Heliyon 8 (2022) e08895

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Mortality due to COVID-19 during the pandemic: A comparison of first, secondo and third SMAtteo COvid19 REgistry (SMACORE)

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ARTICLE INFO

Keywords:
Covid-19
In-hospital mortality

ABSTRACT

COVID-19 tide had shattered on European countries with three distinct and tough waves, from March and April, 2020; October and November, 2020 and March and April, 2021 respectively. We observed a 50% reduction in the hazard of death during both wave II and III compared with wave I (HR 0.54, 95%CI 0.39–0.74 and HR 0.57, 95% CI 0.41–0.80, respectively). Sex and age were independent predictors of death. We compare in-hospital mortality of COVID-19 patients admitted at our Referral Hospital of Northern Italy during the different waves, discuss the reasons of the observed differences and suggest approaches to the challenges ahead.

1. Introduction

Mortality due to SARS-CoV-2 infection provide helpful data on the course of epidemic being a key indicator of the real impact of COVID-19 [1]. The first wave of the SARS-CoV-2 pandemic in Europe occurred on spring 2020. In Italy, three waves occurred: in March–April in October–November 2020, and a third in March–April 2021. In Italy the first death due to SARS-CoV-2 infection was recorded at the end of February. As early as March 2020, In Italy the mortality burden of SARS-CoV-2 was estimated at 50% of overall excess deaths, to decreased to 36% in April, 2020 [1].

The COVID-19 impact on Italy's mortality rate is worse than that in most European countries. The excess of total mortality in Italy was observed in March and April, 2020 followed by a summer lull (in June and July). The excess mortality then increased again and peaked in November 2020 [1]. Finally, as of July 10, 2021 127,768 deaths out of 4, 269,885 cases, were reported in Italy, a number that some expert believe is underestimated [2, 3].

Our hospital, Fondazione IRCCS Policlinico San Matteo, is a large research hospital in Lombardy, Northern Italy, in the eye of the COVID-19 storm and was established as a national SARS-CoV-2 referral center since the beginning of COVID-19 pandemic [4, 5]. Here, we compare the mortality rate of different waves and attempt to understand the reasons behind them.

2. Methods

At the end of July 2020, a second wave was anticipated in Europe, but it only occurred at end of September 2020. A third wave reached Italy in March of 2021. All patients, aged 18 years or more, hospitalized for COVID-19, during the first 5 weeks of each of the first, second and third wave, admitted to the Fondazione IRCCS Policlinico San Matteo, were included. The timeframes were March 1, 2020 to April 4, 2020 (wave I), from October 1, 2020 to November 5, 2020 (wave II) and from March 1, 2021 to April 5, 2021 (wave III). We retrieved demographics

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https://doi.org/10.1016/j.heliyon.2022.e08895
Received 21 April 2021; Received in revised form 22 July 2021; Accepted 29 January 2022

comorbidities, use of invasive mechanical ventilation and intensive care as well as vital status from data included in SMAtteo COvid19 REgistry (SMACORE) to compare overall and age group severity and in-hospital mortality between the three COVID19 waves. The registry was populated with the hospital administrative data. Ethics approval for observational research using SMACORE data was obtained from the local ethics committee.

2.1. Study design and endpoints

Prospective longitudinal study evaluating death at 4 weeks from admission and a combined endpoint at 30 days including death and use of invasive mechanical ventilation (CPAP/nasotracheal intubation).

2.2. Statistical analysis

We used the Stata software (release 16.1, StataCorp, College Station, TX, USA) for computation. We considered a 2-sided p-value<0.05 as statistically significant. We described continuous variables with the mean and standard deviation (SD) and categorical variables as counts and percent. We compared them between waves with the oneway ANOVA and the Fisher exact test, respectively. We computed the rate of events per 100-person week by COVID wave. We compared survival using the log rank test and derived adjusted hazard ratios from a multivariable Cox model, while adjusting for age (grouped as 18–64; 65–80, 81+), sex and presence of multiple comorbidity. We computed the hazard ratio and 95% confidence interval (HR, 95%CI). We performed predefined subgroup analyses in the age categories. We tested the interaction of wave and age, while adjusting for sex. We computed the Harrell's c statistic for model discrimination. In a sensitivity analysis we used a finer breakdown for age (with quinary age groups above 50) as well as age as continuous variable in the multivariable model. The linearity of effect of age was assessed and confirmed.

3. Results

A total of 1461 patients were enrolled, 821 hospitalized for COVID-19 during the first 5 weeks of wave I, 258 during first 5 weeks of wave II and 382 during first 5 weeks of wave III. Their mean age was 67 years (SD 16), 559 (38%) were women. One thousand twenty-seven (80%) had multiple comorbidities. The demographic and clinical characteristics are shown in Table 1: patients observed during wave I were older; the proportion of women was similar; they had more comorbidities. The rate of hospitalization in intensive care was similar; although not statistically significant, there was a trend towards a change during wave III in the ICU admission rate clinical management. Contrary to the first wave, a higher proportion of patients in the second and third wave were not intubated (MV), receiving high flow nasal oxygen (HFNO) or continuous positive airway pressure (CPAP) therapy instead.

Table 1. Patient's characteristics in the three COViD-19 waves.

Variable	Wave I (N = 821)	Wave II (N = 258)	Wave III (N = 382)	p-value
Female, N (%)	283 (34%)	100 (39%)	176 (46%)	0.001
Age (years), mean (SD)	68 (15)	65 (17)	67 (16)	0.003
Age Group				0.471
18–64	307 (37%)	112 (43%)	151 (40%)	
65–80	337 (41%)	91 (35%)	149 (39%)	
81+	177 (22%)	55 (21%)	82 (22%)	
Comorbidities, mean (SD)	3.0 (1.4)	2.7 (1.4)	2.5 (1.4)	0.461
Multiple comorbidities, N (%)	685 (83%)	192 (74%)	150 (72%)	<0.001
Intensive care, N (%)	118 (14%)	29 (11%)	71 (19%)	0.034
High flow oxygen, N (%)	464 (56%)	186 (72%)	105 (50%)	<0.001
CPAP, N (%)	325 (40%)	83 (32%)	73 (35%)	0.073
Mechanical ventilation, N (%)	113 (14%)	19 (7%)	8 (2%)	<0.001
ECMO implant, N (%)	16 (2%)	1 (0.4%)	0 (0%)	0.030

The proportion of deaths decreased from 270 (33%) during wave I to 44 (17%) during wave II and 40 (11%) during wave III, respectively, with corresponding weekly rates of 17% (95%CI 15–19), 10% (95%CI 7–13) and 6% (95%CI 4–8, log rank test p < 0.001 Figure 1, upper panel). At the multivariable Cox model, we observed a 50% reduction in the hazard of death during both wave II and III, respectively, compared with patients in wave I (HR 0.54, 95%CI 0.39–0.74 and HR 0.57, 95%CI 0.41–0.80, respectively), which is independent of age, gender and multiple comorbidities. Sex and age were independent predictors of death, as well (Table 2).

At the subgroup analysis by age group (Figure 1, lower panels), 29, 3 and 2 patients died in the 18–65 years category (log rank test p = 0.017), 140, 16 and 16 in the 65–80 category (log rank test p < 0.001), and 101, 25 and 22 in the 81 + category (log rank test, p < 0.001), in waves I and II and III respectively. When adjusting for sex and multiple comorbidities, the relative risk of dying was still lower for waves II and III with respect to wave I across all age groups (Table 2), though statistical significance remained for the 65–80 years group only. No modifying effect of age on the association of wave and mortality was shown (p for interaction = 0.334).

The sensitivity analysis using finer breakdowns of age and age in continuous yielded the same effect size for waves (HR close to 0.55 for both wave II and III vs. wave I) and excluded similarly a modifying effect of age on wave.

The combined event of invasive mechanical ventilation and death occurred in 334 patients in wave I, 55 in wave II and 41 in wave III with weekly rates of 26% (95%CI 23–29), 14% (95%CI 11–19) and 7% (95% CI 5–10), respectively (log rank test p < 0.001). The adjusted HR from the multivariable Cox model was 0.56 (95%CI 0.420–0.75 and 0.48,95% CI 0.34–0.67 for waves II and III versus wave I, respectively, p < 0.001). No modifying effect of age on the association of wave and mortality was shown (p for interaction = 0.155).

4. Discussion

Despite the magnitude of second and third waves in Italy, fewer patients were hospitalized than in the first wave (821 VS 258 VS 382) and this can be explained partly by increased testing, which, however, does not necessarily reflect a true increase in the number of hospitalizations. Specifically, a two-fold decrease in 30 days mortality was observed in patients admitted in waves II and III, respectively, compared with patients in wave I. At the subgroup analysis by age group, adjusting for sex and multiple comorbidities, the relative risk of dying was still lower for waves II and III than for wave I across all age groups, although statistical significance remained for the 65–80 years group only. Moreover, there was a tendency to use HFNO and CPAP with lower use of MV compared with first wave. Many countries experienced reduction of mortality rate unlike what happened in the United States: in a JAMA editorial, Koh et al underlined the rapid rising COVID- 19 death rates from summer until time of data collection [6]. Our results are in contrast with those by Ioannidis et al, who found no differences in the age distribution of COVID-19 deaths in the same country between the two waves, by analyzing mortality in all countries that had at least 4000 COVID-19 deaths among first and second wave [7]. Similarly, Docherty et al, reported that mortality declined in all age groups, in patients with COVID-19 admitted to 247 acute hospitals in England, Scotland, and Wales with and without comorbidities, between March 9, and Aug 2, 2020 [8]. The observed reduction was greater than expected and was partly attributable to accumulating clinical knowledge and changes in intensive care (IC) management.

As noted, numerous factors can impact in-hospital mortality and the result are not entirely unexpected. This can be explained by several factors. First of all, clinical knowledge of COVID-19, rapidly increased

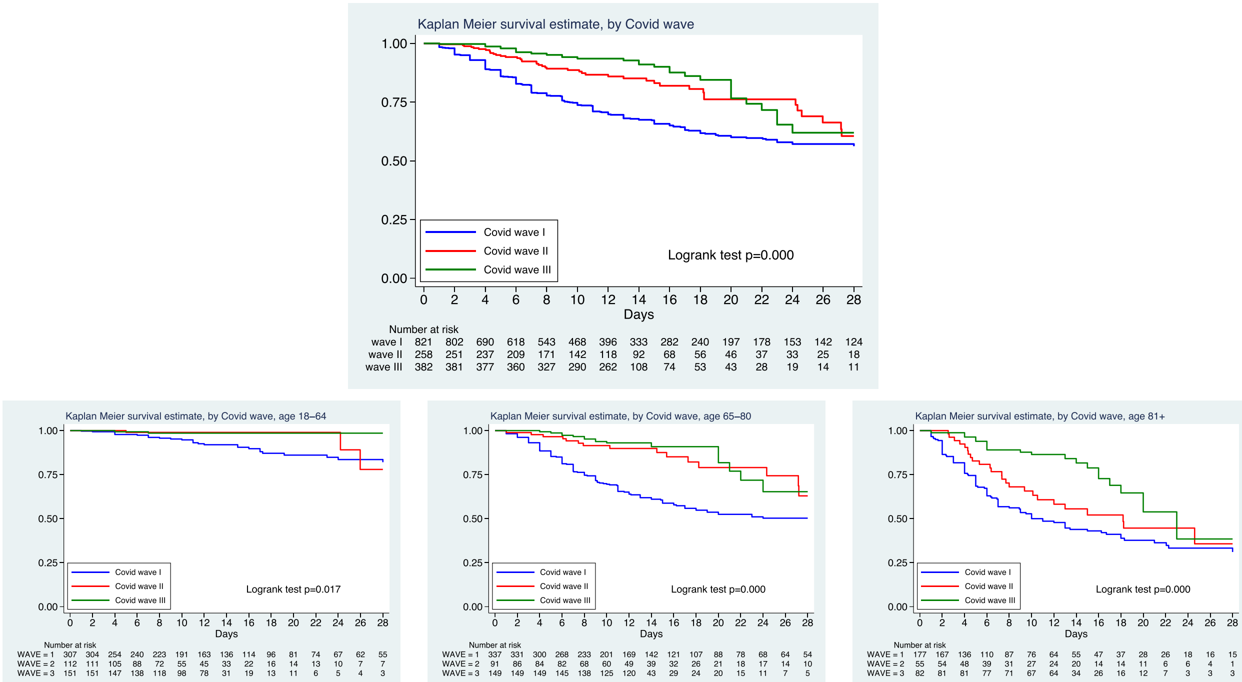

Figure 1. Kaplan Meier survival curves by Covid-19 waves. Upper panel: entire cohort; lower panel: age groups 18–64, 65–80 and 81+.

Table 2. Multivariable Cox Model for in-hospital mortality.

	All cases Model p < 0.001, Harrells' c = 0.74		18–64 yrs Model p = 0.030 Harrell's c = 0.68		65–80 yrs Model p < 0.001 Harrell's c = 0.64		81 + yrs Model p = 0.084 Harrell's c = 0.58	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Wave		<0.001		0.208		<0.001		0.111
I	1		1		1		1	
II	0.53 (0.39–0.73)		0.46 (0.14–1.53)		0.38 (0.23–0.65)		0.70 (0.44–1.09)	
III	0.57 (0.41–0.80)		0.39 (0.09 1.70)		0.62 (0.37–1.05)		0.60 (0.38–0.97)	
Sex		<0.001		0.731		<0.001		0.085
F	1		1		1		1	
M	1.55 (1.23 1.95)		0.88 (0.42–1.85)		2.08 (1.43 3.04)		1.33 (0.96–1.84)	
Age Group		<0.001	-		-		-	
18–64	1							
65–80	4.63 (3.19–6.71)							
81+	9.70 (6.61–14.24)							
Multiple comorbidities		0.083		0.039		0.261		0.489
No	1		1		1		1	
yes	1.52 (0.95–2.44)		8.25 (1.11–61.15)		1.45 (0.76–2.75)		0.77 (0.37–1.60)	

from zero as a result of simultaneous world-wide effort in clinical research, which paid off. Specifically, evidence on the anticoagulant and steroid treatment had progressively accumulated until it was sanctioned by the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial results [9, 10]. Meanwhile changes in the IC management also occurred: in wave I, in the early phase of pandemic, the tendency was to intubate early; but this approach was later questioned [11]. Then, before the start of wave II, high flow oxygen administration was the preferred approach where possible However, while in the early days of pandemic several protocols were adopted and implemented, orienting physicians towards the most uniform therapeutic approach feasible, was not always easy. The same applies to the available guidelines (such as World Health Organization and National Institutes of Health. Guidelines [12, 13]). Hence, reduction in mortality cannot be definitely correlated to the appropriateness of the diagnostic and therapeutic work-up.

Another important aspect is the change in population demographics from the first wave when frail populations (elderly subjects with more comorbidities) were the bulk of those who became ill. The reduction in COVID-19-related hospital mortality can also be attributed to other factors such as circulating variants with lower virulence and severity of disease, development of COVID-19 immunity (natural or due to vaccination) in the population, resulting in milder infections, increased hospital and testing capacity, which was implemented prior to the second wave. The capacity to respond and adapt rapidly to the crisis is another crucial factor. For instance, our hospital coped with the first wave by converting its capacity for COVID patients in less than two weeks, which highlights the role of an early interventions in the reduction of mortality [4]. Mortality could also be affected by community policies such as lockdowns or other restrictive measures, but, as suggested by Meo et al, their influence on COVID mortality seems to be tenuous. It is far more likely that control of in-hospital mortality is a function of adequate resource allocation and saturation of the hospital system [14].

The intrinsic dynamics of infection which, depend on the concomitant occurrence of several factors as suggested by Kissler et al: degree of seasonal variation in transmission, the duration of immunity, cross-immunity between SARS-CoV-2 and other coronaviruses, community behavior. The difference between the two waves reflects the difference between a "rapidly spreading infection" like the first wave and "a slacking one" as well as recurrent wintertime outbreaks of SARS-CoV-2 [15]. Our data fit exactly with this assumption, as we now manage a phase in which the pandemic surge has plateaued.

A limitation of the study lies in being single center with data from an administrative data registry. Also, the subgroup analysis by age classes reduced the power to elicit statistically significant differences between waves, while the corresponding effect size were close.

In conclusion, performing a mortality analysis of our patients elicited important differences in the hospital mortality over three epidemic waves, allowing to speculate on the potential epidemiologic and structural correlates of these findings and their implication for future crises. Our study might represent the foundation for future multicenter studies making use not only of data from the discharge records but also combining them with epidemiological and clinical findings, to further avert an excess of lives being lost in future epidemics of this magnitude.

Declarations

Author contribution statement

Valentina Zuccaro, Marta Colaneri, Raffaele Bruno, Catherine Klersy: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Erika Asperges, Pietro Valsecchi, Margherita Sambo, Laura Maiocchi, Paolo Sacchi, Alba Muzzi, Valeria Musella, Sara Cutti, Marco Rettani, Francesco Mojoli, Stefano Perlini, Angelo Guido Corsico, Antonio Di Sabatino: Performed the experiments; Analyzed and interpreted the data.

Enrico Brunetti: Analyzed and interpreted the data; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2022.e08895.

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