Inpatient Mortality According to Level of Respiratory Support Received for Severe Acute Respiratory Syndrome Coronavirus 2 (Coronavirus Disease 2019) Infection: A Prospective Multicenter Study

Inpatient Mortality According to Level of Respiratory Support Required for SARS-CoV-2 (COVID-19) Infection: A Prospective Multicenter Study

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Abstract

Objective: To describe patients according to the maximum degree of respiratory support and report their inpatient mortality due to COVID-19.

Design: Analysis of the CORACLE registry

Setting: Hospitals in the Piedmont, Lombardy, Tuscany, and Lazio regions of Italy.

Patients: Nine-hundred forty-eight patients hospitalized for COVID-19

Interventions: None

Measurements and Main Results: Among 948 patients, 122 (12.87%) received invasive ventilation, 637 (67.19%) received supplemental oxygen only, and 189 (19.94%) received no respiratory support. The median age was 65 [54, 76.59] years and there was evidence of differential respiratory treatment by decade of life ($p = 0.0046$). There were 606 (63.9%) men in this study, and they were more likely to receive respiratory support than women ($p < 0.0001$). The rate of in-hospital death for invasive ventilation recipients was 22.95%, 12.87% for supplemental oxygen recipients, and 7.41% for those who received neither ($p = 0.0004$). Invasive ventilation recipients who died were significantly older than those who survived (median [quartile 1, quartile3] age: 68.5 [60, 81.36] vs. 62.5 [55.52, 71] years, $p = 0.0145$).

Conclusions: Among patients hospitalized for COVID-19, 13% required mechanical ventilation, which was associated with a mortality rate of 23%.

Key words: SARS-CoV-2 (COVID-19), invasive ventilation, respiratory support, supplemental oxygen, inpatient mortality

Introduction

Early in the outbreak of COVID-19, mechanical ventilators were presented as the primary solution for severe COVID-19 cases, and there were subsequent efforts to increase the number of available ventilators for COVID-19 patients; even methods for ventilator sharing emerged.[1,2,3] However, the outcomes of patients receiving invasive ventilation have been perplexing, with a report from New York revealing that 97% of invasive ventilation recipients over 65 years old died, and a report from China with a similarly high 86% mortality rate.[4,5] Particularly in institutions which may become overwhelmed by large patient volume, providers must consider patients' chances of survival when considering which modality of respiratory support to deliver.[6] Hence, in a registry of patients hospitalized at Italian medical centers, we sought to determine the rate at which hospitalized patients received invasive ventilation, their distinguishing characteristics, and their mortality rate compared to those who received other levels of respiratory support.

Materials and Methods

Data

We used the CORACLE registry (epidemiology, clinical characteristics, and therapy in real life patients affected by Sars-Cov-2), which contains data of COVID-19 patients hospitalized in participating referral centers in the Piedmont, Lombardy, Tuscany, and Lazio regions of Italy, to perform this analysis. All patients in the registry were at least 18 years old and had COVID-19 infection confirmed via positive result of polymerase chain reaction assay of nasal and pharyngeal cultures, on or after February 22, 2020. We limited this analysis to patients whose inpatient mortality status was known (i.e. died in the hospital or discharged alive) as of April 1,

2020. Patients were categorized into 3 mutually exclusive groups according to maximum respiratory support received as follows: invasive ventilation, supplemental oxygen without invasive ventilation, or neither invasive ventilation nor supplemental oxygen. Patients who received both invasive ventilation and supplemental oxygen were analyzed in the invasive ventilation category. Invasive ventilation was initiated for a COVID-19 patient if peripheral oxygen saturation was <92% for patients without chronic obstructive pulmonary disease (COPD) or <88% for patients with COPD. The deterioration of saturation was evaluated in the presence of non-invasive ventilation with high flow oxygen continuous positive airway pressure with positive end expiratory pressure of 10-15 cmH2O. The need for supplemental oxygen therapy was evaluated according to peripheral oxygen saturation <92-96% in patients without COPD or < 88-92% in patients with COPD. Generally, patients aged greater than 80 years with a high comorbidity burden were maintained noninvasively despite desaturation. This work was approved by the ethical committee of Turin (Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino).

Statistical Analysis

Continuous variables were skewed and are presented as median [quartile 1, quartile 3]. We categorized age based on decade of life, to be consistent with the COVID-19 literature.[7] Categorical variables are presented as frequency (%). Differences in patient characteristics between those who received invasive ventilation, supplemental oxygen (without invasive ventilation), or neither were assessed via the Kruskal-Wallis Test and Chi-Square test, or Fisher's Exact Test, as appropriate. Analyses were performed using SAS version 9.4 (Cary, NC).

Results

Of the 1050 patients in the CORACLE registry at the time of analysis, 948 (90.3%) had a known mortality status at discharge. Hence, there were 948 patients included in this analysis, 122 (12.87%) of whom received invasive ventilation, 637 (67.19%) received supplemental oxygen without invasive ventilation, and 189 (19.94%) received no respiratory support (Table 1). The median age was 65 [54, 76.59] years, and although age distribution did not differ significantly according to respiratory support (p=0.1237), there was evidence of differential treatment by decade of life (Figure 1). For example, although 60 – 69 year olds constituted approximately 22% of the entire population, they represented closer to 32% of invasive ventilation recipients; conversely, although patients aged 80 years or more accounted for nearly 19% of the overall population, they only made up 9% of invasive ventilation recipients (p = 0.0046). There were 606 (63.9%) men in this study, and they were more likely to receive supplemental oxygen and/or invasive ventilation compared to women (invasive ventilation: 99 (81.15%), supplemental oxygen without invasive ventilation: 407 (63.89%), neither treatment: 100 (52.91%), p < 0.0001). There were no other significant differences in baseline patient characteristics across treatment groups. Although the overall rate of hypertension was high (51.06%), rates of other comorbidities were fairly low (e.g., diabetes mellitus: 16.16%, chronic heart failure: 7.2%); 59.81% (381/948) of patients had at least 1 comorbidity.

Overall, 124 (13.08%) patients perished in the hospital. The rates of death differed significantly across respiratory support groups, with 22.95% (28/122) of invasive ventilation recipients, 12.87% (82/637) of supplemental oxygen recipients, and 7.41% (14/189) of those who did not receive invasive ventilation or supplemental oxygen dying (p = 0.0004) (Figure 2). Of those who received invasive ventilation, the only distinguishing characteristic of those who perished compared to those who survived was older age (68.5 [60, 81.36] vs. 62.5 [55.52, 71]

years, p = 0.0145). Among invasive ventilation recipients with hypertension, RAASi use was associated with a significantly lower risk of death (44.44% vs 78.72%; p = 0.0074).

Discussion

In this registry study of 948 patients hospitalized for COVID-19, we found that 80.06% required supplemental oxygen and/or invasive ventilation and that 13.08% patients perished in the hospital, overall. We determined that the rates of death differed significantly across treatment modalities, with those receiving invasive ventilation being at the highest risk. Amongst those who required mechanical ventilation, the mortality rate was 23% implying that the survival on mechanical ventilation was much higher in this study than from information available at the time of this writing from China.[8] There were 12.9% of patients in this study who received invasive ventilation, which is nearly identical to the 12.2% reported out of New York.[4] We learned that males in their early-to-mid-60s accounted for the majority of invasive ventilation recipients and that those recipients who perished were significantly older than their counterparts who survived.

We are not the first to find that patients hospitalized with COVID-19 infection are likely males in their mid-60s. Our 64% male prevalence and overall median age of 65 years is comparable to a study of COVID-19 patients in critical care in the United Kingdom, which revealed male predominance (71%) and a median age of 64 years.[9] In Seattle, 63% of such patients were male and had a mean age of 64 years.[10] Similar demographic information has been reported in Hong Kong.[11] Additionally, Grasselli and colleagues (Lombardy region, Italy) observed an 82% prevalence of males and a median age of 63 in their sample of intensive care unit patients.[12] Our 81% male rate of invasive ventilation recipients is nearly identical (median age = 63 years). Several hypotheses exist to explain the differential effect of gender on infection severity and outcomes, including sex hormones' effects on immune and inflammatory responses,

stress hormones, and social isolation.[13] Comorbidities also play a role in the severity of COVID-19; however, the likelihood of having one or more comorbidities also increases with age.

Death rate reports vary widely. Hong Kong reported an 88% 28-day survival rate for COVID-19 patients in the ICU.[11] Our observed rate of inpatient death observed in this study for invasive ventilation recipients is similar to the 26% reported by Grasselli and colleagues from the Lombardy region of Italy; however, not all patients had been removed from ventilation at the time of their paper.[12] Initial reports from Seattle indicate a 50% mortality rate in the ICU (with five-sixths of patients having do-not-resuscitate orders),[10] and critical patients who received invasive ventilation within the first 24 hours of admission in the UK perished at a rate of 66%.[14] Most mortality rates are less than initial reports from (Wuhan) China, in which the 28 day mortality rate among patients who admitted to the ICU and required non-invasive ventilation was 79% (23/29).[5] Similarly, those who required invasive mechanical ventilation had a 28 day mortality rate of 86% (19/22).[5]

This study has limitations inherent to its observational nature, including the inability to fully assess the direct effect of respiratory support on mortality. These data provide information about patients who received respiratory support and do not necessarily inform about patients who may have benefitted from, but did not receive it. We recognize that comparing mortality rates between patients receiving different levels of respiratory therapy does not take into account the underlying severity of disease or comorbidity burden of the patients, which influences treatment decisions. However, we presented information indicating whether treatment was or was not provided in the intensive care unit in an effort to describe the severity. Data pertaining to adjunctive therapies of hydroxychloroquine and tocilizumab were missing at relatively high rates. Additionally, we did not have information available pertaining to do-not-resuscitate orders.

Other variables of interest, including time on ventilator were not available for study. Neither race nor ethnicity were available and data are from the Piedmont, Lombardy, Tuscany, and Lazio regions of Italy, so these results may not be generalizable to other countries.

Conclusion

These data reveal that the majority of patients hospitalized for COVID-19 infection require some level of respiratory support and that most patients are males in their mid-60s with at least 1 comorbidity. Among such patients, 13% required mechanical ventilation, which had an associated in-hospital mortality rate of 23%.

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Disclosures

The authors have no conflicts to disclose.

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Figure Legend

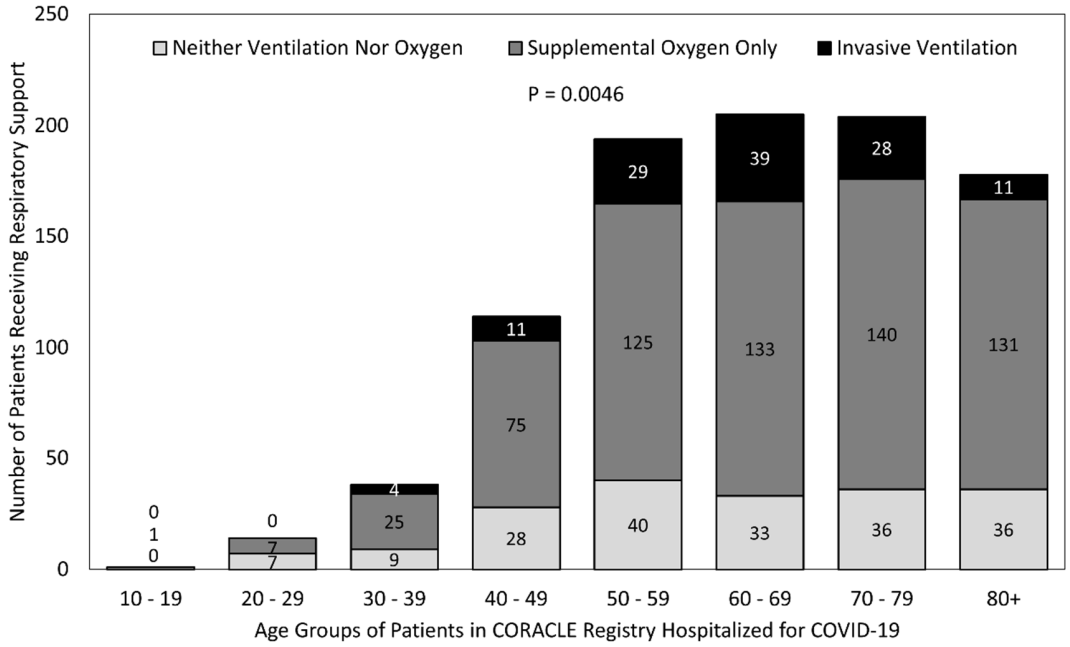
Figure 1. Respiratory support received according to age group of patients in CORACLE registry hospitalized in Italy for COVID-19 infection

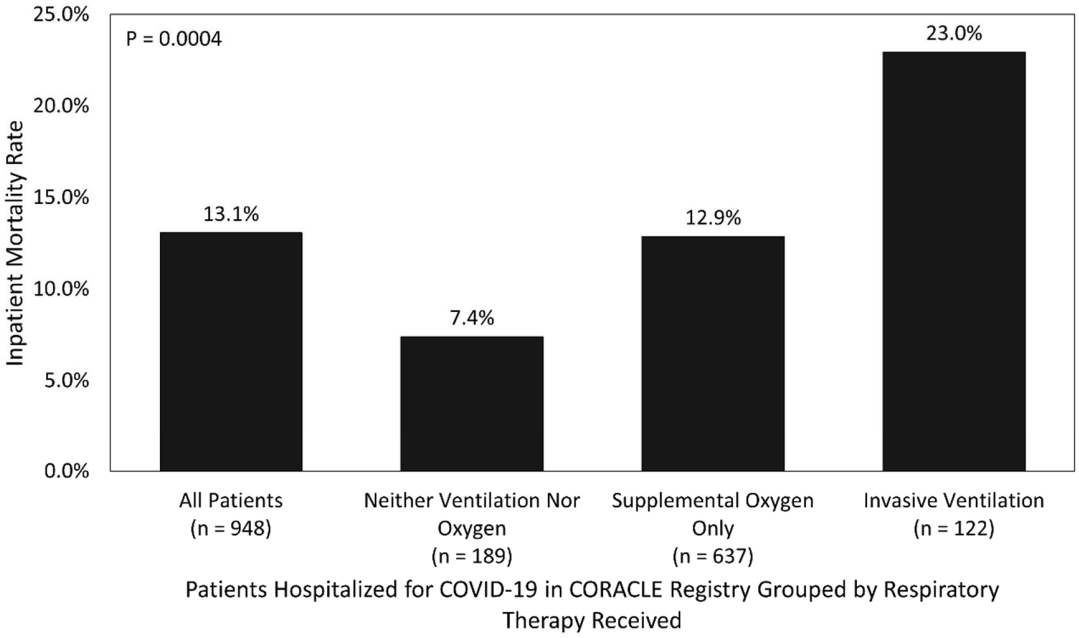
Figure 2. Inpatient survival rates according to age group and respiratory support received of patients in CORACLE registry hospitalized in Italy for COVID-19 infection

Table 1. Characteristics of patients in CORACLE registry hospitalized for COVID-19 according to respiratory support received

Characteristic	Overall (n = 948)	None (n = 189)	Supplemental Oxygen (n = 637)	Invasive Ventilation (n = 122)	P-value
Age (years)	65 [54, 76.59]	63 [50, 76]	66 [54, 77]	63.37 [56, 72]	0.1237
Age category (years)					0.0046
10 - 19	1 (0.11%)	0 (0%)	1 (0.16%)	0 (0%)	
20 - 29	14 (1.48%)	7 (3.7%)	7 (1.1%)	0 (0%)	
30 - 39	38 (4.01%)	9 (4.76%)	25 (3.92%)	4 (3.28%)	
40 - 49	114 (12.03%)	28 (14.81%)	75 (11.77%)	11 (9.02%)	
50 - 59	194 (20.46%)	40 (21.16%)	125 (19.62%)	29 (23.77%)	
60 - 69	205 (21.62%)	33 (17.46%)	133 (20.88%)	39 (31.97%)	
70 - 79	204 (21.52%)	36 (19.05%)	140 (21.98%)	28 (22.95%)	
80+	178 (18.78%)	36 (19.05%)	131 (20.57%)	11 (9.02%)	
Gender (male)	606 (63.92%)	100 (52.91%)	407 (63.89%)	99 (81.15%)	<0.0001
Hypertension[2]	483 (51.06%)	86 (45.74%)	332 (52.12%)	65 (53.72%)	0.2523
Obstructive lung disease[1]	87 (9.19%)	17 (9.04%)	58 (9.11%)	12 (9.84%)	0.9649
Diabetes mellitus[1]	153 (16.16%)	28 (14.81%)	110 (17.3%)	15 (12.3%)	0.3323
Smoking status					0.4678
Yes	82 (8.65%)	13 (6.88%)	54 (8.48%)	15 (12.3%)	
No	803 (84.7%)	166 (87.83%)	539 (84.62%)	98 (80.33%)	
Former	61 (6.43%)	10 (5.29%)	43 (6.75%)	8 (6.56%)	
Missing	2 (0.21%)	0 (0%)	1 (0.16%)	1 (0.82%)	
Chronic heart failure[3]	68 (7.2%)	9 (4.84%)	47 (7.38%)	12 (9.84%)	0.2402
Coronary artery disease	106 (11.18%)	14 (7.41%)	79 (12.4%)	13 (10.66%)	0.1572
Beta blocker[1]	187 (19.75%)	31 (16.4%)	139 (21.82%)	17 (14.05%)	0.0626
Calcium channel blocker[1]	162 (17.11%)	28 (14.81%)	120 (18.84%)	14 (11.57%)	0.0972
Thiazide diuretic[56]	109 (12.22%)	23 (12.17%)	73 (12.27%)	13 (12.04%)	0.9974
Loop diuretic[58]	103 (11.57%)	16 (8.51%)	78 (13.13%)	9 (8.33%)	0.1200
RAASi					0.6297
ACEi	621 (65.51%)	131 (69.31%)	413 (64.84%)	77 (63.11%)	
ARB	181 (19.09%)	34 (17.99%)	120 (18.84%)	27 (22.13%)	
None	146 (15.4%)	24 (12.7%)	104 (16.33%)	18 (14.75%)	
Intensive care unit	265 (27.95%)	2 (1.06%)	148 (23.23%)	115 (94.26%)	<0.0001
Hydroxychloroquine[162]	589 (74.94%)	76 (51.7%)	429 (79.01%)	84 (87.5%)	<0.0001
Anti-IL-6 agent[132]	151 (18.50%)	6 (4.58%)	99 (17.40%)	46 (39.66%)	<0.0001
Length of stay (days)[19]	9 [6, 12]	6 [3, 10]	9 [6, 12]	10 [6, 15]	<0.0001

Age groups were collapsed into a <50 years category for statistical testing due to small counts
Superscripts indicate missing data
RAASi = renin-angiotensin-aldosterone system inhibition; ACEi = angiotensin II-converting enzyme inhibitor; ARB = aldosterone receptor blocker


Neither Ventilation Nor Oxygen
Supplemental Oxygen Only
Invasive Ventilation
P = 0.0046
Number of Patients Receiving Respiratory Support
250
200
150
100
50
0
0
1
0
0
7
7
4
25
9
11
75
28
29
125
40
39
133
33
28
140
36
11
131
36
10 - 19
20 - 29
30 - 39
40 - 49
50 - 59
60 - 69
70 - 79
80+
Age Groups of Patients in CORACLE Registry Hospitalized for COVID-19



Patients Hospitalized for COVID-19 in CORACLE Registry Grouped by Respiratory Therapy Received