CE-RESEARCH LETTER TO THE EDITOR

Determinants of COVID-19-related mortality in an internal medicine setting

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Abbreviations

COVID-19   Coronavirus disease 2019
SARS-CoV-2 Severe acute respiratory syndrome corona-
            virus 2

Dear Editor,

The global community has progressively faced the healthcare and social consequences caused by Coronavirus disease 2019 (COVID-19). To invade the host, SARS-CoV-2 principally exploits the angiotensin-converting enzyme II receptor [1]. SARS-CoV-2 causes a direct cytopathic effect, above all involving the alveolar and the vascular endothelium, but also the gastroenteric system, with mucosal inflammation, leading to an intestinal barrier and enteric nervous system dysfunction [2]. In addition to the more common respiratory manifestations, other alterations have been described, including altered liver function, upper gastrointestinal bleeding and kidney injury, possibly via viral sepsis [2–4]. Moreover, it has been observed that in young adults without comorbidities the presence of gastrointestinal manifestations, anosmia/ageusia and the absence of dyspnoea seem to predict a favourable disease course, whereas in patients older than 65 years, multimorbidity along with major respiratory symptoms were associated with a worse prognosis [5].

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To date, few data are available regarding the clinical characteristics and outcomes of patients hospitalised in internal medicine wards. In Italy, internal medicine practitioners have been rapidly and heavily involved in the management of the pandemic [6], but relevant patient outcomes have been partially described. Hence, we sought to describe patient mortality and other clinical characteristics in an internal medicine setting.

The main aim of this study was to evaluate the in-hospital mortality of the index hospital stay due to COVID-19 in the Internal Medicine Department of our hospital (Fondazione IRCCS Policlinico San Matteo, Pavia) by analysing its associated factors. This was a monocentric, retrospective, observational study, a sub-study of the San Matteo COVID registry (SMACORE). All 540 patients admitted in March–December 2020 (i.e., first and second waves) were included in the study. Data were collected and pseudo-anonymised and entered in the REDCap database. A laboratory diagnosis of SARS-CoV-2-related infection was made according to the nasopharyngeal swab (molecular test) on bronchoalveolar lavage. We included socio-demographic data (age, sex), body mass index, main comorbidities including hypertension, cardiovascular diseases (i.e., coronary heart disease, peripheral vascular disease and heart failure), metabolic diseases (e.g., diabetes mellitus, obesity), chronic obstructive pulmonary disease, chronic kidney disease, neoplastic and onco-haematological disease, psychiatric diseases, dementia and bed confinement status. The symptoms investigated and included in this study upon admission were fever, cough, pulse rate and respiratory rate. Severity of the respiratory disease, as assessed by oxygen exchange parameters and oxygen and non-invasive ventilation requirements support were also assessed. The length of stay was calculated in days, considering the admission day as the beginning of the observation and the discharge day (or death) as the end of study.

Continuous data were presented as median and interquartile range (IQR) or mean and standard deviation. Categorical variables were reported as count and percent. Correlates of hospital mortality were assessed using the Cox regression. Cumulative survival was computed and plotted using the Kaplan–Meier method. Noncollinear variables, with a p value < 0.1, were entered in a multivariable Cox model. Hazard ratios (HR) and 95% confidence intervals were computed. The median follow-up and IQR (corresponding to the length of stay) were computed with the reverse Kaplan–Meier method. The statistical program STATA (release 16, Stata Corp, College Station, TX, USA) was used for computation. The study was approved by the local ethics committee (Fondazione IRCCS Policlinico San Matteo) and all patients provided written informed consent.

All the 540 patients admitted to the Internal Medicine Department were included (median age 71 years, IQR 60–81, 345 males). Table 1 summarises the main clinical and laboratory characteristics of patients. The more frequently reported sign was fever (300, 73.7%), together with cough (148, 47.6%), fatigue (147, 49.2%) and dyspnoea (258, 66.3%). Additionally, 469 patients (86.2%) suffered from at least one associated chronic disease, with 338 (72.1%) having two or more ongoing comorbidities.

Table 1 Clinical and laboratory characteristics of the 540 patients included in the study

Method of SARS-CoV-2 infection diagnosis	n	%
Nasopharyngeal swab	513	95
Bronchoalveolar lavage	27	5
Presenting symptoms	n	%
Fever	300	73.7
Cough	148	47.6
Fatigue	147	49.2
Dyspnoea	258	66.3
Vital signs		Median (IQR)
Fever (°C)		37 (36–38)
HR (beats/min)		88 (78–100)
BF (breaths/min)		20 (17—25)
Severity of disease		Median (IQR)
SO_2 (%)		95 (91–98)
PaO_2 (mmHg)		72 (61–92)
$PaCO_2$ (mmHg)		32 (28–36)
PaO_2/FiO_2		282 (222–353)
Oxygen requirement	n	%
Low flows	95	25.3
High flows	130	34.6
CPAP	114	30.3
Intubation	28	7.4
Comorbidities at admission	n	%
At least 1 comorbidity	469	89.5
≥ 2 chronic diseases	378	72.1
Hypertension	322	77.2
Cardiovascular disease	217	52.4
COPD	48	13.5
Interstitial disease	10	2.8
Asthma	10	2.8
Obesity	66	18.8

Percentages were calculated after the elimination of patients with missing data

BF breath frequency, *COPD* chronic obstructive pulmonary disease, *CPAP* continuous positive airways pressure, *HR* heart rate, *IQR* interquartile range

The overall median hospitalization length was 17 days (IQR 12–28). Patients who died had a median time to death of 10 days. During an overall observation period at risk of 9500 days, 146 deaths (27%) were reported, with a mortality rate of 10.9 per 100 person/week. Figure 1 shows the overall Kaplan–Meier survival curve (upper part) and key clinical variables (lower part). Of note, two-third of deaths occurred within the first 14 days of hospitalisation, with mortality decreasing thereafter having two or more comorbidities, cardiovascular disease, hypertension and dementia were all associated with an increased mortality rate, whereas having mild dyspnoea was a protective factor (as compared to moderate or severe dyspnoea). At multivariable analysis, among the various factors investigated, age ≥ 70 years increased the risk of hospital death by four ($p = 0.001$) and having an onco-haematologic disease by two ($p = 0.062$, Table 2).

We have herein reported data regarding mortality from COVID-19 from an internal medicine ward, finding an in-hospital mortality rate of 10.9 per 100 persons/week, with mortality-related factors being an age ≥ 70 yearsand having and onco-haematologic disease.

By comparing our results with those of studies from other geographical areas (China, Europe and the USA) some interesting differences can be noticed. The mortality was found to be slightly higher in China (28%) [7] and in our Internal Medicine ward in Italy (27%), as compared to the USA (15%) [8]. This finding is probably the result of the geographical areas hit earlier by the pandemic. In the USA, however, some studies showed mortality estimates were much higher than the reported one, possibly reflecting limited access to the private healthcare system [9]. Focusing on the mortality in Europe, a West to East gradient mortality (from major to minor) correlated with a democratization gradient of the countries. In Italy, a mortality rate as high as 54.8% has been reported [10].

Mortality may be expected to be lower in an Internal Medicine unit because critically ill patients would normally be admitted to an intensive care unit (ICU). However, it is also true that during the peak of the pandemic, due to a shortage of available ICU beds, patients might have been admitted to other wards, especially internal medicine, that were among the few where expertise was available to assist these patients with more complex needs. Another factor accounting for the high mortality in our study was the older age (median 71 years) as compared to other studies [7, 8, 11]. This finding probably mirrors the older age of the overall Italian population as compared to others in Europe.

As far as symptoms are concerned, heterogenous data have been reported. Fever and cough were both found to be predictive of mortality in Italy [12], whereas fever was found
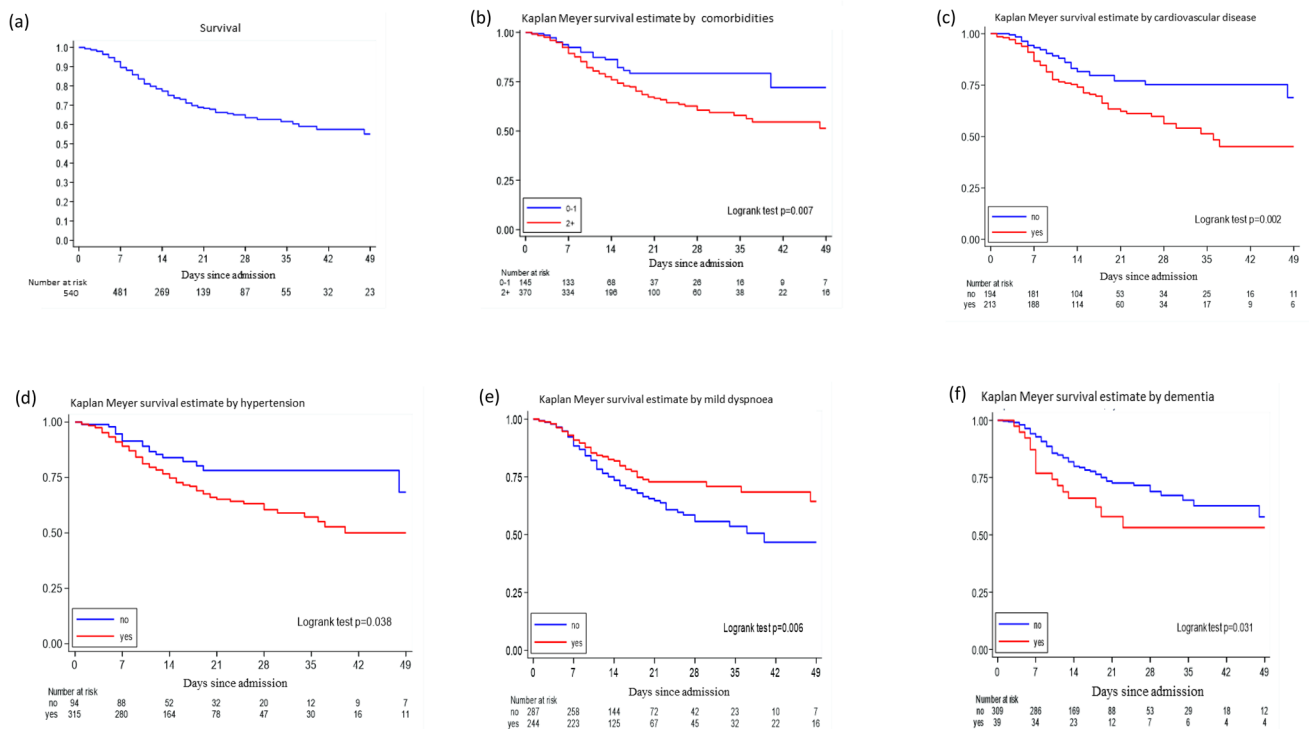

Fig. 1 Kaplan–Meier survival estimate of the whole cohort of patients (**a**) and according to comorbidities (**b**), cardiovascular disease (**c**), hypertension (**d**), mild dyspnoea (**e**) and dementia (**f**) at the time of admission. *p* values from the univariable comparison of curves with the logrank test are shown within the figure

Table 2 Multivariable analysis for factors associated with death

Variable	Hazard ratio	95% confidence interval	p value
Age			
< 70	1		
≥ 70	3.82	2.10–6.93	< 0.001
Dyspnoea			
At rest	1		
Mild or severe exercise	0.89	0.56–1.42	0.619
Bed confinement			
Absent	1		
Present	1.19	0.23–5.99	0.837
Cardiovascular disease			
Absent	1		
Present	1.34	0.82–2.18	0.239
Chronic kidney disease			
Absent	1		
Present	0.78	0.37–1.62	0.499
Dementia			
Absent	1		
Present	1.13	0.50–2.56	0.771
Diabetes mellitus			
Absent	1		
Present	0.98	0.59–1.63	0.947
Hypertension			
Absent	1		
Present	1.23	0.69–2.17	0.480
Obesity			
Absent	1		
Present	0.45	0.16–1.28	0.133
Psychiatric disease			
Absent	1		
Present	1.26	0.60–2.68	0.543
Onco-haematological disease			
Absent	1		
Present	1.98	0.97–4.04	0.062

Model $p < 0.001$, Harrell's $c = 0.71$

to be protective in China [7] and cough was shown to be not significant in the USA [13]. Compared to a large multicentre Italian study in an internal medicine setting [12], we found a higher rate of dyspnoea (66.3% vs 56%) and a lower rate of fever (73.7% vs 85%), possibly suggesting different disease severity and different baseline patients' characteristics. Our study did not find other symptoms to be correlated with mortality and this can be explained by the specific pandemic setting of our geographical region.

Three studies looking at COVID-19 in Lombardy in the first or second wave in an internal medicine setting have been published so far [14–16]. Overall, comparison

among these studies is made difficult by the heterogeneous inclusion criteria and admission modalities, reflecting in different results, despite similar patient age ranges. For example, according to Bandera et al. [15], the number of comorbidities and specific diseases (i.e., cancer, chronic heart failure, dementia and diabetes) were related to in-hospital mortality, while Leidi et al. [14] did not find any association between survival and specific diseases. In the study by Ughi et al. [16], the hazard ratio for mortality markedly increased with increasing Charlson comorbidity index.

Our study has indeed some limitations that should be mentioned. First, this is a monocentric study, with a relatively small number of patients and variables included, conducted in the centre of the first Italian epidemic, and this may have affected our results. Also, some biases should be considered. During the first peak of the epidemic, in March 2020, due to the scarce availability of beds in hospitals, younger patients might have been prioritized for the ICU, on clinical grounds, over older patients. Secondly, older patients with severe comorbidities may have died at home and thus only "more resilient" patients have been included in our cohort, hampering to identify a prognostic role of multiple comorbidities.

To conclude, in our study from a region of Italy, Lombardy, which was the main stage of the National healthcare system crisis, only age ≥ 70 was found to be an independent predictive factor of death, whereas a trend for statistical significance was observed for onco-haematological diseases. Traditional risk factors usually associated with a worse prognosis in COVID-19, such as multiple comorbidities, including cardiovascular and lung disease, the only independently associated factors with death in the previously mentioned Italian study [12], did not have a prognostic role in our cohort. This observation may be accounted for by the local specific population setting. This is supported by the high prevalence of out-of-hospital cardiac arrest found in Lombardy over the first pandemic wave [17]. It is, therefore, likely that many patients died at home before seeking medical advice.

It is possible to postulate that COVID-19 may not only be a pandemic, but also a syndemic, due to its interplay with chronic diseases [18]. COVID-19 clusters with pre-existing conditions, interacts with them, not only on a biological level, but also on a social one and it is influenced by major social factors.

Possible outlooks could be healthcare interventions downstream by paying more attention to older patients and patients with non-communicable diseases. Internal Medicine may play a central role in the future.

Declarations

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