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Original Article

# Serendipitous Adrenal Hyperplasia in Patients Admitted to the Emergency Department for Suspected SARS-CoV-2 Infection is Linked to Increased Mortality

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*Background.* Few data are available on adrenal morphology in patients with acute diseases, although it is known that endogenous glucocorticoids are essential for survival under stress conditions and that an adequate response is driven by activation of the hypothalamic-pituitary-adrenal (HPA) axis.

*Aims.* The aim of this study was to assess adrenal morphology in patients with acute disease compared with patients with non-acute disease.

*Methods.* This cross-sectional study included: 402 patients admitted to the emergency department (ED) for suspected SARS-CoV-2 infection (March–May, 2020) [main cohort]; 200 patients admitted to the ED for acute conditions (December 2018–February 2019) [control group A]; 200 outpatients who underwent radiological evaluation of non-acute conditions (January–February 2019) [control group B]. Chest and/or abdominal CT scans were reviewed to identify adrenal nodules or hyperplasia.

*Results.* In the main cohort, altered adrenal morphology was found in 24.9% of the patients (15.4% adrenal hyperplasia; 9.5% adrenal nodules). The frequency of adrenal hyperplasia was higher both in the main cohort (15.4%) and control group A (15.5%) compared to control group B (8.5%; $p = 0.02$ and $p = 0.03$, respectively). In the main cohort, 14.9% patients died within 30 d. According to a multivariate analysis, adrenal hyperplasia was an independent risk factor for mortality ($p = 0.04$), as were older age ($p < 0.001$) and active cancer ($p = 0.01$).

*Conclusions.* The notable frequency of adrenal hyperplasia in patients with acute diseases suggests an exaggerated activation of the HPA axis due to stressful conditions. The increased risk of short-term mortality found in patients with adrenal hyperplasia suggests that it may be a possible hallmark of worse prognosis. 

*Key Words:* Adrenal enlargement, Adrenal incidentaloma, Adrenal tumor, Critical illness, COVID-19, Acute disease.

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## Introduction

Incidental radiological findings are reported with increasing frequency due to the steep increase in the use of cross-sectional imaging. Extensive literature is available on adrenal incidentalomas, defined as discrete adrenal lesions of 1 cm or more, found serendipitously in patients who presented without overt clinical features of adrenal hormone hypersecretion (1). The frequency of adrenal incidentalomas has reached 5–7% in the most recent studies (2–4), which is close to findings described in autopsy series (5). Conversely, adrenal hyperplasia is neglected outside the context of congenital adrenal hyperplasia. A retrospective radiology study assessing 564 abdominal computerized tomography (CT) scans carried out for different clinical conditions (excluding patients with abdominal trauma, known cancer or endocrine disorders) reported a total of 64 patients with adrenal enlargement, of which 11 had nodular enlargement, with a frequency of serendipitous adrenal hyperplasia of 9.4% (6).

Given that endogenous glucocorticoids are essential for survival under conditions of stress (7), and that an adequate stress response is driven by activation of the hypothalamic-pituitary-adrenal (HPA) axis (8,9), the assessment of adrenal morphology is even more revealing in the context of acute conditions.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which caused the COVID-19 pandemic, has become the most prevalent acute disease globally in the past few years (10). Knowledge of the effects of SARS-CoV-2 infection on the HPA axis is still limited and to date few data are available on adrenal morphology in patients with COVID-19.

Autopsy studies in patients with severe COVID-19 reported microscopic adrenal lesions (ischemic or hemorrhagic necrosis, cortical lipid degeneration and focal adrenalitis) which can result from adrenal hyperactivity in critical illnesses (11,12). Older age and the presence of comorbidities, such as arterial hypertension, cardiovascular disease, diabetes mellitus, and obesity have been identified as risk factors for severe or fatal COVID-19 (13–17). Interestingly, the same comorbidities have been found in patients with cortisol-secreting adrenal tumors (18,19), even when these tumors produce minimal cortisol excess, as happens in adrenal incidentalomas (1,2,20–26).

Given that the adrenal region is usually included in chest CT scans, we designed a study to assess the morphology of the adrenal glands visualized by a chest CT in patients admitted to the emergency department with suspected SARS-CoV-2 infection. We assessed the frequency and features of the alterations observed, and evaluated whether they were linked to specific characteristics, or patient outcomes. We compared the adrenal findings of these patients with those of two control cohorts who had undergone a CT for different reasons before the pandemic.

## Methods

### *Design*

This was a cross-sectional study.

### *Study Participants*

#### *Patients with Suspected SARS-CoV-2 Infection (Main Cohort)*

We retrospectively assessed a consecutive series of patients admitted to the Emergency Department of the San Luigi Gonzaga Hospital in Orbassano (northern Italy) for suspected SARS-CoV-2 infection during the first wave of the pandemic, between March 1 and May 15, 2020.

Inclusion criteria were: age at admission ≥18 years; available nasopharyngeal or oropharyngeal swab for polymerase chain reaction (PCR) testing of SARS-CoV-2 infection; and available chest CT study including the adrenal region. Patients with known adrenal disease, or recent (within one week) glucocorticoid use were excluded.

The following demographic and clinical characteristics were included: date of birth, sex, date of admission, body mass index (BMI), and comorbidities (arterial hypertension, diabetes mellitus, dyslipidemia). Death and related causes were noted over a period of 30 d after admission. Hypertension was defined as blood pressure ≥140/90 mmHg, or current use of antihypertensive medications. Diabetes mellitus was defined when the patient reported fasting glycemia ≥7 mmol/L, glycemia at 2 h during the oral glucose tolerance test ≥11.1 mmol/L, glycated hemoglobin (HbA1c) ≥6.5%, a previous diagnosis of diabetes, or current use of anti-diabetic medications. Dyslipidemia was defined by the current use of cholesterol-lowering medications. Any history of cerebrovascular or cardiovascular disease (TIA, stroke, angina pectoris, myocardial infarction, or revascularization procedures), or history of cancer was carefully investigated.

The study was approved by the ethical committee of San Luigi Gonzaga Hospital (n.11/2020), and was conducted in accordance with the Declaration of Helsinki. The need to obtain informed consent from the study participants was waived due to the observational nature of the study and the use of anonymized data.

### *Control Groups*

We retrospectively reviewed abdominal CT scans and/or chest CT scans including images of the adrenal region of two groups of patients who were referred to our hospital before the first SARS-CoV-2 outbreak. Applying the same exclusion criteria as the main cohort (Figure 1), we retrospectively reviewed abdominal CT scans and/or chest CT scans including the adrenal region of two groups of patients who were referred to our hospital before the first SARS-CoV-2 outbreak.

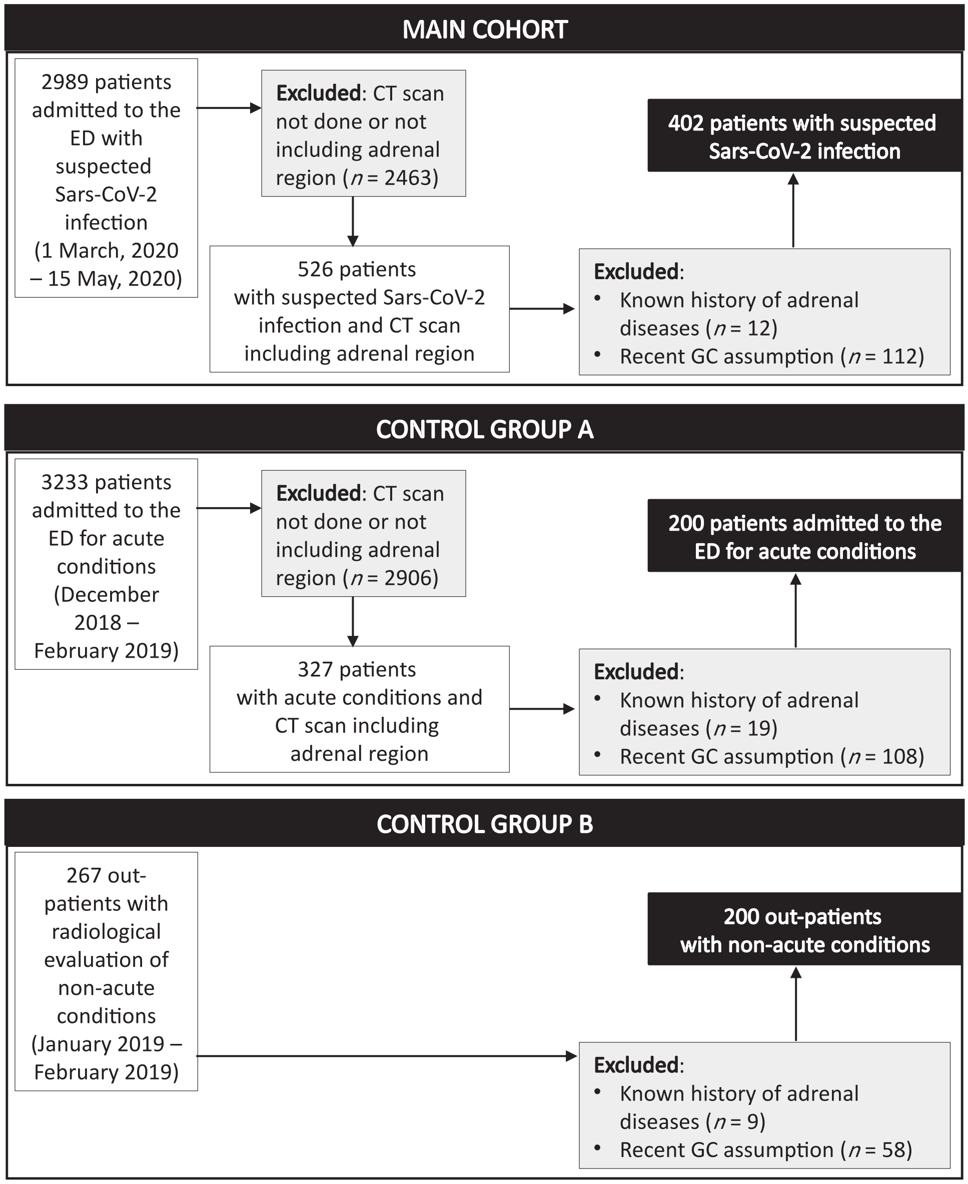


**Figure 1.** Flow diagram of study participants. ED: Emergency department; CT: Computerized tomography; GC: Glucocorticoid.

Group A consisted of 200 patients admitted to the emergency department for a variety of acute conditions (50.5% acute abdominal disease, 20.5% pulmonary embolism, 9% acute renal failure, 8% trauma, 7% aortic dissection, and 5% pulmonary infection) from December 2018–February 2019. Group B consisted of 200 out-patients admitted for radiological evaluation of non-acute conditions (25.5% follow-up of abdominal diseases and 74.5% follow-up of urological diseases) from January 2019–February 2019.

*Adrenal CT Scans*

All CT studies were performed on a Philips Ingenuity CT scanner (Philips Healthcare, Cleveland OH, USA) and on a GE Optima 660 CT scanner (General Electric, Milwaukee, WI, USA). The CT imaging technique was not standardized due to the variety of different clinical indications; however, all scans had a maximum section thickness of 2 mm. For each patient, both adrenal glands were reviewed a posteriori on axial images with an abdominal soft tissue setting (window level 60, width 360) by three independent radiologists (F.S., D.C., G.M.T.) blinded to the clinical data and to the original report. Mismatches between readers were resolved by consensus.

To be included in the study, patients had to have a visible adrenal region on chest CT, with at least one gland entirely visible. All measurements were acquired in consensus using standardized methods, considering the maximum width of the gland as the largest width perpendicular to the long axis of the body, as previously described (19). Diffuse hyperplasia was defined as an enlargement of the gland with a regular outline and no identifiable nodule; maximum width was recorded for each adrenal gland.

To qualify as an enlargement, one of the limbs, or body measurements of either adrenal gland had to exceed the upper limit of normal, which was set at 10 mm for the adrenal body and 5 mm for each adrenal limb (27–29).

Nodular enlargement was defined if the adrenal gland had an irregular outline, included nodules, and had normal adrenal tissue interspersed between the nodules. For each adrenal nodule, size, margin, and mean Hounsfield Unit (HU) values were assessed. A mean unenhanced attenuation value of 10 HU, or less, was considered as suggestive of benign adenomas (1,30). For nodules with an unenhanced attenuation >10 HU, a CT histogram analysis was used to differentiate between lipid-poor adenomas and non-adenomatous lesions (30).

CT histogram measurements were performed on IntelliSpace Portal 11 (Philips Healthcare). For each adrenal nodule, a circular region of interest (ROI) was located to include a large portion of the lesion but avoiding the external portion, to prevent partial volume effects. A CT histogram and a graph of the number of pixels on the y-axis versus the pixel attenuation on the x-axis were obtained from the ROI. The analysis was based on the calculation of the pixels with a negative HU. When available, previous CT scans of the same patients were reviewed to determine whether adrenal enlargement had been reported in the original radiological report.

### *Statistical Analysis*

Continuous variables are presented as the means and standard deviations (SDs), or medians and ranges as measures of variability, as appropriate. Categorical variables were presented with frequencies and percentages. Differences between groups were analyzed with the Mann-Whitney test for continuous variables and the $\chi^2$ test, or Fisher's exact test when appropriate, for categorical variables. To evaluate the factors associated with the risk of mortality, a multivariate analysis was carried out to estimate the odds ratio (OR) and the corresponding 95% confidence interval (95% CI) with the binomial logistic regression analysis.

All reported $p$ values were two-sided. $p$-values less than 0.05 were considered as statistically significant. The statistical analyses were performed with *Jamovi* - v. 2.3.18.

### *Role of the Funding Source*

The University of Turin funded the study but had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

### *Characteristics of the Study Population*

We included 402 patients (Figure 1) who were recruited during the first SARS-CoV-2 outbreak (222 men, 55.2%; 180 women, 44.8%) in the main cohort.

One hundred patients had a PCR-confirmed diagnosis of SARS-CoV-2 infection (24.9%). Table 1 reports the clinical characteristics of the patients stratified by PCR test confirmation of SARS-CoV-2 infection.

Patients in the main cohort and those in group B were comparable in ages, however they were older than patients included in group A ($p$ <0.001) (Table 2). Group B also included mainly males (86%), since most of the patients were referred for follow-up for urological diseases (Table 2).

### *Adrenal CT Findings*

In the main cohort, altered adrenal morphology was found in 100 patients (24.9%), consisting of adrenal hyperplasia in 62 (15.4%), and adrenal nodules in 38 (9.5%) patients. Discrete adrenal nodules were unilateral in 34 (89.4%) patients, and bilateral in 4 (10.6%) patients. No significant differences in adrenal morphology were detected between patients with a positive or negative PCR test for SARS-CoV-2 infection (Table 1).

Of the 38 patients with adrenal nodules, 44 discrete nodules were identified, with a median size of 16 mm (10–50 mm) and a median density of 10 HU (from –41 HU to 42 HU). Twenty-two nodules (50%) had a density ≤10 HU, which is consistent with the diagnosis of adenoma. For the remaining 22 nodules with a mean density >10 HU, the CT histogram analysis revealed that 14 had >10% pixel values below 0 HU, and 8 less than 10% pixel values below 0 HU. In these patients with uncertain radiological characteristics, the histogram analysis was consistent with a presumptive diagnosis of lipid-poor adenomas ($n$ = 10), adrenal metastasis ($n$ = 8), or myelolipoma ($n$ = 1), while three nodules were of indeterminate origin. Note that the eight nodules that qualified as adrenal metastases were found in patients with a previous history of cancer.

In 17 patients with adrenal hyperplasia, a previous CT was available for comparison, which in all cases showed an increase in the thickness of the adrenal glands at the most recent CT, with a median increase of 1.9 mm (1–15 mm).

An increased frequency of adrenal hyperplasia was found both in the main cohort (15.4%) and in the control group A (15.5%) compared to the control group B (8.5%; $p$ = 0.02 and $p$ = 0.03, respectively) (Table 2).

In the main cohort, we did not observe a significant correlation between the presence of adrenal morphological changes with some biochemical indices of disease sever-

**Table 1.** Baseline characteristics of the main cohort

| Characteristics | Overall cohort $N = 402$ | Negative PCR test $N = 302$ (valid cases) | Positive PCR test $N = 100$ (valid cases) | $p$* |
|---|---|---|---|---|
| Age, year | | (302) | (100) | <0.001 |
| Mean (SD) | 72.4 (15.1) | 74.2 (14.8) | 67.1 (14.9) | |
| Female, $N$ (%) | 180 (44.8) | 140 (46.4) | 40 (40) | 0.27 |
| BMI class, | | (302) | (100) | 0.55 |
| Normal, $N$ (%) | 185 (46.1) | 132 (43.7) | 53 (53) | |
| Overweight, $N$ (%) | 144 (35.8) | 117 (38.7) | 27 (27) | |
| Obese, $N$ (%) | 73 (18.1) | 53 (17.6) | 20 (20) | |
| Type 2 Diabetes Mellitus | | (285) | (88) | 0.41 |
| $N$ (%) | 93 (24.9) | 74 (26) | 19 (21.6) | |
| Arterial Hypertension | | (293) | (92) | 0.88 |
| $N$ (%) | 236 (61.3) | 179 (61.1) | 57 (62.0) | |
| Dyslipidemia | | (288) | (89) | 0.33 |
| $N$ (%) | 113 (30.0) | 90 (31.2) | 23 (25.8) | |
| History of CV event | | (283) | (85) | 0.37 |
| $N$ (%) | 96 (26.1) | 77 (27.2) | 19 (22.4) | |
| History of cancer | | (265) | (85) | 0.39 |
| Active cancer, $N$ (%) | 76 (21.7) | 62 (23.4) | 14 (16.5) | |
| Previous cancer, $N$ (%) | 32 (9.1) | 21 (7.9) | 11 (12.9) | |
| Adrenal morphology | | (302) | (100) | |
| Adrenal hyperplasia $N$ (%) | 62 (15.4) | 50 (16.6) | 12 (12.0) | 0.274 |
| Adrenal nodules $N$ (%) | 38 (9.5) | 26 (8.6) | 12 (12.0) | 0.315 |

CT = computed tomography; BMI = body mass index; CV = cardiovascular; SD = standard deviation.
**p* values refer to the comparison between patients with positive or negative PCR test for SARS-CoV-2.

**Table 2.** Comparison of the main cohort and control groups.

| | Main cohort ($N = 402$) | Control Group A ($N = 200$) | Control Group B ($N = 200$) | $p$ |
|---|---|---|---|---|
| Age, years, mean (SD) | 72.4 (15.1) | 64.7 (17.3) | 70.4 (9.3) | Main cohort vs. Group A, <0.001<br>Group A vs. Group B, <0.001 |
| Female, $N$ (%) | 180 (44.8) | 95 (47.5) | 28 (14.0) | Main cohort vs. Group B, <0.001<br>Group A vs. Group B, <0.001 |
| Adrenal nodules, $N$ (%) | 38 (9.5) | 10 (5.0) | 14 (7.0) | 0.141 |
| Adrenal hyperplasia, $N$ (%) | 62 (15.4) | 31 (15.5) | 17 (8.5) | Main cohort vs. Group B, 0.02<br>Group A vs. Group B, 0.03 |

ity, such as white blood cell count, lactate dehydrogenase, ultra-sensitive C-reactive protein and procalcitonin (Supplemental Table 1). Furthermore, we collected data on patient admission from the emergency room (high intensity care unit or low intensity care unit) to assess disease severity. However, even after analyzing these data, we did not observe any differences related to adrenal morphological changes (Supplemental Table 1).

### *Mortality*

In the main cohort, 60 patients (14.9%) died within 30 d. The patients who died were older (80.7 vs. 71.0 years, $p$ <0.001), and showed a higher prevalence of adrenal hyperplasia (26.7 vs. 13.5%, $p = 0.009$) and active cancer (34 vs. 19.7%, $p = 0.04$) (Table 3).

In a multivariate model (overall model test $\chi^2$ 35.6, $p$ <0.001), adrenal hyperplasia was an independent risk factor for mortality ($p = 0.04$), together with older age ($p$ <0.001) and active cancer ($p = 0.01$) (Table 4, Figure 2).

The causes of death were: COVID-related complications in 28.3% of patients, unrelated respiratory diseases in 36.7%, sepsis in 11.7%, cardiovascular disease in 13.3%, and malignancy in 10.0%.

The radiological characteristics of adrenal masses, such as margins, pattern, mean density value, and histogram analysis, did not differ between patients who survived or died (Table 3).

## Discussion

In the present study, the morphology of the adrenal glands was evaluated in a series of consecutive patients admitted to the emergency department with suspected SARS-CoV-2 infection. In order to have a control group of patients with either acute or non-acute conditions, the CT findings of these patients were compared to a group of subjects admitted to the emergency department in the previous winter period, and to a group of outpatients admitted for radiological evaluation for non-acute conditions, before the first

**Table 3.** Comparison between patients stratified by survival status at 30 d

| Characteristics | Alive patients $N = 342$ | Dead patients $N = 60$ | $p$ |
|---|---|---|---|
| Age, years (valid cases) | (342) | (60) | <0.001 |
| Mean (SD) | 71 (15.3) | 80.7 (10.8) | |
| Adrenal hyperplasia (valid cases) | (342) | (60) | 0.009 |
| *N* (%) | 46 (13.5) | 16 (26.7) | |
| Adrenal nodules (valid cases) | (342) | (60) | 0.748 |
| *N* (%) | 33 (9.6) | 5 (8.3) | |
| Nodule size, mm (valid cases) | (33) | (5) | 0.825 |
| Mean (SD) | 18.9 (10.4) | 17.8 (6.5) | |
| Nodule margins (valid cases) | (33) | (5) | 0.951 |
| Regular, *N* (%) | 26 (78.8) | 4 (80.0) | |
| Irregular, *N* (%) | 7 (21.2) | 1 (20.0) | |
| Nodule pattern (valid cases) | (33) | (5) | 0.770 |
| Homogenous, *N* (%) | 22 (66.7) | 3 (60.0) | |
| Inhomogeneous, *N* (%) | 11 (33.3) | 2 (40.0) | |
| Nodule density, HU (valid cases) | (33) | (5) | 0.571 |
| Mean (SD) | 12.2 (17.2) | 17.0 (19.2) | |
| BMI class, (valid cases) | (342) | (60) | 0.558 |
| Normal, *N* (%) | 159 (46.5) | 26 (42.9) | |
| Overweight, *N* (%) | 126 (36.8) | 20 (33.3) | |
| Obese, *N* (%) | 57 (16.7) | 14 (23.8) | |
| Type 2 Diabetes Mellitus (valid cases) | (319) | (54) | 0.601 |
| *N* (%) | 78 (24.5) | 15 (27.8) | |
| Arterial Hypertension (valid cases) | (329) | (56) | 0.923 |
| *N* (%) | 202 (61.4) | 34 (60.7) | |
| Dyslipidemia (valid cases) | (324) | (53) | 0.351 |
| *N* (%) | 100 (30.9) | 13 (24.5) | |
| History of CV event (valid cases) | (315) | (53) | 0.691 |
| *N* (%) | 81 (25.7) | 15 (28.3) | |
| History of cancer (valid cases) | (300) | (50) | 0.039 |
| Active cancer, *N* (%) | 59 (19.6) | 17 (34.0) | |
| Previous cancer, *N* (%) | 26 (8.7) | 6 (12.0) | |
| PCR test for SARS-CoV-2 (valid cases) | (342) | (60) | 0.502 |
| Positive, *N* (%) | 83 (24.3) | 17 (28.3) | |

HU = Hounsfield Unit; CV = cardiovascular.

**Table 4.** Multivariate model for the risk of dying within 30 d

| | OR | 95% CI | $p$ |
|---|---|---|---|
| Age | 1.07 | 1.04–1.10 | <0.001 |
| Active cancer | 2.44 | 1.19–4.99 | 0.01 |
| Adrenal hyperplasia | 2.16 | 1.03–4.55 | 0.04 |
| Confirmed SARS-CoV-2 | 1.73 | 0.81–3.69 | 0.15 |

SARS-CoV-2 outbreak. To the best of our knowledge, this is the largest study on adrenal morphology in patients admitted to the emergency department. The key finding of the study is the notable frequency of serendipitous adrenal hyperplasia (15.4%) found in our patients with acute conditions.

Although a direct comparison with previous studies is difficult due to the different inclusion criteria and methodologies, the frequency of adrenal hyperplasia found in our study is higher than the 9.4% reported in a radiology study which included patients who underwent an abdominal CT for unspecified conditions (6).

There is scant evidence on adrenal morphology in patients with COVID-19. Recently, some case reports showed the presence of bilateral adrenal hemorrhage (31–35), while two retrospective studies reported that patients with a diagnosis of COVID-19 showed features compatible with adrenal infarction on unenhanced CT scans in 23% of 219 patients (36) and 16% of 343 patients (37), respectively. In both studies, radiological signs of acute adrenal infarction were associated with an increased risk of hospitalization in the intensive care unit and a longer length of stay, although association with increased mortality was only found in one study (36,37).

In our study CT features suggestive of adrenal infarction were identified in only five patients with COVID-19. However, other conditions may mimic adrenal infarction on unenhanced CT, which has a lower diagnostic accuracy than enhanced CT. In fact, the typical feature of adrenal infarct is an enlarged hypodense adrenal gland with subtle peripheral rim enhancement after intravenous contrast material injection caused by adrenal venous thrombosis (38).

It is well known that patients with COVID-19 are exposed to thrombotic complications (39), and a few cases have been reported of adrenal insufficiency following COVID-19 infection, mostly due to adrenal infarction

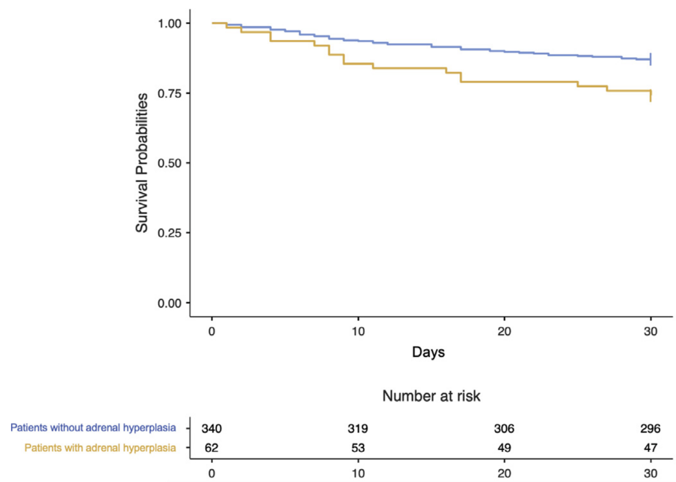


**Figure 2.** Kaplan Meier curves for overall survival in patients with (orange line) or without (blue line) adrenal hyperplasia.

in the context of antiphospholipid syndrome (40). The fact that no significant differences were found in the frequency of adrenal hyperplasia between patients with proven or unproven SARS-CoV-2 infection does not support the view that adrenal infarction is a leading cause of adrenal hyperplasia. Moreover, in our study the frequency of adrenal hyperplasia was comparable between patients recruited during the SARS-CoV-2 outbreak and patients admitted to the emergency department for a variety of acute conditions in the previous winter period, while being significantly higher than findings in out-patients with non-acute conditions.

This suggests that adrenal hyperplasia may be the result of an activated HPA axis in stressful conditions. This hypothesis is corroborated by the other key finding of our study that the presence of adrenal hyperplasia was linked to increased short-term mortality in patients admitted to the emergency department for suspected COVID. Several studies have shown that in patients who need intensive care for medical emergencies, serum cortisol has a prognostic role for both in-hospital and 28 d mortality (41–43). Moreover, higher baseline cortisol values have been found to be associated with increased mortality also in patients with COVID-19 (44,45).

However, studies assessing the volume of adrenal glands in patients with acute conditions have reported mixed findings. Previous studies have shown an increased volume of the adrenal glands in patients with septic shock compared to control subjects; however, they also reported an inverse correlation between adrenal volume and short-term mortality (46,47). Studies have also found that the shape of the adrenal glands and their pattern of enhancement after intravenous contrast were associated with in-hospital mortality in patients with sepsis; however, adrenal volume was not reported in such studies (48,49).

We found serendipitous adrenal masses in 9.5% of patients in the cohort admitted to the emergency department for suspected SARS-CoV-2 infection, without any significant difference between patients with or without confirmed infection. In the two parallel control groups, adrenal incidentalomas were found in 5 and 7% of patients, respectively. These frequency values are expected for the advanced age of our patients (2–4). However, a recent study carried out in a large, unselected population in China found a much lower frequency of adrenal incidentalomas, of 1.4% (50). Interestingly, in the Chinese study patients were relatively young, with a median age of 48 years, while the patients enrolled in other previous studies were older and had medical reasons for undergoing imaging assessment (4).

The findings in a Chinese population apparently free of selection bias challenge the current view of a high frequency of adrenal incidentalomas. In fact, the frequency of serendipitous adrenal masses reported in our cohort is quite high and can be explained by the selection of a diseased population. Our new evidence is that the frequency of adrenal incidentalomas does not seem to be higher in patients with acute medical conditions compared to those with non-acute conditions (4).

We believe that strengths of our study are the availability of different, large cohorts of patients assessed in either acute or non-acute clinical settings which provide new data on the frequency of a neglected entity, serendipitous adrenal hyperplasia, and also of adrenal incidentalomas.

Our study has several limitations including its retrospective design and the lack of hormonal testing.

It is important to take into account the extreme work overload faced by physicians in northern Italy at the time when the study was carried out. In fact, of the 2989 patients admitted to the emergency room for suspected SARS-CoV-2 infection, 2463 were discarded because a CT scan was not performed or the adrenal gland was not visible. This means that we cannot rule out that patients who did not undergo a CT scan were less severely ill, but also other factors, above all clinical judgment, could have influenced this decision. Indeed, the study protocol did not involve capturing data of this cohort.

Given that we do not know the mortality level in group A, there might have been a potential influence of non-included variables on the observed mortality in the main cohort. In fact, factors such as the overall impact of the pandemic, changes in healthcare delivery, and patient demographics could all contribute to variations in mortality rates.

In conclusion, the prevalence of serendipitous adrenal hyperplasia was higher in patients admitted to the emergency department (15%) compared to outpatients (8.5%), who showed a frequency comparable to previous reports in non-acute settings. Conversely, the frequency of serendipitous adrenal nodules did not differ between patients admitted to the emergency department or out-patient clinics, and is line with previous data on elderly subjects with a medical referral.

Adrenal hyperplasia is associated with increased short-term mortality. Although it is biologically plausible to hypothesize that adrenal enlargement may be the expression of enhanced stimulation by the HPA axis in conditions of significant stress, or of destructive processes (i.e., adrenal infarction) triggered by critical diseases leading to adrenal insufficiency, our study cannot definitively prove this hypothesis due to the absence of hormonal evaluation.

The evidence that adrenal hyperplasia is linked to short-term mortality suggests that the assessment of the adrenal glands in critically ill patients may have prognostic implications. Future studies are needed to correlate adrenal imaging data with patient outcome in a controlled prospective setting.

## Funding

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## Declaration of competing interest

Massimo Terzolo has received a research grant from HRA Pharma Rare Diseases, and several advisory board honoraria from HRA Pharma Rare Diseases; the other authors have stated explicitly that they have no conflicts of interest in connection with this article.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2024.103010.

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