Vike (Vike et al., 2023)	The Relationship Between a History of High-risk and Destructive Behaviors and COVID-19 Infection: Preliminary Study.	2023	Outcome
A. Virgolino (Virgolino et al., 2021)	Addictive behaviours during the COVID-19 pandemic: results from a nationwide study in Portugal	2021	Qualitative study
AS. Yahya (Yahya & Khawaja, 2020)	Problem Gambling During the	2020	Qualitative study

	COVID-19 Pandemic.		
T. Zhang (Zhang et al., 2023)	Relieving the Gambling Itch Through Alcohol Consumption: The Impact of COVID-19 Restrictions on Australian Casino Patrons.	2023	Outcome

Albertella, L., Rotaru, K., Christensen, E., Lowe, A., Brierley, M.-E., Richardson, K., Chamberlain, S. R., Lee, R. S. C., Kayayan, E., Grant, J. E., Schluter-Hughes, S., Ince, C., Fontenelle, L. F., Segrave, R., & Yücel, M. (2021). The Influence of Trait Compulsivity and Impulsivity on Addictive and Compulsive Behaviors During COVID-19. *Frontiers in Psychiatry*, *12*, 634583. https://doi.org/10.3389/fpsyt.2021.634583

Alimoradi, Z., Lotfi, A., Lin, C.-Y., Griffiths, M. D., & Pakpour, A. H. (2022). Estimation of Behavioral Addiction Prevalence During COVID-19 Pandemic: A Systematic Review and Meta-analysis. *Current Addiction Reports*, *9*(4), 486–517. https://doi.org/10.1007/s40429-022-00435-6

Andersson, M. J., Balem, M., & Håkansson, A. (2022). An interrupted time series analysis of gambling behavior based on gambling operator revenue-based taxation during the COVID-19 pandemic in Sweden. *Public Health (Elsevier)*, *211*, 14–20. CINAHL Complete. https://doi.org/10.1016/j.puhe.2022.07.003

Avena, N. M., Simkus, J., Lewandowski, A., Gold, M. S., & Potenza, M. N. (2021). Substance Use Disorders and Behavioral Addictions During the COVID-19 Pandemic and COVID-19-Related Restrictions. *Frontiers in Psychiatry*, *12*, 653674. https://doi.org/10.3389/fpsyt.2021.653674

Azevedo, N. P., Santos, P., & Sá, L. (2023). Gambling Disorder among Porto's University Students. *Healthcare (Basel, Switzerland)*, *11*(18). https://doi.org/10.3390/healthcare11182527

Bouza, E., Arango, C., Moreno, C., Gracia, D., Martín, M., Pérez, V., Lázaro, L., Ferre, F., Salazar, G., Tejerina-Picado, F., Navío, M., Granda Revilla, J., Palomo, E., & Gil-Monte, P. R. (2023). Impact of the COVID-19 pandemic on the mental health of the general population and health care workers. *Revista Espanola de Quimioterapia : Publicacion Oficial de La Sociedad Espanola de Quimioterapia*, *36*(2), 125–143. https://doi.org/10.37201/req/018.2023

Brodeur, M., Audette-Chapdelaine, S., Savard, A.-C., & Kairouz, S. (2021a). Gambling and the COVID-19 pandemic: A scoping review. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *111*, 110389. https://doi.org/10.1016/j.pnpbp.2021.110389

Brodeur, M., Audette-Chapdelaine, S., Savard, A.-C., & Kairouz, S. (2021b). Gambling and the COVID-19 pandemic in the province of Quebec (Canada): Protocol for a mixed-methods study. *BMJ Open*, *11*(9), e048785. https://doi.org/10.1136/bmjopen-2021-048785

Brodeur, M., Roberge, P., Cotton, J.-C., Monson, E., Morvannou, A., Poitras, M.-E., Lacasse, A., Jutras-Aswad, D., Couturier, Y., Loignon, C., Audette-Chapdelaine, S., Auger, A.-M., Bertrand, K., Dorceus, S., Simon, O., & Hudon, C. (2023). Experience of LGBTQIA2S+ populations with gambling during the COVID-19 pandemic: Protocol for a mixed-methods study. *BMJ Open*, *13*(2), e066231. https://doi.org/10.1136/bmjopen-2022-066231

Cataldo, I., Casonato, E., Levari, E., Negri, A., Simonato, P., Tomasi, G., Branz, G., Coppola, A., Gianfranceschi, P., Leoni, E., Mistretta, P., Stefani, M., Vanzetta, M., Franceschini, A., Esposito, G., & Corazza, O. (2022). Gambling at the time of COVID-19: Results from interviews in an Italian sample of gamblers. *Emerging Trends in Drugs, Addictions, and Health*, *2*, 100032. https://doi.org/10.1016/j.etdah.2022.100032

Chóliz, M. (2023a). Crisis, What Crisis? The Effect of Economic Crises on Spending on Online and Offline Gambling in Spain: Implications for Preventing Gambling Disorder. *International Journal of Environmental Research and Public Health*, *20*(4). https://doi.org/10.3390/ijerph20042909

Chóliz, M. (2023b). Is gambling like a virus?: A conceptual framework and proposals based on empirical data for the prevention of gambling addiction. *BMC Public Health*, *23*(1), 1686. https://doi.org/10.1186/s12889-023-16610-x

Claesdotter-Knutsson, E., André, F., & Håkansson, A. (2022). Gaming Activity and Possible Changes in Gaming Behavior Among Young People During the COVID-19 Pandemic: Cross-sectional Online Survey Study. *JMIR Serious Games*, *10*(1), e33059. https://doi.org/10.2196/33059

DeCamp, W., & Daly, K. (2023). Loot box consumption by adolescents pre- and post- pandemic lockdown. *PeerJ*, *11*, e15287. https://doi.org/10.7717/peerj.15287

Donati, M. A., Cabrini, S., Capitanucci, D., Primi, C., Smaniotto, R., Avanzi, M., Quadrelli, E., Bielli, G., Casini, A., & Roaro, A. (2021). Being a Gambler during the COVID-19 Pandemic: A Study with Italian Patients and the Effects of Reduced Exposition. *International Journal of Environmental Research and Public Health*, *18*(2). https://doi.org/10.3390/ijerph18020424

Efrati, Y., & Spada, M. M. (2022). Self-perceived substance and behavioral addictions among Jewish Israeli adolescents during the COVID-19 pandemic. *Addictive Behaviors Reports*, *15*, 100431. https://doi.org/10.1016/j.abrep.2022.100431

Englund, A., Sharman, S., Tas, B., & Strang, J. (2022). Could COVID expand the future of addiction research? Long-term implications in the pandemic era. *Addiction*, *117*(8), 2135–2140. CINAHL Complete. https://doi.org/10.1111/add.15790

Fino, E., Hanna-Khalil, B., & Griffiths, M. D. (2021). Exploring the public's perception of gambling addiction on Twitter during the COVID-19 pandemic: Topic modelling and sentiment analysis. *Journal of Addictive Diseases*, *39*(4), 489–503. CINAHL Complete. https://doi.org/10.1080/10550887.2021.1897064

Forsström, D., Lindner, P., Månsson, K. N. T., Ojala, O., Hedman-Lagerlöf, M., El Alaoui, S., Rozental, A., Lundin, J., Jangard, S., Shahnavaz, S., Sörman, K., Lundgren, T., & Jayaram-Lindström, N. (2022). Isolation and worry in relation to gambling and onset of gambling among psychiatry patients during the COVID-19 pandemic: A mediation study. *Frontiers in Psychology*, *13*, 1045709. https://doi.org/10.3389/fpsyg.2022.1045709

George, S. (2020). "Holidays" in People Who Are Addicted to Lotteries: A Window of Treatment Opportunity Provided by the COVID-19 Lockdown. *Indian Journal of Social Psychiatry*, *36*, S6–S6. CINAHL Complete. https://doi.org/10.4103/ijsp.ijsp_318_20

Gjoneska, B., Potenza, M. N., Jones, J., Corazza, O., Hall, N., Sales, C. M. D., Grünblatt, E., Martinotti, G., Burkauskas, J., Werling, A. M., Walitza, S., Zohar, J., Menchón, J. M., Király, O., Chamberlain, S. R., Fineberg, N. A., & Demetrovics, Z. (2022). Problematic use of the internet during the COVID-19 pandemic: Good practices and mental health recommendations. *Comprehensive Psychiatry*, *112*, 152279. https://doi.org/10.1016/j.comppsych.2021.152279

Griffiths, S., Reith, G., Wardle, H., & Mackie, P. (2020). Pandemics and epidemics: Public health and gambling harms. *Public Health*, *184*, 1–2. https://doi.org/10.1016/j.puhe.2020.06.022

Haddad, P., Roukoz, R., Akel, M., & Hallit, S. (2022). Gambling problems among Lebanese adults: Arabic-Language version of the South Oaks Gambling Screen (SOGS) scale validation and correlates. *BMC Psychology*, *10*(1), 18. https://doi.org/10.1186/s40359-022-00727-6

Håkansson, A. (2020a). Effects on Gambling Activity From Coronavirus Disease 2019-An Analysis of Revenue-Based Taxation of Online- and Land-Based Gambling Operators During the Pandemic. *Frontiers in Psychiatry*, *11*, 611939. https://doi.org/10.3389/fpsyt.2020.611939

Håkansson, A. (2020b). Impact of COVID-19 on Online Gambling—A General Population Survey During the Pandemic. *Frontiers in Psychology*, *11*, 568543. https://doi.org/10.3389/fpsyg.2020.568543

Håkansson, A., Fernández-Aranda, F., & Jiménez-Murcia, S. (2021). Gambling-Like Day Trading During the COVID-19 Pandemic—Need for Research on a Pandemic-Related Risk of Indebtedness and Mental Health Impact. *Frontiers in Psychiatry*, *12*, 715946. https://doi.org/10.3389/fpsyt.2021.715946

Håkansson, A., Fernández-Aranda, F., Menchón, J. M., Potenza, M. N., & Jiménez-Murcia, S. (2020). Gambling During the COVID-19 Crisis—A Cause for Concern. *Journal of Addiction Medicine*, *14*(4), e10–e12. https://doi.org/10.1097/ADM.0000000000000690

Håkansson, A., Widinghoff, C., & Berge, J. (2021). Self-Exclusion from Gambling-A Measure of COVID-19 Impact on Gambling in a Highly Online-Based Gambling Market? *International Journal of Environmental Research and Public Health*, *18*(14). https://doi.org/10.3390/ijerph18147367

Hall, L. C., Drummond, A., Sauer, J. D., & Ferguson, C. J. (2021). Effects of self-isolation and quarantine on loot box spending and excessive gaming-results of a natural experiment. *PeerJ*, *9*, e10705. https://doi.org/10.7717/peerj.10705

Hodgins, D. C., & Stevens, R. M. G. (2021). The impact of COVID-19 on gambling and gambling disorder: Emerging data. *Current Opinion in Psychiatry*, *34*(4), 332–343. https://doi.org/10.1097/YCO.0000000000000709

Incerti, C. C., Carenti, M. L., Catalano, G., De Luca, O., Arcangeli, N., Manasse, D., & Casella, P. (2021). Covid-19 and addiction: A comparison between Substance Use Disorder patients and gamblers. *Heroin Addiction & Related Clinical Problems*, *23*(3), 55–60. CINAHL Complete.

Islam, M. S., Sujan, M. S. H., Tasnim, R., Ferdous, M. Z., Masud, J. H. B., Kundu, S., Mosaddek, A. S. M., Choudhuri, M. S. K., Kircaburun, K., & Griffiths, M. D. (2020). Problematic internet use among young and adult population in Bangladesh: Correlates with lifestyle and online activities during the COVID-19 pandemic. *Addictive Behaviors Reports*, *12*, 100311. https://doi.org/10.1016/j.abrep.2020.100311

Jiménez-Murcia, S., & Fernández-Aranda, F. (2022). COVID-19 and Behavioral Addictions: Worrying consequences? *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *56*, 77–79. https://doi.org/10.1016/j.euroneuro.2021.12.004

Jouhki, H., Savolainen, I., Sirola, A., & Oksanen, A. (2022). Escapism and Excessive Online Behaviors: A Three-Wave Longitudinal Study in Finland during the COVID-19 Pandemic. *International Journal of Environmental Research and Public Health*, *19*(19). https://doi.org/10.3390/ijerph191912491

Kim, S. Y., Yoo, D. M., Kwon, M.-J., Kim, J.-H., Kim, J.-H., Bang, W.-J., & Choi, H. G. (2022). Changes in the Mean of and Variance in Psychological Disease Incidences before and during the COVID-19 Pandemic in the Korean Adult Population. *Journal of Personalized Medicine*, *12*(4). https://doi.org/10.3390/jpm12040576

Király, O., Potenza, M. N., Stein, D. J., King, D. L., Hodgins, D. C., Saunders, J. B., Griffiths, M. D., Gjoneska, B., Billieux, J., Brand, M., Abbott, M. W., Chamberlain, S. R., Corazza, O., Burkauskas, J., Sales, C. M. D., Montag, C., Lochner, C., Grünblatt, E., Wegmann, E., & Martinotti, G. (2020). Preventing problematic internet use during the COVID-19 pandemic: Consensus guidance. *Comprehensive Psychiatry*, *100*, N.PAG-N.PAG. CINAHL Complete. https://doi.org/10.1016/j.comppsych.2020.152180

Koós, M., Demetrovics, Z., Griffiths, M. D., & Bőthe, B. (2022). No Significant Changes in Addictive and Problematic Behaviors During the COVID-19 Pandemic and Related Lockdowns: A Three-Wave Longitudinal Study. *Frontiers in Psychology*, *13*, 837315. https://doi.org/10.3389/fpsyg.2022.837315

Kovačić Petrović, Z., Peraica, T., Kozarić-Kovačić, D., & Palavra, I. R. (2022). Internet use and internet-based addictive behaviours during coronavirus pandemic. *Current Opinion in Psychiatry*, *35*(5), 324–331. https://doi.org/10.1097/YCO.0000000000000804

Li, D., Wu, M., Chao, B., & Zhang, L. (2022). Coping efficacy is associated with the domain specificity in risk-taking behaviors during the COVID-19 pandemic. *International Journal of Disaster Risk Reduction : IJDRR*, *82*, 103321. https://doi.org/10.1016/j.ijdrr.2022.103321

Lindner, P., Forsström, D., Jonsson, J., Berman, A. H., & Carlbring, P. (2020). Transitioning Between Online Gambling Modalities and Decrease in Total Gambling Activity, but No Indication of Increase in Problematic Online Gambling Intensity During the First Phase of the COVID-19 Outbreak in Sweden: A Time Series Forecast Study. *Frontiers in Public Health*, *8*, 554542. https://doi.org/10.3389/fpubh.2020.554542

Maraz, A., Katzinger, E., & Yi, S. (2021). Potentially addictive behaviours increase during the first six months of the Covid-19 pandemic. *Journal of Behavioral Addictions*, *10*(4), 912–919. https://doi.org/10.1556/2006.2021.00079

Marionneau, V., & Järvinen-Tassopoulos, J. (2021). From Habit-Forming to Habit-Breaking Availability: Experiences on Electronic Gambling Machine Closures During COVID-19. *Frontiers in Psychology*, *12*, 788586. https://doi.org/10.3389/fpsyg.2021.788586

Marionneau, V., & Järvinen-Tassopoulos, J. (2022). Treatment and help services for gambling during COVID-19: Experiences of gamblers and their concerned significant others. *Nordisk Alkohol- & Narkotikatidskrift : NAT*, *39*(1), 10–24. https://doi.org/10.1177/14550725211030727

Marsden, J., Brown, J., Clark, L., Cousijn, J., Hall, W., Hickman, M., Holmes, J., Humphreys, K., Jackson, S. E., Peacock, A., & Tucker, J. (2022). The impact of the COVID-19 pandemic on addictive disorders—An update. *Addiction*, *117*(11), 2762–2766. CINAHL Complete. https://doi.org/10.1111/add.16033

Marsden, J., Darke, S., Hall, W., Hickman, M., Holmes, J., Humphreys, K., Neale, J., Tucker, J., & West, R. (2020). Mitigating and learning from the impact of COVID-19 infection on addictive disorders. *Addiction*, *115*(6), 1007–1010. CINAHL Complete. https://doi.org/10.1111/add.15080

Masaeli, N., & Farhadi, H. (2021). Prevalence of Internet-based addictive behaviors during COVID-19 pandemic: A systematic review. *Journal of Addictive Diseases*, *39*(4), 468–488. https://doi.org/10.1080/10550887.2021.1895962

Mohamed, M. S., Rukh, G., Schiöth, H. B., Vadlin, S., Olofsdotter, S., Åslund, C., & Nilsson, K. W. (2022). Worsened Anxiety and Loneliness Influenced Gaming and Gambling during the COVID-19 Pandemic. *Journal of Clinical Medicine*, *12*(1). https://doi.org/10.3390/jcm12010249

Niba Rawlings, N., Akwah, E. A., Musisi, J., Awanchiri, K., Babirye, R., Emalieu, D., Nduhukyire, L., Kakeeto, R., & Ngongalah, L. (2022). Perceived risks of COVID-19, attitudes towards preventive guidelines and impact of the lockdown on students in Uganda: A cross-sectional study. *PloS One*, *17*(4), e0266249. https://doi.org/10.1371/journal.pone.0266249

Price, A. (2022a). Health Inequities Among East and South Asian Gamblers During COVID-19: Key Risk Factors and Comorbidities. *International Journal of Mental Health and Addiction*, 1–16. https://doi.org/10.1007/s11469-022-00767-4

Price, A. (2022b). Online Gambling in the Midst of COVID-19: A Nexus of Mental Health Concerns, Substance Use and Financial Stress. *International Journal of Mental Health and Addiction*, *20*(1), 362–379. https://doi.org/10.1007/s11469-020-00366-1

Price, A., Tabri, N., Stark, S., Balodis, I. M., & Wohl, M. J. A. (2022). Mental Health Over Time and Financial Concerns Predict Change in Online Gambling During COVID-19. *International Journal of Mental Health and Addiction*, 1–15. https://doi.org/10.1007/s11469-021-00750-5

Primi, C., Sanson, F., Vecchiato, M., Serra, E., & Donati, M. A. (2022). Loot boxes use, video gaming, and gambling in adolescents: Results from a path analysis before and during COVID-19-pandemic-related lockdown in Italy. *Frontiers in Psychology*, *13*, 1009129. https://doi.org/10.3389/fpsyg.2022.1009129

Pritchard, A., & Dymond, S. (2022). Gambling problems and associated harms in United Kingdom Royal Air Force personnel. *Addictive Behaviors*, *126*, N.PAG-N.PAG. CINAHL Complete. https://doi.org/10.1016/j.addbeh.2021.107200

Quinn, A., Grant, J. E., & Chamberlain, S. R. (2022). COVID-19 and resultant restrictions on gambling behaviour. *Neuroscience and Biobehavioral Reviews*, *143*, 104932. https://doi.org/10.1016/j.neubiorev.2022.104932

Renard. (2022). Impacts of the COVID-19 pandemic on gamblers in Canada: Qualitative analysis of responses to an open-ended question. *Annals of Family Medicine*, *20*, 397–397. CINAHL Complete.

Renard, M., Audette-Chapdelaine, S., Savard, A.-C., Kairouz, S., & Brodeur, M. (2022). Gamblers' Perceptions of the Impact of the COVID-19 Pandemic on Their Gambling Behaviours: Analysis of Free-Text Responses Collected through a Cross-Sectional Online Survey. *International Journal of Environmental Research and Public Health*, *19*(24). https://doi.org/10.3390/ijerph192416603

Rodda, S. N., Park, J. J., Wilkinson-Meyers, L., & King, D. L. (2022). The impact of COVID-19 on addiction treatment in New Zealand. *Addictive Behaviors*, *127*, 107230. https://doi.org/10.1016/j.addbeh.2021.107230

Sachdeva, V., Sharma, S., & Sarangi, A. (2022). Gambling behaviors during COVID-19: A narrative review. *Journal of Addictive Diseases*, *40*(2), 208–216. https://doi.org/10.1080/10550887.2021.1971942

Savolainen, I., Vuorinen, I., Sirola, A., & Oksanen, A. (2022). Gambling and gaming during COVID-19: The role of mental health and social motives in gambling and gaming problems. *Comprehensive Psychiatry*, *117*, 152331. https://doi.org/10.1016/j.comppsych.2022.152331

Scafuto, F., Ciacchini, R., Orrù, G., Crescentini, C., Conversano, C., Mastorci, F., Porricelli, M., & Gemignani, A. (2023). COVID-19 Pandemic and Internet Addiction in Young Adults: A Pilot Study on Positive and Negative Psychosocial Correlates. *Clinical Neuropsychiatry*, *20*(4), 240–251. https://doi.org/10.36131/cnfioritieditore20230403

Sharman, S., Roberts, A., Bowden-Jones, H., & Strang, J. (2021). Gambling in COVID-19 Lockdown in the UK: Depression, Stress, and Anxiety. *Frontiers in Psychiatry*, *12*, 621497. https://doi.org/10.3389/fpsyt.2021.621497

Sirola, A., Nyrhinen, J., & Wilska, T.-A. (2023). Psychosocial Perspective on Problem Gambling: The role of Social Relationships, Resilience, and COVID-19 Worry. *Journal of Gambling Studies*, *39*(3), 1467–1485. CINAHL Complete. https://doi.org/10.1007/s10899-022-10185-9

Smith, E., Michalski, S., Knauth, K. H. K., Kaspar, K., Reiter, N., & Peters, J. (2023). Large-Scale Web Scraping for Problem Gambling Research: A Case Study of COVID-19 Lockdown Effects in Germany. *Journal of Gambling Studies*, *39*(3), 1487–1504. CINAHL Complete. https://doi.org/10.1007/s10899-023-10187-1

Smith, N. D. L., Jones, G. M., & Lucia, M. B. (2022). Telehealth treatment for gambling disorder in the COVID-19 era: Seismic shifts and silver linings. *Current Opinion in Psychiatry*, *35*(4), 265–269. https://doi.org/10.1097/YCO.0000000000000799

Vike, N. L., Bari, S., Stetsiv, K., Woodward, S., Lalvani, S., Stefanopoulos, L., Kim, B. W., Maglaveras, N., Katsaggelos, A. K., & Breiter, H. C. (2023). The Relationship Between a History of High-risk and Destructive Behaviors and COVID-19 Infection: Preliminary Study. *JMIR Formative Research*, *7*, e40821. https://doi.org/10.2196/40821

Virgolino, A., Santos, O., Fialho, M., Heitor, M. J., Costa, A., Rasga, C., Martiniano, H., Costa, J., Vicente, A., & de Almeida, T. C. (2021). Addictive behaviours during the COVID-19 pandemic: Results from a nationwide study in Portugal...14th European Public Health Conference (Virtual), Public health futures in a changing world, November 10-12, 2021. *European Journal of Public Health*, *31*, iii384–iii385. CINAHL Complete.

Yahya, A. S., & Khawaja, S. (2020). Problem Gambling During the COVID-19 Pandemic. *The Primary Care Companion for CNS Disorders*, *22*(4), 20com02690. https://doi.org/10.4088/PCC.20com02690

Zhang, T., Seet, P.-S., Redmond, J., & Sharafizad, J. (2023). Relieving the Gambling Itch Through Alcohol Consumption: The Impact of COVID-19 Restrictions on Australian Casino Patrons. *Journal of Gambling Studies*. https://doi.org/10.1007/s10899-023-10252-9

Supplementary Table 3. Specific ratings for each Newcastle-Ottawa Scale (NOS) item in each longitudinal study that meets the inclusion criteria after selection by text.

Study	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysi	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Overall
M. Auer, 2022 (Auer & Griffiths, 2022)	1	1	1	1	2	1	1	1	9
M. Auer, 2023 (Auer et al., 2023)	1	1	1	1	2	1	1	1	9
M. Balem, 2023 (Balem et al., 2023)	1	1	1	1	2	1	1	1	9
ME. Bellringer, 2021 (Bellringer et al., 2021)	1	1	1	1	2	0	1	1	8
N. Black, 2022 (Black et al., 2022)	1	1	1	1	2	0	1	1	8
A. Emond, 2022 (Emond et al, 2022)	1	1	1	1	2	0	1	0	7
M. Fluharty, 2022 (Fluharty et al., 2022)	1	1	1	1	2	0	1	1	8
S. Lischer, 2021 (Lischer et al., 2021)	1	1	1	1	2	0	1	1	8
V. Månsson, 2021 (Månsson et al., 2021)	1	1	1	1	2	0	1	1	8
CA. Shaw 2022 (Shaw et al., 2022)	1	1	1	1	2	0	1	1	8

Auer, M., & Griffiths, M. D. (2022). Gambling Before and During the COVID-19 Pandemic Among Online Casino Gamblers: An Empirical Study Using Behavioral Tracking Data. *International Journal of Mental Health and Addiction*, *20*(3), 1722–1732. https://doi.org/10.1007/s11469-020-00462-2

Auer, M., Malischnig, D., & Griffiths, M. D. (2023). Gambling Before and During the COVID-19 Pandemic Among European Regular Sports Bettors: An Empirical Study Using Behavioral Tracking Data. *International Journal of Mental Health and Addiction*, *21*(1), 20–27. https://doi.org/10.1007/s11469-020-00327-8

Balem, M., Karlsson, A., Widinghoff, C., Perrot, B., Challet-Bouju, G., & Håkansson, A. (2023). Gambling and COVID-19: Swedish national gambling data from a state-owned gambling sports and casino operator. *Journal of Behavioral Addictions*, *12*(1), 230–241. https://doi.org/10.1556/2006.2022.00089

Bellringer, M. E., & Garrett, N. (2021). Risk Factors for Increased Online Gambling during COVID-19 Lockdowns in New Zealand: A Longitudinal Study. *International Journal of Environmental Research and Public Health*, *18*(24). https://doi.org/10.3390/ijerph182412946

Black, N., Swanton, T. B., Burgess, M. T., & Gainsbury, S. M. (2022). Impact of Gambling Supply Reduction During COVID-19 Shutdowns on Gambling Problems and Gambling Behaviour in Australia: A National Longitudinal Study. *Journal of Gambling Studies*, *38*(2), 353–365. https://doi.org/10.1007/s10899-021-10067-6

Emond, A., Nairn, A., Collard, S., & Hollén, L. (2022). Gambling by Young Adults in the UK During COVID-19 Lockdown. *Journal of Gambling Studies*, *38*(1), 1–13. https://doi.org/10.1007/s10899-021-10029-y

Fluharty, M., Paul, E., & Fancourt, D. (2022). Predictors and patterns of gambling behaviour across the COVID-19 lockdown: Findings from a UK cohort study. *Journal of Affective Disorders*, *298*(Pt A), 1–8. https://doi.org/10.1016/j.jad.2021.10.117

Lischer, S., Steffen, A., Schwarz, J., & Mathys, J. (2021). The Influence of Lockdown on the Gambling Pattern of Swiss Casinos Players. *International Journal of Environmental Research and Public Health*, *18*(4). https://doi.org/10.3390/ijerph18041973

Månsson, V., Wall, H., Berman, A. H., Jayaram-Lindström, N., & Rosendahl, I. (2021). A Longitudinal Study of Gambling Behaviors During the COVID-19 Pandemic in Sweden. *Frontiers in Psychology*, *12*, 708037. https://doi.org/10.3389/fpsyg.2021.708037

Shaw, C. A., Hodgins, D. C., Williams, R. J., Belanger, Y. D., Christensen, D. R., El-Guebaly, N., McGrath, D. S., Nicoll, F., Smith, G. J., & Stevens, R. M. G. (2022). Gambling in Canada During the COVID Lockdown: Prospective National Survey. *Journal of Gambling Studies*, *38*(2), 371–396. https://doi.org/10.1007/s10899-021-10073-8

Supplementary Table 4. Specific ratings for each Newcastle-Ottawa Scale (NOS) item in each cross-sectional study that meets the inclusion criteria after selection by text.

Study	Representativeness of the cases	Sample size	Non response-rate	Ascertainment of the screening/surveillance tool	The potential confounders were investigated by subgroup analysis or multivariable analysis	Assessment of the outcome	Statistical test	Overall
MC. Alessi, 2022 (Alessi et al., 2022)	1	0	0	2	1	1	1	6
A. Amerio, 2022 (Amerio et al., 2022)	1	1	0	2	1	1	1	7
H. Bonny-Noach, 2021 (Bonny-Noach et al., 2021)	1	0	0	2	1	1	1	6
I. Cataldo, 2022 (Cataldo et al., 2022)	0	0	0	2	1	1	0	4
E. Claesdotter-Knutsson, 2021 (Claesdotter-Knutsson, et al., 2021)	1	1	0	2	1	1	1	7
SM. Gainsbury, 2021 (Gainsbury et al.,	1	1	0	2	1	1	1	7

A. Håkansson (Changes in gambling), 2020 (Håkansson et al., 2020)	1	1	0	2	1	1	1	7
A. Håkansson (Gambling and self-), 2021 (Håkansson et al., 2021)	1	1	0	2	1	1	1	7
A. Håkansson (Psychological distress), 2020, (Håkansson et al., 2020)	0	0	0	2	1	1	1	5
A. Håkansson (Changes of gambling), 2021 (Håkansson et al., 2021)	1	1	0	2	1	1	1	7
J. Kalke, 2022 (Kalke et al., 2022)	1	1	0	2	1	1	1	7
A. Lugo, 2021 (Lugo et al., 2021)	1	1	0	2	1	1	1	7
V. Mravčík, 2021 (Mravčík et al., 2021)	1	1	0	2	0	1	0	5
E. Otis, 2022 (Otis et al., 2022)	1	0	0	2	1	1	1	6
A. Pérez-Albéniz, 2022 (Pérez-Albéniz et al., 2022)	0	1	0	2	0	1	1	5
K. Rantis, 2022 (Rantis et al., 2022)	1	1	0	2	0	1	1	6
L. Salerno, 2021 (Salerno et al., 2021)	1	0	0	2	0	1	1	5
S. Sharman, 2022 (Sharman	1	1	0	2	1	1	1	7

et al., 2022)								
H. Wardle, 2021 (Wardle et al., 2021)	1	1	0	2	1	1	1	7

Alessi, M. C., Martinotti, G., De Berardis, D., Sociali, A., Di Natale, C., Sepede, G., Cheffo, D. P. R., Monti, L., Casella, P., Pettorruso, M., Sensi, S., & Di Giannantonio, M. (2022). Craving variations in patients with substance use disorder and gambling during COVID-19 lockdown: The Italian experience. *World Journal of Clinical Cases*, *10*(3), 882–890. https://doi.org/10.12998/wjcc.v10.i3.882

Amerio, A., Stival, C., Lugo, A., Fanucchi, T., Gorini, G., Pacifici, R., Odone, A., Serafini, G., & Gallus, S. (2022). COVID-19 lockdown: The relationship between trait impulsivity and addictive behaviors in a large representative sample of Italian adults. *Journal of Affective Disorders*, *302*, 424–427. https://doi.org/10.1016/j.jad.2022.01.094

Bonny-Noach, H., & Gold, D. (2021). Addictive behaviors and craving during the COVID-19 pandemic of people who have recovered from substance use disorder. *Journal of Addictive Diseases*, *39*(2), 257–264. https://doi.org/10.1080/10550887.2020.1856298

Cataldo, I., Casonato, E., Levari, E., Negri, A., Simonato, P., Tomasi, G., Branz, G., Coppola, A., Gianfranceschi, P., Leoni, E., Mistretta, P., Stefani, M., Vanzetta, M., Franceschini, A., Esposito, G., & Corazza, O. (2022). Gambling at the time of COVID-19: Results from interviews in an Italian sample of gamblers. *Emerging Trends in Drugs, Addictions, and Health*, *2*, 100032. https://doi.org/10.1016/j.etdah.2022.100032

Claesdotter-Knutsson, E., & Håkansson, A. (2021). Changes in Self-Reported Web-Based Gambling Activity During the COVID-19 Pandemic: Cross-sectional Study. *JMIR Serious Games*, *9*(4), e30747. https://doi.org/10.2196/30747

Gainsbury, S. M., Swanton, T. B., Burgess, M. T., & Blaszczynski, A. (2021). Impacts of the COVID-19 Shutdown on Gambling Patterns in Australia: Consideration of Problem Gambling and Psychological Distress. *Journal of Addiction Medicine*, *15*(6), 468–476. https://doi.org/10.1097/ADM.0000000000000793

Håkansson, A. (2020a). Changes in Gambling Behavior during the COVID-19 Pandemic-A Web Survey Study in Sweden. *International Journal of Environmental Research and Public Health*, *17*(11). https://doi.org/10.3390/ijerph17114013

Håkansson, A. (2021). Gambling and self-reported changes in gambling during COVID-19 in web survey respondents in Denmark. *Heliyon*, *7*(7), e07506. https://doi.org/10.1016/j.heliyon.2021.e07506

Håkansson, A., Jönsson, C., & Kenttä, G. (2020). Psychological Distress and Problem Gambling in Elite Athletes during COVID-19 Restrictions-A Web Survey in Top Leagues of Three Sports during the Pandemic. *International Journal of Environmental Research and Public Health*, *17*(18). https://doi.org/10.3390/ijerph17186693

Håkansson, A., & Widinghoff, C. (2021). Changes of Gambling Patterns during COVID-19 in Sweden, and Potential for Preventive Policy Changes. A Second Look Nine Months into the Pandemic. *International Journal of Environmental Research and Public Health*, *18*(5). https://doi.org/10.3390/ijerph18052342

Kalke, J., Schütze, C., Lahusen, H., & Buth, S. (2022). Parameters for Change in Offline Gambling Behavior After the First COVID-19 Lockdown in Germany. *Frontiers in Psychology*, *13*, 857234. https://doi.org/10.3389/fpsyg.2022.857234

Lugo, A., Stival, C., Paroni, L., Amerio, A., Carreras, G., Gorini, G., Mastrobattista, L., Minutillo, A., Mortali, C., Odone, A., Pacifici, R., Tinghino, B., & Gallus, S. (2021). The impact of COVID-19 lockdown on gambling habit: A cross-sectional study from Italy. *Journal of Behavioral Addictions*, *10*(3), 711–721. https://doi.org/10.1556/2006.2021.00033

Mravčík, V., & Chomynová, P. (2021). Substance use and addictive behaviours during COVID-19 confinement measures increased in intensive users: Results of an online general population survey in the Czech Republic. *Epidemiologie, Mikrobiologie, Imunologie : Casopis Spolecnosti pro Epidemiologii a Mikrobiologii Ceske Lekarske Spolecnosti J.E. Purkyne*, *70*(2), 98–103.

Otis, E., Kim, A. J., Stewart, S. H., Sherry, S. B., & Yakovenko, I. (2022). Changes in sports gambling behavior during the COVID-19 pandemic in Canada. *Frontiers in Psychiatry*, *13*, 1018234. https://doi.org/10.3389/fpsyt.2022.1018234

Pérez-Albéniz, A., Nuez, C., Lucas-Molina, B., Ezquerra, M., & Fonseca-Pedrero, E. (2022). Impact of lockdown on the addictive behavior of university students in La Rioja. *Adicciones*, *0*(0), 1646. https://doi.org/10.20882/adicciones.1646

Rantis, K., Panagiotidis, P., Parlapani, E., Holeva, V., Tsapakis, E. M., & Diakogiannis, I. (2022). Substance use during the COVID-19 pandemic in Greece. *Journal of Substance Use*, *27*(3), 231–238. CINAHL Complete. https://doi.org/10.1080/14659891.2021.1941344

Salerno, L., & Pallanti, S. (2021). COVID-19 Related Distress in Gambling Disorder. *Frontiers in Psychiatry*, *12*, 620661. https://doi.org/10.3389/fpsyt.2021.620661

Sharman, S., Roberts, A., Bowden-Jones, H., & Strang, J. (2022). Gambling and COVID-19: Initial Findings from a UK Sample. *International Journal of Mental Health and Addiction*, *20*(5), 2743–2754. https://doi.org/10.1007/s11469-021-00545-8

Wardle, H., Donnachie, C., Critchlow, N., Brown, A., Bunn, C., Dobbie, F., Gray, C., Mitchell, D., Purves, R., Reith, G., Stead, M., & Hunt, K. (2021). The impact of the initial Covid-19 lockdown upon regular sports bettors in Britain: Findings from a cross-sectional online study. *Addictive Behaviors*, *118*, N.PAG-N.PAG. CINAHL Complete. https://doi.org/10.1016/j.addbeh.2021.106876

4. DISCUSSION

In this doctoral project, several topics related to COVID-19 were explored: the association between patient's clinical conditions, including specific diseases and multimorbidity, and different COVID-19-related outcomes; the role played by the severity of the clinical picture of the patients in the association between multimorbidity and some SARS-CoV-2 endpoints; the possible differences in the demographic, socioeconomic, and clinical characteristics of infected, hospitalized, admitted to ICU, and dead patients among the first three waves of COVID-19 pandemic; the evaluation of the impact of COVID-19 pandemic on gambling habits, focusing on frequency, expenditure, and transitions among different types of gambling.

The first finding concerned the greater risk of performing at least a SARS-CoV-2 swab in patients with clinical conditions, including oncological, cardiovascular, cerebrovascular, and respiratory diseases, as well as multimorbidity, during the first wave of the pandemic in Piedmont Region. While limited research specifically examined the relationship between patient clinical conditions and the probability of performing swab testing in the early months of the pandemic in Italy, similar trends were identified also in another study (125). There are many possible explanations for this increased risk. Firstly, during the initial wave, the Italian Government directed COVID-19 testing toward patients with both worsened clinical conditions and specific epidemiological criteria, given the limited availability of tests (125). Secondly, patients with multimorbidity were more prone to experiencing severe symptoms if infected with the virus and had more frequent interactions with the healthcare system due to their complex clinical picture. This increased susceptibility to severe illness and higher frequency of healthcare interactions might lead them to seek COVID-19 testing more frequently. Additionally, starting in April 2020, patients with chronic diseases had to be swabbed to access outpatient services, such as dialysis, radiotherapy, or chemotherapy, further increasing their probability of being tested for SARS-CoV-2.

The first part of this research also assessed the likelihood of testing positive for the COVID-19 swab. An important peculiarity is that these results completely changed based on the reference population used: the general Piedmont population or the population that performed at least one swab during the first wave. When considering the entire population, the results showed an increased risk of being tested positive for the virus among those who suffered from clinical conditions and have a higher comorbidity burden. This finding is in line with other studies (69,126). The rationale behind this was that subjects with a greater comorbidity burden, reflecting a poorer clinical picture, generally performed more swabs compared to healthy subjects, thereby increasing their risk of testing positive. In addition, the compromised immune system or other physiological vulnerabilities of ill subjects made them more susceptible to viral infections, including COVID-19 (127). In contrast, the investigation of the risk of testing positive within the population that underwent a SARS-CoV-2 test revealed that patients with certain pre-existing pathologies, particularly oncological diseases, exhibited a lower probability of testing positive for the virus. Moreover, the risk decreased as the comorbidity burden increased. The primary explanation for this finding lies in the fact that patients with more severe clinical profiles or compromised immune statuses, such as those undergoing cancer treatments, and individuals living with these vulnerable individuals, took greater precautions and were more attentive to adhering to recommended protective measures (128). These measures included social distancing, mask-wearing, hand hygiene, and avoidance of crowded places, the main protective strategies emphasized by local authorities to limit the spread of COVID-19 and prevent infection during the initial phases of the pandemic (129).

Another important finding is that both specific previous health conditions and multimorbidity were identified as strong risk factors for hospitalization and death due to SARS-CoV-2 infection. These results emerged both considering only those who tested positive for the virus during the first wave and the entire Piedmont population, are consistent with other several studies involving other countries (130–132). The first possible explanation is that chronic conditions such as cardiovascular diseases, respiratory disorders, and diabetes could weaken the immune response, making it more challenging for the body to combat SARS-CoV-2 infection and leading to worse outcomes (133). Moreover, patients with underlying health conditions might have limited physiological reserves, making it challenging for their bodies to cope with the additional stress imposed by a severe viral infection like COVID-19 (134). Therefore, the compromised immune system functions and decreased reserves were likely significant contributors to the higher likelihood of hospitalization and death. On the contrary, when examining ICU admission, the results, while aligning with those observed for death and hospitalization in the general population, seem to be different when focusing exclusively on the subgroup of positive cases. In fact, this research showed that multimorbidity, except in a few cases, such as cardiovascular diseases and diabetes, was not a risk factor for ICU admission. The main reason for this counterintuitive finding lies in the severe scarcity of resources during the initial phase of the pandemic, particularly in ICU bed availability. Healthcare professionals had to make critical decisions on ICU admissions based on the patients' health conditions and the potential effectiveness of treatments and care they could receive. Consequently, numerous symptomatic individuals with pre-existing diseases, facing a dramatic clinical picture, were not admitted to the ICU. This situation also explains the remarkably high estimates OR estimates associated with death among those who tested positive for COVID-19 with a CCI greater than 4 (males, 45-59 years old: OR: 17.32, 95% CI: 7.91-37.90; males, 60-74 years old: OR: 3.26, 95% CI: 2.29-4.64; females, 45-59 years old: OR: 31.88, 95% CI: 5.96-170.43; females 60-74 years old: OR: 5.90, 95% CI: 3.31-10.52).

Furthermore, the results of this first part of the research give another notable insight. Specifically, when assessing deaths in both populations, it emerged that the OR estimates were consistently higher for the younger population (45-59 years old) compared to the older population (60-74 years old). This aligns with findings reported by other researchers (80,135). This means that although pre-existing clinical conditions were risk factors for a worse prognosis of COVID-19 regardless of age, younger patients with underlying health conditions had an even greater risk compared to their healthy counterparts in the same age group, as opposed to the older population, whose differences were less pronounced. Therefore, specific pre-existing clinical health conditions and multimorbidity were significant risk factors, particularly in the younger population.

Focusing specifically on the association between certain diseases and COVID-19 outcomes, each disease considered in this research is found to be a risk factor for worse disease.

From the results of the first part of the projects, it emerged that oncological diseases were one of the strongest risk factors. This finding is in line with studies conducted in Italy and in other countries (136,137). The primary reason for this result is the immunosuppressive state generally caused by cancer treatments, such as chemotherapy and radiotherapy, which could lead to a greater susceptibility to the infection (138). Moreover, the more recent the antitumor therapies, the greater the risk of developing a more severe COVID-19 (139). While these findings apply to any cancer, regardless of the site, the literature suggests that certain types of cancer, such as lung cancer, had a more significant impact. In fact, according to a systematic review conducted in Italy and published in 2022 (140), patients with lung cancer had a 91 percent greater risk of dying than those with other malignancies. Certain cancers that directly affect the respiratory system could result in more severe complications related to COVID-19.

Furthermore, also the other pre-existing respiratory diseases constituted significant risk factors. Several studies showed that specific pathologies affecting the respiratory tract and impairing lung function increased the risk of contracting more severe SARS-CoV-2 infection (77,141). These health respiratory conditions included chronic obstructive pulmonary disease, asthma, interstitial lung disease, bronchiectasis, and obstructive sleep apnea. The airways hypersensitive, immune alteration, hypercapnia, hypoxemia, surges of sympathetic activation, and increased inflammatory markers, resulting from respiratory injuries, were the main contributors to a worse COVID-19 prognosis (142).

In this research, alongside oncological and respiratory pathologies, cardiovascular and cerebrovascular diseases were also identified to be strongly associated with COVID-19-related hospitalization, ICU admission, and death. This aligns with the findings of the literature, also considering specific cardio- and cerebrovascular pathologies such as hypertension, myocardial injury, heart failure, coronary artery disease, and stroke (143–145). The link between these diseases and worse COVID-19 outcomes could be attributed to the drugs used to manage cardiovascular and cerebrovascular risk, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). These medications increase the expression of ACE2, the viral receptor for SARS-COV-2, facilitating the virus's entry into pneumocytes. The interplay of drugs, compromised vascular health, and endothelial dysfunction amplified the severity of COVID-19 outcomes in patients with pre-existing cardiovascular and cerebrovascular diseases (146,147). Furthermore, several studies identified a greater risk in patients with cardiovascular conditions affected also by diabetes (72,143). Therefore, in line with the results of this doctoral project and other studies (76,148), it seemed that diabetes was an additional very significant risk factor for a worse COVID-19 prognosis. Several factors contributed to this association. Firstly, as above discussed, diabetes is often accompanied by other health conditions such as cardiovascular diseases and obesity (72,143,149), which independently pose risks for severe COVID-19 outcomes. Secondly, patients with diabetes have hyperglycemia, a higher risk of uncontrolled inflammatory response, greater levels of tissue injury–related enzymes, a hypercoagulable state, and higher serum levels of inflammatory biomarkers, such as C-reactive protein, D-dimer, interleukin-6 (IL-6), serum ferritin, and coagulation index, all of which contributed to a heightened susceptibility to SARS-CoV-2 infection (150,151). Finally, the presence of diabetes creates an environment conducive to a dysregulated immune system. This immune dysregulation in diabetic individuals manifests as dysfunction in phagocytic cells, ineffective clearance of microbes, impaired T-cell-mediated immune responses, inhibition of neutrophil chemotaxis, and altered cytokine production. These impairments collectively hindered the body's ability to mount an effective defense against viral infections, including SARS-CoV-2 (150,152).

Moreover, alongside the performance of at least one SARS-CoV-2 swab, positivity to COVID-19, hospitalization, ICU admission, and death, this doctoral research assessed two other outcomes related to COVID-19: non-discharge from the Emergency Department and the length of hospitalization. The results indicated that in the younger population (<65 years old), multimorbidity was a strong risk factor for these two outcomes.

The results concerning hospital stays align with other studies present in the literature. According to a study conducted by Bähler et al. (153), the length of hospitalization doubled for patients with multimorbid conditions. Once again, a compromised immune system and reduced physiological reserves resulting from co-existing clinical conditions seem to play a key role in prolonging hospital stays for surviving patients. Furthermore, it was found that in the older population (65+ years old) the association between CCI and death within 30 days from the first infection was the only statistically significant relationship in the second sample analyzed in this project. However, descriptive statistics indicated that elderly patients had lower rates of discharge from the ED, higher percentages of ICU admission, higher mortality in the first 30 days, and longer hospital stays. Therefore, it appeared that older age was an independent and significant risk factor for more severe COVID-19 outcomes. This trend was also shown in other studies (55,154).

Other important findings were identified through the mediation analyses. Focusing on the younger subgroup, direct significant effects were observed when evaluating the association between CCI and non-discharge from ED and between multimorbidity and length of hospitalization. On the other hand, the NEWS2 Score, used as a proxy of the severity of the patient's clinical conditions, did not appear to play a mediating role in these associations. Shifting the focus to the subgroup of the elderly, the results were found to be markedly different. According to the OR and HR estimates, no direct effect estimate was found to be statistically significant, while NEWS2 Score was identified as a mediator in the association between multimorbidity and non-discharge, as well as between CCI and the combined outcome consisting of ICU admission and death. Therefore, it appeared that in older patients, multimorbidity was associated with COVID-19 outcomes only when mediated by the NEWS2 Score, and that CCI was not directly associated with a worse prognosis of COVID-19. These results confirm that multimorbidity directly affected the younger population in relation to more severe COVID-19 outcomes, but not the elderly.

The main reason NEWS2 Score played the role of mediator exclusively in the older population and not in the younger group might be due to the different levels of homeostatic reserve present in the two subgroups. The homeostatic reserve refers to the body's ability to maintain stability and balance in its internal environment despite external challenges or stressors and reflects the capacity of physiological systems to adapt and respond to various demands, maintaining essential functions within a normal range. Some authors explained how much the severe loss of this reserve can impact the overall health of a person, specifically on frailty (155).

Considering that aging is widely recognized as one of the primary factors in the decline of organ reserve, that is the ability of an organ to successfully return to its original physiological state following repeated episodes of stress, some studies showed that this reserve is supported by an excess of metabolic capacity which, once compromised or depleted, reduces the cell's ability to cope with added workload and stress (156). Therefore, a hypothesis can be made to explain why the course of SARS-CoV-2 in the younger subgroup, especially in severe cases, exhibited a sudden deterioration even when the patient's conditions were stable. In fact, the NEWS2 Score had a limited impact on outcome prediction in the younger population, as the high physiological reserve limited organ dysfunction during the first phases of the infection. This resulted in the NEWS2 deteriorating only in the later phases of COVID-19 illness, which in the meantime had caused a drastic reduction in the homeostatic reserve. On the contrary, the older population’s physiological reserve was already low in the early stages of SARS-CoV-2 infection, and therefore the NEWS2 Score resulted in predictive at arrival at the Emergency Department. The process of losing reserve, which may culminate in the frailty syndrome, is characterized by aging and several factors associated with it. These factors can contribute to a worse condition in the elderly and a more challenging recovery of stable physiological functions. Notably, the development of a mild pro-inflammatory state, commonly known as inflammageing (157), and the resulting dysregulation in the organism (158) have a significant impact, especially in conjunction with a pre-existing clinical condition or multimorbidity (159,160). This phenomenon could explain how the severity of patient’s conditions at the time of accessing the Emergency Department played a key role in the relationship between the Charlson Index and the negative COVID-19-related outcomes assessed in this doctoral project.

In addition to focusing on certain COVID-19 outcomes related to the first wave, an additional aim of this doctoral thesis was to compare different COVID-19 endpoints among the first three pandemic waves (1st wave: 01/03/2020-15/04/2020, 2nd wave: 15/10/2020-15/12/2020, 3rd wave: 01/03/2021-15/04/2021).

The first notable finding that emerged from the comparison among the first three waves of the COVID-19 pandemic was that the number of cases detected during the second and third waves was significantly higher than in the first phase (1st wave: 405.0 cases per day; 2nd wave: 2366.4 cases per day; 3rd wave: 1778.8 cases per day). This aligns with other studies (161,162). The possible explanations for this finding were related to the policies implemented by the local government and the availability of tests, whose scarcity might lead to underestimation during the first wave. In fact, on one hand, the restrictive measures implemented during the first wave were much more stringent than in the second and third waves, and the strict national lockdown played a key role in reducing SARS-CoV-2 infections and shortening the peak period (163,164). On the other hand, the increased availability of tests, more laboratories performing RT-PCR, and the introduction of rapid antigenic testing both within hospitals and in the community in the last two waves played a crucial role in the greater capacity and ability to detect positive SARS-CoV-2 cases.

When assessing the demographic and clinical characteristics of infected patients across the first three waves, it was observed that positive patients were younger and with fewer comorbidities, both considering specific diseases and the Charlson Index. This finding, consistent with other research (165,166), reflects the higher diffusion of COVID-19 occurred in the active working population during the second and third wave, who meanwhile resumed work thanks to milder restrictive measures. Furthermore, during the initial wave, numerous residents in nursing homes were infected from the onset of the pandemic until April 2020, when visitor access was forbidden, and isolation and tracking protocols were implemented for staff and patients to reduce SARS-CoV-2 transmission. This contributed to the increase in the median age of infected patients during the first phase of the COVID-19 pandemic and a significant reduction from April 2020.

Even though the number of positive cases increased five to sixfold, only a slight rise in hospitalizations, ICU admissions, and deaths was observed in the latter two waves, although there was a significant decrease in percentage terms due to a strong increment in the number of asymptomatic infected subjects. Possible explanations include heightened awareness and knowledge of healthcare professionals in diagnosing and treating COVID-19 disease and a better organization for out-of-hospital COVID-19 care, such as Special Units for Continuing Care at Home (167). Another crucial factor is the most prevalent virus lineage present in Italy during this period. According to a report from the Italian National Institute of Health (168), the predominant variant circulating in Italy during the later phases was the B.1.1.7 lineage (Alpha variant), known for its high transmissibility. In contrast, other more lethal SARS-CoV-2 variants, such as the Delta variant (0.2% of cases in the period from December 28, 2020, to May 19, 2021), were less prevalent in the Italian territory. This would explain the high number of SARS-CoV-2-positive cases and the lower severity of the disease.

Focusing on the infected patients who were hospitalized due to illness, from the results of the project emerged that between the first and second waves, the percentages and number of admissions to the hospital slightly increased over time, particularly among those aged 75 years and older and with pre-existing clinical conditions. However, during the third wave, a significant reduction was observed. In addition to the evidence that elderly patients could be safely treated at home or in nursing homes (169), another important factor that could explain this result was the impact of prioritizing vaccination of frail and older patients. In fact, as discussed in the "Introduction" section, the first categories of subjects to be vaccinated in Italy included the older population and those with a higher burden of comorbidity. Therefore, the marked reduction in SARS-CoV-2 infections observed in elderly subjects and patients with certain clinical conditions, such as dementia (from 3.4% to 1.2%), could be largely attributed to the vaccination campaign. Moreover, in line with the results concerning infected subjects discussed above and with the literature (170,171), a reduction in the percentage of hospitalized subjects who were admitted to the ICU or who died was noted during the latter waves. Also in this case, the possible reasons were the increased knowledge of health professionals in treating patients with COVID-19, several improvements in care and treatment of the illness, and the predominant presence of a highly transmissible variant that, while more contagious, was not among the most lethal.

Another indication of the improvement in the national healthcare system's response to the COVID-19 pandemic is reflected in the results concerning the health procedures implemented towards infected patients. The data revealed a trend comparing the first and the latter two waves, indicating a decrease in the use of invasive mechanical ventilation and tracheostomy, and a parallel increase in Continuous positive airway pressure (CPAP) and non-invasive ventilation, both in ICUs, in high dependency units, and low intensity-of-care wards. This trend, in line with other studies conducted in other countries (172,173), reflects enhanced resource availability within national health systems, better-trained health staff, and improved knowledge on treating SARS-CoV-2 patients, on ventilation, and on its weaning during subsequent waves (173,174). Comparing the second and third waves, instead, slight increases in the use of CPAP (both in and out of the ICU), intubation, tracheotomy, and invasive ventilation were observed. These differences might be attributed to the fact that, during the third wave, COVID-19 patients who were hospitalized were younger, more severely ill, and treated for more severe respiratory failures. The possible factors contributing to this shift were the presence of the Delta variant, albeit limited in the Italian territory until summer 2021 (175), and age-related differences in the immune response.

Examining the length of hospital stay, this research observed a reduction over time both in ICU (from 28.0 to 24.8 days) and in other hospital wards (from 18.8 to 16.4 days). Similar findings were also noted in-hospital mortality. These trends, consistent with the existing literature (165,176), could be attributed to the improvements in therapeutic approaches, resource optimization, and several organizational enhancements (164,172–174). These improvements encompassed a greater availability of beds in ICUs, other hospital wards, and external facilities, which contributed to the reduction of hospital overload, and a more efficient allocation of resources and timely admission of COVID-19 patients.

Another significant finding that emerged from the comparison of the first three waves of COVID-19 was related to the subgroup of subjects who died from SARS-CoV-2. While those who died were predominantly over 76 throughout the analysis period, during the third wave there was an increase, in percentage terms, in mortality among younger individuals and those with fewer comorbidities. Even when analyzing specific diseases separately, a reduction in mortality was observed among those with pre-existing clinical conditions during the third wave of the pandemic. This pattern, statistically significant in assessing cerebrovascular diseases, cardiovascular diseases, kidney injuries, neoplasia, and dementia, could be attributed to the Italian government's vaccination policy that chose to prioritize vaccination of elderly and frail patients.

Furthermore, combining more adverse outcomes (ICU admission and death), OR estimates indicated that being male, older, and having one or more clinical conditions were independent risk factors for a worse prognosis of COVID-19. Nevertheless, after controlling for the possible confounding factors, the results demonstrated that patients infected in the second and third waves experienced a significant and independent reduction in the risk of developing severe outcomes. This insight is very important, as it reflects the fact that great improvement occurred over time.

In addition to identifying multimorbidity or certain previous diseases as significant risk factors for a worse prognosis in COVID-19, this research showed how various aspects of individuals' lives, habits, routines, and behaviors, whether they were students or healthcare workers, young or elderly, with or without comorbidities, were profoundly disrupted by the pandemic. These disruptions extended far beyond the realm of physical health, impacting mental well-being, social interactions, and professional environments. From sudden shifts to remote work and online learning to heightened stress levels and challenges in accessing healthcare services, the pandemic reshaped daily life for millions worldwide, highlighting the interconnectedness of health outcomes with broader societal factors. For this reason, in the last part of this doctoral thesis, the impact of the SARS-CoV-2 pandemic on one of the most important addictions and habits was examined: gambling.

According to gambling data in Italy, significant shifts in gambling expenditure from 2019 to 2021 were observed. In 2019, the total amount gambled was 110.54 billion euros, while in 2020 there was a significant 20% decrease, with a total expenditure of 88.38 billion euros (177,178). When distinguishing between land-based and online gambling, a sharp contrast emerged: land-based gambling experienced a notable 47.2% decline in 2020, while online gambling had a substantial increase of 35%. By 2021, data showed that gambling settled back to pre-pandemic values, with the total amount returning to pre-pandemic levels at 111.17 billion euros. However, a significant change occurred between 2019 and 2021: in 2019, 67% of gambling was concentrated in land-based activities; in 2021, this percentage plummeted to just under 40%, signaling a remarkable shift as online gambling exceeded 60% (179). Similar results were also observed when analyzing data on gambling around the world (180). Therefore, from the data, it seemed that the COVID-19 pandemic had a great impact on gambling habits.

These findings were confirmed by the systematic review conducted on this topic in this doctoral thesis. From the twenty-eight studies included in this review, the first important result was that a significant decrease in the frequency and expenditure of land-based gambling emerged (109,181–184). This significant decrease in land-based activities could be attributed primarily to the closure of several physical gambling activities, including casinos, bingo halls, poker rooms, and betting stores (185). This was coupled with stringent restrictions imposed on citizens, prohibiting them from leaving their homes except for essential reasons.

Focusing on online gambling, instead, the findings presented a more intricate picture. Specifically, while certain studies indicated a significant decline in sports betting, others demonstrated a notable increase in online casino activities and skill games (183,184,186). Moreover, in line with gambling-related data, some studies addressing overall online gambling noted an increase both in frequency and expenditure (106,187). The possible factors contributing to this rise in online gambling included the prolonged time spent at home due to restrictive measures that required people to stay at home, especially during the more challenging phases of the pandemic (182,188), and the worsened mental well-being of individuals, who experienced higher levels of anxiety, depression, and stress during this difficult period (189,190). As reported by different studies, these heightened mental health issues were linked to risky behaviors, including increased involvement in gambling activities (191–193). Regarding sports betting, instead, the main reason for this strong decline was the cancellation or suspension of major sporting events during the first months of the pandemic, rendering it essentially impossible for subjects to bet on sports events such as football, basketball, tennis, and volleyball, which they traditionally engaged in before the onset of SARS-CoV-2 (102).

A further outcome investigated in this systematic review was the transitions among different types of gambling. According to the studies, it emerged that there was a migration of subjects from land-based venues to online platforms (106,108,109). However, it was observed that subjects accustomed to specific types of gambling, such as land-based slot machines or casinos, mainly shifted to the online version of the same type of gambling without changing the game. Only a minority transitioned to other games. For this reason, especially among sports bettors, a lower gambling frequency was noted compared to pre-pandemic levels (184,194,195), due to the suspension of sports events on which the subjects used to bet. One possible explanation for the lack of initiation of new online gambling habits in most cases could lie in the demographic characteristics of individuals who engage in specific types of gambling. Those who play video poker or engage in sports betting tend to be younger, more educated, and better informed about the dynamics of these specific games (196).

Although these results are generalizable to the entire population, certain most vulnerable subgroups experienced a more pronounced impact from the restrictions (106,182,183,194,195,197–199). These groups encompassed the unemployed, precarious workers, subjects with psychological conditions, and those struggling with addictions such as alcohol, drugs, and gambling. The increase in free time resulting from stay-at-home measures exacerbated addictive behaviors and mental health issues (189,200). For this reason, these subgroups faced a worsening of their conditions during the COVID-19 pandemic, and subjects with pathological addictions experienced a heightened risk of relapse due to the limitations imposed by stay-at-home policies and the resulting increased desire (201). In this scenario, these vulnerable subgroups were more susceptible to an escalation in their gambling habits. Also focusing on the subgroups of gamblers before the SARS-CoV-2 outbreak, the systematic review identified a significant worsening in gambling habits in the most vulnerable populations (104,182,194,197,198,202). In addition to vulnerable populations, the pandemic also significantly impacted another subgroup: the younger population. The closure of schools, universities, and other places generally frequented by youths such as pubs, discos, cinemas, gyms, and sports centers, coupled with social distancing restrictions, led to a substantial increase in the time spent at home, resulting in elevated levels of anxiety, stress, and depression (203–205). In this context, the technological skills and abilities of the younger populations played a crucial role: while enabling them to maintain social connections remotely, such as through the use of social media and free online games, it also led to some negative behaviors, such as engaging in gambling on online platforms, which, unlike land-based gambling, continued to operate even during the most challenging phases of the pandemic. Nevertheless, it is important to observe that the findings were not totally consistent across the studies included in this systematic review (104,108,182,183,194,195,197,198,202,206,207). This heterogeneity was one of the reasons behind the decision to conduct a systematic review without a meta-analysis. Indeed, it is acknowledged that in the presence of high heterogeneity among studies, a systematic review is more suitable for describing and summarizing the literature on a particular topic. Another significant reason was the low number of studies that have analyzed the same type of gambling (online or land-based), with the same designs (longitudinal or case-control study), and estimating the same association or occurrence measures, making the implementation of a meta-analysis unfeasible.

Another notable aspect emerged by conducting this systematic review is that all the included studies were conducted in the most developed countries, and particularly in the European continent. One plausible reason for this could be that gambling, especially in specific forms such as online gambling, may be more prevalent and subject to heightened attention from researchers and policymakers in most developed countries, including Europe. Moreover, these countries possess greater availability of data and resources for gambling research compared to other regions of the world, where data are often scarce and frequently unreliable. Furthermore, most developed countries might have more advanced regulatory systems and public policies aimed at addressing the issue of gambling, thereby increasing the likelihood of studies and research being conducted on this topic in such regions.

This doctoral project has several strengths. The first lies in the type of data utilized in this project. The first and third studies were conducted using the Piedmont Longitudinal Study (PLS), which encompasses approximately 4 million subjects. The PLS databases contain a wealth of clinical, hospital-related, and sociodemographic information collected over time, enabling the identification of pre-existing clinical conditions, the therapies or procedures implemented in the hospital during the pandemic, and the calculation of the CCI at an individual level. Additionally, the second study was conducted using the EPICLIN platform, whose information was gathered by analyzing patients' medical records one by one, providing detailed and precise information. The second important strength lies in the very large sample size of subjects involved in both the first and third studies. To date, these are among the first studies involving such a large cohort (the entire Piedmont population in this case) to investigate various COVID-19-related outcomes, including swab access, positivity to SARS-CoV-2, hospitalization, ICU admission, and death. Another strength lies in the methods used throughout this doctoral project. The use of multistate models, mediation analyses, and systematic review allowed for the investigation of these topics in an advanced and innovative manner. Moreover, this project is the first to explore the role played by the severity of a patient's clinical conditions upon arrival in the Emergency Department in the association between multimorbidity and different SARS-CoV-2 outcomes, revealing crucial findings. In addition, the systematic review conducted is the first systematic research, in the literature, to entirely focus on the impact of the COVID-19 pandemic and related restrictive measures on gambling.

In addition to these strengths, another crucial aspect of this research lies in its profound utility. Indeed, by scrutinizing various dimensions of the SARS-CoV-2 pandemic, including the identification of major risk factors such as previous diseases or multimorbidity, tracking its evolution over time, and examining the adaptability and speed of response within our national healthcare system, we can establish a framework for proactive measures and enhance preparedness against potential future pandemics. Through a comprehensive exploration of the intricacies surrounding COVID-19, we acquire the essential knowledge necessary for refining public health policies, bolstering surveillance systems, and devising swift response mechanisms. This multifaceted understanding not only empowers us to mitigate the immediate impacts of the current crisis but also equips us with invaluable insights to navigate and mitigate the challenges posed by future global health emergencies.

However, this doctoral project has some limitations. The first is related to the fact that the first three studies focus exclusively on the Piedmont population (or only some hospitals in Piedmont). Differences in the regional healthcare systems and the spread of SARS-CoV-2 among regions imply that the results are not totally generalizable to the entire country. However, Piedmont was one of the most affected populations, at least during the first phases of the pandemic. A second limitation concerns the use of some proxies, such as the NEWS2 Score and CCI, which could lead to a deviation from the real patient's clinical condition in some cases, although they are two indicators using validated algorithms. For this reason, these deviations should be minimized.

Finally, about gambling, the limitation concerns the information present in the studies included in the systematic review. As most of the studies collected information about gambling from questionnaires, responses regarding gambling frequency and expenditure during the pre-pandemic period may be affected by recall bias. Moreover, some authors offered a reward in exchange for filling out the questionnaire, which could potentially lead respondents to provide inaccurate answers to obtain the reward (information bias).

5. CONCLUSIONS

This doctoral project presents several significant findings.

Primarily, this thesis found that, during the first wave, patients with pre-existing clinical conditions or multimorbidity underwent more vigilant monitoring and COVID-19 testing, and as the Charlson Index increased, this risk was gradually higher. Despite the increased monitoring, these subjects had a lower risk of testing positive for the virus when compared with the overall swabbed population. This lower risk could be attributed to the heightened adherence of those with pre-existing clinical conditions to anti-COVID measures, such as social distancing, mask usage, and frequent handwashing. However, this likelihood became significantly higher only when the overall Piedmont population was considered. Furthermore, among infected patients, pre-existing diseases and multimorbidity were found to increase the risk of hospitalization and death within 30 days of the first positive swab, while previous clinical conditions emerged as risk factors for increased ICU admission only when considering the entire population.

When comparing the younger and older populations, from the OR estimates emerged that multimorbidity was a risk factor for a worse prognosis of COVID-19 especially in the younger population. Focusing on specific diseases, respiratory and oncological conditions were found to be the most crucial risk factors affecting the course of COVID-19. This finding could be attributed to the immunocompromised state of oncological patients due to cancer therapies and the various respiratory challenges faced by subjects with respiratory diseases, such as hypersensitive airways, hypercapnia, hypoxemia, and increased inflammatory markers, all contributing to the exacerbation of the disease.

In the early stages of the pandemic, these results held significant importance for both healthcare professionals and policymakers. Healthcare professionals gained valuable insights into which categories were more prone to developing severe COVID-19 outcomes, while policymakers could use this information to organize and strategize vaccination campaigns, prioritizing specific subgroups to effectively reduce their risk.

Two additional outcomes examined in this project were the non-discharge after accessing the ED and the length of hospitalization during the first wave. The results indicated that a higher CCI value increased the risk of not being discharged and significantly prolonged the length of hospitalization in the younger population. Conversely, these estimates were not significant when considering the subgroup of the elderly. Moreover, evaluating whether the NEWS2 Score, used as a proxy for the severity of the patient's clinical condition during ED access, played a mediating role in the association between multimorbidity and various COVID-19 outcomes, it was observed that in the younger subgroup, multimorbidity was directly associated with an increased risk of non-discharge and longer hospitalization. Instead, for the older population, it emerged that the NEWS2 Score played the role of mediator in the association between CCI and the combined outcome of ICU admission/death as well as between multimorbidity and non-discharge.

These findings are very important, emphasizing that when healthcare professionals decide on procedures and treatments, they should consider not only the comorbidity burden of patients but also their clinical condition upon arriving at the ED. The NEWS2 Score has proven to be a reliable indicator in this regard.
Comparing the first three waves of the COVID-19 pandemic, a substantial increase in the number of cases was observed during the second and third waves compared to the first wave. Examining the clinical and demographic characteristics of infected subjects revealed that those who tested positive in the later waves were younger and with fewer comorbidities. This finding may be attributed to the fact that patients contracting the virus during these phases, during which lockdown measures were less stringent, were primarily active working subjects. However, despite this surge in the number of positive cases, there was only a small increase in absolute terms in hospitalization, ICU admission, and deaths, while the percentages were significantly lower.
Analyzing the subgroup of infected subjects who were hospitalized, a slight increase in hospitalizations among the elderly was observed between the first and second waves, while a significant decrease was noted in the third wave, potentially attributable to the effectiveness of the vaccination campaign implemented by the Italian government. In addition, overall, the percentage of those who were admitted to the ICU or died decreased over time, indicating that healthcare professionals made more informed decisions regarding the care and treatment of COVID-19 patients. This was also evident when analyzing the therapies and procedures implemented during the first three waves: compared to the initial stages of the pandemic, less use of tracheotomy, intubation, and invasive ventilation occurred, while the use of CPAP and non-invasive ventilation increased. Simultaneously, the length of hospitalization in both ICUs and other hospital wards decreased over time. Further findings were found by investigating deceased subjects. While the majority of deaths were among individuals aged 76 and above, during the third wave an increase in mortality percentages among younger individuals and a reduction among those with pre-existing conditions emerged. Again, therefore, it appears that vaccination had a significant effect.
The last important finding observed comparing the first three waves concerns the risk of poorer outcomes of COVID-19 (ICU admission and death) over time, after removing possible confounding. The results showed a substantial and independent reduction in the risk of ICU admission or mortality during the second and third waves. This is very important because suggests remarkable improvements over time. The natural course of the pandemic, the appearance of new viral variants, the starting of vaccination, and the improvements in the tracking of new cases and patient management influenced these trends.
Finally, when assessing the impact of the COVID-19 pandemic on gambling, a significant reduction in land-based gambling, and a parallel surge in the risks associated with online gambling, especially considering virtual casino and skill games, emerged. Additionally, migration from land-based venues to online platforms was observed, especially among individuals who engaged in gambling before the pandemic. This shift involved a change in the location of play, transitioning from land-based venues to the comfort of home through tablet and smartphone apps. Focusing on sports bettors, the systematic

review revealed a strong reduction in this type of activity.

The main contributing factors to these findings were: the physical closure of gambling venues, including casinos, bingo halls, poker rooms, and betting stores, while, online platforms continued to operate; the cancelation or suspension of major sporting events such as male and female football, tennis, volleyball, and basketball championships, on which the subjects used to bet; the increased time spent at home due to restrictive measures that imposed to stay at home; the elevated levels of anxiety, frustration, depression, and distress experienced by the subjects during this challenging period. Notably, the impact of restrictions on gambling habits was more pronounced among the most vulnerable subgroups. The most vulnerable categories include the unemployed, precarious workers, those with psychological conditions, and those with specific addictions such as alcohol, drugs, and gambling before the pandemic outbreak.

To date, despite four years having passed since the first cases of SARS-CoV-2 were detected, a comprehensive and ongoing study of the COVID-19 pandemic remains crucial, offering invaluable insights that can shape our preparedness and response strategies for potential future global health crises. Analyzing the multifaceted aspects of this pandemic, from its origins and transmission dynamics to the effectiveness of public health measures can lay the foundation for proactive measures against potential future pandemics. By delving into the complexities of COVID-19, we gain the knowledge needed to refine public health policies, enhance surveillance systems, and develop rapid response mechanisms.

6. REFERENCES

1. Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, et al. Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. Cell Host Microbe. 2020 Mar 11;27(3):325–8.

2. Kim D, Lee JY, Yang JS, Kim JW, Kim VN, Chang H. The Architecture of SARS-CoV-2 Transcriptome. Cell. 2020 May 14;181(4):914-921.e10.

3. Al-Qaaneh AM, Alshammari T, Aldahhan R, Aldossary H, Alkhalifah ZA, Borgio JF. Genome composition and genetic characterization of SARS-CoV-2. Saudi J Biol Sci. 2021 Mar 1;28(3):1978–89.

4. Hao Y, Wang Y, Wang M, Zhou L, Shi J, Cao J, et al. The origins of COVID-19 pandemic: A brief overview. Transbound Emerg Dis. 2022 Oct 20;10.1111/tbed.14732.

5. Wu XD, Shang B, Yang RF, Yu H, Ma ZH, Shen X, et al. The spike protein of severe acute respiratory syndrome (SARS) is cleaved in virus infected Vero-E6 cells. Cell Res. 2004 Oct;14(5):400.

6. Jiang Y, Yin W, Xu HE. RNA-dependent RNA polymerase: Structure, mechanism, and drug discovery for COVID-19. Biochem Biophys Res Commun. 2021 Jan 29;538:47–53.

7. World Health Organization. Listings of WHO's response to COVID-19 [Internet]. [cited 2023 Nov 29]. Available from: https://www.who.int/news/item/29-06-2020-covidtimeline

8. Spiteri G, Fielding J, Diercke M, Campese C, Enouf V, Gaymard A, et al. First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020. Eurosurveillance. 2020 Mar 5;25(9):2000178.

9. Vestergaard LS, Nielsen J, Richter L, Schmid D, Bustos N, Braeye T, et al. Excess all-cause mortality during the COVID-19 pandemic in Europe - preliminary pooled estimates from the EuroMOMO network, March to April 2020. Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull. 2020 Jul;25(26):2001214.

10. Rossen LM, Nørgaard SK, Sutton PD, Krause TG, Ahmad FB, Vestergaard LS, et al. Excess all-cause mortality in the USA and Europe during the COVID-19 pandemic, 2020 and 2021. Sci Rep. 2022 Nov 3;12(1):18559.

11. Fouillet A, Pontais I, Caserio-Schönemann C. Excess all-cause mortality during the first wave of the COVID-19 epidemic in France, March to May 2020. Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull. 2020 Aug;25(34):2001485.

12. Pani SM, Cadoni F, Minerba L. Study of the excess mortality associated with the SARS-CoV-2 pandemic in the Local Health Authorities and Districts of the Autonomous Region of Sardinia - quinquennium 2017-2021. Ann Ig Med Prev E Comunita. 2023 Nov 23;

13. Griffin S. Covid-19: England had worst excess mortality in Europe in April. BMJ. 2020 Jul 31;370:m3058.

14. French G. Impact of Hospital Strain on Excess Deaths During the COVID-19 Pandemic — United States, July 2020–July 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021 [cited 2023 Nov 29];70. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7046a5.htm

15. Morley C, Unwin M, Peterson GM, Stankovich J, Kinsman L. Emergency department crowding: A systematic review of causes, consequences and solutions. PloS One. 2018;13(8):e0203316.

16. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. [cited 2023 Nov 28]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

17. World Health Organization. WHO Director-General's opening remarks at the media briefing – 5 May 2023 [Internet]. [cited 2023 Nov 28]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing---5-may-2023

18. World Health Organization. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data [Internet]. [cited 2023 Nov 28]. Available from: https://covid19.who.int/

19. COVID-19 US STATE POLICIES (CUSP). Policies to Prevent COVID-19 – CUSP [Internet]. [cited 2023 Nov 29]. Available from: https://statepolicies.com/policy-by-topic/covid-prevention/

20. Wilder-Smith A, Freedman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. J Travel Med. 2020 Mar 13;27(2):taaa020.

21. Babuna P, Yang X, Gyilbag A, Awudi DA, Ngmenbelle D, Bian D. The Impact of COVID-19 on the Insurance Industry. Int J Environ Res Public Health. 2020 Aug 10;17(16):5766.

22. Açikgöz Ö, Günay A. The early impact of the Covid-19 pandemic on the global and Turkish economy. Turk J Med Sci. 2020 Apr 21;50(SI-1):520–6.

23. Aigbedo H. Impact of COVID-19 on the hospitality industry: A supply chain resilience perspective. Int J Hosp Manag. 2021 Sep;98:103012.

24. Pompili M, Innamorati M, Sampogna G, Albert U, Carmassi C, Carrà G, et al. The impact of Covid-19 on unemployment across Italy: Consequences for those affected by psychiatric conditions. J Affect Disord. 2022 Jan 1;296:59–66.

25. Geranios K, Kagabo R, Kim J. Impact of COVID-19 and Socioeconomic Status on Delayed Care and Unemployment. Health Equity. 2022;6(1):91–7.

26. Saladino V, Algeri D, Auriemma V. The Psychological and Social Impact of Covid-19: New Perspectives of Well-Being. Front Psychol [Internet]. 2020 [cited 2023 Nov 30];11. Available from: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.577684

27. Rajkumar RP. COVID-19 and mental health: A review of the existing literature. Asian J Psychiatry. 2020 Aug;52:102066.

28. Zhu C, Zhang T, Li Q, Chen X, Wang K. Depression and Anxiety During the COVID-19 Pandemic: Epidemiology, Mechanism, and Treatment. Neurosci Bull. 2023 Apr 1;39(4):675–84.

29. Jones EAK, Mitra AK, Bhuiyan AR. Impact of COVID-19 on Mental Health in Adolescents: A Systematic Review. Int J Environ Res Public Health. 2021 Mar 3;18(5):2470.

30. Patt D, Gordan L, Diaz M, Okon T, Grady L, Harmison M, et al. Impact of COVID-19 on Cancer Care: How the Pandemic Is Delaying Cancer Diagnosis and Treatment for American Seniors. JCO Clin Cancer Inform. 2020 Nov 30;4:CCI.20.00134.

31. Aras D, Tang A, Ahmad H. Analysis of the Covid-19 pandemic impact on osteoarthritis patient visits at physiotherapy clinics in Indonesia - A retrospective cohort study. Ann Med Surg 2012. 2022 Dec;84:104826.

32. Ciddi PK, Bayram GA. Impact of COVID-19 on rehabilitation experiences of physiotherapists. Work Read Mass. 2022;71(1):31–9.

33. Choi SE, Mo E, Sima C, Wu H, Thakkar-Samtani M, Tranby EP, et al. Impact of COVID-19 on Dental Care Utilization and Oral Health Conditions in the United States. JDR Clin Transl Res. 2023 Apr 21;23800844231165016.

34. Michalowsky B, Hoffmann W, Bohlken J, Kostev K. Effect of the COVID-19 lockdown on disease recognition and utilisation of healthcare services in the older population in Germany: a cross-sectional study. Age Ageing. 2020 Nov 17;50(2):317–25.

35. Bansal S, Roy M, Chatterjee T, Roy AK. Deaths due to delayed presentation to the hospital from fear of contracting COVID-19 during lockdown period: a tertiary care center experience. J Community Hosp Intern Med Perspect. 2021;11(3):299–301.

36. Maung KK, Marques-Vidal P. Impact of COVID-19 pandemic on cardiovascular diseases hospitalisation, management and mortality in Switzerland. Open Heart. 2023 Mar 28;10(1):e002259.

37. Zhang X, Elsaid MI, DeGraffinreid C, Champion VL, Paskett ED, Impact of COVID-19 on Behaviors across the Cancer Control Continuum in Ohio group. Impact of the COVID-19 Pandemic on Cancer Screening Delays. J Clin Oncol Off J Am Soc Clin Oncol. 2023 Jun 10;41(17):3194–202.

38. Fazli G, Moineddin R, Ling V, Booth G. Changes to Diabetes Screening During the Early Waves of the COVID-19 Pandemic. Can J Diabetes. 2022 Nov;46(7):S13–4.

39. Hirschfeld CB, Shaw LJ, Williams MC, Lahey R, Villines TC, Dorbala S, et al. Impact of COVID-19 on Cardiovascular Testing in the United States Versus the Rest of the World. Jacc Cardiovasc Imaging. 2021 Sep;14(9):1787–99.

40. World Health Organization. Tracking SARS-CoV-2 variants [Internet]. [cited 2023 Nov 30]. Available from: https://www.who.int/activities/tracking-SARS-CoV-2-variants

41. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021 Apr 9;372(6538):eabg3055.

42. Frampton D, Rampling T, Cross A, Bailey H, Heaney J, Byott M, et al. Genomic characteristics and clinical effect of the emergent SARS-CoV-2 B.1.1.7 lineage in London, UK: a whole-genome sequencing and hospital-based cohort study. Lancet Infect Dis. 2021 Sep;21(9):1246–56.

43. Davies NG, Jarvis CI, Edmunds WJ, Jewell NP, Diaz-Ordaz K, Keogh RH. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. Nature. 2021 May;593(7858):270–4.

44. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, Yassine HM, Benslimane FM, Al Khatib HA, et al. Severity, Criticality, and Fatality of the Severe Acute Respiratory Syndrome Coronavirus 2

(SARS-CoV-2) Beta Variant. Clin Infect Dis Off Publl Infect Dis Soc Am. 2022 Aug 24;75(1):e1188–91.

45. Jassat W, Mudara C, Ozougwu L, Tempia S, Blumberg L, Davies MA, et al. Difference in mortality among individuals admitted to hospital with COVID-19 during the first and second waves in South Africa: a cohort study. Lancet Glob Health. 2021 Sep;9(9):e1216–25.

46. Aleem A, Akbar Samad AB, Vaqar S. Emerging Variants of SARS-CoV-2 and Novel Therapeutics Against Coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Nov 30]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK570580/

47. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido D da S, Mishra S, et al. Genomics and epidemiology of a novel SARS-CoV-2 lineage in Manaus, Brazil. medRxiv. 2021 Mar 3;2021.02.26.21252554.

48. Mlcochova P, Kemp SA, Dhar MS, Papa G, Meng B, Ferreira IATM, et al. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. Nature. 2021 Nov;599(7883):114–9.

49. Zhan Y, Yin H, Yin JY. B.1.617.2 (Delta) Variant of SARS-CoV-2: features, transmission and potential strategies. Int J Biol Sci. 2022;18(5):1844–51.

50. Varea-Jiménez E, Aznar Cano E, Vega-Piris L, Martínez Sánchez EV, Mazagatos C, García San Miguel Rodríguez-Alarcón L, et al. Comparative severity of COVID-19 cases caused by Alpha, Delta or Omicron SARS-CoV-2 variants and its association with vaccination. Enfermedades Infecc Microbiol Clin Engl Ed. 2023 Feb 1;S2529-993X(23)00039-4.

51. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021 Aug 12;385(7):585–94.

52. Ren SY, Wang WB, Gao RD, Zhou AM. Omicron variant (B.1.1.529) of SARS-CoV-2: Mutation, infectivity, transmission, and vaccine resistance. World J Clin Cases. 2022 Jan 7;10(1):1–11.

53. Callaway E, Ledford H. How bad is Omicron? What scientists know so far. Nature. 2021 Dec;600(7888):197–9.

54. Hyams C, Challen R, Marlow R, Nguyen J, Begier E, Southern J, et al. Severity of Omicron (B.1.1.529) and Delta (B.1.617.2) SARS-CoV-2 infection among hospitalised adults: a prospective cohort study in Bristol, United Kingdom. Lancet Reg Health – Eur [Internet]. 2023 Feb 1 [cited 2023 Dec 1];25. Available from: https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(22)00252-6/fulltext

55. Starke KR, Reissig D, Petereit-Haack G, Schmauder S, Nienhaus A, Seidler A. The isolated effect of age on the risk of COVID-19 severe outcomes: a systematic review with meta-analysis. BMJ Glob Health. 2021 Dec 1;6(12):e006434.

56. Luo H, Liu S, Wang Y, Phillips-Howard PA, Ju S, Yang Y, et al. Age differences in clinical features and outcomes in patients with COVID-19, Jiangsu, China: a retrospective, multicentre cohort study. BMJ Open. 2020 Oct 1;10(10):e039887.

57. Fabião J, Sassi B, Pedrollo EF, Gerchman F, Kramer CK, Leitão CB, et al. Why do men have worse COVID-19-related outcomes? A systematic review and meta-analysis with sex adjusted for age. Braz J Med Biol Res. 2022 Feb 16;55:e11711.

58. Ballering AV, Oertelt-Prigione S, olde Hartman TC, Rosmalen JGM. Sex and Gender-Related Differences in COVID-19 Diagnoses and SARS-CoV-2 Testing Practices During the First Wave of the Pandemic: The Dutch Lifelines COVID-19 Cohort Study. J Womens Health. 2021 Dec 1;30(12):1686–92.

59. Pan D, Sze S, Minhas JS, Bangash MN, Pareek N, Divall P, et al. The impact of ethnicity on clinical outcomes in COVID-19: A systematic review. EClinicalMedicine. 2020 Jun 1;23:100404.

60. Ugarte-Gil MF, Alarcón GS, Seet AM, Izadi Z, Montgomery AD, Duarte-García A, et al. Association Between Race/Ethnicity and COVID-19 Outcomes in Systemic Lupus Erythematosus Patients From the United States: Data From the COVID-19 Global Rheumatology Alliance. Arthritis Care Res. 2023 Jan;75(1):53–60.

61. National Public Health (NHS). Disparities in the risk and outcomes of COVID-19. 2020 Aug;

62. House of Commons Women and Equalities Committee. Unequal impact? Coronavirus and BAME people. 2020 Dec 8;

63. Yoshikawa M, Asaba K. Educational Attainment Decreases the Risk of COVID-19 Severity in the European Population: A Two-Sample Mendelian Randomization Study. Front Public Health. 2021 Jun 3;9:673451.

64. Zhuo J, Harrigan N. Low education predicts large increase in COVID-19 mortality: the role of collective culture and individual literacy. Public Health. 2023 Aug 1;221:201–7.

65. Nafilyan V, Pawelek P, Ayoubkhani D, Rhodes S, Pembrey L, Matz M, et al. Occupation and COVID-19 mortality in England: a national linked data study of 14.3 million adults. Occup Environ Med. 2022 Jul 1;79(7):433–41.

66. Mutambudzi M, Niedzwiedz C, Macdonald EB, Leyland A, Mair F, Anderson J, et al. Occupation and risk of severe COVID-19: prospective cohort study of 120 075 UK Biobank participants. Occup Environ Med. 2021 May 1;78(5):307–14.

67. Apenyo T, Vera-Urbina AE, Ahmad K, Taveira TH, Wu WC. Association between median household income, state Medicaid expansion status, and COVID-19 outcomes across US counties. PLoS ONE. 2022 Aug 11;17(8):e0272497.

68. Fernández-Martínez NF, Ruiz-Montero R, Gómez-Barroso D, Rodríguez-Torronteras A, Lorusso N, Salcedo-Leal I, et al. Socioeconomic differences in COVID-19 infection, hospitalisation and mortality in urban areas in a region in the South of Europe. BMC Public Health. 2022 Dec 12;22(1):2316.

69. de Lusignan S, Dorward J, Correa A, Jones N, Akinyemi O, Amirthalingam G, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. Lancet Infect Dis. 2020 Sep;20(9):1034–42.

70. K C M, Oral E, Straif-Bourgeois S, Rung AL, Peters ES. The effect of area deprivation on COVID-19 risk in Louisiana. PloS One. 2020;15(12):e0243028.

71. Mateo-Urdiales A, Fabiani M, Rosano A, Vescio MF, Del Manso M, Bella A, et al. Socioeconomic patterns and COVID-19 outcomes before, during and after the lockdown in Italy (2020). Health Place. 2021 Sep;71:102642.

72. Burhan E, Mubarak F, Adilah SASU, Sari CYI, Ismail E, Astuti P, et al. Association between cardiovascular diseases and COVID-19 pneumonia outcome in Indonesia: a multi-center cohort study. Front Med. 2023;10:1190148.

73. Li X, Guan B, Su T, Liu W, Chen M, Bin Waleed K, et al. Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis. Heart Br Card Soc. 2020 Aug;106(15):1142–7.

74. Xu J, Xiao W, Liang X, Shi L, Zhang P, Wang Y, et al. A meta-analysis on the risk factors adjusted association between cardiovascular disease and COVID-19 severity. BMC Public Health. 2021 Aug 11;21(1):1533.

75. Nia AM, Srinivasan VM, Hayworth MK, Lall RR, Kan P. A History of Cerebrovascular Disease Is Independently Associated with Increased Morbidity and Mortality in Patients with COVID-19: A Cohort Study of 369,563 COVID-19 Cases in the USA. Cerebrovasc Dis. 2021 Aug 6;51(1):20–8.

76. Gęca T, Wojtowicz K, Guzik P, Góra T. Increased Risk of COVID-19 in Patients with Diabetes Mellitus—Current Challenges in Pathophysiology, Treatment and Prevention. Int J Environ Res Public Health. 2022 Jan;19(11):6555.

77. Aveyard P, Gao M, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, et al. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. Lancet Respir Med. 2021 Aug;9(8):909–23.

78. Johansson ALV, Skog A, Johannesen TB, Myklebust TÅ, Skovlund CW, Mørch LS, et al. Were cancer patients worse off than the general population during the COVID-19 pandemic? A population-based study from Norway, Denmark and Iceland during the pre-vaccination era. Lancet Reg Health – Eur [Internet]. 2023 Aug 1 [cited 2023 Dec 11];31. Available from: https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(23)00099-6/fulltext

79. Schiffl H, Lang SM. Long-term interplay between COVID-19 and chronic kidney disease. Int Urol Nephrol. 2023 Feb 24;1–8.

80. McConnell KH, Hajat A, Sack C, Mooney SJ, Khosropour CM. Association between any underlying health condition and COVID-19-associated hospitalization by age group, Washington State, 2020-2021: a retrospective cohort study. BMC Infect Dis. 2023 Mar 30;23(1):193.

81. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968 May;16(5):622–6.

82. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol. 1992 Feb;45(2):197–203.

83. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998 Jan;36(1):8–27.

84. Groll DL, To T, Bombardier C, Wright JG. The development of a comorbidity index with physical function as the outcome. J Clin Epidemiol. 2005 Jun 1;58(6):595–602.

85. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987 Jan 1;40(5):373–83.

86. Christensen DM, Strange JE, Gislason G, Torp-Pedersen C, Gerds T, Fosbøl E, et al. Charlson Comorbidity Index Score and Risk of Severe Outcome and Death in Danish COVID-19 Patients. J Gen Intern Med. 2020 Sep;35(9):2801–3.

87. Tuty Kuswardhani RA, Henrina J, Pranata R, Anthonius Lim M, Lawrensia S, Suastika K. Charlson comorbidity index and a composite of poor outcomes in COVID-19 patients: A systematic review and meta-analysis. Diabetes Metab Syndr. 2020 Dec;14(6):2103–9.

88. Royal College of Physicians. RCP London. 2017 [cited 2023 Nov 28]. National Early Warning Score (NEWS) 2. Available from: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2

89. Kostakis I, Smith GB, Prytherch D, Meredith P, Price C, Chauhan A, et al. The performance of the National Early Warning Score and National Early Warning Score 2 in hospitalised patients infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Resuscitation. 2021 Feb;159:150–7.

90. CR P, Vanidassane I, Pownraj D, Kandasamy R, Basheer A. National Early Warning Score 2 (NEWS2) to predict poor outcome in hospitalised COVID-19 patients in India. PLoS ONE. 2021 Dec 15;16(12):e0261376.

91. Baker KF, Hanrath AT, Schim van der Loeff I, Kay LJ, Back J, Duncan CJ. National Early Warning Score 2 (NEWS2) to identify inpatient COVID-19 deterioration: a retrospective analysis. Clin Med. 2021 Mar;21(2):84–9.

92. Mesas AE, Cavero-Redondo I, Álvarez-Bueno C, Cabrera MAS, Andrade SM de, Sequí-Dominguez I, et al. Predictors of in-hospital COVID-19 mortality: A comprehensive systematic review and meta-analysis exploring differences by age, sex and health conditions. PLOS ONE. 2020 Nov 3;15(11):e0241742.

93. Wang QQ, Kaelber DC, Xu R, Volkow ND. COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States. Mol Psychiatry. 2021 Jan;26(1):30–9.

94. Friske MM, Spanagel R. Chronic alcohol consumption and COVID-19 infection risk: A narrative review. Alcohol Clin Exp Res. 2023;47(4):629–39.

95. Esposito G, Pesce M, Seguella L, Sanseverino W, Lu J, Corpetti C, et al. The potential of cannabidiol in the COVID-19 pandemic. Br J Pharmacol. 2020;177(21):4967–70.

96. Morojele NK, Shenoi SV, Shuper PA, Braithwaite RS, Rehm J. Alcohol Use and the Risk of Communicable Diseases. Nutrients. 2021 Oct;13(10):3317.

97. Muhammad JS, Siddiqui R, Khan NA. COVID-19: Is There a Link between Alcohol Abuse and SARS-CoV-2-Induced Severe Neurological Manifestations? ACS Pharmacol Transl Sci. 2021 Apr 9;4(2):1024–5.

98. Hamer M, Kivimäki M, Gale CR, Batty GD. Lifestyle risk factors, inflammatory mechanisms, and COVID-19 hospitalization: A community-based cohort study of 387,109 adults in UK. Brain Behav Immun. 2020 Jul 1;87:184–7.

99. Pollard MS, Tucker JS, Green HD. Changes in Adult Alcohol Use and Consequences During the COVID-19 Pandemic in the US. JAMA Netw Open. 2020 Sep 1;3(9):e2022942.

100. Killgore WDS, Cloonan SA, Taylor EC, Lucas DA, Dailey NS. Alcohol dependence during COVID-19 lockdowns. Psychiatry Res. 2021 Feb 1;296:113676.

101. Chacon NC, Walia N, Allen A, Sciancalepore A, Tiong J, Quick R, et al. Substance use during COVID-19 pandemic: impact on the underserved communities. Discoveries. 9(4):e141.

102. Håkansson A. Effects on Gambling Activity From Coronavirus Disease 2019-An Analysis of Revenue-Based Taxation of Online- and Land-Based Gambling Operators During the Pandemic. Front Psychiatry. 2020;11:611939.

103. Cataldo I, Casonato E, Levari E, Negri A, Simonato P, Tomasi G, et al. Gambling at the time of COVID-19: Results from interviews in an Italian sample of gamblers. Emerg Trends Drugs Addict Health. 2022;2:100032.

104. Fluharty M, Paul E, Fancourt D. Predictors and patterns of gambling behaviour across the COVID-19 lockdown: Findings from a UK cohort study. J Affect Disord. 2022 Feb 1;298(Pt A):1–8.

105. Amerio A, Stival C, Lugo A, Fanucchi T, Gorini G, Pacifici R, et al. COVID-19 lockdown: The relationship between trait impulsivity and addictive behaviors in a large representative sample of Italian adults. J Affect Disord. 2022 Apr 1;302:424–7.

106. Shaw CA, Hodgins DC, Williams RJ, Belanger YD, Christensen DR, El-Guebaly N, et al. Gambling in Canada During the COVID Lockdown: Prospective National Survey. J Gambl Stud. 2022 Jun;38(2):371–96.

107. Emond A, Nairn A, Collard S, Hollén L. Gambling by Young Adults in the UK During COVID-19 Lockdown. J Gambl Stud. 2022 Mar;38(1):1–13.

108. Kalke J, Schütze C, Lahusen H, Buth S. Parameters for Change in Offline Gambling Behavior After the First COVID-19 Lockdown in Germany. Front Psychol. 2022;13:857234.

109. Rantis K, Panagiotidis P, Parlapani E, Holeva V, Tsapakis EM, Diakogiannis I. Substance use during the COVID-19 pandemic in Greece. J Subst Use. 2022 Jun;27(3):231–8.

110. Scortichini M, Schneider dos Santos R, De' Donato F, De Sario M, Michelozzi P, Davoli M, et al. Excess mortality during the COVID-19 outbreak in Italy: a two-stage interrupted time-series analysis. Int J Epidemiol. 2020 Dec 1;49(6):1909–17.

111. Dorrucci M, Minelli G, Boros S, Manno V, Prati S, Battaglini M, et al. Excess Mortality in Italy During the COVID-19 Pandemic: Assessing the Differences Between the First and the Second Wave, Year 2020. Front Public Health. 2021 Jul 16;9:669209.

112. Gazzetta Ufficiale. Disposizioni urgenti per il potenziamento del Servizio sanitario nazionale in relazione all'emergenza COVID-19 [Internet]. 2020 [cited 2023 Dec 12]. Available from: https://www.gazzettaufficiale.it/eli/id/2020/03/09/20G00030/sg

113. Bongiovanni M, Arienti R, Bini F, Bodini BD, Corbetta E, Gianturco L. Differences between the waves in Northern Italy: How the characteristics and the outcome of COVID-19 infected patients admitted to the emergency room have changed. J Infect. 2021 Jul 1;83(1):e32–3.

114. Borghesi A, Golemi S, Carapella N, Zigliani A, Farina D, Maroldi R. Lombardy, Northern Italy: COVID-19 second wave less severe and deadly than the first? A preliminary investigation. Infect Dis. 2021 May 4;53(5):370–5.

115. Bertolotti M, Betti M, Giacchero F, Grasso C, Franceschetti G, Carotenuto M, et al. Long-Term Survival among Patients Hospitalized for COVID-19 during the First Three Epidemic Waves: An Observational Study in a Northern Italy Hospital. Int J Environ Res Public Health. 2022 Nov 19;19(22):15298.

116. Zuccaro V, Colaneri M, Asperges E, Valsecchi P, Sambo M, Maiocchi L, et al. Mortality due to COVID-19 during the pandemic: A comparison of first, second and third SMAtteo COvid19 REgistry (SMACORE). Heliyon. 2022 Feb 1;8(2).

117. Istituto Superiore di Sanità - EpiCentro. National COVID-19 vaccination plan [Internet]. [cited 2023 Dec 12]. Available from: https://www.epicentro.iss.it/en/vaccines/covid-19-vaccination-plan

118. Sacco C, Mateo-Urdiales A, Petrone D, Spuri M, Fabiani M, Vescio MF, et al. Estimating averted COVID-19 cases, hospitalisations, intensive care unit admissions and deaths by COVID-19 vaccination, Italy, January−September 2021. Eurosurveillance. 2021 Nov 25;26(47):2101001.

119. Marziano V, Guzzetta G, Mammone A, Riccardo F, Poletti P, Trentini F, et al. The effect of COVID-19 vaccination in Italy and perspectives for living with the virus. Nat Commun. 2021 Dec 14;12(1):7272.

120. Mannucci PM, Galbussera AA, D'Avanzo B, Tettamanti M, Remuzzi G, Fortino I, et al. Two years of SARS-CoV-2 pandemic and COVID-19 in Lombardy, Italy. Intern Emerg Med. 2023 Aug;18(5):1445–51.

121. Crivellari S, Pasquali M, Aiosa G, Daniele A, Bertolotti M, Salerno C, et al. Outcomes of patients with COVID-19 hospitalized during the fourth pandemic wave in relation to their clinical features and vaccination status. Ital J Med. 2022 Dec 30;16(1).

122. Gallo V, Chiodini P, Bruzzese D, Bhopal R. Age-and sex-adjustment and the COVID-19 pandemic – transformative example from Italy. Int J Epidemiol. 2020 Oct 1;49(5):1730–2.

123. Gallo V, Chiodini P, Bruzzese D, Kondilis E, Howdon D, Mierau J, et al. Comparing the COVID-19 pandemic in space and over time in Europe, using numbers of deaths, crude rates and adjusted mortality trend ratios. Sci Rep. 2021 Aug 12;11(1):16443.

124. EPICLIN. Il progetto EPICLIN [Internet]. [cited 2023 Nov 28]. Available from: https://new.epiclin.it/

125. Trevisan C, Pedone C, Maggi S, Noale M, Di Bari M, Sojic A, et al. Accessibility to SARS-CoV-2 swab test during the Covid-19 pandemic: Did age make the difference? Health Policy Amst Neth. 2021 Dec;125(12):1580–6.

126. McQueenie R, Foster HME, Jani BD, Katikireddi SV, Sattar N, Pell JP, et al. Multimorbidity, polypharmacy, and COVID-19 infection within the UK Biobank cohort. PloS One. 2020;15(8):e0238091.

127. Suardi C, Cazzaniga E, Graci S, Dongo D, Palestini P. Link between Viral Infections, Immune System, Inflammation and Diet. Int J Environ Res Public Health. 2021 Mar 2;18(5):2455.

128. Kale D, Herbec A, Beard E, Gold N, Shahab L. Patterns and predictors of adherence to health-protective measures during COVID-19 pandemic in the UK: cross-sectional and longitudinal findings from the HEBECO study. BMC Public Health. 2022 Dec 14;22(1):2347.

129. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet Lond Engl. 2020 Jun 27;395(10242):1973–87.

130. Semenzato L, Botton J, Drouin J, Cuenot F, Dray-Spira R, Weill A, et al. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. Lancet Reg Health - Eur. 2021 Sep 1;8:100158.

131. López-Bueno R, Torres-Castro R, Koyanagi A, Smith L, Soysal P, Calatayud J. Associations Between Recently Diagnosed Conditions and Hospitalization due to COVID-19 in Patients Aged 50 Years and Older-A SHARE-Based Analysis. J Gerontol A Biol Sci Med Sci. 2022 Apr 1;77(4):e111–4.

132. Chudasama YV, Zaccardi F, Gillies CL, Razieh C, Yates T, Kloecker DE, et al. Patterns of multimorbidity and risk of severe SARS-CoV-2 infection: an observational study in the U.K. BMC Infect Dis. 2021 Sep 4;21(1):908.

133. Bigdelou B, Sepand MR, Najafikhoshnoo S, Negrete JAT, Sharaf M, Ho JQ, et al. COVID-19 and Preexisting Comorbidities: Risks, Synergies, and Clinical Outcomes. Front Immunol. 2022 May 27;13:890517.

134. Endeshaw Y, Campbell K. Advanced age, comorbidity and the risk of mortality in COVID-19 infection. J Natl Med Assoc. 2022 Oct 1;114(5):512–7.

135. Bae S, Kim SR, Kim MN, Shim WJ, Park SM. Impact of cardiovascular disease and risk factors on fatal outcomes in patients with COVID-19 according to age: a systematic review and meta-analysis. Heart. 2021 Mar 1;107(5):373–80.

136. Salvatore M, Hu MM, Beesley LJ, Mondul AM, Pearce CL, Friese CR, et al. COVID-19 Outcomes by Cancer Status, Site, Treatment, and Vaccination. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2023 Jun 1;32(6):748–59.

137. Cherri S, Lemmers DHL, Noventa S, Abu Hilal M, Zaniboni A. Outcome of oncological patients admitted with COVID-19: experience of a hospital center in northern Italy. Ther Adv Med Oncol. 2020 Sep 30;12:1758835920962370.

138. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol Off J Eur Soc Med Oncol. 2020 Jul;31(7):894–901.

139. Tian J, Yuan X, Xiao J, Zhong Q, Yang C, Liu B, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020 Jul;21(7):893–903.

140. Oldani S, Petrelli F, Dognini G, Borgonovo K, Parati MC, Ghilardi M, et al. COVID-19 and Lung Cancer Survival: An Updated Systematic Review and Meta-Analysis. Cancers. 2022 Nov 21;14(22):5706.

141. Huang BZ, Chen Z, Sidell MA, Eckel SP, Martinez MP, Lurmann F, et al. Asthma Disease Status, COPD, and COVID-19 Severity in a Large Multiethnic Population. J Allergy Clin Immunol Pract. 2021 Oct;9(10):3621-3628.e2.

142. Lohia P, Sreeram K, Nguyen P, Choudhary A, Khicher S, Yarandi H, et al. Preexisting respiratory diseases and clinical outcomes in COVID-19: a multihospital cohort study on predominantly African American population. Respir Res. 2021 Feb 5;22(1):37.

143. Maddaloni E, D'Onofrio L, Siena A, Luordi C, Mignogna C, Amendolara R, et al. Impact of cardiovascular disease on clinical outcomes in hospitalized patients with Covid-19: a systematic review and meta-analysis. Intern Emerg Med. 2021 Oct;16(7):1975–85.

144. Vasbinder A, Meloche C, Azam TU, Anderson E, Catalan T, Shadid H, et al. Relationship Between Preexisting Cardiovascular Disease and Death and Cardiovascular Outcomes in Critically Ill Patients With COVID-19. Circ Cardiovasc Qual Outcomes. 2022 Oct;15(10):e008942.

145. Huang H, Chen J, Fang S, Chen X, Pan X, Lei H, et al. Association Between Previous Stroke and Severe COVID-19: A Retrospective Cohort Study and an Overall Review of Meta-Analysis. Front Neurol [Internet]. 2022 [cited 2023 Dec 21];13. Available from: https://www.frontiersin.org/articles/10.3389/fneur.2022.922936

146. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020 Sep;17(9):543–58.

147. Pranata R, Huang I, Lim MA, Wahjoepramono EJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19–systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis. 2020 Aug 1;29(8):104949.

148. Hartmann-Boyce J, Rees K, Perring JC, Kerneis SA, Morris EM, Goyder C, et al. Risks of and From SARS-CoV-2 Infection and COVID-19 in People With Diabetes: A Systematic Review of Reviews. Diabetes Care. 2021 Dec;44(12):2790–811.

149. Russell CD, Lone NI, Baillie JK. Comorbidities, multimorbidity and COVID-19. Nat Med. 2023 Feb;29(2):334–43.

150. Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabetes Metab Syndr. 2020 Aug;14(4):535–45.

151. Giorda CB, Picariello R, Tartaglino B, Nada E, Doglio M, Romeo F, et al. From swab testing to health outcomes within the T2DM population: Impact of diabetes background on COVID19 progression. Diabetes Res Clin Pract. 2021 Oct;180:109021.

152. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol. 1999 Dec;26(3–4):259–65.

153. Bähler C, Huber CA, Brüngger B, Reich O. Multimorbidity, health care utilization and costs in an elderly community-dwelling population: a claims data based observational study. BMC Health Serv Res. 2015 Jan 22;15:23.

154. Sundaram SS, Melquist S, Kalgotra P, Srinivasan S, Parasa S, Desai M, et al. Impact of age, sex, race, and regionality on major clinical outcomes of COVID-19 in hospitalized patients in the United States. BMC Infect Dis. 2022 Jul 29;22(1):659.

155. Mendiratta P, Schoo C, Latif R. Clinical Frailty Scale. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Nov 28]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK559009/

156. Atamna H, Tenore A, Lui F, Dhahbi JM. Organ reserve, excess metabolic capacity, and aging. Biogerontology. 2018 Apr;19(2):171–84.

157. Morrisette-Thomas V, Cohen AA, Fülöp T, Riesco É, Legault V, Li Q, et al. Inflamm-aging does not simply reflect increases in pro-inflammatory markers. Mech Ageing Dev. 2014 Jul;139:49–57.

158. Bektas A, Schurman SH, Sen R, Ferrucci L. Aging, inflammation and the environment. Exp Gerontol. 2018 May;105:10–8.

159. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018 Sep;15(9):505–22.

160. Friedman EM, Mroczek DK, Christ SL. Multimorbidity, inflammation, and disability: a longitudinal mediational analysis. Ther Adv Chronic Dis. 2019;10:2040622318806848.

161. Graichen H. What is the difference between the first and the second/third wave of Covid-19? - German perspective. J Orthop 2021. 24: A1–A3. DOI: 10.1016/j.jor.2021.01.011.

162. Wei Y, Guan J, Ning X, Li Y, Wei L, Shen S, et al. Global COVID-19 Pandemic Waves: Limited Lessons Learned Worldwide over the Past Year. Engineering. 2022 Jun 1;13:91–8.

163. Karako K, Song P, Chen Y, Tang W, Kokudo N. Overview of the characteristics of and responses to the three waves of COVID-19 in Japan during 2020-2021. Biosci Trends. 2021 Feb 28;15(1):1–8.

164. Vinceti M, Filippini T, Rothman KJ, Di Federico S, Orsini N. SARS-CoV-2 infection incidence during the first and second COVID-19 waves in Italy. Environ Res. 2021 Jun 1;197:111097.

165. Hoogenboom WS, Pham A, Anand H, Fleysher R, Buczek A, Soby S, et al. Clinical characteristics of the first and second COVID-19 waves in the Bronx, New York: A retrospective cohort study. Lancet Reg Health – Am [Internet]. 2021 Nov 1 [cited 2023 Dec 27];3. Available from: https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00033-8/fulltext

166. Acuña-Castillo C, Inostroza-Molina A, Castro SA, Molina-Cabrera S, Leiva-Salcedo E, Riquelme D, et al. Comparison of the First and Second Wave of Infections by SARS-CoV-2: A Retrospective and Longitudinal Study From a Primary Health Care Center in Santiago of Chile. Front Public Health. 2022 Jun 30;10:913519.

167. Chirico F, Sacco A, Nucera G, Magnavita N. Coronavirus disease 2019: the second wave in Italy. J Health Res. 2021;35:359–63.

168. Istituto Superiore di Sanità - Epicentro. Prevalenza e distribuzione delle varianti del virus SARS-CoV-2 di interesse per la sanità pubblica in Italia [Internet]. 2021 May. Available from: https://www.epicentro.iss.it/coronavirus/pdf/sars-cov-2-monitoraggio-varianti-rapporti-periodici-19-maggio-2021.pdf

169. Costantino G, Solbiati M, Elli S, Paganuzzi M, Massabò D, Montano N, et al. Utility of hospitalization for elderly individuals affected by COVID-19. PloS One. 2021;16(4):e0250730.

170. Karagiannidis C, Windisch W, McAuley DF, Welte T, Busse R. Major differences in ICU admissions during the first and second COVID-19 wave in Germany. Lancet Respir Med. 2021 May;9(5):e47–8.

171. Oladunjoye O, Gallagher M, Wasser T, Oladunjoye A, Paladugu S, Donato A. Mortality due to COVID-19 infection: A comparison of first and second waves. J Community Hosp Intern Med Perspect. 2021;11(6):747–52.

172. Martinot M, Eyriey M, Gravier S, Kayser D, Ion C, Mohseni-Zadeh M, et al. Evolution of baseline characteristics and severe outcomes in COVID-19 inpatients during the first and second waves in Northeastern France. Infect Dis Now. 2022 Feb;52(1):35–9.

173. Iftimie S, López-Azcona AF, Vallverdú I, Hernández-Flix S, de Febrer G, Parra S, et al. First and second waves of coronavirus disease-19: A comparative study in hospitalized patients in Reus, Spain. PLoS ONE. 2021 Mar 31;16(3):e0248029.

174. Chalmers JD, Crichton ML, Goeminne PC, Cao B, Humbert M, Shteinberg M, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. Eur Respir J [Internet]. 2021 Apr 1 [cited 2023 Dec 28];57(4). Available from: https://erj.ersjournals.com/content/57/4/2100048

175. De Marco C, Veneziano C, Massacci A, Pallocca M, Marascio N, Quirino A, et al. Dynamics of Viral Infection and Evolution of SARS-CoV-2 Variants in the Calabria Area of Southern Italy. Front Microbiol. 2022 Jul 28;13:934993.

176. Saito S, Asai Y, Matsunaga N, Hayakawa K, Terada M, Ohtsu H, et al. First and second COVID-19 waves in Japan: A comparison of disease severity and characteristics. J Infect. 2021 Apr;82(4):84–123.

177. Enti locali e regioni contro mafie e corruzione. Avviso Pubblico. [cited 2024 Jan 3]. I dati ufficiali sul gioco d'azzardo in Italia nel 2019. Available from: https://www.avvisopubblico.it/home/home/cosa-facciamo/informare/documenti-tematici/gioco-dazzardo/i-primi-dati-sul-gioco-dazzardo-in-italia-nel-2019/

178. Enti locali e regioni contro mafie e corruzione. Avviso Pubblico. [cited 2024 Jan 3]. I dati ufficiali sul gioco d'azzardo in Italia nel 2020. Available from: https://www.avvisopubblico.it/home/home/cosa-facciamo/informare/documenti-tematici/gioco-dazzardo/i-dati-ufficiali-sul-gioco-dazzardo-in-italia-nel-2020/

179. Enti locali e regioni contro mafie e corruzione. Avviso Pubblico. [cited 2024 Jan 3]. I dati ufficiali sul gioco d'azzardo in Italia nel 2021. Available from: https://www.avvisopubblico.it/home/home/cosa-facciamo/informare/documenti-tematici/gioco-dazzardo/i-dati-ufficiali-sul-gioco-dazzardo-in-italia-nel-2021/

180. Gambling Industry News. Global Gambling Statistics & Trends 2024 [Internet]. [cited 2024 Jan 3]. Available from: https://gamblingindustrynews.com/global-gambling-statistics/

181. Lischer S, Steffen A, Schwarz J, Mathys J. The Influence of Lockdown on the Gambling Pattern of Swiss Casinos Players. Int J Environ Res Public Health. 2021 Feb 18;18(4).

182. Lugo A, Stival C, Paroni L, Amerio A, Carreras G, Gorini G, et al. The impact of COVID-19 lockdown on gambling habit: A cross-sectional study from Italy. J Behav Addict. 2021 Jul 20;10(3):711–21.

183. Månsson V, Wall H, Berman AH, Jayaram-Lindström N, Rosendahl I. A Longitudinal Study of Gambling Behaviors During the COVID-19 Pandemic in Sweden. Front Psychol. 2021;12:708037.

184. Wardle H, Donnachie C, Critchlow N, Brown A, Bunn C, Dobbie F, et al. The impact of the initial Covid-19 lockdown upon regular sports bettors in Britain: Findings from a cross-sectional online study. Addict Behav. 2021 Jul;118:106876.

185. Hodgins DC, Stevens RMG. The impact of COVID-19 on gambling and gambling disorder: emerging data. Curr Opin Psychiatry. 2021 Jul 1;34(4):332–43.

186. Balem M, Karlsson A, Widinghoff C, Perrot B, Challet-Bouju G, Håkansson A. Gambling and COVID-19: Swedish national gambling data from a state-owned gambling sports and casino operator. J Behav Addict. 2023 Mar 30;12(1):230–41.

187. Bonny-Noach H, Gold D. Addictive behaviors and craving during the COVID-19 pandemic of people who have recovered from substance use disorder. J Addict Dis. 2021 Jun;39(2):257–64.

188. McQuade A, Gill P. The role of loneliness and self-control in predicting problem gambling behaviour. Gambl Res J Natl Assoc Gambl Stud Aust. 2020 Aug 23;24(1):18–30.

189. Rossi R, Socci V, Talevi D, Mensi S, Niolu C, Pacitti F, et al. COVID-19 Pandemic and Lockdown Measures Impact on Mental Health Among the General Population in Italy. Front Psychiatry [Internet]. 2020 [cited 2024 Jan 3];11. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00790

190. Santomauro DF, Herrera AMM, Shadid J, Zheng P, Ashbaugh C, Pigott DM, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. The Lancet. 2021 Nov 6;398(10312):1700–12.

191. Barrault S, Bonnaire C, Herrmann F. Anxiety, Depression and Emotion Regulation Among Regular Online Poker Players. J Gambl Stud. 2017 Dec 1;33(4):1039–50.

192. Huțul TD, Karner-Huțuleac A. The Level of Gambling Prediction Using Depression and Anxiety in the Romanian Population. J Gambl Stud. 2022 Jun 1;38(2):653–62.

193. Kessler RC, Hwang I, LaBrie R, Petukhova M, Sampson NA, Winters KC, et al. DSM-IV pathological gambling in the National Comorbidity Survey Replication. Psychol Med. 2008 Sep;38(9):1351–60.

194. Håkansson A. Changes in Gambling Behavior during the COVID-19 Pandemic-A Web Survey Study in Sweden. Int J Environ Res Public Health. 2020 Jun 5;17(11).

195. Håkansson A, Jönsson C, Kenttä G. Psychological Distress and Problem Gambling in Elite Athletes during COVID-19 Restrictions-A Web Survey in Top Leagues of Three Sports during the Pandemic. Int J Environ Res Public Health. 2020 Sep 14;17(18).

196. Gainsbury SM, Russell A, Hing N. An investigation of social casino gaming among land-based and Internet gamblers: A comparison of socio-demographic characteristics, gambling and co-morbidities. Comput Hum Behav. 2014 Apr 1;33:126–35.

197. Håkansson A. Gambling and self-reported changes in gambling during COVID-19 in web survey respondents in Denmark. Heliyon. 2021 Jul;7(7):e07506.

198. Håkansson A, Widinghoff C. Changes of Gambling Patterns during COVID-19 in Sweden, and Potential for Preventive Policy Changes. A Second Look Nine Months into the Pandemic. Int J Environ Res Public Health. 2021 Feb 27;18(5).

199. Sharman S, Roberts A, Bowden-Jones H, Strang J. Gambling and COVID-19: Initial Findings from a UK Sample. Int J Ment Health Addict. 2022;20(5):2743–54.

200. Rolland B, Haesebaert F, Zante E, Benyamina A, Haesebaert J, Franck N. Global Changes and Factors of Increase in Caloric/Salty Food Intake, Screen Use, and Substance Use During the Early COVID-19 Containment Phase in the General Population in France: Survey Study. JMIR Public Health Surveill. 2020 Sep 18;6(3):e19630.

201. Alessi MC, Martinotti G, De Berardis D, Sociali A, Di Natale C, Sepede G, et al. Craving variations in patients with substance use disorder and gambling during COVID-19 lockdown: The Italian experience. World J Clin Cases. 2022 Jan 21;10(3):882–90.

202. Gainsbury SM, Swanton TB, Burgess MT, Blaszczynski A. Impacts of the COVID-19 Shutdown on Gambling Patterns in Australia: Consideration of Problem Gambling and Psychological Distress. J Addict Med. 2021 Dec 1;15(6):468–76.

203. Lee J, Solomon M, Stead T, Kwon B, Ganti L. Impact of COVID-19 on the mental health of US college students. BMC Psychol. 2021 Jun 8;9(1):95.

204. Sundler AJ, Bergnehr D, Haffejee S, Iqbal H, Orellana MF, Vergara Del Solar A, et al. Adolescents' and young people's experiences of social relationships and health concerns during COVID-19. Int J Qual Stud Health Well-Being. 2023 Dec;18(1):2251236.

205. Volpe U, Orsolini L, Salvi V, Albert U, Carmassi C, Carrà G, et al. COVID-19-Related Social Isolation Predispose to Problematic Internet and Online Video Gaming Use in Italy. Int J Environ Res Public Health. 2022 Jan;19(3):1539.

206. Bellringer ME, Garrett N. Risk Factors for Increased Online Gambling during COVID-19 Lockdowns in New Zealand: A Longitudinal Study. Int J Environ Res Public Health. 2021 Dec 8;18(24).

207. Claesdotter-Knutsson E, Håkansson A. Changes in Self-Reported Web-Based Gambling Activity During the COVID-19 Pandemic: Cross-sectional Study. JMIR Serious Games. 2021 Nov 3;9(4):e30747.

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