COVID-19 in sub-intensive care unit: An italian single-center experience along the three epidemic waves

Fabrizio Vallelonga,* Francesco Arcangelo Diella,* Marcella Converso, Giovanna De Filippi, Francesca Bosco, Francesco Panero, Franco Aprà, Fabrizio Elia

Emergency Medicine, San Giovanni Bosco Hospital, Turin, Italy

**These authors equally contributed to this study*

Abstract

The goal was to characterize COVID-19 patients who needed treatment in Sub-Intensive Care Units (SICUs) for hypoxemic respiratory failure, describe their six-month mortality, and identify clinical and laboratory characteristics that were associated with death. Data from 216 consecutive patients admitted to the COVID-SICU of Turin's San Giovanni Bosco Hospital were analyzed retrospectively. A total of 216 patients (24.5% of whom were female) were enrolled. The average age was 63±11.9 years. In the three waves, the six-month mortality rate was 32.8%, 35.1%, and 26.6%, respectively (p=0.52). The mortality rate was significantly higher in intubated patients compared to those not requiring intubation (60.8% versus 29.9%, p<0.01). On admission, deceased patients were older (69±7.7 versus 60.2±12.6 y.o., p<0.01), with a higher prevalence of dyslipidemia, coronary artery disease, chronic heart failure, and higher serum creatinine. However, only age was predictive of death at multivariate analysis (OR 5.29, p<0.01), with 63 years old as the best cut-point. At six months, mortality in COVID patients managed in a SICU is around 30%. Age is a significant negative prognostic factor, with 63 years of age being the best predicting cut-off.

Correspondence: Fabrizio Vallelonga, Emergency Medicine, San Giovanni Bosco Hospital, Piazza del Donatore di Sangue 3, 10154, Turin, Italy. Tel.: +39.0112402240 - Fax: +39.0112402236.
E-mail: vallelonga.fabrizio@gmail.com

Key words: COVID-19; sub-intensive care unit; mortality; prognostic factors.

Contributions: study concept and design: FV, FD, FE; acquisition of the data: FD, MC, GDF, FB, FP; analysis and interpretation of the data: FV, FA, FE; drafting of the manuscript: FV, FD; critical revision of the manuscript for important intellectual content: all authors; statistical expertise: FV.

Conflict of interest: The authors have no conflicts of interest to declare.

Financial support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Ethics approval and informed consent: The institutional ethics board "Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino" approved this study and waived the need for informed consent, due to the retrospective nature of the analysis.

Acknowledgments: A special gratitude to all medical and nursing staff of the Emergency Department of San Giovanni Bosco Hospital.

Received for publication: 31 May 2022.
Revision received: 28 July 2022.
Accepted for publication: 9 September 2022.

Emergency Care Journal 2022; 18:10648
doi:10.4081/ecj.2022.10648

Introduction

From March 2020, the world will face the COVID-19 pandemic.[1] Following China, Italy was the second country to be severely affected, putting the health system's capacity under enormous strain,[2-4] even with indirect damages primarily related to reduced medical care for non-COVID-related emergencies.[5] According to the Istituto Superiore di Sanità, Intensive Care Units (ICUs) were rapidly saturated, with COVID-related occupation rates approaching 60% of total capacity. This condition prompted a rapid reorganization of hospital facilities, culminating in the establishment of Europe's first Sub-intensive Respiratory Unit entirely dedicated to COVID-19 patients in Northern Italy.[6] Following the summer period's reduction in contagions, a second epidemic wave has engulfed the country since the end of October 2020, with a third wave expected in March 2021. The global impacts on the economic, social, and health domains resulted in an exponential increase in medical literature from independent groups and global coalitions,[7] with a corresponding decrease in scientific publication quality. There are studies describing cohorts of patients admitted to ICUs,[8] comparative studies between patients requiring and not requiring ICUs,[9] and studies regarding patients undergoing Non-Invasive Ventilation (NIV) outside ICUs,[10] but data collection specifically concerning patients referred to true Sub-Intensive Care Units (SICUs) is currently scarce. This is due in part to the lack of standard criteria for defining SICUs, as well as the frequently disparate terminology used to refer to the same facility (SICU, High Dependency Unit, Intermediate Care Unit).

The primary goals of this study were to characterize COVID-19 patients who needed SICU treatment for hypoxemic respiratory failure leading to non-invasive ventilation (NIV), to describe their six-month mortality, and to identify clinical and laboratory characteristics associated with death. The secondary goal was to compare the population and outcome of the three epidemic waves.

Materials and Methods

During the three Italian epidemic waves, data from consecutive patients admitted to the COVID-SICU of San Giovanni Bosco Hospital in Turin were retrospectively analyzed. This SICU had 12 SICU beds with a 1:3 nurse-to-patient ratio in accordance with the Italian Group for the Evaluation of Intervention in Intensive Care Medicine (GiViTi) standards for the intermediate level of care.[11]

All enrolled patients had a laboratory-confirmed SARS COV2 infection, as evidenced by a positive Real-Time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) assay of nasal or pharyngeal swabs or lower respiratory tract aspirates, as needed,[12] and severe respiratory failure necessitating Non-Invasive Ventilation (NIV) or Continuous Positive Airway Pressure (CPAP), as determined by clinical judgment. The timing of the start of NIV/CPAP support, whether immediate in the ED (Emergency Department) or delayed upon admission to the SICU, was always determined by clinical judgment. There were no age restrictions for admission to the COVID-SICU; cases where the indication was uncertain were discussed collaboratively before hospitalization, taking age, comorbidities, and performance status into account.

Two independent researchers collected the following data from medical records (ED report and electronic hospital database for double-check): age, gender, past medical history, ongoing therapy, symptoms duration before hospitalization, vital signs on ED admission, and biochemical data on ED admission.

Patients with COVID admitted to the SICU for reasons other than respiratory failure were not included (septic shock, haemorrhagic shock, cardiogenic shock, post-surgery management).

Past medical history

The following data were collected: smoking habit, history of arterial hypertension, diabetes mellitus, dyslipidemia, obesity (*i.e.* body mass index >30 kg/m^2), coronary artery disease, chronic heart failure (*i.e.* known ejection fraction <40%), atrial fibrillation (paroxysmal, persistent, and permanent), chronic kidney disease (*i.e.* glomerular filtration rate <60 mL/min/1.73m^2), known chronic lung disease, active cancer.

Ongoing cardiovascular therapy

Antihypertensive (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, diuretics, calcium channel blockers, beta blockers, alpha blockers, alpha-2 agonists), antiplatelet, and anticoagulant (vitamin K antagonists, direct oral anticoagulants) data were gathered.

Vital signs

During the initial medical evaluation on ED admission, the following vital signs were recorded: arterial blood pressure (mmHg), heart rate (beats per minute), respiratory rate (acts per minute), PaO_2/FiO_2 ratio (mmHg), defined as the ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction), and body temperature (°C).

Biochemical data

On admission to the emergency department, the following biochemical data were collected: complete blood count with formula, creatinine, lactate dehydrogenase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), D-dimer, C-reactive protein, and ferritin.

Six-months mortality

When possible, six-month mortality was assessed using the hospital's electronic database. For patients discharged from our hospital, data was obtained through telephone contact with family members six months after admission.

The institutional ethics board "Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino" approved this study and waived the need for informed consent, due to the retrospective nature of the analysis.

Statistical analysis

Analyses were performed with SPSS (Statistical Package for the Social Sciences – version 22 - © 2014 IBM). Normal distribution of continuous variables was tested using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation. Qualitative variables were expressed as absolute values of frequency and percentage values. Differences between two independent groups were evaluated using Student's t-test for continuous variables with normal distribution and Mann-Whitney test for continuous variables with non-normal distribution; multiple comparisons (between more than 2 groups) were evaluated with One-way ANOVA analysis and Bonferroni's correction. Categorical variables were compared using chi-square test or Fisher's exact test according to sampling number of analysed groups.

Predictors of mortality

The correlation between 6-month mortality (dependent variable) and selected clinical and demographical parameters was examined using univariate and multivariate logistic regression analysis (independent variables). A receiver operating characteristic (ROC) analysis was used to estimate the predictive accuracy of continuous variables (state variable: 6-months mortality). After determining the best ROC cut point based on the balance of sensitivity and specificity, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated (highest Youden index).

Results

A total of 216 patients (24.5 % female) were enrolled: 58 patients during the first, 94 during the second and 64 during the third epidemic wave. Overall mean age was 63 ± 11.9 years old, with patients in the second wave older than those in the first one (65.7 ± 11.7 versus 60 ± 11.7 years old, p=0.01). A higher prevalence of obesity was found in the third wave (39.1% versus 17.2% and 19.1% of first and second wave, respectively – p=0.01) while more patients with active cancer were enrolled in the first one (17.2% versus 3.2% and 3.1% of the second and third wave, respectively – p<0.01; Supplementary Table 1). The average time of stay in SICU was 7.4±6.6 days (with a significantly longer duration in the first wave than in subsequent ones: 11.5±9.7, 6.3±6.3, 5.6±5.1 days, p<0.01), while the whole hospitalization lasted 21.4±15.2 days (with no difference in the three waves).

The proportion of deceased patients at 6 months was similar in the three waves (32.8%, 35.1% and 26.6%, p=0.52), as that of orotracheal intubation (25.9%, 18.1% and 30.2%, p=0.20). Deceased patients had longer SICU stay (8.4±7.4 days versus 5.9±6.2 days, p=0.02), but similar total hospitalization stay (18.1±15.2 days versus 22.5±15.1 days, p=0.11) compared to survived patients. A total of 54 (25% of the cohort) patients started NIV/CPAP as soon as they entered the emergency room in the ED; 16 of them (29%) underwent intubation during hospitalization. The remaining 162 (75%) patients were treated with venturi masks, oxygen mask with reservoir or high-flow nasal canula in the ED, thereby initiating NIV/CPAP only once admitted to the SICU; the intubation rate in this group was not statistically different, namely 19% (p=0.11).

Clinical and demographic characteristics of the three cohorts are summarized in Table 1 and Supplementary Table 1.

Considering the entire population, the intubation rate was 23.6% (51 out of 216 patients); the mortality rate was significantly higher in intubated patients compared to patients not requiring intubation (60.8% versus 29.9%, respectively, p <0.01). Duration of symptoms before intubation were similar in the three waves (13±7.3 versus 16.1±8.1 versus 11.7±5.9 days, p=0.17); taking into account the overall population of intubated patients, those who survived had a shorter disease duration at the time of intubation than the deceased ones, although this difference has only a trend toward statistical significance (11±5.7 versus 15±7.6 days, p=0.06).

Deceased patients were older (69 ± 7.7 versus 60.2 ± 12.6 years old, p<0.01), with higher prevalence of dyslipidemia (37.7% versus 19%, p<0.01), coronary artery disease (17.4% versus 7.5%, p=0.03), chronic heart failure (15.9% versus 5.4%, p=0.01), and higher serum creatinine on admission (1.5 ± 1 versus 1.2 ± 1.1 mg/dl, p=0.03) compared to survived patients. These differences were even evident, though not always significant, in any single waves (Table 2; Supplementary Table 2).

These variables were all associated with 6-month mortality at univariate logistic regression, but only age retained significance at multivariate analysis (OR 1.08, CI 1.04-1.12, p<0.01; Table 3). The accuracy of mere age in predicting 6-month mortality was therefore assessed through Receiver-Operating Characteristic (ROC) analysis, revealing an AUC of 0.71 (CI 0.64-0.78, p<0.01) with 63 years old as the best cut-point (sensitivity 83%, specificity 57%, positive predictive value 48%, negative predictive value 88% - OR 5.29 at multivariate logistic regression analysis; Figure 1).

Patients over 63 years old had higher prevalences of cardiovascular comorbidities, and more frequently three or more comorbidities simultaneously (41.7% versus 16.7%, p<0.01) compared to younger patients. Moreover, they presented lower PaO2/FiO2 ratio (180 ± 67.3 versus 218 ± 81.4 mmHg, p<0.01), lower Hemoglobin level (13.8 ± 2.3 versus 14.4 ± 1.9 mg/dl), higher Neutrophils to Lymphocytes ratio (9.6 ± 7.4 versus 7.3 ± 5.6, p=0.01) and serum C-reactive protein (13.3 ± 8.9 versus 10.8 ± 7.7 gm/dl, p=0.03) on ED admission (Table 4; Supplementary Table 3). The proportion of patients undergoing oro-

Table 1. Clinical and demographical characteristics along the three waves.

	FIRST wave [58]	SECOND wave [94]	THIRD wave [64]	p
Age [years]	60 ± 11.7	65.7 ± 11.8	61.9 ± 11.8	0.01
Female [% (n)]	20.7 (12)	23.4 (22)	29.7 (19)	0.49
Smoking habit [% (n)]	8.6 (5)	8.5 (8)	14.1 (9)	0.47
Vital parameters (ED admission)				
Systolic Blood Pressure [mmHg]	128 ± 19.7	130 ± 19.8	131 ± 20.9	0.72
Diastolic Blood Pressure [mmHg]	77 ± 10.2	75 ± 11.4	76 ± 9.6	0.48
Heart Rate [bpm]	99 ± 15.3	93 ± 15.3	92 ± 14.3	0.06
PaO_2/FiO_2 ratio [mmHg]	229 ± 65.6	185 ± 79.6	192 ± 68.9	0.01
$PaCO_2$ [mmHg]	31 ± 5	33 ± 6.4	31 ± 4.4	0.12
Respiratory Rate [apm]	26 ± 7.9	27 ± 14.2	26 ± 8.2	0.87
Temperature [°C]	37.9 ± 0.9	37.6 ± 1.1	37.5 ± 1.1	0.13
Symptom onset before admission [days]	7.3 ± 2.7	7.5 ± 3.2	7.2 ± 3.1	0.81
Laboratory exams (ED admission)				
White Blood Cells [10^3/μL]	8.4 ± 4.4	10.4 ± 5.3	8.8 ± 4.7	0.03
Neutrophils [10^3/μL]	6.6 ± 4	8.6 ± 4.6	7.1 ± 4.3	0.01
Lymphocytes [10^3μL]	1.5 ± 2.3	1.1 ± 0.6	1.1 ± 0.6	0.15
Neutrophils/Lymphocytes ratio	8.1 ± 8.4	9.3 ± 5.9	7.9 ± 6.1	0.36
Hemoglobin [g/dL]	14.3 ± 1.7	13.9 ± 2.2	14.1 ± 2.3	0.49
Platelets [10^3/μL]	193 ± 75	234 ± 85.7	202 ± 85.2	0.01
Creatinine [mg/dL]	1.4 ± 1.5	1.3 ± 1	1.2 ± 0.7	0.46
Aspartate aminotransferase [IU/L]	62 ± 64.4	56 ± 40.1	48 ± 26.9	0.27
Alanine aminotransferase [IU/L]	54 ± 77.7	59 ± 67.4	42 ± 28.2	0.27
Lactate dehydrogenase [U/L]	446 ± 189.4	479 ± 266.8	438 ± 129.7	0.51
D-dimer [μg/mL]	2.1 ± 2.3	5.4 ± 10.8	1.3 ± 0.8	0.01
C-Reactive Protein [mg/dL]	11.5 ± 8.6	13.3 ± 8.8	11.2 ± 7.7	0.25
Ferritin [ng/mL]	1045 ± 420.6	1566 ± 1618	1660 ± 1247	0.66
Length of hospital stay, mortality and intubation rate				
SICU stay [days]	11.5±9.7	6.3±6.3	5.6±5.1	< 0.01
Total hospital stay [days]	24±14.2	21.9±15.9	19.8±14.5	0.52
Deceased at 6-months [% (n)]	32.8 (19)	35.1 (33)	26.6 (17)	0.52
Orotracheal intubation [% (n)]	25.9 (15)	18.1 (17)	30.2 (19)	0.20
Symptom onset before intubation [days]	13±7.3	16.1±8.1	11.7±5.9	0.17

DOAC: Direct Oral AntiCoagulants; ED: Emergency Department; IU: Internationl Units; SICU: Sub-Intensive Care Unit.

tracheal intubation was similar in the two groups (27% versus 24%, respectively in over- and under-63 years old).

No relevant differences in comorbidities, vital signs, or laboratory parameters emerged by still dichotomizing each age category into survived and deceased patients (Table 5; Supplementary Table 4). Orotracheal intubation was more frequent in deceased than in survived patients (35.1% versus 11.1%, p<0.01, in over-63 years old; 91.7% versus 15.7%, p<0.01, in under-63 years old).

Table 2. Clinical and demographical characteristics of survived and deceased patients along the three waves

	FIRST wave [58]			SECOND wave [94]			THIRD wave [64]			OVERALL		
	Survived [39]	Deceased [19]	p	Survived [61]	Deceased [33]	p	Survived [47]	Deceased [17]	p	Survived [147]	Deceased [69]	p
Age [years]	57.8 ± 12.1	64.7 ± 9.3	0.03	62.2 ± 12.7	72.1 ± 5.9	< 0.01	59.7 ± 12.6	67.9 ± 6.5	< 0.01	60.2 ± 12.6	69 ± 7.7	< 0.01
Female [% (n)]	25.6 (10)	10.5 (2)	0.18	24.6 (15)	21.2 (7)	0.71	34 (16)	17.6 (3)	0.21	27.9 (41)	17.4 (12)	0.10
Smoking habit [% (n)]	5.1 (2)	15.8 (3)	0.18	6.6 (4)	12.1 (4)	0.36	12.8 (6)	17.6 (3)	0.62	8.2 (12)	14.5 (10)	0.15
Vital parameters (ED admission)												
Systolic Blood Pressure [mmHg]	130 ± 19.9	124 ± 19.3	0.34	130 ± 21.1	130 ± 17.5	0.86	134 ± 21.1	125 ± 19.6	0.13	131 ± 20.7	128 ± 18.4	0.23
Diastolic Blood Pressure [mmHg]	78 ± 9.1	74 ± 12	0.16	75 ± 13.5	75 ± 6.4	0.91	77 ± 9.4	74 ± 10.1	0.33	76 ± 11.2	75 ± 8.9	0.25
Heart Rate [bpm]	101 ± 16.1	94 ± 12.5	0.13	94 ± 18.5	92 ± 15.9	0.50	92 ± 14.9	94 ± 12.6	0.60	95 ± 17.1	93 ± 14.1	0.31
PaO_2/FiO_2ratio [mmHg]	236 ± 65.7	215 ± 79.9	0.41	195 ± 80.4	165 ± 75.2	0.09	192 ± 69.2	191 ± 70.1	0.94	203 ± 75.3	182 ± 76	0.09
$PaCO_2$ [mmHg]	31 ± 5.1	31 ± 5.2	0.88	33 ± 6.6	33 ± 6	0.74	31 ± 4.6	32 ± 3.8	0.46	32 ± 5.7	32 ± 5.1	0.74
Respiratory Rate [apm]	24 ± 6.6	30 ± 9.4	0.03	28 ± 16.3	26 ± 8.1	0.55	26 ± 6.9	27 ± 10.8	0.72	26 ± 12.2	27 ± 9.2	0.71
Temperature [°C]	37.9 ± 0.8	37.7 ± 1.3	0.44	37.6 ± 1.1	37.8 ± 1.1	0.33	37.5 ± 1.1	37.5 ± 1.2	0.85	37.6 ± 1	37.7 ± 1.2	0.68
Symptom onset before admission [days]	7.2 ± 2.7	7.4 ± 3	0.48	7.5 ± 3.4	7.4 ± 2.7	0.42	7.2 ± 2.7	6.9 ± 4	0.50	7.4 ± 3	7.3 ± 3.1	0.91
Laboratory exams (ED admission)												
White Blood Cells [10^3/μL]	7.9 ± 3.9	9.5 ± 5.2	0.18	10.9 ± 5.6	9.5 ± 4.1	0.21	8.4 ± 3.9	9.6 ± 6.5	0.37	9.3 ± 4.9	9.5 ± 4.9	0.75
Neutrophils [10^3/μL]	5.9 ± 3.4	7.8 ± 4.9	0.15	9 ± 5.1	7.8 ± 3.6	0.22	6.8 ± 3.6	7.9 ± 5.8	0.38	7.5 ± 4.4	7.8 ± 4.6	0.62
Lymphocytes [10^3μL]	1.7 ± 2.7	1.1 ± 0.6	0.38	1.1 ± 0.5	1.1 ± 0.7	0.70	1.1 ± 0.5	1.1 ± 0.8	0.93	1.3 ± 1.5	1.1 ± 0.7	0.37
Neutrophils/Lymphocytes ratio	6.9 ± 6.2	10.3 ± 11.6	0.16	9.2 ± 5.3	9.6 ± 7.1	0.74	7.6 ± 5.9	8.9 ± 6.4	0.46	8.1 ± 5.8	9.6 ± 8.3	0.17
Hemoglobin [g/dL]	14.6 ± 1.5	13.8 ± 2	0.10	14.1 ± 2	13.5 ± 2.5	0.27	13.9 ± 2.4	14.6 ± 2.1	0.30	14.1 ± 2	13.9 ± 2.3	0.36
Platelets [10^3/μL]	196 ± 71.9	188 ± 82.8	0.72	240 ± 84.9	222 ± 87.2	0.34	214 ± 89.7	165 ± 59.5	0.04	220 ± 84.7	199 ± 82.5	0.08
Creatinine [mg/dL]	1.3 ± 1.6	1.7 ± 1.3	0.37	1.2 ± 1.1	1.4 ± 0.9	0.23	1.1 ± 0.5	1.5 ± 0.9	0.04	1.2 ± 1.1	1.5 ± 1	0.03
Aspartate aminotransferase [IU/L]	54 ± 28.6	78 ± 105.8	0.23	60 ± 45.6	50 ± 26.6	0.31	49 ± 26.1	45 ± 29.8	0.64	55 ± 36.2	56 ± 58.6	0.85
Alanine aminotransferase [IU/L]	46 ± 40.2	71 ± 127.6	0.30	68 ± 76.9	41 ± 39.6	0.08	45 ± 31.3	32 ± 14.4	0.12	55 ± 57.8	47 ± 70.9	0.38
Lactate dehydrogenase [U/L]	428 ± 189.4	484 ± 189.1	0.31	468 ± 300.1	502 ± 188.6	0.61	438 ± 127.4	439 ± 140.3	0.99	447 ± 226.8	480 ± 176.9	0.28
D-dimer [μg/mL]	2.3 ± 2.5	1.5 ± 1.4	0.59	5.3 ± 11.4	5.7 ± 9.8	0.87	1.4 ± 0.9	1.2 ± 0.7	0.60	3.4 ± 8.2	3.8 ± 7.7	0.76
C-Reactive Protein [mg/dL]	10.9 ± 8	12.8 ± 9.8	0.44	13.4 ± 8.7	13.1 ± 9.3	0.90	11 ± 6.6	11.8 ± 10.4	0.70	11.9 ± 7.9	12.7 ± 9.6	0.53
Ferritin [ng/mL]	1479±1125	1749±1912	0.37	1389±1259	1894±2120	0.19	1670±1096	1636±1583	0.93	1484±1169	1798±1922	0.24
Intubation rate												
Orotracheal intubation [% (n)]	17.9 (7)	42.1 (8)	0.04	6.6 (4)	39.4 (13)	< 0.01	19.6 (9)	58.8 (10)	< 0.01	13.7 (20)	44.9 (31)	< 0.01
Symptom onset before intubation [days]	9±2.6	15.3±8.3	0.10	16.5±9.9	16±7.9	0.92	9.6±2.9	13.7±7.5	0.13	11±5.7	15±7.6	0.06

DOAC: Direct Oral AntiCoagulants; ED: Emergency Department; IU: Internationl Units

Table 3. Univariate and multivariate logistic regression analysis.

Predictive variables		Outcome 6-months mortality	
		Univariate analysis (CI 95%)	Multivariate analysis (CI 95%)
Age (continuous variable)	OR p-value	1.09 (1.05 – 1.12) <0.01	1.08 (1.04 – 1.12) <0.01
Dyslipidemia	OR p-value	2.57 (1.36 – 4.86) 0.01	1.34 (0.61 – 2.94) 0.47
Coronary artery disease	OR p-value	2.60 (1.09 – 6.24) 0.03	1.19 (0.35 – 4.02) 0.78
Chronic heart failure	OR p-value	3.30 (1.26 – 8.61) 0.02	1.44 (0.36 – 5.76) 0.61
Creatinine (continuous variable)	OR p-value	1.3 (0.9 – 2) 0.16	1.23 (0.93 – 1.64) 0.15

OR: odds ratio; CI: Confidence Interval.

Discussion

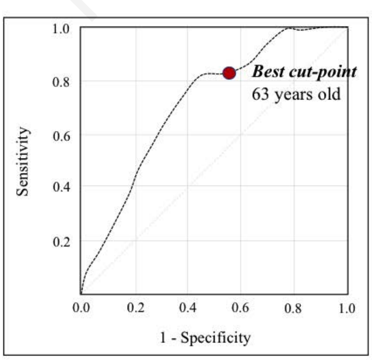
To the best of our knowledge, this is the first study specifically describing patients admitted to a COVID-SICU and evaluating long-term mortality along the three Italian epidemic waves; additionally, we emphasize age as the sole predictor of mortality at 6 months for the first time, being able to rely on 0% of patients still hospitalized at the time of writing, in contrast to most previous studies, where this percentage could even reach 58%.[13]

In our global cohort of 216 patients, the 6-month mortality rate was 31.9%. At univariate logistic regression, age, dyslipidemia, coronary artery disease, chronic heart failure, and higher serum creatinine on admission were all associated with 6-month mortali-

Table 4. Clinical and demographical characteristics of patients according to age category.

	Patients ≤63 y.o. [96]	Patients >63 y.o. [120]	p
Age [years]	52.1 ± 9	71.8 ± 4.5	<0.01
Female [% (n)]	26 (25)	23.3 (28)	0.65
Smoking habit [% (n)]	11.5 (11)	9.2 (11)	0.58
Vital parameters (ED admission)			
Systolic Blood Pressure [mmHg]	127 ± 19.1	133 ± 20.5	0.04
Diastolic Blood Pressure [mmHg]	76 ± 11.4	76 ± 9.9	0.73
Heart Rate [bpm]	99 ± 15.3	93 ± 15.3	0.04
PaO_2/FiO_2 ratio [mmHg]	218 ± 81.4	180 ± 67.3	<0.01
$PaCO_2$ [mmHg]	32 ± 6.2	32 ± 4.9	0.81
Respiratory Rate [apm]	26 ± 8.5	27 ± 13.1	0.56
Temperature [°C]	37.7 ± 1	37.6 ± 1.1	0.28
Symptom onset before admission [days]	7.4 ± 2.7	7.2 ± 3.3	0.62
Laboratory exams (ED admission)			
White Blood Cells [10^3/µL]	9.5 ± 5.4	9.2 ± 4.5	0.66
Neutrophils [10^3/µL]	7.6 ± 4.8	7.6 ± 4.2	0.99
Lymphocytes [10^3µL]	1.4 ± 1.8	1 ± 0.7	0.04
Neutrophils/Lymphocytes ratio	7.3 ± 5.6	9.6 ± 7.4	0.01
Hemoglobin [g/dL]	14.4 ± 1.9	13.8 ± 2.3	0.02
Platelets [10^3/µL]	217 ± 86.8	211 ± 82.8	0.58
Creatinine [mg/dL]	1.1 ± 1.1	1.4 ± 1.1	0.06
Aspartate aminotransferase [IU/L]	57 ± 40.1	54 ± 47.7	0.63
Alanine aminotransferase [IU/L]	60 ± 63.5	47 ± 60.4	0.14
Lactate dehydrogenase [U/L]	458 ± 267.5	457 ± 154.8	0.98
D-dimer [µg/mL]	4.3 ± 10.2	3 ± 6.2	0.38
C-Reactive Protein [mg/dL]	10.8 ± 7.7	13.3 ± 8.9	0.03
Ferritin [ng/mL]	1741 ± 1491	1476 ± 1424	0.30
Mortality and intubation rate			
Deceased at 6-months [% (n)]	12.5 (12)	47.5 (57)	<0.01
Orotracheal intubation [% (n)]	25.3 (24)	22.5 (27)	0.64
Symptom onset before intubation [days]	13.4±7.5	13.6±7	0.89

DOAC: Direct Oral AntiCoagulants; ED: Emergency Department; IU: Internationl Units.



AUC	Standard Error	p-value	C.I.
0.71	0.035	< 0.01	0.64 - 0.78

Age accuracy		Outcome: Survived	Outcome: Deceased	
Age	≤ 63 y.o.	84	12	96
Age	> 63 y.o.	63	57	120
		147	69	216
Accuracy		65%		
Sensitivity		● 83%		
Specificity		● 57%		
PPV		48%		
NPV		88%		

Variable	Logistic regression analysis	Univariate	Multivariate
Age > 63 y.o.	OR	**6.33** (3.14 – 12.8)	**5.29** (2.53 – 11.1)
	p-value	< 0.01	< 0.01

Figure 1. Prognostic value of the age variable. AUC: Area Under the Curve; C.I.: confidence interval; PPV: positive predictive value; NPV: negative predictive value; y.o.: years old; OR: odds ratio.

ty, but only age remained significant at multivariate analysis, with 63 years old being the best predicting cut-point (OR 5.29 - sensitivity 83%, specificity 57%, positive predictive value 48%, negative predictive value 88%). To support this finding, although patients older than 63 years have more comorbidities than younger ones (Supplementary Table 3), when each age category was further dichotomized according to mortality (Supplementary Table 4), no differences in comorbidities or clinical characteristics were found between survived and deceased patients.

The comparison of the three waves revealed similar population characteristics and mortality rates; the longer SICU stay of the first wave was most likely due to the lower possibility of step-down wards compared to those established in subsequent waves, at least in our hospital setting.

Santus and colleagues[14] found similar results: among 412 COVID patients enrolled in three respiratory high dependency units and three general wards, the only independent risk factors for death were age 65 years and respiratory failure at admission. Even when only short-term in-hospital mortality was considered, Santus' cohort had a mortality rate of 25%.

A meta-analysis including thirteen studies indicated the same cut-point, age ≥65 years, as important predictor of death.[15]

In comparison to our findings, the rate of intubation among COVID patients admitted to a Madrid Intermediate Respiratory Care Unit was higher (37.1%), which was justified by a much lower PaO2/FiO2 ratio.[16] The deceased patients in this cohort were older; the 28-day mortality rate of those requiring intubation was 53.8% compared to 6.8% in those who could have avoided it (overall 24.3%) (16), highlighting a trend similar to ours, albeit with a larger difference.

Our cohort's mortality rate of 60.8% among patients who required intubation and thus ICU management is also comparable to the value described by the larger Italian ICU series.[8] These mortality rates are unquestionably higher than those described in the initial reports,[17] but they are invalidated by a large number of patients who were still hospitalized at the time of publication, and thus likely underestimated, given the prolonged duration of hospitalization, particularly in patients managed in the most intensive settings.

Only patients requiring intubation, and thus invasive mechanical ventilation, were managed in our hospital's COVID-ICU; this type of organization is worth considering because it can be decisive for the interpretation of the analysis, as a Chinese study shows, with mortality being 39% for their entire ICU population, but reaching 97% in the subgroup of patients requiring invasive mechanical ventilation.[18]

These disparities may be explained by differences in management policies, case mixes, follow-up durations, or definitions of critically ill patients, as well as differences in other studies, in which mortality in patients admitted to the Intermediate Care Unit did not differ between those who required and did not require ICU transfer (15.2% vs 9.6%, p=0.44).[19]

A progressive improvement in COVID patient mortality has been described,[20,21] but this was not demonstrated in our cohort's three consecutive waves. The reduction in mortality is most likely the result of a multifactorial process that cannot be well interpreted

Table 5. Clinical and demographical characteristics of survived and deceased patients according to age category.

	Patients ≤ 63 y.o. [96]			Patients > 63 y.o. [120]		
	Survived[84]	Deceased [12]	p	Survived [61]	Deceased [33]	p
Age [years]	51.7 ± 9.5	55.3 ± 2.8	0.01	71.7 ± 4.3	71.9 ± 4.7	0.77
Female [% (n)]	28.6 (24)	8.3 (1)	0.14	27 (17)	19.3 (57)	0.32
Smoking habit [% (n)]	9.5 (8)	25 (3)	0.12	6.3 (4)	12.3 (7)	0.26
Vital parameters (ED admission)						
Systolic Blood Pressure [mmHg]	127 ± 19.2	123 ± 18.9	0.48	136 ± 21.7	128 ± 18.4	0.04
Diastolic Blood Pressure [mmHg]	76 ± 11.5	76 ± 11.1	0.91	77 ± 10.9	74 ± 8.5	0.19
Heart Rate [bpm]	98 ± 15.2	91 ± 11.1	0.17	92 ± 18.9	93 ± 14.7	0.61
PaO_2/FiO_2 ratio [mmHg]	215 ± 81.8	242 ± 79.1	0.42	186 ± 62.7	174 ± 72.4	0.34
$PaCO_2$ [mmHg]	33 ± 6.4	30 ± 3.3	0.39	32 ± 4.4	32 ± 5.4	0.59
Respiratory Rate [apm]	26 ± 8.7	27 ± 6.5	0.84	27 ± 15.9	27 ± 9.6	0.96
Temperature [°C]	37.7 ± 1	38.1 ± 0.8	0.28	37.5 ± 0.9	37.6 ± 1.2	0.68
Symptom onset before admission [days]	7.4 ± 2.7	7.5 ± 2.5	0.94	7.3 ± 3.4	7.2 ± 3.2	0.92
Laboratory exams (ED admission)						
White Blood Cells [10^3/µL]	9.6 ± 5.4	8.9 ± 5.5	0.66	8.9 ± 4.1	9.7 ± 4.9	0.34
Neutrophils [10^3/µL]	7.7 ± 4.8	7 ± 4.8	0.74	7.2 ± 3.8	8 ± 4.6	0.34
Lymphocytes [10^3µL]	1.4 ± 1.9	1.3 ± 0.7	0.74	1 ± 0.6	1 ± 0.7	0.70
Neutrophils/Lymphocytes ratio	7.5 ± 5.8	6 ± 3.2	0.39	8.9 ± 5.7	10.4 ± 8.9	0.27
Hemoglobin [g/dL]	14.5 ± 1.9	14.2 ± 1.3	0.62	13.7 ± 2.1	13.8 ± 2.4	0.86
Platelets [10^3/µL]	217 ± 85.4	217 ± 100.5	0.99	225 ± 84.3	195 ± 78.8	0.06
Creatinine [mg/dL]	1.1 ± 1.1	1.3 ± 0.6	0.66	1.3 ± 1.1	1.6 ± 1.1	0.14
Aspartate aminotransferase [IU/L]	58 ± 41.9	50 ± 25.8	0.57	50 ± 26.4	57 ± 63.9	0.47
Alanine aminotransferase [IU/L]	60 ± 65.8	57 ± 47.3	0.89	48 ± 44.1	44 ± 75.2	0.74
Lactate dehydrogenase [U/L]	469 ± 279.8	396 ± 176.4	0.39	479 ± 128.4	503 ± 172	0.81
D-dimer [µg/mL]	4 ± 9.9	7.1 ± 13.4	0.53	2.7 ± 5.8	3.4 ± 6.8	0.59
C-Reactive Protein [mg/dL]	10.5 ± 7.6	12.4 ± 8.6	0.45	13.7 ± 8.1	12.8 ± 9.8	0.57
Ferritin [ng/mL]	1679 ± 1301	2371 ± 2952	0.63	1252 ± 953.2	1723 ± 1789	0.14
Intubation rate						
Orotracheal intubation [% (n)]	15.7 (13)	91.7 (11)	<0.01	11.1 (7)	35.1 (20)	<0.01
Symptom onset before intubation [days]	11.3±6.6	16±8.2	0.14	10.2±2.6	14.5±7.5	0.23

DOAC: Direct Oral AntiCoagulants; ED: Emergency Department; IU: Internationl Units in a small population.

Male sex, cardiovascular comorbidities, acute cardiac or kidney injury, lymphocytopenia, and D-dimer were all associated with an increased risk of in-hospital death,[8,22,23] but none of these variables were found to be predictors in our study.

Similarly, despite initial data linking drugs acting on the renin angiotensin system and mortality, this lack of relationship has now been established through large case series and metanalysis.[24-26]

Higher aspirin use was observed in our deceased patients, most likely due to a higher prevalence of ischemic heart disease, but was unrelated to mortality in univariate and multivariate analyses. Our findings are consistent with those of a recent meta-analysis in COVID-19 patients,[27] despite the fact that antiplatelet therapy has previously been associated with lower mortality and ARDS incidence in critically ill patients with predisposing conditions.[28]

The mortality rate was significantly higher in intubated patients compared to patients not requiring intubation (60.8% versus 29.9%, respectively, p<0.01). Although statistical significance is never reached in the various subgroups for the duration of symptoms before intubation (Table 2, 4, 5), there is a trend toward statistical significance for a shorter delay to intubation in survived patients than in deceased ones (11±5.7 versus 15±7.3 days, p=0.06). Although the design of our study does not allow for more in-depth analysis, Camous,[29] who described a mortality rate of 50% and 87% in patients intubated before and after 7 days of dexamethasone therapy, recently suggested that intubation delay could be a negative prognostic factor. To answer this question, studies with appropriate designs are required.

Limitations

The information presented is the result of a single-center analysis. The study's retrospective nature imposes some limitations; however, we strived to conduct the most comprehensive chart review possible, using the analysis of two independent revisors and being able to rely on 0% missing data. We chose not to reveal the cause of death because, while the data collected by phone contact constitute a small percentage, being provided by non-medical personnel may introduce uncertainty about the true cause of death. Similarly, because of the high risk of interpretive bias due to the retrospective nature of the analysis, we did not include important data such as NIV/CPAP setting and duration, radiological findings, and drug therapy; however, drug therapy provided during hospitalization always followed the standard of care based on the best evidence at the time of admission. The decision to start NIV/CPAP immediately in the ED or to delay it until admission to the SICU was influenced not only by clinical severity but also by logistical concerns (availability of SICU beds, consequent expected length of stay in the ED, number of ventilators in the ED). Although there is a possibility that a subset of patients was undertreated in the early stages of the disease (in terms of ventilatory support), the nature of the study does not allow for a more thorough discussion of this point; nonetheless, the rate of intubation did not differ between those who began ventilatory support in the ED and those who began it in the SICU. Furthermore, no data on the percentage of "do-not-intubate" patients were reported, which may represent a category at increased risk of mortality; however, the inability to distinguish the clinical or organizational (available resources) aetiology of this data, as well as the difficulty in determining when a patient is classified as such (on SICU admission or only later at the time of further deterioration), could lead to misinterpretation. Finally, the sample size is small, but it is comparable to that of a 12-bed ward, with the added benefit of being extrapolated from a setting with true semi-intensive care criteria.

Conclusions

In summary, mortality in COVID patients managed in a SICU is high, reaching about the 30% at six months, with similar data along the three Italian epidemic in our single center experience. Age is an important negative prognostic factor, with 63 years old as the best predicting cut-point (OR 5.29).

References

1. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565–74.
2. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020;395:1225–8.
3. Lorettu L. Key words for 2020: Pandemic, emergency, anomie. Emerg Care J 2021;17:9436.
4. Poggiali E, Barbieri G, Salvatore V, Salinaro F. The Emergency Rooms and Emergency Medicine should not be the answer to the weakness of the Italian National Health System. Emerg Care J [Internet]. 2021 Dec 20;17(4 SE-Letters to the Editor). Available from: https://www.pagepressjournals.org/index.php/ecj/article/view/10304
5. Giostra F, Mirarchi MG, Farina G, et al. Impact of COVID-19 pandemic and lockdown on emergency room access in Northern and Central Italy. Emerg Care J 2021;17:9705
6. Henchi S, Conti CB, Vanoni N, et al. First COVID-19 sub-intensive respiratory unit in Europe: the Italian experience. Multidiscip Respir Med 2020;15:682.
7. COVID-19 Clinical Research Coalition. Global coalition to accelerate COVID-19 clinical research in resource-limited settings. Lancet 2020;395:1322-5.
8. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 2020;323:1574–81.
9. Cattelan AM, Di Meco E, Trevenzoli M, et al. Clinical Characteristics and laboratory biomarkers changes in COVID-19 patients requiring or not intensive or sub-intensive care: a comparative study. BMC Infect Dis 2020;20:934.
10. Bellani G, Grasselli G, Cecconi M, et al. Noninvasive ventilatory support of patients with COVID-19 outside the Intensive Care Units (WARd-COVID). Ann Am Thorac Soc 2021;18:1020–6.
11. Iapichino G, Radrizzani D, Rossi C, et al. Proposal of a flexible structural-organizing model for the Intensive Care Units. Minerva Anestesiol 2007;73:501–6.
12. Boodman C, Lagacé-Wiens P, Bullard J. Diagnostic testing for SARS-CoV-2. CMAJ 2020;192:E713.
13. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
14. Santus P, Radovanovic D, Saderi L, , et al. Severity of respiratory failure at admission and in-hospital mortality in patients with COVID-19: a prospective observational multicentre study. BMJ Open 2020;10:e043651.
15. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-

analysis. J Infect 2020;81:e16–25.
16. Carrillo Hernandez-Rubio J, Sanchez-Carpintero Abad M, Yordi Leon A, et al. Outcomes of an intermediate respiratory care unit in the COVID-19 pandemic. PLoS One 2020;15:e0243968.
17. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
18. Wang Y, Lu X, Li Y, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med 2020;201:1430–4.
19. Grosgurin O, Leidi A, Farhoumand PD, et al. Role of intermediate care unit admission and noninvasive respiratory support during the COVID-19 pandemic: a retrospective cohort study. Respiration 2021;100:786–93.
20. Ciceri F, Ruggeri A, Lembo R, et al. Decreased in-hospital mortality in patients with COVID-19 pneumonia. Pathog Glob Health 2020;114:281–2.
21. Ruggeri A, Landoni G, Ciceri F. Trend towards reduction in COVID-19 in-hospital mortality. Lancet Reg Heal Eur 2021;3:100059.
22. Figliozzi S, Masci PG, Ahmadi N, et al. Predictors of adverse prognosis in COVID-19: A systematic review and meta-analysis. Eur J Clin Invest 2020;50:e13362.
23. Barbieri G, Cipriano A, Carrara S, et al. SARS-CoV-2 management in Emergency Department: risk stratification and care setting identification proposal based on first pandemic wave in Pisa University Hospital. Emerg Care J 2021;17:9859
24. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;323:2052–9.
25. Mancia G, Rea F, Ludergnani M, et al. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. N Engl J Med 2020;382:2431–40.
26. Biswas M, Kali MSK. Association of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers with risk of mortality, severity or SARS-CoV-2 test positivity in COVID-19 patients: meta-analysis. Sci Rep 2021;11:5012.
27. Salah HM, Mehta JL. Meta-analysis of the effect of aspirin on mortality in COVID-19. The Am J Cardiol 2021;142:158–9.
28. Wang L, Li H, Gu X, et al. Effect of antiplatelet therapy on acute respiratory distress syndrome and mortality in critically ill patients: a meta-analysis. PLoS One 2016;11:e0154754.
29. Camous L, Pommier J-D, Martino F, et al. Very late intubation in COVID-19 patients: a forgotten prognosis factor? Crit Care