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The importance of patients' case-mix for the correct interpretation of the hospital fatality rate in COVID-19 disease

Antonella d'Arminio Monforte[a,*], Alessandro Tavelli[a], Francesca Bai[a], Daniele Tomasoni[a], Camilla Falcinella[a], Roberto Castoldi[a], Diletta Barbanotti[a], Giovanni Mulè[a], Marina Allegrini[a], Daniele Tesoro[a], Gianmarco Tagliaferri[a], Debora Mondatore[a], Matteo Augello[a], Andrea Cona[a], Giuseppe Ancona[a], Lidia Gazzola[a], Nathalie Iannotti[a], Camilla Tincati[a], Ottavia Viganò[a], Anna De Bona[a], Teresa Bini[a], Alessandro Cozzi-Lepri[b], Giulia Marchetti[a]

[a] Clinic of Infectious Diseases, Department of Health Science, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy
[b] Centre for Clinical Research, Epidemiology, Modelling and Evaluation, Institute for Global Health, University College London, London, UK

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ABSTRACT

Objective: We aimed to document data on the epidemiology and factors associated with clinical course leading to death of patients hospitalised with COVID-19.
Methods: Prospective observational cohort study on patients hospitalised with COVID-19 disease in February-24th/May-17th 2020 in Milan, Italy. Uni-multivariable Cox regression analyses were performed. Death's percentage by two-weeks' intervals according to age and disease severity was analysed.
Results: A total of 174/539 (32.3%) patients died in hospital over 8228 person-day follow-up; the 14-day Kaplan–Meier probability of death was 29.5% (95%CI: 25.5–34.0). Older age, burden of comorbidities, COVID-19 disease severity, inflammatory markers at admission were independent predictors of increased risk, while several drug-combinations were predictors of reduced risk of in-hospital death. The highest fatality rate, 36.5%, occurred during the 2nd–3rd week of March, when 55.4% of patients presented with severe disease, while a second peak, by the end of April, was related to the admission of older patients (55% ≥80 years) with less severe disease, 30% coming from long-term care facilities.
Conclusions: The unusual fatality rate in our setting is likely to be related to age and the clinical conditions of our patients. These findings may be useful to better allocate resources of the national healthcare system, in case of re-intensification of COVID-19 epidemics.

Introduction

SARS CoV-2 epidemic is one of the most devastating worldwide epidemics in the last century. From the initial outbreak in China, it reached Europe by the end of February 2020. Lombardy was the first region to be affected, thus representing an unexpected challenge for region governors and causing a dramatic overload of hospitals and intensive care units (ICU). In a short time span, all the hospitals were overwhelmed by dozens of citizens suffering from acute respiratory distress and the different departments were rapidly shifted to areas for COVID-19 patients. On March 11, WHO declared the state of pandemic (World Health Organisation, 2020).

We faced a number of deaths that seemed to be higher than what could be expected from the data of the Chinese epidemic, where a fatality rate on hospitalised patients ranging from 1.4 to 2.3% (Guan et al., 2020; Wu et al., 2020) to 28% was documented in an early report from Wuhan by Zhou et al. (2020).

When reporting fatality rates, several factors should be taken in consideration, that include the reference population, disease severity, but also presence of comorbidities and the availability of ICU beds; all these factors might contribute to disentangle differences on COVID-19 fatality rates in different settings.

* Corresponding author at: Institute of Infectious and Tropical Diseases, Department of Health Sciences, ASST Santi Paolo e Carlo, University of Milan, Via A. di Rudinì, 8, 20142 Milan, Italy.
E-mail address: antonella.darminio@unimi.it (A. d'Arminio Monforte).

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Table 1
Demographic and clinical characteristics of 539 patients hospitalised for COVID-19 disease according to in-hospital death.

	In-hospital survival N = 367 (67.7)	In-hospital death N = 174 (32.3)	Total N = 539	p
Gender, male, N (%)	230 (63.0)	117 (67.2)	347 (64.4)	0.338
Age, years, median (IQR)	60 (50–72)	78 (67–84)	66 (54–78)	<0.001
Age strata, years, N (%)				
18–39	43 (11.8)	0 (0.0)	43 (8.0)	<0.001
40–59	134 (36.7)	23 (13.2)	157 (29.1)	
60–79	139 (38.1)	82 (47.1)	221 (41.0)	
≥80	49 (13.4)	69 (39.7)	118 (21.9)	
Ethnicity, N (%)				<0.001
Caucasian	285 (78.1)	163 (93.7)	448 (83.1)	
Latin/Hispanic	37 (10.1)	5 (2.9)	42 (7.8)	
Black	8 (2.2)	0 (0.0)	8 (1.5)	
Asian	12 (3.3)	3 (1.7)	15 (2.8)	
Other	23 (6.3)	3 (1.7)	26 (4.8)	
Risk factors, N (%)				<0.001
Close contact/household	88 (24.1)	23 (13.2)	111 (20.6)	
Healthcare worker	37 (10.1)	2 (1.2)	39 (7.2)	
High risk zone	17 (4.7)	10 (5.7)	27 (5.0)	
Hospitalisation last 30 days	18 (4.9)	9 (5.2)	27 (5.0)	
Long-term care facility	23 (6.3)	33 (19.0)	56 (10.4)	
Unknown	182 (49.9)	97 (55.8)	279 (51.8)	
Smoking, N (%)				0.001
Never	47 (12.9)	6 (3.5)	53 (9.8)	
Former	35 (9.6)	20 (11.5)	55 (10.2)	
Actual	12 (3.3)	1 (0.6)	13 (2.4)	
Unknown	271 (74.2)	147 (84.5)	418 (77.6)	
Obesity, N (%)				0.153
No	141 (38.4)	52 (30.2)	193 (35.8)	
Yes	50 (13.6)	27 (15.8)	77 (14.3)	
Unknown	174 (47.7)	94 (54.3)	268 (49.8)	
Number of concomitant comorbidities, N (%)				
0	151 (41.1)	36 (20.7)	186 (34.5)	<0.001
1	114 (31.2)	35 (20.1)	149 (27.6)	
2	50 (13.7)	40 (23.0)	90 (16.7)	
3	27 (7.4)	30 (17.2)	57 (10.6)	
≥4	24 (6.6)	33 (19.0)	57 (10.6)	
Comorbidities, N (%)				
Hypertension	145 (39.7)	105 (60.3)	250 (46.4)	<0.001
Diabetes	49 (13.4)	46 (26.4)	95 (17.6)	<0.001
Cardiovascular diseases[a]	72 (19.7)	75 (43.1)	147 (27.3)	<0.001
Cerebrovascular diseases[b]	21 (5.7)	24 (13.8)	45 (8.3)	0.002
Chronic obstructive pulmonary disease/asthma	43 (11.8)	31 (17.8)	74 (13.7)	0.057
Chronic liver diseases/cirrhosis	12 (3.3)	7 (4.0)	19 (3.5)	0.665
Solid or haematological malignancy	17 (4.7)	21 (12.1)	38 (7.0)	0.002
Chronic kidney disease	17 (4.7)	24 (138)	41 (7.6)	<0.001
HIV infection/AIDS	3 (0.82)	1 (0.6)	4 (0.7)	0.755
Reumathic diseases	6 (1.6)	8 (4.6)	14 (2.6)	0.044
Age unadjusted Charlson score, median (IQR)	0 (0–1)	1 (0–3)	0 (0–2)	<0.001
Days from symptoms onset to hospitalisation, median (IQR)	7 (3–10)	5 (2–8)	6 (3–10)	0.001
Signs and symptoms at admission, N (%)				
Fever	312 (85.5)	153 (87.9)	465 (86.3)	0.439
Dyspnea	191 (52.3)	109 (62.6)	300 (55.7)	0.024
Cough	205 (56.2)	67 (38.5)	272 (50.5)	<0.001
Dyspnea	191 (52.3)	109 (62.6)	300 (55.7)	0.024
Asthenia	62 (17.0)	23 (14.9)	88 (16.3)	0.553
Gastrointestinal symptoms	64 (17.5)	12 (6.9)	76 (14.1)	0.001
Myalgia	24 (6.6)	3 (1.7)	27 (5.0)	0.016
Arhytmia	14 (3.8)	12 (6.9)	26 (4.8)	0.121
Chestpain	18 (4.9)	6 (3.5)	24 (4.4)	0.435
Anosmia/dysgeusia	16 (4.4)	1 (0.6)	17 (3.1)	0.018
Headache	9 (2.5)	2 (1.2)	11 (2.0)	0.312
Other respiratory symptoms	18 (4.9)	5 (2.9)	23 (4.3)	0.269
Other non respiratory symptoms	26 (7.1)	32 (18.4)	58 (10.8)	<0.001
COVID-19 severity at admission, N (%)				<0.001
Mild	28 (7.7)	7 (4.0)	35 (6.5)	
Moderate	197 (54.0)	45 (25.9)	242 (44.9)	
Severe	137 (37.5)	107 (61.5)	244 (45.3)	
Critical	3 (0.8)	15 (8.6)	18 (3.4)	
PO_2/FiO_2 at admission, mmHg, median (IQR)	322 (275–371)	242 (150–308)	301 (231–352)	<0.001
>300	206 (56.4)	42 (24.1)	248 (50.2)	<0.001
100–300	131 (35.9)	97 (55.7)	228 (46.1)	
<100	3 (0.8)	15 (8.6)	18 (3.6)	
Missing	25 (6.8)	20 (11.5)	45 (8.3)	
Respiratory rate at admission, breaths/min, median (IQR)	22 (18–28)	28 (22–32)	24 (20–29)	<0.001
X-ray or CT scan findings, N (%)				0.059
No signs of pneumonia	33 (9.0)	10 (5.7)	43 (7.9)	

Table 1 (*Continued*)

	In-hospital survival N = 367 (67.7)	In-hospital death N = 174 (32.3)	Total N = 539	p
Pulmanary infiltrates/ground glass opacities and lung consolidation	182 (49.9)	79 (45.4)	261 (48.4)	
Lung consolidation	24 (6.6)	24 (13.8)	48 (8.9)	
Pulmanary infiltrates/ground glass opacities	123 (33.7)	60 (34.5)	183 (33.9)	
Bilateral involvement	292 (87.9)	137 (83.5)	429 (86.5)	0.372
Pleural effusion	42 (11.5)	27 (15.5)	69 (12.8)	0.193
Hemoglobin, g/dL, median (IQR)	13.7 (12.4–14.8)	13.2 (11.6–14.5)	13.5 (12.2–14.8)	0.015
CRP, mg/L, median (IQR)	46.1 (21.3–85.7)	87.1 (54.9–126.1)	60.1 (27.8–103.0)	<0.001
LDH, U/L, median (IQR)	273 (211–353)	355 (275–482)	296 (229–393)	<0.001
Leukocytes count, 10^3/μL, median (IQR)	6.35 (4.74–8.61)	7.06 (5.20–10.79)	6.56 (4.93–9.11)	0.001
Lymphocyte count, 10^3/μL, median (IQR)	1.09 (0.74–1.45)	0.80 (0.58–1.14)	1.01 (0.67–1.36)	<0.001
Platelets,10^3/μL, median (IQR)	214 (167–267)	192 (145–261)	204 (159–266)	0.007
Creatine phosphokinase, U/L, median (IQR)	82 (52–154)	140 (66–350)	94 (54–184)	<0.001
D-dimer, ng/mL, median (IQR)	305 (153–584)	563 (314–2340)	358 (170–809)	<0.001
ALT, U/L, median (IQR)	30 (20–52)	28 (19–43)	30 (20–49)	0.168
AST, U/L, median (IQR)	40 (30–56)	46 (32–68)	41 (31–60)	0.009
Creatinin, mg/dL, median (IQR)	0.8 (0.7–1.1)	1.1 (0.8–1.7)	0.9 (0.7–1.2)	<0.001
Procalcitonin, ng/mL, median (IQR)	0.1 (0.05–0.29)	0.69 (0.18–2.49)	0.18 (0.07–0.84)	<0.001
Ferritin, ng/mL median (IQR)	389 (182–758)	701 (334–1320)	447 (215–860)	<0.001
Pharmacological support, N (%) lopinavir/r or darunavir/c or remdesivir	89 (24.2)	45 (26.2)	134 (24.8)	0.632
Hydroxychloroquine ± azithromycin	306 (83.8)	121 (69.5)	427 (79.2)	<0.001
Heparin prophylaxis	242 (66.3)	113 (64.9)	355 (65.9)	0.756
Corticosteroids	80 (21.9)	42 (24.1)	122 (22.6)	0.565
Immunomodulator (tocilizumab, sarilumab)	29 (7.9)	14 (8.1)	43 (8.0)	0.968
Drugs combination, N (%)				0.001
No drugs	29 (8.0)	22 (12.6)	51 (9.5)	
Hydroxychloroquine + heparin (±lopinavir/r or darunavir/c or azithromycin)	214 (58.6)	87 (50.0)	301 (55.8)	
Hydroxychloroquine + lopinavir/r or darunavir/c	41 (11.2)	11 (6.3)	52 (9.6)	
Hydroxychloroquine ± azithromycin	49 (13.4)	23 (13.2)	72 (13.4)	
Heparin only	11 (3.0)	18 (10.3)	29 (5.4)	
Other combinations	21 (5.8)	13 (7.5)	34 (6.3)	
Highest grade of O_2 therapy, N (%)				<0.001
Mechanical ventilation	62 (17.0)	55 (31.6)	117 (21.7)	
cPAP	82 (22.5)	74 (42.5)	156 (28.9)	
O_2 low/high flow	159 (43.6)	43 (24.7)	202 (37.5)	
No O_2 therapy	62 (17.0)	2 (1.2)	64 (11.9)	
Follow-up, median days (IQR)	13 (7–25)	6 (5–12)	10 (6–21)	<0.001

[a] Cardiovascular diseases: coronary artery disease or congestive heart failure or vascular diseases.
[b] Cerebrovascular diseases: stroke or transient ischemic attack or hemiplegia.

Bearing this in mind, we aimed to identify factors associated with the risk of in-hospital death in a cohort of hospitalised patients with COVID-19 disease in a single hospital in Milan.

Methods

Setting

San Paolo hospital is a University hospital with 426 beds of all specialities, including ICU, infectious diseases, and pneumology. Since end of February, increasing number of ICU and non-ICU beds were saved for COVID-19 patients (Supplemental Figure 1). Doctors and nurses converged in multidisciplinary teams leaded by infectious diseases, pneumology and intensive care physicians.

Design

Prospective observational cohort study including all patients admitted to the San Paolo Hospital in Milan with symptomatic SARS CoV-2 infection between February 24 and May 17, 2020.

Subjects and methods

Inclusion criteria were: -confirmed diagnosis of symptomatic SARS CoV-2 infection by RT-PCR on naso-pharyngeal or oro-pharyngeal or broncho-alveolar swab specimens; -age ≥18 years; -hospitalisation in February 24–May 17. Patients who died in the emergency room within 24 h and patients not hospitalised were not included.

Data were entered into an electronic database, including: age; sex; ethnicity; risk factors for SARS CoV-2; ongoing or previous comorbidities; age-unadjusted Charlson comorbidity index (Charlson et al., 1987); symptoms; obesity; respiratory rate (RR), oxygen saturation percent (SO_2); computerised tomography (CT); laboratory examinations.

CT scan was evaluated as: no pathological findings; interstitial pneumonia; consolidation; pleural effusion. Mono- or bilateral extension was collected.

Disease severity at admission was classified as mild (no pneumonia); moderate (radiological demonstration of pneumonia; RR > 26/min; SO_2 > 96% in room air; PaO_2/FiO_2 > 300 mmHg); severe (RR < 24/min; SO_2 < 92%; PaO_2/FiO_2 100–300 mmHg); critical disease (PaO_2/FiO_2 < 100 mmHg).

The highest intensity of ventilation was recorded as: no need; low/high flow supplemental oxygen by nasal cannula/face mask; continuous positive airway pressure device (cPAP); mechanical non-invasive or invasive ventilation.

Criteria for invasive mechanical ventilation were acute respiratory distress (PaO_2/FiO_2 <100 mmHg) and no major conditions determining short life expectancy.

Antivirals; low molecular weight heparin; hydroxychloroquine ± azithromycin; immunomodulatory agents; high-dose corticosteroids were collected and grouped according to the combinations used.

Primary end-point was time to in-hospital death. Factors associated were evaluated in the whole cohort and in patients

undergoing mechanical ventilation, with a special focus on the possible role of comorbidities. We also evaluated the dynamics of the disease in terms of severity at presentation, age of patients, availability of ICU beds, and fatality-rate according to two-week time frames.

The study was approved by Ethic Committee Area 1, Milan (2020/ST/049 and 2020/ST/049_BIS, 11/03/2020). Informed consent was obtained whenever possible.

Statistics

Follow-up was censored at June 17, so that each patient had at least 30 days' observation. Statistics included: Chi-square and Kruskal–Wallis test, to compare characteristics of in-hospital survivors vs non survivors and characteristics of population according to 2-week time-span of admission.

We calculated the in-hospital mortality by age strata according to the number of comorbidities and formally tested for interaction between age and number of comorbidities using Wald test.

Kaplan–Meier curves were used to estimate the probability of in-hospital death. The time-to event was calculated from the date of hospital admission to the date of death or last day of hospitalisation or to June 17th, whichever occurred first. We evaluated the possible association between burden of comorbidities and time to in-hospital death using 2 Cox-proportional hazard regression models with 2 different definitions of the exposure: age-unadjusted Charlson index (Model 1) or individual comorbidities (Model 2). We also evaluated the possible association of other variables at admission including demographics, period of

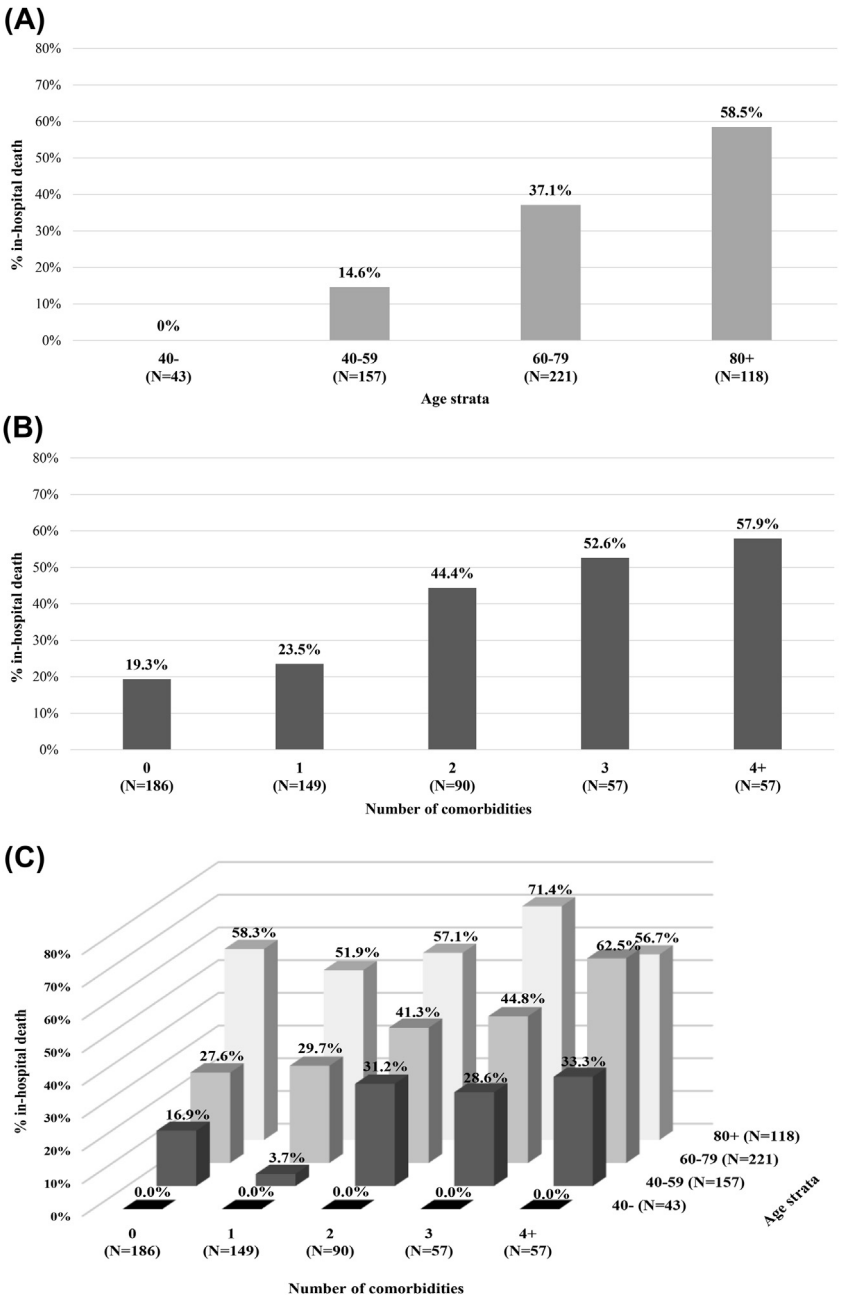

Figure 1. In-hospital fatality according to (A) age strata, (B) number of comorbidities and (C) age strata and number of comorbidities combined.

admission, disease severity; CRP, D-dimer; use of anti-Covid-19 drug combinations. A sensitivity analysis in the patients undergoing mechanical ventilation was performed.

All analyses were done using Stata v.14.

Results

Of the 687 patients entered the emergency room of the San Paolo hospital in the period February 24–May 17, 2020, 43 (6.2%) died within 24 h and 105 (15.3%) did not require hospitalisation and were excluded. A total of 539 (78.5%) patients were hospitalised for SARS CoV-2 symptomatic infection.

In a median follow-up of 71 days (IQR: 14–89), 174 patients (32.3%) died in hospital, 3 (0.6%) were still hospitalised by June 17, and 362 (67.7%) were discharged: 254 at home, 99 in intermediate-care facilities and 9 in other ICUs.

Demographic and clinical variables according to in-hospital death are shown in Table 1. Overall, 347 (64.4%) patients were males; median age was of 66 years (Interquartile range—IQR: 54–78); 448 (83.1%) were Caucasian; 111 (20.6%) had close contacts with subjects affected by COVID-19 disease, 56 (10.4%) were resident in long-term facilities. A total of 77 (14.3%) were obese (e.g. BMI > 30 kg/m^2); 65.5% suffered from at least one comorbidity: 250 (46.4%) suffered from hypertension, 95 (17.6%) from diabetes, 147 (27.3%) from cardiovascular disease. Median days from onset of symptoms to admission were 6 (IQR: 3–10). Fever was present in 86% of cases, dyspnoea in 55.7% and cough in 50.5%; in 16.9% non-respiratory symptoms were only present. At admission, 35 cases (6.5%) were affected by mild disease, with no radiological signs of pneumonia; in 242 patients (44.9%) the disease was moderate; in 244 patients (45.3%) the disease was severe and in 18 (3.6%) critical with high-grade respiratory distress. In half of the patients (262, 48.7%) the PO_2/FO_2 was below 300 mmHg. A number of laboratory markers were elevated, indicating the presence of an ongoing infection: CRP, procalcitonin, leukocytes, lymphocytes, D-dimer, CPK, LDH, ferritin.

During hospitalisation, most of the patients received hydroxychloroquine ± azithromycin (427, 79.2%) and low weight heparin at prophylactic doses (355, 65.8%), 134 (24.8%) received antivirals (lopinavir/r or darunavir/c in 126, remdesivir n 8 cases), 122 (22.6%) corticosteroids and 43 (8.0%) immunomodulatory drugs. More than half of the patients were given combinations including hydroxychloroquine + heparin ± lopinavir/r or darunavir/c or azithromycin (301, 55.8%).

A total of 117 patients (21.9%) required mechanical invasive (N = 68) or non-invasive (N = 49) ventilation, 156 (29.0%) required cPAP, 202 (37.5%) only high or low flow oxygen support and 64 (11.9%) no oxygen at all.

A number of factors were differently distributed among survivors and non survivors: non survivors were older, more frequently Caucasian, more frequently affected by comorbidities, suffered by a more severe disease at presentation, and showed more frequently higher serum inflammatory parameters than survivors. During hospitalisation, oxygen support was more intensive in those patients who subsequently died (Table 1).

We also observed that the highest percentage of deaths occurred in the oldest patients, being 58.5% in those aged 80 or above (Figure 1A). Percentages of deaths also increased with number of comorbidities, being 19.3% in patients with no comorbidity and 58% in those with at least 4 comorbidities (Figure 1B). By analyzing the percentage of deaths in relation to the age groups and comorbidities together, we verified that no one under the age of 40 died independently of comorbidities, while comorbidities weighed on the number of deaths in other age groups, apart from the oldest one, aged 80 years and over, in which the percentage of deaths is very high independently from comorbidities (Figure 1C). We confirmed this different effect of comorbidities on in-hospital death according to age, by identifying an interaction between age and number of comorbidities (interaction p-value <0.001).

Over 8228 person-day follow-up (PDFU), 174 patients died in hospital. The Kaplan Meir probability of in-hospital death by 14 days was of 29.5% (IQR: 25.5–34.0) (Figure 2A). The 14-day probability of death was associated with age, being 0% in patients below 40, and highest in those above 80 (52.0%, 95%CI: 43.1–61.6) (Figure 2B).

In the unadjusted analysis, a number of factors were associated with time to in-hospital death: age, individual comorbidities and Charlson index, inflammatory markers and D-dimer, severity of disease and therapy combinations.

A severe burden of comorbidity as by age unadjusted Charlson index (Model 1) and not individual comorbidities (Model 2) was independently associated with the risk of in-hospital death (Table 2). A number of other variables were independently associated with risk of time to in-hospital death: age, with every 10 years older showing 53% higher risk (AHR 1.53, 95% CI: 1.32–1.78); CRP >60 mg/dL (AHR 2.14,95% CI:1.49–3.08); D-dimer >1000 ng/mL (AHR 1.67; 95% CI:1.12–2.46), severe and critical COVID-19 disease at presentation (AHR: 1.77, 95%CI: 1.24–2.53 and AHR 5.27, 95% CI: 2.82–9.85); finally, the use of most of the drugs combinations was associated with reduced risk of in-hospital death (Table 2, Model 1). Data were similar when individual comorbidities replaced Charlson index in the model (Table 2, Model 2).

A total of 55/117 (47.0%) patients who underwent mechanical ventilation died in hospital; again age, Charlson index,

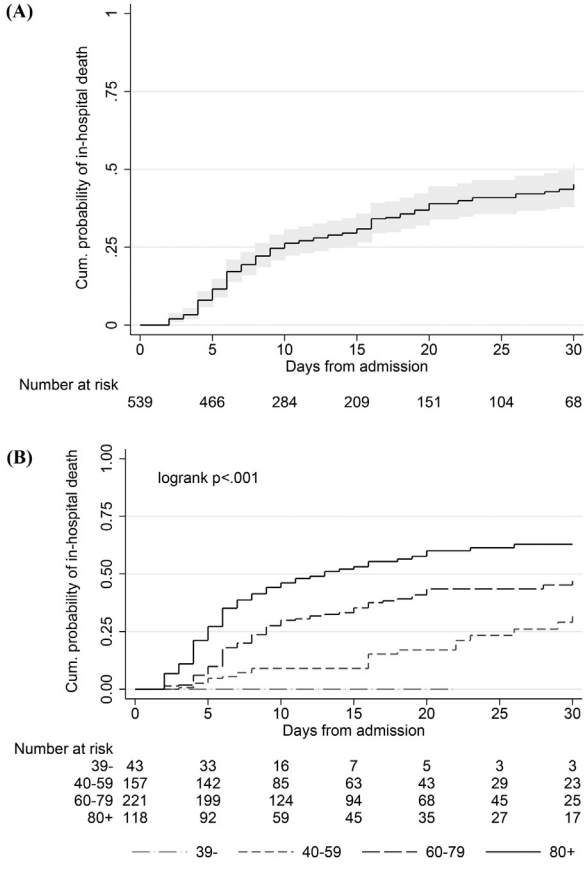

Figure 2. Kaplan–Meier estimates of cumulative probability of in-hospital death (A) and according to age strata (B).

Table 2
Unadjusted (HR) and Adjusted Hazard Ratio (AHR) of in-hospital death in 539 patients with COVID-19 disease, by univariable and multivariable Cox regression analyses.

	Unadjusted				Model1 (w Charlson index)				Model2 (w single comorbidities)			
	HR	95%CI		p	AHR[a]	95%CI		p	AHR[a]	95%CI		p
Age, per 10 years older	**1.55**	**1.39**	**1.74**	<**0.001**	1.53	1.32	1.78	<**0.001**	1.60	1.37	1.86	<**0.0001**
Gender, male (vs female)	1.11	0.81	1.52	0.531	1.36	0.96	1.93	0.082	1.34	0.94	1.90	0.108
Hypertension (vs no)	1.72	1.27	2.33	<**0.001**					1.00	0.69	1.44	0.996
Diabetes (vs no)	1.71	1.22	2.40	**0.002**					1.32	0.89	1.95	0.161
Cardio-vascular diseases (vs no)	1.99	1.48	2.69	<**0.001**					1.13	0.77	1.65	0.525
Cerebro-vascular diseases (vs no)	1.79	1.16	2.76	**0.008**					0.85	0.50	1.44	0.549
Cancer (vs no)	1.85	1.17	2.92	**0.008**					1.31	0.78	2.21	0.304
Chronic obstructive pulmonary disease (vs no)	1.66	1.06	2.59	**0.027**					1.25	0.77	2.05	0.369
Chronic liver diseases	0.97	0.45	2.07	0.935								
Chronic kidney diseases	1.30	1.05	1.62	0.017					1.00	0.78	1.28	0.994
Obesiy (BMI >30 kg/m^2)												
No	1.00				1.00				1.00			
Yes	1.31	0.82	2.08	0.256	1.50	0.92	2.46	0.106	1.50	0.91	2.48	0.115
Unknown	1.32	0.94	1.86	0.105	1.17	0.82	1.68	0.384	1.25	0.86	1.80	0.236
Charlson age unadjsuted index												
0	1.00				1.00							
1	1.82	1.20	2.77	**0.005**	1.50	0.96	2.35	0.073				
2	2.29	1.45	3.64	<**0.001**	2.10	1.27	3.48	**0.004**				
≥3	2.97	2.05	4.31	<**0.001**	1.78	1.16	2.73	**0.008**				
CRP >60 mg/L (vs ≤60 mg/L)	2.59	1.85	3.62	<**0.001**	2.14	1.49	3.08	<**0.001**	2.08	1.44	3.01	<**0.001**
D-dimer >1.000 ng/mL (vs ≤1.000 ng/mL)	2.33	1.62	3.34	<**0.001**	1.66	1.12	2.46	**0.012**	1.57	1.06	2.32	**0.023**
Severity												
Mild/moderate	1.00				1.00				1.00			
Severe	2.14	1.5	3.0	<**0.001**	1.77	1.24	2.53	**0.002**	1.76	1.23	2.54	**0.002**
Critical	7.61	4.3	13.6	<**0.001**	5.27	2.82	9.85	<**0.001**	4.97	2.65	9.31	<**0.001**
Thearapy combinations												
No drugs	1.00				1.00				1.00			
Hydroxychloroquine + heparin (±lopinavir/r or darunavir/c or azithromycin)	0.33	0.20	0.53	<**0.001**	0.30	0.17	0.50	<**0.001**	0.28	0.16	0.47	<**0.001**
Hydroxychloroquine + lopinavir/r or darunavir/c	0.45	0.22	0.92	**0.029**	0.42	0.20	0.91	**0.028**	0.42	0.20	0.90	**0.025**
Hydroxychloroquine or Hydroxychloroquine + azithromycin	0.55	0.31	1.00	**0.048**	0.57	0.30	1.07	0.080	0.53	0.28	1.00	**0.048**
Heparin	0.85	0.45	1.58	0.600	0.65	0.34	1.26	0.201	0.66	0.33	1.31	0.239
Other combinations	0.44	0.22	0.89	0.021	0.37	0.18	0.79	**0.010**	0.34	0.16	0.72	**0.005**
Week of admission												
24 Feb–08 Mar 2020	1.00				1.00				1.00			
09 Mar–22 Mar 2020	0.85	0.53	1.37	0.509	1.33	0.80	2.22	0.267	1.47	0.87	2.47	0.146
23 Mar–05 Apr 2020	0.68	0.41	1.11	0.122	1.05	0.60	1.86	0.857	1.11	0.61	2.01	0.739
06 Apr–19 Apr 2020	0.62	0.34	1.11	0.107	0.79	0.40	1.54	0.484	0.92	0.46	1.83	0.802
20 Apr–03 May 2020	0.88	0.45	1.73	0.717	1.48	0.67	3.27	0.338	1.69	0.76	3.76	0.195
04 May–17 May 2020	0.40	0.15	1.05	0.063	0.58	0.20	1.67	0.313	0.72	0.25	2.04	0.535

Bold values are those p values below 0.05, as statistically significant.
[a] Adjsuted for all the factors showed.

inflammatory markers were associated with increased risk of death. In this setting obesity was independently associated with a 2-fold higher risk of in-hospital death (AHR 2.45; 95%CI: 1.11–5.42) (Supplemental Table 1).

Looking at the 174 died patients, 32 received invasive mechanical ventilation and 147 not. Among these last ones, 67 patients showed P/F <100 and were not admitted in ICU and died. Main reasons for not admission were age, presence of severe comorbidities and short life expectancy.

We then studied the dynamics of COVID-19 disease, by investigating patients admitted and disease severity in the 2-week time frames. We observed a first peak of deaths in patients hospitalised in the 2nd–3rd week of March (36.5%), and a second one in the last two weeks of April (32.5%). While during the first peak most of the patients presented with severe disease (55.4%) but only 13% were older than 79, during the second peak the disease was less frequently severe (35%) but more than half of the patients (55%) were aged ≥80 and 30% acquired the infection in long-term facilities residency (Table 3).

Discussion

In our study population of 539 patients hospitalised for COVID-19 disease we found an in-hospital mortality of 32%, reaching 44% in patients undergoing mechanical ventilation. Patients' age, disease severity at presentation, level of inflammation and concomitant comorbidities appeared to be the main drivers of fatality events. We also observed different waves of patients' admissions by calendar time characterized by different demographic and clinical profiles.

The unusually high fatality rate should be interpreted with attention. Our analysis was only focused on hospitalised patients, the large majority (93.5%) with pneumonia, most of them (88%) requiring oxygen support. Data on Chinese population show fatality rates ranging from 2.3% (Wu and McGoogan, 2020) among 44,672 cases, mostly (81%) with mild disease, to 28% among 191 patients hospitalised in Wuhan (Zhou et al., 2020); older age was associated with poor outcome in all the studies (Guan et al., 2020; Wu et al., 2020; Wu and McGoogan, 2020; Zhou et al. 2020). Other data coming from the Milano area, show 23.1% of fatality rates among 410 hospitalised patients (Ciceri et al., 2020). Further, Vena et al described an in-hospital fatality rate of 44% among 317 COVID-

Table 3
Dynamic characteristics of patients with COVID-19, according to 2-weeks periods of admission.

	24 Feb–08 Mar 2020	09–22 Mar 2020	23 Mar–05 Apr 2020	06–19 Apr 2020	20 Apr–03 May 2020	04–17 May 2020	p
Hospital admissions, N	69	178	148	77	40	27	
ICU admission, N (%)	16 (23.2)	27 (15.2)	14 (9.5)	8 (10.4)	2 (5.0)	3 (11.1)	0.042
ICU beds, N	6	9	18	19	15	6	
ICU deaths, N (%)	9 (56.2)	15 (55.6)	5 (35.7)	2 (25.0)	1 (50.0)	0 (0.0)	0.282
In-hospital death, N (%)	24 (34.8)	65 (36.5)	46 (31.1)	21 (27.3)	13 (32.5)	5 (18.5)	0.418
Age of patients admitted, N (%)							<0.001
39–	6 (8.7)	15 (8.4)	9 (6.1)	7(9.1)	5 (12.5)	1 (3.7)	
40–59	14 (20.3	62 (34.8)	47 (31.8)	20 (26.0)	7 (17.5)	7 (25.9)	
60–79	43 (62.3)	78(43.8)	56 (37.8)	28 (36.4)	6 (15.0)	10 (37.0)	
80+	6 (8.7)	23 (12.9)	36 (24.3)	22 (28.6)	22 (55.0)	9 (33.3)	
Risk factors, N(%)							<0.001
Close contact/household	18 (26.1)	29 (16.3)	31 (20.9)	20 (26)	8 (20.0)	5 (18.5)	
Healthcare worker	3 (4.3)	11 (6.2)	9 (6.1)	9 (11.7)	2 (5.0)	5 (18.5)	
High Risk zone	19 (27.5)	7 (3.9)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Hospitalisation last 30 days	3 (4.3)	8 (4.5)	8 (5.4)	4 (5.2)	3 (7.5)	1 (3.7)	
Long-term care facility	2 (2.9)	7 (3.9)	7 (4.7)	20 (26)	12 (30.0)	8 (29.6)	
Unknown	24 (34.8)	116 (65.2)	92 (62.2)	24 (31.2)	15 (37.5)	8 (29.63)	
Severity at admission, N (%)							0.334
Mild	5 (7.3)	8 (3.9)	8 (4.8)	5 (6.5)	6 (15.0)	3 (11.1)	
Moderate	27 (39.1)	72 (40.7)	67 (45.6)	42 (54.5)	20 (50.0)	14 (51.9)	
Severe	35 (50.7)	91 (51.4)	67 (45.6)	28 (36.4)	13 (32.5)	10 (37.0)	
Critical	2 (2.9)	7 (4.0)	6 (4.1)	2 (2.6)	1 (2.5)	0 (0.0)	

19 patients in Genoa, being age and CVD independent predictors (Vena et al., 2020). The reasons for such differences need to be disentangled, to properly describe the weight of the epidemics and the impact in the different settings on medical care organisation. First, in all the reports age is a predictor of worse outcome (Ciceri et al., 2020; Guan et al., 2020; Wu et al., 2020; Wu and McGoogan, 2020; Zhou et al., 2020). With a median age of 66 years and 63% over 60, our is the oldest study population of all the studies mentioned. Moreover, in our study 65% are affected by at least one comorbidity. The presence of comorbidities is associated with a worse prognosis (Ciceri et al., 2020; Wu et al., 2020; Zhou et al., 2020). Comparing our data with those reported by Ciceri et al., from the same geographical area, we observed that the difference in overall mortality rate (23% vs 32%) might account for different percentages of patients with at least two comorbidities (19% vs 39%) (Ciceri et al., 2020).

Looking at our results in detail, the association of age and comorbidities is particularly evident in the age stratum 60–79, showing a fatality rate ranging from 27% in case of no comorbidity, to 62% when 4 or more comorbidities are present.

Main drivers of high in-hospital mortality rate in our cohort are age, disease severity at admission and weight of comorbidities, as represented by Charlson index, as well as inflammatory and pro-coagulatory markers, as shown by others (Ciceri et al., 2020; Wu et al., 2020; Zhou et al., 2020). We did not find an association between individual comorbidities and risk of death, differently from other reports (Ciceri et al., 2020; Cummings et al., 2020).

We also observed a reduced risk of in-hospital death according to the treatment received. Most of the patients were receiving combinations containing hydroxychloroquine ± azithromycin ± antivirals. The possible effectiveness and toxicity of hydroxychloroquine in Covid-19 disease is debated: laboratory studies showed antiviral properties (Devaux et al., 2020; Liu et al., 2020), while clinical studies showed contrasting results (Gautret et al., 2020; Tang et al., 2020). A multinational analysis showing decreased survival has been retracted by the Authors leaving great uncertainty in this area (Mehra et al., 2020). It should be considered that immune-mediated and vascular mechanisms, and not only viral-related ones, might have a role in disease progression/death (Totura and Baric, 2012). Unfortunately, the low number of patients receiving immunomodulatory drugs does not allow any considerations on their efficacy by interfering with cytokine storm, as suggested and recently demonstrated in a real-life setting (Guaraldi et al., 2020; Pedersen and Ho, 2020). Similarly, remdesivir was given only to 8 patients, so we were unable to test the possible positive effect of the drug (Beigel et al., 2020; Goldman et al., 2020; Grein et al., 2020).

Looking at critically ill patients, we observed a very high mortality rate, of 47% (55/117), in agreement with Wu et al., reporting 52.4% fatality rate among patients with ARDS (Wu et al., 2020). Cummings et al. (2020) reported 39% of deaths among 257 critically ill patients from New York City; in their study they defined critically ill all those requiring mechanical ventilation or high-level supplemental oxygen. When applying the same definition, 273 patients were identified in our cohort, 129 of which (47%) died in hospital. The in-hospital fatality rate is consistently very high in all studies on critically ill patients.

In our setting obesity was associated with death in critically ill patients who underwent mechanical ventilation. This result seems to be inconsistent with the 'obesity paradox' identified for ARDS (Zhi et al., 2016), but bias is the most likely explanation for the 'paradox findings' (Lennon et al., 2016; Banack and Stokes, 2017).

Interesting is the dynamics of the epidemics in our hospital. Looking at data on the characteristics of patients admitted in the different 2-weeks periods, from the beginning of outbreak, we can observe two different waves, the first one represented by severely ill patients, and the second one, one month later, by very old patients, with less severe disease, in 20% coming from long-term care facilities. The scandal of elderly people getting infected and dying in long-term care facilities occurred in Lombardy, other Italian regions and European countries, determining an epidemic inside the epidemic, affecting fragile people (Surveillance of COVID-19 at long-term care facilities in the EU/EEA, 2020; Survey nazionale sul contagio COVID-19 nelle strutture residenziali e sociosanitarie, 2020)

Finally, we cannot exclude that the high fatality rate found in our setting could be related to the limited number of beds in ICU, even if these were increased every day while facing the wave of admissions. Actually, to date there are no standardised criteria for invasive mechanical ventilation in COVID-19 patients (Wunsch, 2020). A multidisciplinary equip of intensive care, infectious diseases and pneumology specialists, evaluated all the 67 patients

with P/F < 100 taking into account level of respiratory distress, age, comorbidities and life expectancy.

It is reasonable that the weight of each of these reasons was largely dependent of ICU beds availability, given that theoretically all the patients should have the opportunity of being ventilated even if their life expectancy is short. The balance between health care system offer and individual patient request applies for all health care systems and all diseases, but high income countries give better opportunities to their citizens as compared to low income ones.

Our study has several limitations. First, a number of variables have not been adequately collected, in particularly obesity (Simonnet et al., 2020), 50% of patients with unknown BMI. Second, we are not aware whether patients died for COVID-19 disease or with COVID-19 disease: actually, the association of risk of death with number of comorbidities might suggest either that COVID-19 was more aggressive in fragile patients, or that the cause of death was the pre-existing condition, and COVID-19 acted as a trigger on a precarious condition.

In conclusion, we showed a high rate of in-hospital death in patients with COVID-19 disease in a University hospital in Milan, the first European city to be overwhelmed by the epidemic of SARS CoV-2 infection in Europe. The severity of disease at presentation, the advanced age of patients, the level of inflammation, and the presence of comorbidities, together with the small number of ICU beds are the most likely explanations for the outcome observed. These findings may be useful to better allocate resources of the national healthcare systems, in case of re-intensification of COVID-19 epidemics.

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Competing interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.09.037.

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