



Trends in all-cause mortality of hospitalized patients due to SARS-CoV-2 infection from a monocentric cohort in Milan (Lombardy, Italy)

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Abstract

Background Robust data on case fatality rate (CFR) among inpatients with COVID-19 are still lacking, and the role of patient characteristics in in-hospital deaths remains under-investigated. This study quantified the overall CFR and described its trend in a cohort of hospitalized patients with SARS-CoV-2 in Italy. Admission to ICU, death, or discharge were the secondary outcomes.

Methods This retrospective study is based on administrative health data and electronic case records of inpatients consecutively admitted to Niguarda Hospital between 21 February and 8 November 2020.

Results An overall CFR of 18% was observed. CFR was significantly reduced during the second wave of contagion (1 June to 30 September, 16%) compared with the first wave (21 February to 31 May, 21% $p = 0.015$). Such reduction was mainly observed among male inpatients between 40 and 80 years with limited comorbidities. Admission to ICU was associated with a high risk of mortality in both waves. The incidence of severe disease and the need for ICU admission were lower in the second wave.

Conclusion CFR in SARS-CoV-2 inpatients was demonstrated to decrease over time. This reduction may partly reflect the changes in hospital strategy and clinical practice. The reasons for this improvement should be further investigated to plan an exit strategy in case of future outbreaks.

Key messages

What is already known on this topic

Before the advent of anti-COVID-19 vaccines, a multi-wave pattern of contagion was observed, and this trend conditioned the inpatient case fatality rate (CFR), which varied over time accordingly to the waves of contagion.

Only preliminary results on the in-hospital mortality trend are available, along with a partial analysis of its determinants. Consequently, robust data on CFR among inpatients with SARS-CoV-2 infection are still lacking, and the role of patient characteristics in in-hospital deaths remains under-investigated.

What this study adds

This study shows that the in-hospital mortality in patients with SARS-CoV-2 infection decreases over time. Such reduction was mainly observed among male inpatients between 40 and 80 years with limited comorbidities. Admission to ICU was invariably associated with a high risk of mortality during the whole study period (21 February to 8 November 2020), but the incidence of severe disease and the need for ICU admission were lower in the second wave of contagions (1 October to 8 November 2020). This reduction may partly reflect the impact of changes in hospital strategy and clinical practice. The reasons for this improvement should be further investigated to inform the response to future outbreaks and to plan exit strategy by prioritizing high-risk populations.

Keywords SARS-CoV-2 infection · COVID-19 · Case fatality rate · Inpatients with COVID-19 · Trend of case fatality rate

Introduction

By the end of 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had spread as coronavirus disease 2019 (COVID-19) (Hu et al. 2021). Since the WHO

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announced the COVID-19 outbreak to be a pandemic (12 March 2020) (WHO 2020), a burden imposed upon global health and excess mortality was observed, concerning both COVID-19 and the delayed care due to overwhelmed health-care systems (Woolf et al. 2021; Reese 2019).

Before the advent of anti-COVID-19 vaccines, a multi-wave pattern of contagion was observed globally, and this reflected on national health policies, which had to face up different levels of hospital care burden (Cacciapaglia et al. 2021). In addition, this multi-wave pattern also conditioned the inpatient case fatality rate (CFR), which varied over time according to the wave of contagion (Madahar et al. 2021; Horwitz et al. 2021; Saito et al. 2021).

To better characterize this phenomenon, the host characteristics were substantially investigated, and age, gender, and the presence of comorbidities were considered as major factors related to infection mortality, from the first months of the pandemic onset (Li et al. 2021). The impact of such determinants on in-hospital deaths seems to have been confirmed through the pandemic waves (Navaratnam et al. 2021), but this issue remains under-investigated.

Italy was among the first countries that faced the COVID-19 health emergency; the first case of pneumonia due to SARS-CoV-2 was diagnosed in northern Italy on 20 February 2020 (Onder et al. 2020). Since then, a bimodal pattern of the pandemic spread was observed throughout 2020. The first wave subsided by the end of May (Alicandro et al. 2020) and a second wave was registered in the second half of 2020. Even if preliminary results on the in-hospital mortality trend in northern Italy are available (Borghesi et al. 2021), along with a partial analysis about its determinants (Navaratnam et al. 2021), robust data on CFR among inpatients with SARS-CoV-2 infection are still lacking and the role of patient characteristics in in-hospital deaths remains under-investigated.

This study aimed to assess the overall CFR and to describe its trend during 2020 in a monocentric cohort of hospitalized patients with a diagnosis of SARS-CoV-2 infection in northern Italy. Furthermore, admission to ICU, death, or discharge from the moment of admission have been considered as secondary outcomes.

Patients and methods

Study design, setting, and participants

This is a retrospective cohort study based on the review of administrative health data and electronic case records of the inpatients who were consecutively admitted to Niguarda Hospital between 21 February and 8 November 2020. Niguarda is one of the largest General Hospital in the north of Milan within a Metropolitan Area of 3,279,944 inhabitants (January 2020) and hosts all the

medical and surgical disciplines for adults and children, including a 24-hour Emergency Department with 96,588 visits and 32,612 hospital admissions covering every intensity of care in 2019. In this hospital context, all inpatients were eligible if diagnosed with SARS-CoV-2 infection, certified by the positivity of nasopharyngeal swab to SARS-CoV-2 genome, regardless of the presence of the respiratory disease. Most of the swab tests were processed at Niguarda Hospital, and a documented result of test positivity from other health facilities was not a reason for exclusion. Inpatients who developed COVID-19 symptoms and/or tested positive for the SARS-CoV-2 genome after 48 hours from the admission were excluded, as their infections could be considered to be possibly hospital-acquired. All the included patients were followed up from the first day of either elective or urgent admission in the hospital until the day of discharge, death, or 17 January 2021.

This study conformed to the Helsinki Declaration and was approved by the ethics committee for Milano Area 3 (register number 249-13052020). Informed consent was provided by the participants.

Outcome measurements

The overall CFR was the main outcome, and it was calculated as the proportion of observed in-hospital deaths (all-cause mortality) over the total number of included inpatients with a diagnosis of SARS-CoV-2 infection in the period of observation. Then, time-specific CFRs were calculated and to this end, the study period was divided into the following three periods, consistent with the trends of hospital admissions due to SARS-CoV-2 infection: 1) *first wave*: from 21 February to 31 May 2020, 2) *intermediate phase*: between 1 June and 30 September 2020, and 3) *second wave*: from 1 October to 8 November 2020. CFRs were compared between the first- and second-wave patient groups.

Finally, specific CFRs were estimated with respect to the following subgroups, according to the first and second wave time intervals: gender, age levels in terms of decades (between < 20 years and \geq 90 years), admission to an intensive care unit (ICU), and comorbidity burden defined under the Charlson comorbidity index (Charlson et al. 1987) and stratified in five categories (from score 0 to \geq 5). Moreover, CFR was also investigated by subgrouping patients based on disease severity — i.e., whether pulmonary involvement was detected.

Secondary outcomes were defined from the time of admission to the following events: admission to ICU, death, or discharge. Both single and composite outcomes reflecting complex definitions of in-hospital SARS-CoV-2 infection

prognosis were considered to investigate the secondary endpoints.

Statistical analysis

The distribution of patients' characteristics at admission was described using numbers and frequencies for categorical variables, median, and interquartile range (IQR) or mean and standard deviation (SD) for continuous variables. These characteristics were compared between the first- and second-wave patient groups using the Chi-square test, Mann–Whitney test or *t*-test, as appropriate. A description of the patients hospitalized during the intermediate phase was also performed. Point estimates of overall and subgroup-specific CRFs and their 95% confidence intervals (CI), according to the Wald method, were calculated.

To analyze the incidence of all-cause mortality and admission to ICU, a time-to-event analysis was performed accounting for discharge (treated as a competing risk) and the presence of patients that were still in hospital at the moment of data extraction (treated as censored observations). The Aalen–Johansen estimator was used to estimate the crude incidence of the two following competing events within the two waves: admission to ICU or death before ICU (composite outcome) and discharge before ICU. The curves were compared between the two waves using the Gray test (Gray 1988). A similar analysis was performed on the three following competing endpoints: admission to ICU, death before ICU, and discharge before ICU. An additional analysis was conducted for the two following unique competing events: in-hospital death and discharge.

To assess the association of patients' characteristics (age, gender, Charlson comorbidity index) at baseline with the afore-mentioned outcomes, univariate cause-specific Cox models were fitted, separately for each wave. Finally, a multiple cause-specific Cox model jointly on the populations of both waves was fitted to compare the hazard of each event between the two waves by adjusting for age, gender and Charlson comorbidity index. All these analyses were based on complete cases.

All the analyses were performed using R 4.0.3 (R Core Team, 2020. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

In the study period, 1859 individuals admitted to Niguarda Hospital presented with the SARS-CoV-2 infection. In total, 74 patients who developed COVID-19 symptoms and/or

tested positive for SARS-Cov-2 after 48 hours from admission were excluded (Supplementary Fig. S1). The remaining 1785 patients were classified according to the period of admission: first wave (920, 52%), intermediate phase (133, 7%), or second wave (732, 41%). A comparison of the characteristics of the patients between the first and second waves is shown in Table 1.

The median time between the onset of symptoms and hospital admission was significantly shorter for the second wave (median [IQR]: 5 days [3–8] vs 6 [3–9], $p = 0.016$).

Patients of the second-wave group were significantly older (median [IQR]: 66 years [54.37–78.82] vs 64 [51.74–77.07], $p = 0.020$) and with more comorbidities (Charlson comorbidity index mean [SD]: 4 [3] vs 3 [3], $p < 0.001$) compared with the first-wave group. In particular, more patients with a history of myocardial infarction (13% vs 8%, $p = 0.001$), cerebrovascular accident or transient ischemic attack (12% vs 8%, $p = 0.004$) and solid tumors (15% vs 10%, $p = 0.006$) were observed in the second-wave group.

Nevertheless, admissions to ICU were significantly higher in the first-wave group (18% vs 9%, $p < 0.001$).

Patients admitted during the intermediate phase were markedly different from those of the two waves, as shown in Supplementary Table 1.

The trend of admissions and outcomes (deaths and discharges), in terms of absolute numbers, occurred in each week from 21 February to 31 December 2020 is reported in Supplementary Fig. S2. The peak of admissions per week during the second wave is higher than in the first wave (218 vs 171) but with a similar peak of deaths (37 vs 34). The peaks of discharges occurring later than 2 weeks after admissions are also evident in both waves.

Overall CFR

The overall CFR in the study period was 18.5% (95% CI: 16.7–20.3; the number of deaths/number of cases: 330/1785).

Over a median of 14 [IQR 8–23] days of follow-up for patients of the first wave and 11 [IQR 7–17] days for patients of the second wave, 197 and 121 fatalities were observed respectively (number of cases: 920 in the first wave, 732 in the second wave), with a CFR (95% CI) significantly lower in the second-wave group of patients: 21.4% (18.8–24.1) vs 16.5% (13.8–19.2), $p = 0.015$.

CFR of the intermediate phase was 9% (95% CI: 4.2–13.9), considering 12 deaths out of 133 patients.

A comparison of the CFR between the two waves calculated in population subgroups (gender, age categories, admission to ICU, Charlson comorbidity index) is shown in Fig. 1. The CFR was lower in the second wave than in the first for all subgroups but especially within males (17% vs 24%), age ≥ 60 to < 70 (11% vs 21%), ≥ 70 to < 80

Table 1 Comparison of patients' characteristics at admission between waves

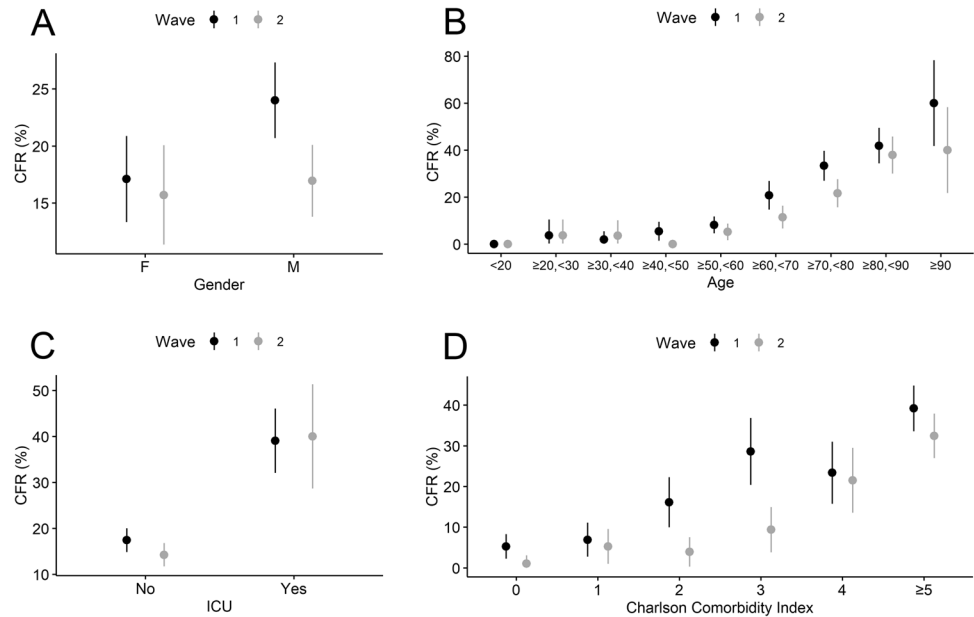
Variables	Wave 1 (<i>n</i> = 920)	Wave 2 (<i>n</i> = 732)	<i>P</i> -value*
Gender (male), <i>n</i> (%)	575 (62.5)	490 (66.9)	0.069
Age (years), median (IQR)	64.06 (51.74–77.07)	66.44 (54.37–78.82)	0.020
Age (years), <i>n</i> (%)			0.060
< 20	27 (2.9)	27 (3.7)	
≥ 20 to < 30	52 (5.7)	28 (3.8)	
≥ 30 to < 40	111 (12.1)	62 (8.5)	
≥ 40 to < 50	197 (21.4)	136 (18.6)	
≥ 50 to < 60	154 (16.7)	149 (20.4)	
≥ 60 to < 70	192 (20.9)	162 (22.1)	
≥ 70 to < 80	148 (16.1)	132 (18.0)	
≥ 80 to < 90	14 (1.5)	11 (1.5)	
≥ 90	25 (2.7)	25 (3.4)	
Current pregnancy, <i>n</i> (%)	3 (0.3)	4 (0.5)	0.761
Days from first symptoms to admission, median (IQR)	6 (3–9)	5 (3–8)	0.016
Severe disease (any pulmonary involvement), <i>n</i> (%)	789 (85.8)	648 (88.5)	0.113
Admission to ICU	169 (18.4)	65 (8.9)	<0.001
History of:			
Asthma, <i>n</i> (%)	33 (4.8)	23 (3.1)	0.146
Myocardial infarction, <i>n</i> (%)	72 (7.8)	94 (12.9)	0.001
Congestive heart failure, <i>n</i> (%)	55 (6.0)	33 (4.5)	0.224
Peripheral vascular disease, <i>n</i> (%)	52 (5.7)	53 (7.3)	0.225
Cerebrovascular accident or transient ischemic attack, <i>n</i> (%)	71 (7.7)	88 (12.0)	0.004
Dementia, <i>n</i> (%)	62 (6.8)	48 (6.6)	0.954
Chronic obstructive pulmonary disease, <i>n</i> (%)	58 (6.3)	64 (8.8)	0.074
Peptic ulcer disease, <i>n</i> (%)	17 (1.8)	20 (2.7)	0.298
Hemiplegia, <i>n</i> (%)	16 (1.7)	16 (2.2)	0.643
Liver disease, <i>n</i> (%)	22 (2.4)	25 (3.4)	0.277
Moderate to severe chronic kidney disease, <i>n</i> (%)	81 (8.8)	67 (9.2)	0.877
Solid tumor, <i>n</i> (%)	95 (10.3)	109 (14.9)	0.006
AIDS, <i>n</i> (%)	2 (0.2)	6 (0.8)	0.163
Diabetes mellitus, <i>n</i> (%)	146 (15.9)	128 (17.5)	0.427
Leukemia, <i>n</i> (%)	12 (1.3)	5 (0.7)	0.318
Lymphoma, <i>n</i> (%)	18 (2.0)	11 (1.5)	0.609
Charlson comorbidity Index, 0–37 score, mean (SD)	3 (3)	4 (3)	<0.001
Charlson comorbidity index, estimated 10-year survival (%), mean (SD)	62 (39)	57 (39)	0.003
Charlson comorbidity index, <i>n</i> (%)			0.001
Score 0	263 (28.6)	253 (34.6)	
Score 1	190 (20.7)	92 (12.6)	
Score 2	130 (14.1)	95 (13.0)	
Score 3	124 (13.5)	102 (14.0)	
Score 4	105 (11.4)	96 (13.1)	
Score ≥ 5	107 (11.6)	93 (12.7)	

*Chi-square test for categorical, Mann–Whitney test or *t*-test for numerical variables; ICU, intensive care unit; IQR, interquartile range; sd, standard deviation. *P*-values reported in bold are statistically significant

(22% vs 33%), ≥ 90 (60% vs 40%), patients not admitted to ICU (14% vs 17%) and patients with Charlson comorbidity index [2 (4% vs 16%) and 3 (9% vs 29%)]. Moreover, the

decrease in CFR in the second wave was more evident within patients with mild disease (2% vs 13%) than with severe disease (18% vs 23%), as shown in Supplementary Table 2.

Fig. 1 Comparison of case fatality rate (CFR) between the two waves in subgroups: gender (A), age (B), admission to intensive care unit (C), Charlson Comorbidity Index (D). Bars are 95% CIs.



Secondary outcomes

The crude cumulative incidence as estimated by the Aalen–Johansen estimator of the competing risks (ICU or death without ICU and discharge without ICU) in the two waves are depicted in Fig. 2. At 30 days after admission, the estimated cumulative incidence of ICU or death without ICU (Fig. 2A) was 33% (95% CI: 30–36.2) and 22% (19–25.3) respectively for waves 1 and 2 ($p < 0.001$). The estimated incidence of discharge without ICU (Fig. 2B) was 54% (50.1–57) in wave 1 and 65% (61.6–69.3) in wave 2 ($p < 0.001$). At 30 days we also observed an incidence of only ICU (Fig. 2C) of 19% (16–21.1) vs 9% (7–11.3), $p < 0.001$, and an incidence of death with or without ICU (Fig. 2C) of 21% (18.5–24) vs 17% (13.6–19.6), $p = 0.109$ respectively for wave 1 versus wave 2.

According to the Cox univariate analysis, older age and higher Charlson comorbidity index were significantly associated with a higher hazard of ICU or death and a lower hazard of discharge in both waves, while male gender was a stronger predictor of worse outcome during the first than during the second wave (Table 2).

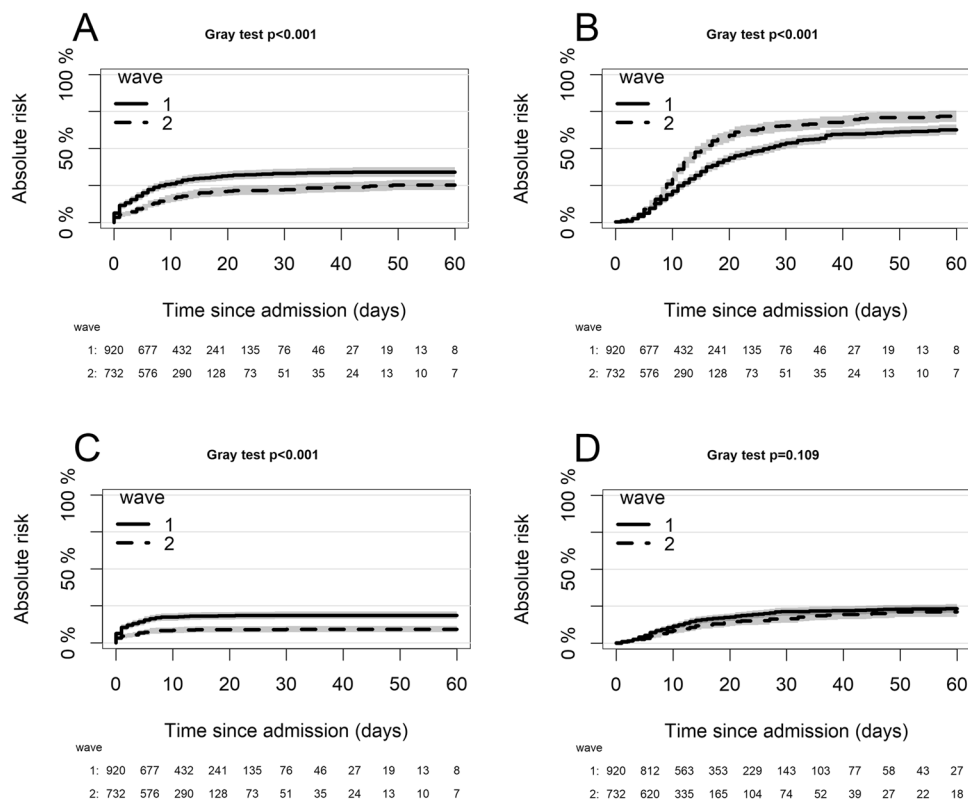
Multiple Cox model analysis adjusting for age, gender, and Charlson comorbidity index indicates that the hazard of ICU or death during wave 2 was significantly lower than during wave 1 (HR with 95% CI: 0.65, 0.54–0.79). The hazard of discharge without ICU was significantly higher during wave 2 (1.46, 1.28–1.67) than the hazard of discharge with or without ICU (1.50, 1.32–1.71) while the hazard of death with or without ICU was not significantly different (0.83, 0.66–1.04), as shown in Supplementary Table 3.

Discussion

Between February and November 2020, a CFR of 18% (95% CI: 16.7–20.3) was observed among patients admitted to Niguarda Hospital with SARS-CoV-2 infection; this was significantly reduced during the second wave (16.5%, 95% CI: 13.8–19.2) compared to the first one (21.4%, 95% CI: 18.8–24.1; $p = 0.015$). Such reduction was mainly observed among male inpatients who were over 40 years and under 80 years and with a limited burden of comorbidities, while the CFR was steadily low in young females with no comorbidities and high among elderly in-patients with multiple comorbidities. Admission to ICU was invariably associated with a high risk of mortality in both waves, but the incidence of severe disease (i.e., requiring intensive care or leading to death before ICU admission) and the need for ICU admission was lower in the second wave compared to the first one.

In-hospital mortality in patients with SARS-CoV-2 infection was variably high across several international studies, and consistent with our findings. The estimate of CFR during the first months of the outbreak in 2020 was 17% (95% CI: 12.7–22.7, $n = 13,398$) in a meta-analysis on 33 studies between January and April 2020, and mortality was lower in general inpatients (11%, 95% CI: 7.7–16.9) compared with critically ill patients (40%, 95% CI: 31.2–50.6) (Macedo et al. 2021). However, these reports unraveled a degree of heterogeneity with geographical differences, and mortality up to 31% was reported, as in the case of 522,167 patients hospitalized with SARS-CoV-2 infection in Brazil by December 2020 (Castro et al. 2021). Further to the issues related to CFR calculation methods, such diversity of results might reflect

Fig. 2 Crude incidence (Aalen–Johansen estimates) of admission to intensive care unit or death before intensive care unit (A), discharge before intensive care unit (B), admission to intensive care unit (C), and death in hospital (D)



the SARS-CoV-2 virulence on different populations, as well as the local capacity of the national healthcare systems.

A worldwide change in the trend of in-hospital mortality of SARS-CoV-2 infection over the year 2020 was described by several studies—from Japan (Saito et al. 2021), USA (Horwitz et al. 2021; Roth et al. 2021; Finelli et al. 2021), UK (Navaratnam et al. 2021; Docherty et al. 2021) and Spain (Domingo et al. 2021; Garcia-Vidal et al. 2021)—and a drop in in-hospital mortality rates were also confirmed in our Italian cohort. It is not known if this change may be primarily attributed to the accrual of clinical knowledge on pharmacological treatment, such as the optimization of the management of corticosteroids (Pulakurthi et al. 2021) or to the training of healthcare workers to rapidly provide support during hospital overflow. Conversely, disease mortality was also observed to be unchanged over time, as in the case of Brazil (Castro et al. 2021), and additional factors such as peculiar health policies of infection prevention and inequities in healthcare systems might have a role.

An older age (> 60 years) and the presence of comorbidities were found to be independent predictors of severe outcomes in hospitalized patients with SARS-CoV-2 infection, in line with other case studies from Spain and Italy (Corradini et al. 2021; Moreno-Torres et al. 2021). The role of the male gender is controversial. Sex differences in COVID-19 case fatality were observed in the first half of 2020, and male gender seemed to be associated with

poor outcomes (Li et al. 2021). However, this association was inconsistently reported across studies (Dehingia and Raj 2021). In our results, a significant association was observed with regard to the first wave (HR 1.40, 95% CI: 1.03–1.89, female as reference), and yet not in the second one (HR 0.81, 95% CI: 0.55–1.19). This apparent gender gap was hypothesized to reflect other factors such as the access to health services and its representation in hospital settings, rather than biological differences in response to SARS-CoV-2 pathology (Dehingia and Raj 2021).

This study had several limitations. First, the monocentric nature of data source and analysis may reflect regional and local health policies and might not be generalized to all the hospital settings on a country level. Secondly, all-cause death and all cases requiring ICU were considered as outcomes independently of the association with the severity of COVID-19, and the inclusion of SARS-CoV-2 patients without a severe disease might over- or under-estimate CFR and outcome predictors. Finally, several major predictors, such as in-hospital treatment, concurrent complications due to hospitalization, social determinants and its proxies, such as ethnicity, were not considered in the analysis, and the effect size of age, sex, and comorbidities may reflect other features, such as social status.

In conclusion, the observed in-hospital mortality in patients with SARS-CoV-2 infection was shown to decrease over time, and this reduction may partly reflect

Table 2 Univariate cause-specific Cox models hazard ratios with 95% confidence interval to assess the association of patients' characteristics at baseline with each event, separately on each wave.

Factors	ICU or death without ICU, HR (95% CI)		Discharge without ICU, HR (95% CI)	
	Wave 1 <i>n</i> = 920 <i>N</i> events = 300	Wave 2 <i>n</i> = 732 <i>N</i> events = 160	Wave 1 <i>n</i> = 920 <i>N</i> events = 489	Wave 2 <i>n</i> = 732 <i>N</i> events = 429
Age (per 10-year increment)	1.171 (1.092–1.256)	1.293 (1.156–1.446)	0.790 (0.755–0.826)	0.756 (0.719–0.800)
Gender, female as reference	1.625 (1.265–2.088)	1.128 (0.799–1.594)	0.962 (0.804–1.153)	0.830 (0.677–1.016)
Charlson comorbidity index, Score 0 as reference				
Score 1	1.695 (1.078–2.667)	1.431 (0.593–3.454)	1.091 (0.820–1.452)	0.734 (0.530–1.017)
Score 2	1.898 (1.222–2.950)	1.310 (0.549–3.125)	0.716 (0.531–0.964)	0.550 (0.397–0.761)
Score 3	1.736 (1.100–2.740)	1.532 (0.655–3.585)	0.608 (0.443–0.834)	0.469 (0.334–0.659)
Score 4	1.372 (0.855–2.203)	1.783 (0.791–4.021)	0.497 (0.366–0.676)	0.243 (0.168–0.353)
Score ≥5	1.737 (1.190–2.535)	2.550 (1.230–5.288)	0.302 (0.232–0.393)	0.201 (0.148–0.272)
Factors	Death, HR (95% CI)		Discharge, HR (95% CI)	
	Wave 1 <i>n</i> = 920 <i>N</i> events = 197	Wave 2 <i>n</i> = 732 <i>N</i> events = 121	Wave 1 <i>n</i> = 920 <i>N</i> events = 555	Wave 2 <i>n</i> = 732 <i>N</i> events = 443
Age (per 10-year increment)	1.689 (1.515–1.883)	1.969 (1.669–2.322)	0.808 (0.770–0.848)	0.778 (0.738–0.820)
Gender (female as reference)	1.396 (1.028–1.894)	0.812 (0.552–1.195)	0.899 (0.758–1.065)	0.789 (0.646–0.964)
Charlson comorbidity index, Score 0 as reference				
Score 1	1.012 (0.448–2.714)	3.758 (0.439–32.18)	0.789 (0.609–1.021)	0.671 (0.487–0.923)
Score 2	2.287 (1.069–4.897)	2.619 (0.293–23.44)	0.551 (0.418–0.728)	0.573 (0.418–0.787)
Score 3	4.574 (2.233–9.370)	6.341 (0.803–50.08)	0.627 (0.465–0.844)	0.513 (0.368–0.715)
Score 4	3.689 (1.771–7.684)	12.870 (1.725–96.03)	0.641 (0.481–0.854)	0.345 (0.241–0.494)
Score ≥5	6.535 (3.413–12.515)	18.448 (2.564–132.72)	0.416 (0.323–0.536)	0.279 (0.208–0.373)

HR, hazard ratio; CI, confidence interval

the impact of changes in hospital strategy and clinical practice. The reasons for this improvement should be further investigated to inform the response to future outbreaks and to plan exit strategy by prioritizing high-risk populations.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10389-021-01675-y>.

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Authors' contributions Study conception and design: Nicola Ughi, Davide Paolo Bernasconi, Maria Grazia Valsecchi, Oscar Massimiliano Epis, Claudio Rossetti. Data collection: Nicola Ughi, Francesca Del Gaudio, Armanda Dicuonzo, Laura Beltrami, Michaela Bertuzzi. Data interpretation: all. Statistical analysis: Davide Paolo Bernasconi, Maria Grazia Valsecchi, Nicola Ughi. Manuscript drafting: Nicola Ughi, Davide Paolo Bernasconi. Manuscript editing and approval to submit: all.

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Availability of data and material Data may be made available upon reasonable request.

Code availability Not applicable

Declarations

Conflicts of interest None of the authors declared conflict of interests.

Ethics approval This study was approved by the ethics committee Milano Area 3 (register number 249-13052020).

Consent to participate All the participants signed an informed consent form.

Consent for publication Not required as this manuscript doesn't include details, images, or videos related to the participants


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