COVID-19

Clinical characteristics and risk factors associated with COVID-19 mortality in a non-Intensive Care Unit

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Keywords

COVID-19 • SARS-CoV-2 • Risk factors • Mortality

Summary

Introduction. *The Coronavirus disease 2019 caused by a new Coronavirus (SARS-CoV-2) throughout the pandemic period has been characterised by a wide spectrum of clinical manifestations, courses, and outcomes. In particular, most patients with severe or critical symptoms re-quired hospitalization. The demographic and clinical characteristics of patients upon admission to the hospital, as well as pre-existing medical conditions, seem to have affected the clinical out-come. Predictive factors of inauspicious outcome in non-Intensive Care Unit hospitalized patients were investigated.*

Methods. *A retrospective, single-centre, observational study of 239 patients with confirmed COVID-19 disease admitted during the first waves of the pandemic to the Infectious Disease Operative Unit of a hospital in Southern Italy was conducted. Demographic characteristics, under-lying diseases, and clinical, laboratory, and radiological findings were collected from the patient's medical records. Information about in-hospital medications, days of admission, and out-come were also considered. Inferential statistical analysis was performed to evaluate the association between patients' characteristics upon hospital admission and during in-hospital length of stay and death.*

Results. *Mean age was 67.8 ± 15.8 years; 137/239 (57.3%) patients were males, and 176 (73.6%) had at least one comorbidity. More than half of patients (55.3%) suffered from hypertension. The length of stay in hospital was 16.5 ± 9.9 days and mortality rate of 12.55%. In multivariable logistic regression analysis, predictors of mortality of COVID-19 patients included age (OR, 1.09; CI, 1.04-1.15), Chronic Kidney Disease (OR, 4.04; CI, 1.38-11.85), and need of High Flow Oxygen therapy (OR, 18.23; CI, 5.06-65.64).*

Conclusions. *Patients who died in the hospital had shorted length of stay than that of the surviving patients. Older age, pre-existent chronic renal disease and need of supplemental oxygen represented independent predictors of mortality in patients hospitalized in non-Intensive Care Unit with COVID-19. The determination of these factors allows retrospectively a greater understanding of the disease also in comparison with the successive epidemic waves.*

Introduction

The novel Coronavirus (2019-nCoV), known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), responsible for Coronavirus Disease 2019 (COVID-19), originated in Wuhan, Hubei province, in China at the end of 2019 [1]. COVID-19 rapidly spread around the world and, on March 11, 2020, the World Health Organization (WHO) declared this disease pandemic [2].

The clinical spectrum of infection can be seen in COVID-19 patients ranging from asymptomatic to severe disease with pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), and sepsis [3, 4]. The pandemic has caused the death of more than 6.7 million people out of approximately 664 million infected as of 25 January 2023 [5].

Most patients with severe or critical symptoms require hospitalization. Substantial differences in length of stay (LoS) in the hospital and the mortality of patients with COVID-19 have been reported worldwide; the results of a recent systematic review showed that the mean LoS in hospital was 14.49 days, with 13 days as the median and minimum and maximum hospital LoS reported of 3.5 and 53.8 respectively [6]. Another study showed that among Intensive Care Unit (ICU) admissions, the median stay ranged from 5 to 19 days. Furthermore, the LoS of patients discharged alive was longer than those who died in the hospital [7].

However, the duration varies depending on several factors such as the patient's age, comorbidities, availability, and accessibility to health services [6, 7].

The global mortality rate among hospitalized COVID-19 patients was around 18%, although with notable differences between countries [8, 9]. The mortality risk among ICU admitted patients was higher than that among non-ICU patients [9].

Chronic conditions such as hypertension, cardiovascular disease, type-2 diabetes, respiratory disease, cancer, and renal disease were the most prevalent underlying causes among hospitalized patients with COVID-19 [10, 11].

Since the first reports on COVID-19, older age, and comorbidity were identified as risk factors for death among COVID-19 patients [12-15]. Some investigations have reported that pre-existing chronic conditions, such as type-2 diabetes, Chronic Obstructive Pulmonary

Disease (COPD), heart, liver, and kidney disease, hypertension, obesity, cancers have been associated with ICU admission and death, as well as high serum levels of Interleukin-6 (IL-6), C-Reactive Protein (CRP), and D-Dimer have also been identified as independent factors for predicting COVID-19 severity, and in-hospital mortality [16-19].

This study aimed to describe the demographics and clinical features in a cohort of hospitalized COVID-19 patients in a non-ICU Unit and identify the risk factors associated with mortality.

Information about in-hospital medications and laboratory findings were also considered and the risk factors associated with COVID-19 related death in this group of non-ICU hospitalized patients were evaluated.

Methods

Study population

In this retrospective, single-center, observational study, patients with SARS-CoV2 infection admitted to the Infectious Disease Operative Unit (OU) of Vito Fazzi Hospital, Lecce, Italy, between March 1, 2020, and December 31, 2020, were considered. Diagnosis of COVID-19 was established by real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) assay on nasopharyngeal swabs. Demographic characteristics, underlying diseases, and clinical, laboratory and radiological findings were collected from the patients' medical records upon admission to the OU. Obesity, type 2 diabetes, hypertension, heart disease, Chronic Kidney Disease (CKD), dialysis and cancer were the pre-existing comorbidities investigated. The following laboratory data were recorded: Arterial partial pressure of oxygen (PO2): Fraction of inspired oxygen (FiO2) ratio, IL-6, CRP, D-Dimer and Glomerular Filtration Rate (GFR). Data on medications, high-flow oxygen therapy, LoS in hospital and outcome were also collected.

This research was approved by the Ethics Committee of the Health Local Unit of Lecce (Report n. 57 of 22, January 2021) and conducted in accordance with the Helsinki declaration. The informed consent was retrospectively obtained from participants if possible.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as frequency and percentage. Comparison between continuous variables was performed using independent samples t test and between categorical variables using chi-square test or fisher exact test, as needed.

Univariate and multivariate logistic regression analyses were performed to determine the independent risk factors associated with mortality. Variables emerging from univariate analysis with p-value < 0.05 were included in the multivariate analysis. Statistical calculations were performed by MedCalc software, version 14.8.1 (MedCalc Sofware Ltd, Ostend, Belgium).

Results

A total of 239 consecutive patients diagnosed with COVID-19 were admitted to the Infectious Disease Unit of "Vito Fazzi" Hospital, Lecce, Italy, between March 1, 2020, and December 31, 2020. Clinical characteristics and outcome of patients are described. Mean age was 67.8 ± 15.8 years; 137/239 (57.3%) patients were males, and 176 (73.6%) had at least one chronic comorbidity. More than half of patients (55.3%) were suffered by hypertension.

The majority of patients (81%) did not need high flow oxygen therapy and, 164/239 (68.6%) patients had interstitial pneumonia with ground glass patterns.

The mean LoS in the hospital was 16.5 ± 9.9 days and the overall in-hospital mortality rate was 12.55% (30/239).

Almost all patients, 225/239 (94.1%) received Low-Molecular Weight Heparin (LMWH) and a total of 191/239 (79%) patients received combination therapy with dexa-methasone (DEX) and UFH. On the basis on clinical judgment and high IL-6 levels, five patients were treated with tocilizumab (TL) double dose. 48/239 (20.1%) patients received remdesevir (RDV) (Tab. I).

From the comparison between Survivors and Non-Survivors patients, those who died were older, with significant difference between the two groups ($p < 0.0001$) and more likely to have a history of CKD ($p < 0.0001$) or dialysis ($p = 0.044$).

Concerning the laboratory findings, the 36.7% of Non-Survivors patients had $PO_2/FiO_2 < 200$ compared to the 17.7% of Survivors, with a significant difference ($p = 0.029$) between the two groups.

Kidney function assessed as GFR was also significantly different ($p < 0.0001$) between the two groups; with a lower value (39.9 ± 21.3 mL/min) among dead patients compared to those discharged alive from the hospital (68.9 ± 23.1 mL/min).

Finally, the mean LoS in the hospital of patients who died was 10.5 ± 7.7 days and of those survived 17.4 ± 9.8 days, with a significant difference ($p = 0.0003$) between the two categories (Tab. I).

Univariate logistic regression analysis, shown in Table II, revealed a significant association between in-hospital mortality and age of patients, CKD ($p < 0.0001$), $PO_2/FiO_2 < 200$ ($p < 0.05$), high flow oxygen therapy ($p < 0.0001$) and more than two comorbidities ($p < 0.001$). Using multivariate logistic regression, we found that age (OR 1.09, 95% CI 1.04-1.5; $p < 0.001$), CKD (OR 4.04, 95% CI 1.38-11.82; $p = 0.01$) and high-flow oxygen therapy (OR 18.23, 95% CI 5.06-65.64; $p < 0.0001$) were significant predictors of in-hospital mortality (Tab. II).

Discussion

This retrospective study described the demographic characteristics and clinical presentation of a cohort of COVID-19 patients hospitalized during the first waves of the pandemic in an Infectious Diseases UO, who were

Tab. I. Demographic and clinical characteristics of 239 patients with COVID-19 admitted to the Infectious Disease Operative Unit.

Characteristics	Total (n = 239)	Survivors (n = 209)	Non-survivors (n = 30)	P-value
Age, years (mean ± SD)	67.8 ± 15.8	65.8 ± 15.6	81.7 ± 8.6	< 0.0001 [a]
Sex, male N (%)	137 (57.3)	121 (57.9)	16 (53.3)	0.783 [b]
Age group, years				
20-29 N (%)	2 (0.8)	2 (0.96)	0 (0.0)	
30-39 N (%)	13 (5.4)	13 (6.2)	0 (0.0)	
40-49 N (%)	13 (5.4)	13 (6.2)	0 (0.0)	
50-59 N (%)	41 (17.1)	40 (19.1)	1 (3.3)	
60-69 N (%)	48 (20.8)	47 (17.1)	1 (3.3)	
70-79 N (%)	60 (25.1)	53 (25.4)	7 (23.3)	
80-89 N (%)	52 (21.8)	33 (15.8)	19 (63.3)	
≥ 90 N (%)	10 (4.2)	8 (3.8)	2 (6.7)	< 0.0001 [b]
No. of comorbidities				
None N (%)	63 (26.4)	57 (27.3)	6 (20.0)	
1 N (%)	52 (21.8)	51 (24.4)	1 (3.3)	
2 N (%)	62 (25.9)	54 (25.8)	8 (26.7)	
3 N (%)	43 (18.0)	35 (16.7)	8 (26.7)	
> 3 N (%)	19 (7.9)	12 (5.8)	7 (23.3)	0.0015 [b]
Comorbidities				
Obesity N (%)	50 (20.9)	45 (21.5)	5 (16.7)	0.619 [b]
Type 2 diabetes N (%)	57 (23.8)	47 (22.5)	10 (33.3)	0.756 [b]
Hypertension N (%)	132 (55.2)	117 (56.0)	15 (50.0)	0.675 [b]
Heart disease N (%)	79 (33.1)	64 (30.6)	15 (50.0)	0.087 [b]
Chronic kidney disease N (%)	63 (26.4)	43 (20.6)	20 (66.7)	< 0.0001 [b]
Dialysis N (%)	7 (2.9)	4 (1.9)	3 (10.0)	0.044 [c]
Cancer N (%)	13 (5.4)	11 (5.3)	2 (6.7)	0.670 [c]
Pneumonia N (%)	164 (68.6)	140 (67.0)	24 (80.0)	0.220 [b]
LoS (d ± SD)	16.5 ± 9.9	17.4 ± 9.8	10.5 ± 7.7	0.0003 [a]
Laboratory panel				
PO_2/FiO_2 ratio (mmHg), (mean ± SD)	297.9 ± 105.4	303.5 ± 104.1	259.1 ± 107.6	0.031 [a]
PO_2/FiO_2 < 200 N (%)	48 (20.1)	37 (17.7)	11 (36.7)	0.029 [b]
IL-6 (pg/ml), (mean ± SD)	40.7 ± 117.2	37.9 ± 114.2	65.9 ± 141.3	0.277 [a]
D-Dimer (mg/ml), (mean ± SD)	2782.6± 6048.9	2734.7 ± 6246.8	3140.0 ± 4364.3	0.666 [a]
CRP (mg/dl), (mean ± SD)	51.8 ± 50.5	49.0 ± 48.0	72.5 ± 63.7	0.070 [a]
GFR (mL/min), (mean ± SD)	65.3 ± 24.8	68.9 ± 23.1	39.9 ± 21.3	< 0.0001 [a]
Respiratory support				
None N (%)	192 (81.0)	181 (87.0)	11 (37.9)	
High flow oxygen therapy N (%)	45 (19.0)	27 (13.0)	18 (62.1)	< 0.0001 [b]
Treatment				
HCQ N (%)	59 (24.7)	51 (24.4)	8 (26.7)	0.966 [b]
LPV N (%)	42 (17.6)	36 (17.2)	6 (20.0)	0.008 [b]
UFH N (%)	225 (94.1)	197 (94.3)	28 (93.3)	0.831 [b]
DEX N (%)	194 (81.2)	171 (81.8)	23 (76.7)	0.671 [b]
TL N (%)	5 (2.1)	5 (2.4)	0 (0.0)	1.000 [c]
RDV N (%)	49 (20.6)	46 (22.1)	3 (10.0)	0.152 [c]
HCQ + LMWE + LPV N (%)	40 (16.7)	34 (16.3)	6 (20.0)	0.604 [b]
DEX + LMWE N (%)	191 (79.9)	169 (80.9)	22 (73.3)	0.376 [b]
DEX + LMWE + RDV N (%)	48 (20.1)	46 (22.0)	2 (6.7)	0.053 [c]

[a] Independent samples t-test. [b] Chi-square test; [c] Fisher's exact test.
LoS: length of hospital stay; PO_2: partial pressure of oxygen; FiO_2: fraction of inspired oxygen; IL-6: interleukin 6; CRP: C-reactive protein; GFR: glomerular filtration rate; HCQ: Hydroxychloroquine; LPV: Lopinavir; LMWE: Low-Molecular Weight Heparin; DEX: Dexamethasone; TL: Tocilizumab; RDV: Remdesivir.

not admitted to the ICU. Large proportion of patients did not require high flow oxygen therapy.

We found that in-hospital mortality rate among patients diagnosed with COVID-19 was 12.55% with a mean LoS in the hospital of 16.5 ± 9.9 days for all patients. Patients who died in the hospital had shorted LoS than that of the surviving patients. This confirms the evidence of other studies, in which LoS of patients discharged alive was between 4 and 53 days compared to 4 and 21 days of patients who died [7].

Tab. II. Univariate e multivariate analysis of risk factors associated with mortality in COVID-19 patients.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	1.10 (1.06-1.15)	< 0.0001	1.09 (1.04-1.15)	0.000
PO_2/FiO_2 < 200	2.69 (1.18-6.13)	0.018	0.42 (0.11-1.66)	0.217
Comorbidities > 2	3.45 (1.57-7.56)	0.002	1.31 (0.47-3.62)	0.607
Chronic kidney disease	7.72 (3.37-17.70)	< 0.0001	4.04 (1.38-11.85)	0.011
High flow oxygen therapy	10.97 (4.68-25.72)	< 0.0001	18.23 (5.06-65.64)	< 0.0001

OR: odds ratio; 95% CI: 95% confidence interval; PO_2: partial pressure of oxygen; FiO_2: fraction of inspired oxygen.

The death count in our population is consistent with that reported in an Italian multicenter study involving 26 hospitals representative of national population sample, in which the mortality rate was 11.8% [13].

By the multivariate logistic regression analysis, we observed that age, high flow oxygen therapy and pre-existing CKD were independent predictors of in-hospital mortality.

Age is prominent in the literature as a frequently reported independent factors associated with in-hospital mortality [20].

Our results are similar to data of a cohort of over 17 million NHS patients that demonstrated that patients with reduced kidney function had a very high risk of COVID-19 mortality [21], even higher than that of other high-risk factors. In several other international studies, it was observed that CKD patients have a higher risk of intubation and death [13, 22, 23]. A possible explanation is that patients with CKD have alteration of the immune system [24] and increased concentrations of pro-inflammatory cytokines [25] with a possible increase in lung inflammation.

Finally, the need of high flow oxygen therapy was found to be the last independent predictor of mortality in our cohort, although few patients in our hospital ward had used respiratory support. It has been showed that respiratory failure and a PaO_2/FiO_2 < 200 mmHg at admission were factors independently associated with a higher mortality rate [26].

Xie et colleagues demonstrated that patients with oxygen saturation lower than 90% had high risk to die respect patient with oxygen saturation more than 90% [27].

Studies comparing the prognosis of patients with PaO_2/FiO_2 < 200 requiring mechanical ventilation during different waves document that in-hospital mortality did not improve during subsequent epidemic waves [28, 29].

This study has several limitations. It is a retrospective study from a single center in a limited sample and the findings may not be generalizable to other populations.

The data are related to the first pandemic waves that present peculiar characteristics compared to subsequent epidemic periods due to the lack of knowledge of the etiological agent and of the clinical manifestations of the disease.

Despite limitations, our results illustrate the effect of baseline morbidity factors such as increasing age and chronic pathology, particularly chronic kidney disease, dialysis, and, more than two comorbidities on the mortality of patients with COVID-19.

The differences between the different epidemic waves should be the subject of a thorough analysis. The comparison between the characteristics of the patients treated in the same center in the first and subsequent epidemiological waves will be the subject of a subsequent study by the same authors.

Conclusions

We identified demographic factors and baseline comorbidities as independent predictors of mortality in non-ICU hospitalized COVID-19 patients during the first epidemic waves when knowledge of the SARS-CoV-2 was still limited and the outcome associated with the risk factors in COVID-19 patients was still partially unknown. Several chronic comorbidities, complications, and demographic variables for COVID-19 mortality were recognized. A better understanding of all the factors associated with a serious evolution of the disease can help to define more effective programs in the clinical management and prevention of the disease.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

PG acquired data; MG and AZ carried out the analysis of data. All authors conceived the study and contributed to the preparation of the manuscript related to their sections and approved the final version to be submitted.

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