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First and second waves among hospitalised patients with COVID-19 with severe pneumonia: a comparison of 28-day mortality over the 1-year pandemic in a tertiary university hospital in Italy

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ABSTRACT

Objective The first COVID-19–19 epidemic wave was over the period of February–May 2020. Since 1 October 2020, Italy, as many other European countries, faced a second wave. The aim of this analysis was to compare the 28-day mortality between the two waves among COVID-19 hospitalised patients.

Design Observational cohort study. Standard survival analysis was performed to compare all-cause mortality within 28 days after hospital admission in the two waves. Kaplan-Meier curves as well as Cox regression model analysis were used. The effect of wave on risk of death was shown by means of HRs with 95% CIs. A sensitivity analysis around the impact of the circulating variant as a potential unmeasured confounder was performed.

Setting University Hospital of Modena, Italy. Patients admitted to the hospital for severe COVID-19 pneumonia during the first (22 February–31 May 2020) and second (1 October–31 December 2020) waves were included.

Results During the two study periods, a total of 1472 patients with severe COVID-19 pneumonia were admitted to our hospital, 449 during the first wave and 1023 during the second. Median age was 70 years (IQR 56–80), 37% women, 49% with PaO_2/FiO_2 <250 mm Hg, 82% with ≥1 comorbidity, median duration of symptoms was 6 days. 28-day mortality rate was 20.0% (95% CI 16.3 to 23.7) during the first wave vs 14.2% (95% CI 12.0 to 16.3) in the second (log-rank test p value=0.03). After including key predictors of death in the multivariable Cox regression model, the data still strongly suggested a lower 28-day mortality rate in the second wave (aHR=0.64, 95% CI 0.45 to 0.90, p value=0.01).

Conclusions In our hospitalised patients with COVID-19 with severe pneumonia, the 28-day mortality appeared to be reduced by 36% during the second as compared with the first wave. Further studies are needed to identify factors that may have contributed to this improved survival.

Strengths and limitations of this study

- ► Our study provides a precise evaluation of the 28-day mortality among a homogeneous cohort of hospitalised patients affected by severe COVID-19 and a valid comparison between the two waves adjusted for all key predictors throughout the whole of 2020.
- ► We offer the calculation of the e-value to rule out that the lower mortality risk observed during the second wave could be due to the lower pathogenicity of the virus circulating.
- ► We show a comparison of the mortality risk also in subsets of patients treated in critical areas with different respiratory supports.
- ► One key limitation is that our study is monocentric and retrospective; thus, our results are not directly generalisable to other settings with a different case-mix of the included populations.

INTRODUCTION

After the first cases in Wuhan, China, COVID-19 has become a global pandemic, showing devastating effects in the period of March–May 2020 in Europe.[1–3] In response to that, measures of containment have been introduced worldwide with variability in the extent of imposed lockdowns. In June–August, almost all countries, including Italy, started to decrease containment measures

in the attempt to balance economic crisis with the epidemic morbidity and mortality.[4–6] As a consequence, and not unexpectedly, Italy faced a second COVID-19 wave over the period of October–December, with more than 1.8 million cases and over 50 000 deaths, almost doubling the number of deaths reported until August 2020.[7 8] In Europe indeed, the COVID-19 epidemiological trend exhibited three distinct time periods: daily new COVID-19 cases rose to mid-April, plateaued until mid-May then increased again at the end of the summer period, and deaths followed a similar three-phase pattern. Unfortunately, to date, all published studies analysed data censored up to September 2020,[6 9–14] whereas in many countries, the second wave occurred in October 2020 and onwards.[15]

These studies, which compared mortality rates between the two waves using country reports either on COVID-19 case fatality rate or excess risk of mortality, showed a slightly decreased mortality during the second wave.[6 9–14] Many hypotheses regarding the factors that could have contributed to a change over time in mortality rate have been proposed: first, the possibility that vulnerable groups have died in the first wave; second, that healthcare systems could be more prepared to treat timely severe cases; third, SARS-CoV-2 could have evolved and led to the circulation of new variants carrying different risks of transmission or pathogenicity.[10] Concerning the second point, it is important to consider that clinical management and treatment of severe cases changed considerably in the short period that separated the two waves. Indeed, the first wave was characterised, especially at the beginning, by the use of hydroxychloroquine or lopinavir, followed by the introduction of prophylactic dose of low-molecular weight heparin to reduce the risk of thrombosis.[16–18] Standard of care (SoC) dramatically changed during the second wave due to the publication of negative results concerning the efficacy of lopinavir and hydroxychloroquine in the SOLIDARITY trial,[19] the positive results associated with the use of dexamethasone and, more recently, of tocilizumab in the RECOVERY trial and of the combination baricitinib +remdesivir in the ACCT2 trial.[20–23] As a consequence, during the second wave, the Italian Society of Infectious and Tropical Diseases, National Institutes of Health, UK, and USA Department of Health and Human Services (DHHS) guidelines recommended the use of remdesivir in early stages of the disease and dexamethasone in patients who needed oxygen supplementation as SoC.[24–27] In some centres, included ours, in both the first and second waves, tocilizumab was also used in case of severe gas exchange impairment and detection of a 'cytokine storm', a strategy which is now recommended by international guidelines.[24] The knowledge on COVID-19 is increasing very rapidly in an unprecedented way, changing constantly our clinical practice. Importantly, in this ever-changing scenario dominated by the advent of vaccine campaigns and new viral variants, further waves might still occur in most parts of the world; thus, it is crucial to monitor changes in mortality over time and identify the main factors that may induce these changes. The aim of the present study was to perform a comparison of the mortality risk in a well-defined population of hospitalised patients recruited during the first and second waves, after careful consideration of key potential confounding factors.

METHODS

Study design and population

This study is a retrospective, single centre, observational cohort study conducted at the University Hospital of Modena, which is a 'COVID-19 hospital' designated to receive the largest number of patients affected by SARS-CoV-2 pneumonia of the province. The study enrolled consecutively all adult patients (≥18 years) with a confirmed diagnosis of SARS-CoV-2 infection by PCR testing on nasopharyngeal swab and severe COVID-19 pneumonia as previously defined.[28] Because we assisted to a marked decrease in the rate of hospitalisation for severe disease in the summer period due to containment measures and lockdown implementation in the previous months,[8] in agreement with national statistics reporting the number of new infections by calendar time,[15] we defined second wave patients as those enrolled between 1 October and 31 December 2020, while those admitted between 22 February and 31 May 2020 represented the first-wave hospitalisations.

Concerning treatment, during the first wave, patients were treated according to SoC consisting of hydroxychloroquine, lopinavir and low-molecular weight heparin (LMWH) at a prophylactic dose, while in the second wave, protease inhibitors and hydroxychloroquine were no longer used. In both waves, an intermediate dose of LMWH or therapeutic dosage was considered for patients with severe–critical COVID-19, depending on clinical judgement or based on ongoing randomised clinical trials.[29] Remdesivir, during the first wave, was available through compassionate use only for patients in intensive care unit (ICU), while that during the second one could be routinely prescribed accordingly to the recommendations of regulatory agencies.[30] Corticosteroids, which were not routinely administered during the first wave outside of the ICU, were universally prescribed during the second wave. Dexamethasone was used according to SoC at 6 mg/day for 10 days.[20] Methylprednisolone 2 mg/kg/day was initiated in patients admitted to ICU.[31] In both waves, in case of respiratory deterioration tocilizumab was administered as described in our previous publications.[28 32]

Indications for applying non-invasive or invasive respiratory support at our centre were based on national and international recommendations,[33–35] which matched both clinical and physiological severity. For patients with COVID-19 with a PaO_2:FiO_2 ratio of <200 mm Hg, respiratory rate of >30 breaths/min or respiratory distress without an immediate indication for invasive mechanical ventilation (IMV), non-invasive respiratory support (NIS) was delivered through high-flow nasal oxygen

(HFNO) and non-invasive ventilation (NIV) via oronasal facemask or helmet interface. It is important to note that HFNO was used during the first wave only in critical care areas since it was perceived as a possible means of increasing airborne SARS-CoV-2 contamination. In contrast, during the second wave, it was used in all the medical wards equipped with negative pressure rooms.[36] Moreover, given supporting evidence, awake prone position manoeuvres were systematically introduced during the second wave for patients undergoing NIS, particularly in those receiving HFNO.[37]

Patient and public involvement statement

Patients and the public were not directly involved in this research.

Data collection

At admission, demographic data such as age and sex, full medical history to evaluate the presence of chronic comorbidities and symptoms were collected. An age-unadjusted Charlson Comorbidity Index (CCI) was also calculated. The Subsequent Organ Failure Assessment score was assessed at baseline. Data from arterial blood gas performed on admission, together with the PaO_2:FiO_2 ratio and laboratory parameters, were prospectively collected from electronic medical and laboratory records. Electronic missing data were filled, when possible, by accessing clinical charts of the patients. Data on performed treatments in terms of medications, type of respiratory support, as well as death or discharge were collected after the end of hospital stay through electronic medical records.

Outcome measures

The primary outcome of the study was 28-day mortality rate.

Statistical analysis

Baseline characteristics of the participants were compared after stratification by wave. Continuous variables were expressed as median (IQR) and compared by Mann-Whitney U test. Categorical variables were expressed as numbers and percentages and compared by χ^2 test or Fisher's exact test by wave.

Standard survival analysis was performed with participants' follow-up accrued from the date of hospital entry until the date of death or discharge. Patients discharged from the hospital within 28 days were assumed to survive to 28 days. This was done because we thought it would be important to give an unbiased estimate of the 28-day mortality, taking into account the competing risk of early discharge. We also used administrative censoring on 31 December 2020 for those still in the hospital at the date of the analysis.

The 28-day mortality rates were compared by means of unweighted Kaplan-Meier curves and univariable and multivariable Cox regression models. HRs of death for second wave versus first wave with 95% CI are shown.

The underlying causal structure of the model is described in figure 1 through the visual aid of a direct acyclic graph. Potential confounders were identified a priori on the basis of established causal links or axiomatic knowledge. According to our assumptions, circulating SARS CoV-2 variants were the only confounders for

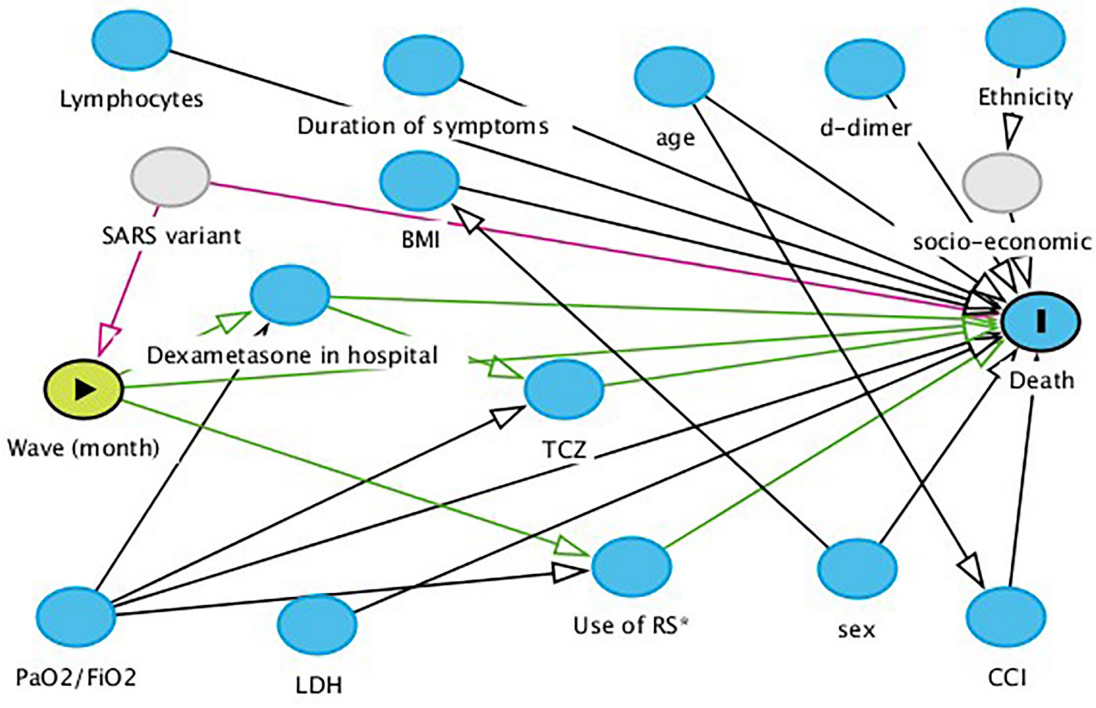

Figure 1 DAG of assumptions on causal structure of the data. BMI, body mass index; CCI, Charlson Comorbidity Index; DAG, direct acyclic graph; LDH, lactate dehydrogenase; RS, respiratory support; TCZ, tocilizumab.

the question of interest. In addition, we identified age, ethnicity, duration of symptoms, baseline PaO_2/FiO_2, lactate dehydrogenase, D-dimer, lymphocytes and presence of comorbidities as key predictors of the outcome. CCI was age-unadjusted in order to minimise possible collinearity with age. These key predictors were included in the multivariable model to increase efficiency.

In addition, the change in treatment strategy (with incremental use of dexamethasone in participants recruited during the second wave) and the type of respiratory support required (eg, more use of HFNO in the second wave) were considered as mediators in this analysis and therefore were not included in the multivariable model. In general, we made no adjustment for postbaseline potential confounding factors as to evaluate possible mechanisms leading to a difference in mortality rates was beyond the scope of this initial analysis. Importantly, SARS-CoV-2 variant is an unmeasured confounder so, by definition, it could not be controlled for in the analysis. We have therefore performed a sensitivity analysis under the assumption that, contrary to current belief, the original Wuhan strain is more pathogenic than the present B1.1.1.7 variant and calculated the bias factor based on the concept of e-value.[38] The e-value is defined as the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the main exposure and the outcome to fully explain the specific exposure–outcome association, conditional on other measured covariates. Specifically, we made the following assumptions: the prevalence of the B.1.1.7 variant in our region in the months of October–December was a maximum of 10% across all age groups.[39] We then assumed that the original Wuhan strain is associated with an 80% increase of mortality risk, the opposite of what has been shown in some reports, although results are conflicting.[40–43]

We also performed two other sensitivity analyses. The first was done after excluding patients aged >75 years and those with a diagnosis of cancer for whom ICU treatment might have been precluded. The second analysis was done after excluding patients enrolled after 3 December 2020 in order to guarantee the same duration of potential follow-up for people enrolled in the two waves.

Moreover, we performed three additional secondary subset analyses restricted to patients who required the use of respiratory support (HFNO, NIV and IMV). This was done mainly to describe 14-day mortality in patients who required access to critical areas of the hospital and to compare rates between waves specifically in this setting. Baseline for these survival analyses was the date of starting use of the specific respiratory support and maintaining death as the endpoint. Mortality in these subsets were estimated using weighted Kaplan-Meier methods with weights constructed on the basis of the level of gas exchange impairment recorded at baseline, which was considered a key confounder in this setting.

A two-sided test of less than 0.05 was considered statistically significant. All statistical analyses were performed using the SAS software V.9.4.

RESULTS

During the two study periods, a total of 1472 patients with severe COVID-19 pneumonia were admitted to our hospital, 449 during the first wave and 1023 during the second. Epidemiological characteristics are shown in table 1. Overall, 541 (36.8%) were women and the median age was 70 years (range 56–80); almost 95% of participants were Caucasian. Median duration of symptoms before hospital admission was 6 days with no difference between the two waves (p=0.040). Concerning comorbidities, age-unadjusted CCI did not differ between the two waves, but the prevalence of those with ≥1 comorbidity was higher during the second wave (84.6% vs 77.3%, p<0.001), especially with regard to ischaemic cardiomyopathy, connective tissue disease, diabetes, dementia and hypertension. In contrast, although the median baseline PiO_2/FiO_2 was not different between the two waves, when looking at the rank distributions, gas exchange levels were significantly less compromised in patients recruited during the second wave with a lower fraction of participants showing a baseline $PiO_2/FiO_2 \leq 150$ mm Hg (27.2% vs 36.6%, p<0.001) (table 2). Laboratory parameters are shown in table 3: patients of the second wave showed significantly higher levels of haemoglobin (13.4 vs 12.8 g/L), lower lymphocytes (926.4 vs 1645/mm^3) and lower D-dimer (920 vs 1165 ng/mL).

Drug use was consistent with the change in guidelines and clinical practice between the first and the second waves. In particular, the use of remdesivir decreased from 4.5% (20/449) to 1.8% (18/1023) (p=0.003) in the second wave, while dexamethasone increased from 36.5% to 67.5% (p<0.001). Prophylactic heparin usage increased and was used in all patients recruited in the second wave, while bridging and therapeutic dosage was similar in the two waves (p=0.13 and p=0.39, respectively). Tocilizumab was more frequently prescribed in the first wave than in the second one when it was prescribed only to rescue patients failing on dexamethasone (40.3% vs 29.7 %, p<0.001) (table 4). Concerning respiratory support, there was more frequent use of HFNO during the second wave (16.1% vs 5.3%, p<0.001) and a less frequent use of NIV (11.4% vs 21.2%; p<0.001) and IMV (8.0% vs 19.4%; p<0.001). Time from admission to IMV tended to be longer in the second wave (9.0 vs 11.0 median days, p=0.06), while in the second wave, patients underwent both HFNO, that is, when median PaO_2:FiO_2 ratio was higher than that recorded during the first wave (100 mm Hg vs 74 mm Hg, p=0.047), and NIV (92 mm Hg vs 79 mm Hg, p=0.39) earlier. Moreover, there was evidence for a reduction over time in the frequency of use of IMV with 87 patients who underwent endotracheal intubation in the first wave (19.4 %) vs 82 (8.0%) during the second wave (p<0.001) (table 5).

Table 1 Demographic comorbidities and main delays by wave

Characteristics	Enrolment period			
	February–May	October–December	P value*	Total
	n=449	n=1023		N=1472
Age (years)			<0.001	
Median (IQR)	65 (54–77)	71 (58–81)		70 (56–80)
Gender, n (%)			0.100	
Female	151 (33.6)	390 (38.1)		541 (36.8)
Ethnicity, n (%)			0.771	
Caucasian	427 (95.1)	969 (94.7)		1396 (94.8)
Black	11 (2.4)	22 (2.2)		33 (2.2)
Asian	10 (2.2)	26 (2.5)		36 (2.4)
Hispanic	1 (0.2)	6 (0.6)		7 (0.5)
BMI				
Median (IQR)	27.6 (24.9–31.1)	28.1 (25.7–32.3)	0.050	27.8 (25.3–31.5)
Comorbidities, n (%)				
≥1	347 (77.3)	865 (84.6)	<0.001	1212 (82.3)
Obesity	93 (32.2)	134 (36.9)	0.208	227 (34.8)
Ischaemic cardiomyopathy	222 (50.1)	559 (55.0)	0.088	781 (53.5)
COPD	161 (36.3)	400 (39.3)	0.281	561 (38.4)
Connective tissue disease	154 (34.8)	396 (38.9)	0.130	550 (37.7)
Cerebrovascular disease	146 (33.0)	365 (35.9)	0.280	511 (35.0)
Mild liver disease	1 (0.4)	3 (1.0)	0.449	4 (0.7)
Diabetes	203 (45.8)	538 (52.9)	0.013	741 (50.8)
Chronic kidney failure	154 (34.8)	375 (36.9)	0.441	529 (36.2)
Solid tumour	195 (44.0)	474 (46.6)	0.361	669 (45.8)
Liver failure	130 (29.3)	335 (32.9)	0.175	465 (31.8)
Haematological disease	13 (5.6)	13 (4.3)	0.510	26 (4.9)
Peptic ulcer disease	6 (2.6)	6 (2.0)	0.659	12 (2.2)
Dementia	139 (31.4)	384 (37.8)	0.019	523 (35.8)
Arterial hypertension	161 (46.4)	244 (31.4)	<0.001	405 (36.0)
Chronic heart failure	28 (12.0)	43 (14.3)	0.433	71 (13.3)
Peripheral vascular disease	52 (22.2)	62 (20.6)	0.649	114 (21.3)
CCI, mean (SD)	5.9 (4.9)	5.9 (5.2)	0.475	5.9 (5.1)
Main delays				
Days from symptoms onset to hospitalisation, median (IQR)	6 (3–9)	6 (3–8)	0.040	6 (3–9)
Days from symptoms onset to ICU, median (IQR)	9 (6–12)	8 (6–11)	0.062	9 (6–11)
Days from hospitalisation to ICU, median (IQR)	1 (0–3)	1 (0–4)	0.437	1 (0–4)

*χ^2 or Mann-Whitney test as appropriate.
BMI, body mass index; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

Concerning the main findings, the Kaplan-Meier analysis suggests that the cumulative risk of death by day 28 from hospital admission was significantly lower during the second wave: 14.2% (95% CI 12.0% to 16.3%) vs 20.0% (95% CI 16.3% to 23.7%) (figure 2, log-rank test p value=0.03) (figure 2).

After including key predictors of outcome in the multivariable Cox regression model, the data still strongly suggested a reduction in the 28-day mortality rate comparing the second wave with the first wave (aHR=0.64, 95% CI 0.45 to 0.90, p=0.01). Results were similar in the sensitivity analyses: (1) after excluding participants with solid cancers and those aged >75 (aHR: 0.65, 95% CI 0.29 to 1.47, p=0.30) and (2) after excluding participants who were enrolled after 3 December 2020 (aHR:0.78, 95% CI 0.56 to 1.09, p=0.15) (online supplemental figures 1 and 2).

Table 2 Vital signs at admission by wave

Characteristics	Enrolment period N	February–May	October–December	P value*	Total
Systolic blood pressure	901			<0.001	
Median (IQR)		123 (110–137)	130 (120–145)		130 (117–140)
Diastolic blood pressure	900			0.173	
Median (IQR)		75 (70–80)	75 (70–80)		75 (70–80)
SOFA score	694			0.735	
Median (IQR)		2 (2–4)	2 (2–4)		2 (2–4)
Baseline PaO_2/FiO_2 (mm Hg)	1392			0.017	
Median (IQR)		248 (84– 319)	257 (133–318)		254 (120–319)
0–250, n (%)		218 (51.5)	459 (47.4)	0.153	677 (48.6)
0–150, n (%)		155 (36.6)	264 (27.2)	<0.001	419 (30.1)
HFNO PaO_2/FiO_2 (mm Hg)	161			0.047	
Median (IQR)		74 (62–95)	100 (69–156)		96 (66–150)
NIV PaO_2/FiO_2 (mm Hg)	173			0.387	
Median (IQR)		79 (58–137)	92 (65–115)		88 (63–123)
IMV PaO_2/FiO_2 (mm Hg)	127			0.707	
Median (IQR)		77 (54–147)	86 (63–113)		81 (58–125)
Respiratory rate	919			0.386	
Median (IQR)		22 (18–28)	22 (18–28)		22 (18–28)

*χ or Mann-Whitney test as appropriate.
HFNO, high-flow nasal oxygen; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; SOFA, Subsequent Organ Failure Assessment.

Concerning the sensitivity analysis around the possible confounding effect of the circulating variant, under the assumptions described in the Methods section, using the online bias factor calculator developed at Harvard University, we estimated a bias factor of 1.27 and a maximum attenuation of the relative risk of death comparing the first wave with the second wave from 1.56 to 1.23 (https://bias-factor.hmdc.harvard.edu/).

Finally, similar differences in 14-day mortality rates by wave were observed after restricting the analysis to patients needing HFNO, NIV or IMV (online supplemental figure 3). In all these secondary subset analyses, the effect size associated with wave remained similar, although sample size was greatly reduced so that comparisons are potentially underpowered.

DISCUSSION

Our analysis reports a significant reduction in 28-day mortality, from 20% to 14%, among hospitalised patients with severe SARS-CoV2-associated pneumonia, comparing the two epidemic waves of COVID-19 in a tertiary care University Hospital in Northern Italy, one of the most affected areas in the world.

At present, only a few studies worldwide compared in-hospital mortality risk by pandemic wave. In these studies, a non-standardised definition of waves was used; exact inclusion criteria were often unclear; follow-up was short; and none provided transparent and reasonable assumptions regarding the underlying causal structural of the data.[6 9–14] Indeed, it is also important to remark that the heterogeneity of study designs, including censoring time and the severity of population collected (critical or severe), varies widely and these factors could strongly influence the estimated mortality and its predictors. For example, in Japan, during the second wave, which was defined as the period from 1 June to 31 July, hospitalised patients with severe COVID-19 disease were significantly younger with fewer underlying diseases, and consequently, as expected, mortality rates were lower (17% vs 7%).[9] In a Spanish cohort study, also in line with our results, authors reported a significant decrease in the case mortality from 24.0% to 13.2%.[14] However, again, results are not fully comparable as waves have been defined differently (first wave includes the summer month of June and the second wave was truncated in mid-October).

In contrast, in our analysis by excluding the summer period, we were able to include two cohorts with more homogenous characteristics, including the proportion of patients affected by severe or critical disease and with small imbalances for other predictors of death between the two waves. Moreover, any small differences in these measured characteristics were controlled for by multivariable regression modelling. Interestingly, an Italian study based on mortality survey data showed a similar

Table 3 Basal laboratory parameters by wave

Baseline laboratory parameters	Enrolment period			
	February–May	October–December	P value	Total
	N=443	N=1009		N=1452
Leucocytes (/mm^3), median (IQR)	6100 (4820–8400)	6660 (4770–9420)	0.052	6440 (4790–9060)
% neutrophiles, median (IQR)	11.0 (8.7–78.9)	64.3 (8.7–80.5)	0.063	60.9 (8.7–80.1)
Lymphocytes, median (IQR)	1645 (870.0–2285)	926.4 (660.0–1317)	<0.001	1090 (710.0–1824)
Haemoglobin (g/L), median (IQR)	12.8 (11.4–14.1)	13.4 (12.1–14.3)	<0.001	13.2 (11.9–14.2)
Platelets (10^9/L), median (IQR)	209.0 (155.0–272.0)	203.0 (156.0–261.0)	0.428	204.0 (156.0–264.0)
Alanine amino transferase, U/L, median (IQR)	29.5 (18.0–47.0)	26.0 (17.0–43.0)	0.033	27.0 (17.0–45.0)
INR, median (IQR)	1.1 (1.0–1.1)	1.0 (1.0–1.1)	<0.001	1.0 (1.0–1.1)
D-dimer (ng/mL), median (IQR)	1165 (610.0–2300)	920.0 (540.0–1710)	<0.001	970.0 (550.0–1920)
0–500 ng/mL, n (%)	80 (18.3)	204 (21.7)	0.050	284 (20.7)
501–4000 ng/mL, n (%)	303 (69.5)	655 (69.8)		958 (69.7)
4000+ ng/mL, n (%)	53 (12.2)	79 (8.4)		132 (9.6)
Lactate dehydrogenase (U/L)	547.0 (426.0–715.0)	528.0 (425.0–682.0)	0.079	535.0 (425.0–695.0)
Creatinine (mg/dL), median (IQR)	0.9 (0.7–1.1)	0.9 (0.7–1.2)	0.020	0.9 (0.7–1.1)
eGFR (mL/min), median (IQR)	86.4 (64.2–99.9)	80.3 (55.7–94.5)	<0.001	82.5 (57.3–96.5)
60+ mL/min, n (%)	345 (77.9)	724 (71.7)	0.040	1069 (73.6)
31–60 mL/min, n (%)	68 (15.3)	208 (20.6)		276 (19.0)
0–30 mL/min, n (%)	30 (6.8)	78 (7.7)		108 (7.4)
C reactive protein (mg/L), median (IQR)	6.0 (3.0–16.0)	6.0 (3.0–14.0)	0.066	6.0 (3.0, 14.0)
IL-6, mg/L, median (IQR)	165.1 (54.0–326.4)	101.5 (29.2–381.8)	0.058	125.7 (37.2–359.8)
Procalcitonin (ng/mL), median (IQR)	0.1 (0.1–0.4)	0.1 (0.1–0.4)	0.602	0.1 (0.1–0.4)

χ^2 or Mann-Whitney test.
eGFR, estimated glomerular filtration rate; IL, interleukin; INR, international noarmalised ratio.

distribution of comorbidities when comparing COVID-19 deaths which occurred over March–May 2020 and those recorded over June–August 2020.[6] Our trend in mortality is also consistent with those shown in the ICNARC report, including only critically ill patients and comparing mortality risk of COVID-19 between those admitted up to 31 August 2020 with those admitted from 1 September 2020 to March 2021 in England, Wales and Northern Ireland.[44] Indeed, using a risk prediction model to adjust for changes in the characteristics of patients admitted to critical care, they observed a decreasing trend in 28-day mortality over time.

Table 4 Therapies used by wave

Therapies ever used	Enrolment period			
	February–May	October–December	P value*	Total
	N=449	N=1023		N=1472
Heparin, n *(%)*				
Intermediate	4 (0.9)	3 (0.3)	0.125	7 (0.5)
Full dose	16 (3.6)	28 (2.7)	0.391	44 (3.0)
Remdesivir, n *(%)*	20 (4.5)	18 (1.8)	0.005	18 (1.2)
Glucocorticoids, n *(%)*				
Standard dose	164 (36.5)	691 (67.5)	<0.001	855 (58.1)
High dose	17 (3.8)	41 (4.0)	0.841	58 (3.9)
Tocilizumab, n *(%)*	181 (40.3)	304 (29.7)	<0.001	485 (32.9)
Anakinra, n *(%)*	16 (3.6)	0 (0.0)	<0.001	16 (1.1)

*χ test.

Table 5 Postbaseline respiratory support and outcomes by wave

	Enrolment period			
Respiratory support	**February–May**	**October–December**	**P value***	**Total**
	N=449	N=1023		N=1472
HFNO, n (%)	24 (5.3)	165 (16.1)	<0.001	189 (12.8)
NIV, n (%)	95 (21.2)	117 (11.4)	<0.001	212 (14.4)
IMV, n (%)	87 (19.4)	82 (8.0)	<0.001	169 (11.5)
Outcomes				
Days between hospital admission and NIV, median (IQR)	2.0 (1.0–4.0)	2.0 (1.0–6.0)	0.632	2.0 (1.0–5.0)
Days between disease onset and IMV, median (IQR)	9.0 (6.0–12.0)	11.0 (7.0–16.0)	0.062	10.0 (7.0–14.0)
Days free from HFNO (days), median (IQR)	25.0 (22.0–27.0)	25.0 (22.0–27.0)	0.876	25.0 (22.0–27.0)
Days free from NIV (days), median (IQR)	25.0 (23.0–26.0)	25.0 (22.5–27.0)	0.677	25.0 (23.0–27.0)
Days free from IMV (days), median (IQR)	23.0 (17.0–25.0)	20.0 (14.0–24.0)	0.065	21.0 (16.0–25.0)
Days free from hospital (days), median (IQR)	15.0 (6.0–21.0)	20.0 (14.0–23.0)	<0.001	19.0 (12.0–23.0)
Days free from ICU (days), median (IQR)	21.0 (16.0–25.0)	23.0 (20.0–26.0)	0.022	23.0 (18.0–25.5)
Death, n (%)	102 (22.7)	164 (16.0)	0.002	266 (18.1)
Death in those requiring HFNO, n (%)	10 (41.7)	47 (28.5)	0.190	57 (30.2)
Death in those requiring NIV, n (%)	40 (42.1)	40 (34.2)	0.238	80 (37.7)
Death in those requiring IMV, n (%)	40 (46.0)	36 (43.9)	0.787	76 (45.0)

*$\chi 2$ or Mann-Whitney test.
HFNO, high-flow nasal oxygen; ICU, intensive care unit; IMV, Invasive mechanical ventilation; NIV, non-invasive ventilation.

Several reasons might explain the observed difference in 28-day mortality between the two waves. First, a better organisation of care improved clinical and therapeutic pathways. Indeed, during the second wave, the improved strict collaboration between infectious disease, pulmonary medicine and intensive care specialists in our

Figure 2 Survival Kaplan-Meier estimates stratified by pandemic wave.

hospital allowed for a timely choice of therapy administration, respiratory support use and intensive care admission, which was, understandably, less organised during the first wave. Second, the pharmacological interventions have also changed over time. The real difference concerns the use of steroids, given that the percentage of patients treated with glucocorticoids nearly doubled from the first to the second wave. Notably, tocilizumab was used in both waves, but only in those clinically failing glucocorticoids during the second wave. In agreement with the results shown in a preliminary report from the RECOVERY trial,[45] data from our hospital indeed support that intensification with tocilizumab improved survival in people with severe gas exchange impairment when compared with glucocorticoids alone (separate analyses submitted). Third, indications for respiratory supports varied over time in line with data from the literature.[34 35] In detail, comparing the two waves, we observed some relevant differences both in the frequency of use of different modes of respiratory support, including IMV and non-invasive modes of support (HFNO and NIV) and in the related mortality rates. In fact, the cumulative proportion of patients requiring respiratory support, both invasive and non-invasive, was lower in the second wave as compared with the first period of the pandemic (35.5% vs 45.9%, p=0.002). Indeed, whereas the proportion of patients requiring NIS did not change over time (26.5% vs 27.5 p=0.7), the use of HFNO increased by >3-fold during the second wave also for logistic reasons. Moreover, during the second wave, there was extensive use of pronation, which may slow respiratory deterioration in selected COVID-19 spontaneously breathing patients, thus reducing the need for NIV or IMV as compared with standard oxygen.[46–49]

Importantly, all the three described factors which changed between the first and second wave may have reduced the need for IMV, and it is well known in literature that a 41.9% decrease in IMV rate is associated with a 20.9% decrease in 28-day mortality.[50] Unfortunately, our analysis does not dwell into the investigation of the potential mechanisms which might have determined the observed difference, and a follow-up analysis has already been planned to include data of the third wave in order to examine in detail the possible impact of these mediation factors.

Our study has other limitations. First of all, our model correctly estimates the total effect of time of admission on the risk of mortality only if our underlying assumptions are correct. These are untestable assumptions and include the absence of other unmeasured confounding besides the bias due to the change in circulating SARS-CoV-2 variants and the fact that the model is correctly specified. Of note, even in the far-fetched scenario that the reduction in mortality appreciated could be due to lower pathogenicity of the B.1.1.7 strain compared with that of the strain circulating during the first wave, our sensitivity calculations exclude that the relative risk could be attenuated to the null value after controlling for such unmeasured factor. In addition, it is likely that the B.1.1.7 strain is actually more pathogenic,[40] and therefore, our estimate of the difference in mortality during the second wave is potentially even underestimated. Second, although the results of the sensitivity analyses conducted in subsets of the study population treated in critical areas are similar to those seen in the main analysis, these are likely to be underpowered. Additionally, despite all the efforts in filling the gap in the dataset, there are still missing values in some parameters. Although some of these are key predictors and their inclusion in the multivariable analysis would have increased the efficiency of the estimates, none are potential confounders according to our assumptions. The analysis does not explore possible mechanisms (post baseline factors) that led to the decrease in mortality seen in second wave as opposed to first wave in our setting. Also, our analysis does not cover a period in which the delta variant of concern (VoC) was widely circulating in our region. Higher risk of transmission has been documented with this variant,[51] and it would be interesting to repeat this same analysis at later stages to evaluate the in-hospital mortality rate associated with the delta VoC. Finally, our results are not directly generalisable to other settings with a different case-mix of the populations studied.

Nevertheless, this analysis also has many strengths. A key strength is the large sample size, and furthermore, the inclusion of the cohort of patients seen for care after October 2020 allowed us to evaluate the 28-days mortality among COVID-19 hospitalised patients throughout the whole year 2020, a data previously not available in the literature. Our analysis was conducted under transparent assumptions regarding the underlying causal structure of data, and a sensitivity analysis was performed to evaluate the impact of virus variants, a key potential unmeasured confounding factor. Finally, as this is a monocentric study, inclusion criteria were the same in the two waves, and patients belonged to a well-characterised hospital cohort.

In conclusion, our analysis shows a significant reduction in the 28-day mortality rates in our hospital during the second wave of the pandemic compared with the first. Our findings also have a psychological impact on healthcare workers committed to the fight against COVID-19, showing that their efforts were not vain. Additional research is warranted on this topic with the aim of identifying factors that may have led to the difference observed, including the role of improved hospital organisation and healthcare interventions, involving both pharmacological and respiratory support.

While we are waiting for the achievement of herd immunity from vaccination, which is likely to vary by country, a better understanding of the potential impact of these factors could help the daily management of hospitalised patients and lead to a further decrease in hospital mortality.

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