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Clinical and organizational factors associated with mortality during the peak of first COVID-19 wave: the global UNITE-COVID study

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Abstract

Purpose: To accommodate the unprecedented number of critically ill patients with pneumonia caused by coronavirus disease 2019 (COVID-19) expansion of the capacity of intensive care unit (ICU) to clinical areas not previously used for critical care was necessary. We describe the global burden of COVID-19 admissions and the clinical and organizational characteristics associated with outcomes in critically ill COVID-19 patients.

Methods: Multicenter, international, point prevalence study, including adult patients with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) and a diagnosis of COVID-19 admitted to ICU between February 15th and May 15th, 2020.

Results: 4994 patients from 280 ICUs in 46 countries were included. Included ICUs increased their total capacity from 4931 to 7630 beds, deploying personnel from other areas. Overall, 1986 (39.8%) patients were admitted to surge capacity beds. Invasive ventilation at admission was present in 2325 (46.5%) patients and was required during ICU stay in 85.8% of patients. 60-day mortality was 33.9% (IQR across units: 20%–50%) and ICU mortality 32.7%. Older age, invasive mechanical ventilation, and acute kidney injury (AKI) were associated with increased mortality. These associations were also confirmed specifically in mechanically ventilated patients. Admission to surge capacity beds was not associated with mortality, even after controlling for other factors.

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Conclusions: ICUs responded to the increase in COVID-19 patients by increasing bed availability and staff, admitting up to 40% of patients in surge capacity beds. Although mortality in this population was high, admission to a surge capacity bed was not associated with increased mortality. Older age, invasive mechanical ventilation, and AKI were identified as the strongest predictors of mortality.

Keywords: COVID-19, SARS-CoV-2, Pneumonia, Critical care, Surge capacity

Introduction

Coronavirus disease 2019 (COVID-19) is arguably the most significant challenge critical care medicine has been confronted with since its conception [1]. In the past 2 years, critical care services worldwide have admitted a large number of critically ill COVID-19 patients presenting with severe respiratory failure who often require prolonged treatment in the intensive care unit (ICU). Unfortunately, despite the support provided, mortality remains high, particularly in ventilated patients [2]. Although many groups and societies have studied diagnostic, therapeutic and prognostic aspects of COVID-19 in the critically ill, these studies were mostly limited to a group of hospitals or geographical areas, and very few reports offer a global perspective.

Many ICUs needed to extend their capacity at the peaks of the pandemic and to do so often recruited healthcare workers (HCW) from outside critical care [3, 4]. The extent of this practice in hospitals worldwide and its impact on the survival outcomes of critically ill COVID-19 patients have only concisely been reported [5].

Although there are important geographical differences in the spread of the coronavirus, and new variants create new challenges, the future remains unpredictable, particularly in areas with low vaccination rates. It can, therefore, be expected that COVID-19 will remain a continued challenge in ICUs globally for some time to come. Efforts to study the disease should continue to advance our understanding of the disease and improve patient management and treatment [6].

The European Society of Intensive Care Medicine (ESICM), therefore, set out to describe the extent of COVID-19 ICU surge worldwide and to describe the clinical characteristics, management, and outcomes of critically ill COVID-19 patients. Additionally, the goal was to study the impact of critically ill COVID-19 patients being admitted to a surge capacity bed on the treatment and outcomes. We hypothesized that admission to surge capacity beds increased mortality compared to standard ICU beds, and that need for early invasive mechanical ventilation was associated with higher mortality.

Take-home message

This study including data on the peak of the pandemic from 240 centers in 46 countries shows the global impact of the first wave of coronavirus disease 2019 (COVID-19) wave on intensive care units (ICUs), which responded by increasing their capacity and opening ICU beds in non-ICU locations in two thirds of cases. A large proportion of patients (40%) were admitted to surge capacity beds, and most needed invasive mechanical ventilation (85%); admission to a surge capacity bed was not associated with survival, while age, acute kidney injury and ventilation were strongest predictors for mortality.

Methods

The ESICM UNITE-COVID study was a multicenter, international, anonymized point prevalence study. An international steering committee of experts was established in 2020 by the ESICM. A network of national coordinators recruited investigators, coordinated study participation, and monitored local ethics committee approval at each participating center in the individual countries. The Ghent University Hospital Ethics Committee approved the study (registration number BC07826). The study was not funded, and participation was voluntary. The trial was registered at ClinicalTrials.gov (NCT04836065).

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational were followed throughout this manuscript [7].

Participants

For inclusion in the study, subjects had to fulfill all of the following: (1) age 18 or older; (2) present in an ICU or in any other area in the hospital under the care of the critical care team on the day between February 15th and May 15th, 2020 with the highest number of COVID-19 patients under the care of intensivists; (3) Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection confirmed through polymerase chain reaction (PCR) or equivalent diagnostic technique; (4) Clinical manifestation of COVID-19. Patients who tested positive for SARS-CoV-2 without COVID-19 were excluded from the study. Intermediate care/progressive care unit patients not under the care of the critical care team were not included. Patients could only be included once.

Patients were selected by the local investigator, who identified the day with the highest number of patients that fulfilled the inclusion criteria. Other than data collection no additional interventions or measurements other than those that were standard of care were performed. Informed consent was either obtained or waived according to the local ethics committee's decision.

Variables

The data collected included the demographic characteristics of the patients, their comorbidities, duration of COVID-19 symptoms, clinical status at the time of admission to the ICU, complications during ICU stay, drugs used as part of routine care or because of participation in a research study (including antimicrobials, sedatives, neuromuscular blockers, anticoagulation, and anti-inflammatory therapies), as well as any organ support during ICU stay. Patient data were collected from the day of ICU admission until day 60 following admission to the ICU.

Center data were collected separately and included hospital type and unit characteristics, number of beds before the COVID-19 pandemic and on the day with the highest number of COVID-19 patients under intensivist care, and ICU beds in non-ICU locations that were available and managed by the ICU team. We also gathered data specifically on ICU staffing—the patient/nurse ratio, the number of physicians working in the unit and the number of non-ICU HCWs employed on the study day.

Data sources and curation

The requested information was collected in a structured format. All data were submitted by the participating centers through a secure cloud-based electronic Data Capture platform (Clinfile, Vélizy-Villacoublay, France). A comprehensive data curation exercise was undertaken and Data Acquisition, Quality and Curation for Observational Research Designs (DAQCORD) checklist is included in the supplementary materials [8]. Curation scripts and curated data dictionary which include data missingness are available on GitHub and archived [9].

To address information bias, we performed several subanalyses, and considered missingness both at patient and at unit level. There was no apparent bias for considered outcomes due to loss to follow up. Bias related to heterogeneity between centers (differences in data reporting and in medical practice) were considered using random effect model at unit level, and variation between centers is reported in the results. Sensitivity analyses minimizing potential effects of missing data and focused on heterogeneous population were included. We report the non-missing number of patients for each variable in the tables in the manuscript and supplemental material. As ICU admission criteria may vary between countries and indication for mechanical ventilation is more objective, we decided a priori to consider the subgroup of mechanical ventilation at admission for sensitivity analysis.

The study was conducted in emergency setting, and across several countries. No formal sample size analysis was performed in the emergency phase of a new pandemic, we aimed to enroll 1000 patients in a multi-centric study.

Statistical methods

Categorical variables are expressed as frequencies (percentages) and continuous variables are described as medians with interquartile range (IQR) (25th–75th percentile). For comparisons between groups, we sought differences in categorical variables using a Pearson chi-squared test or Fisher's exact test when appropriate. The Mann–Whitney U test was used for comparison of grossly non-normally distributed continuous variables. Statistical significance was defined as $p < 0.05$.

A multivariable mixed-effect model was built to assess the relation of different covariates with survival, dividing the population into two cohorts: development (70%) and testing (30%). Methods on handling of missing data and of collinear variables, and methods on multiple imputation of missing data are reported in the supplemental material. Numeric variables were centered and scaled before inclusion in the model, except age which was categorized by decades. Site ID was included as random effect in the model, while admission to a surge capacity bed was included a priori in the model as a fixed effect.

Three multivariable models were subsequently developed starting from baseline comorbidities, next including ICU admission and ventilation data, and finally ICU complications. Variables associated with mortality in univariable analysis and associated with surge capacity beds were included (threshold for inclusion set at $p < 0.2$). Survival was included as reference value. For each model, variables were first automatically ordered in terms of importance to assure maximal model convergence and backward selection was employed to retain the most significant variables, selecting the best model according to likelihood-ratio test based on chi-squared mixtures ($p < 0.05$ as exclusion threshold) [10]. The final model was built with variables retained from previous steps. Model performance was calculated on the test cohort after excluding collinearity and singularity and again on the full cohort after multiple imputation for missing data. Other methods on model development and testing, on multiple imputation procedure and database curation are reported in the supplemental material. A sensitivity analysis was conducted including only patients on invasive ventilation at ICU admission and admitted for respiratory failure due to COVID-19.

Statistical analyses were all performed using R Statistical Software (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, version 4.1.1).

Results

Participating ICUs

Two hundred and eighty ICUs located in 46 countries in 5 continents contributed patient data to the study (Europe [60%], Asia [22%], South America [6%], North America [6%], and Africa [6%] (Supplemental material Table 1, Supplemental material Fig. 1).

The majority of the participating centers were public (86%), teaching (83%) hospitals. Eighty-four percent of units were mixed ICUs, and closed ICUs were most common (61%).

The median number of operational beds in the participating ICUs was 15 (IQR 10–22). Median number of patients included per unit was 12 (IQR 6–21; range 1–121) Overall 66% of the units increased their capacity during the pandemic surge. The resulting surge capacity of the participating units was 21 (IQR 15–32) beds ($p < 0.001$). The total standard ICU capacity was 4931 beds, which increased to 7630 during the pandemic surge. In 66% of the participating centers, ICU beds were opened in non-ICU locations where patients were cared for by the ICU team with support from surge staff; the median number of such beds was 18 (12–24), while the median number of patients in surge capacity beds was 7 (IQR 3–15, range 1–64).

ICU workforce

The number of patients per ICU nurse increased from 2.0 (SD 0.85) to 2.4 (SD 1.1) during the pandemic surge ($p < 0.001$). The number of intensivists available for clinical care increased from 4.5 (SD 4.66) to 5.4 (SD 5.38) ($p < 0.001$) while the number of residents available for clinical care increased from 4.3 (SD 5.72) to 6.2 (SD 9.69) ($p < 0.001$). Non-ICU nurses and physicians were employed in 85% and 58% of the participating ICUs, respectively.

Demographics and baseline comorbidities

A total of 4994 patients were included in the study. Baseline data and comorbidities are reported in Table 1. The majority of patients (71.4%, IQR across units 60%-86%) were male and the median age was 62 years (IQR 53–70). 5.6% of the patients were healthcare workers, and 2.5% of female patients were pregnant.

The most common comorbidities included arterial hypertension, chronic cardiac disease, chronic pulmonary disease, and asthma. The median BMI was 27.9 (25.3–32.3); 37.3% of the patients were obese, while 39.1% were overweight. The rates of most baseline comorbidities were similar in patients on invasive mechanical ventilation (IMV) at the time of admission and in patients not on IMV at admission but requiring IMV at a later stage. The exceptions to this rule were diabetes and chronic liver disease which were more common in the latter. Patients who never needed IMV were younger than patients needing mechanical ventilation (age 59 [48–68] vs 62 [54–70], $p < 0.001$), and more frequently had diabetes and chronic cardiac disease (4.3% vs 2.2%, $p = 0.014$, 20.4% vs 14.3%, $p < 0.001$, respectively).

Patient status at the time of ICU admission

The median time between first symptoms and hospital admission was 7 days (IQR 4–9). Most patients were admitted to a hospital ward before being admitted to the ICU; the median length of stay in hospital before ICU admission was 1 (IQR 0–4) day(s).

Respiratory insufficiency was the primary indication for ICU admission (Table 1). Other COVID-19 complications were rarely the indication for ICU admission (2.2%), as were other diagnoses in patients with active COVID-19 (2.1%). This distribution varied according to need for IMV at admission or later during ICU stay, with a higher number of patients who needed IMV at admission being referred from other centers compared to the other categories, and a higher number of patients who never needed IMV being admitted to ICU for a reason other than respiratory failure.

While in hospital, pre-ICU respiratory support was commonly required (72.7%, IQR across centers: 60–98%). Most of these patients received standard oxygen (76.3%, IQR across centers 71.1–100%); non-invasive respiratory support [continuous positive airway pressure (CPAP) and non-invasive ventilation (NIV)] or high-flow nasal oxygen (HFNO)] was also used in 10.7% (IQR across centers 9.1–66.7%), 5.2% (IQR 9.1–33.3%), and 7.9% (IQR 6.0–33.3%) of patients, respectively.

Thromboembolic complications were diagnosed in 7.4% of patients at the time of ICU admission. These included deep vein thrombosis (0.8%), pulmonary embolism (1.9%), and other thromboembolic events (1.4%).

Fever was common at admission, with a median temperature of 38.0 °C (IQR 37.0–38.7).

The highest C-reactive protein (CRP) and procalcitonin (PCT) values within 24 h of admission were 165 mg/L (IQR 77–259.5) and 0.42 ng/mL (IQR 0.18–1.30), respectively; ferritin concentrations were elevated, with a median concentration of 135.5 mg/L (IQR 1.4–1095.6). Median D-dimer levels (999 ng/mL, IQR 356 – 2900) were also elevated on admission. The highest median white cell count on admission was 9.9×10^9/L

Table 1 Baseline characteristics

Characteristic	All patients ($N=4994$)[1]	Patients intubated at admission ($N=2325$)[1]	Patients intubated during ICU stay ($N=1677$)[1]	Not invasively ventilated during ICU stay ($N=682$)	*p* values[2]	*p* values[2]
		A	B	C	A vs B	A vs C
Demographics						
Sex	28.6% Female 71.4% Male (4975)	27.3% Female 72.7% Male (2323)	29.2 Female 70.8% Male (1676)	32% Female 68% Male (682)	0.2	0.018
Pregnancy	0.68% (0)	0.4% (0)	0.3% (0)	2.5% (0)	0.6	< 0.001
Age (years)	62 [53–70] (4908)	62 [54–70] (2320)	62.5 [54–71] (1674)	59 [48–68] (678)	0.3	< 0.001
BMI	27.97 [25.3–32.27] (4528)	28.4 [25.7–32.87] (2146)	27.78 [25–31.92] (1546)	27.44 [24.8–31.18] (619)	< 0.001	< 0.001
Healthcare worker	5.6% (4571)	4.5% (2154)	4.4% (1570)	11.5% (644)	0.9	< 0.001
Comorbidities						
Chronic cardiac disease	15.6% (4766)	14.3% (2292)	15.8% (1643)	20.4% (678)	0.2	< 0.001
History of hypertension	49.7% (4781)	50.1% (2304)	49.8% (1647)	48.7% (676)	0.9	0.5
Chronic liver disease	2.6% (4755)	2% (2287)	3.2% (1643)	3.4% (674)	0.017	0.034
Chronic neurological disease	5.9% (4753)	5.5% (2284)	6.3% (1643)	6.7% (673)	0.3	0.2
Chronic pulmonary disease	9% (4767)	8.4% (2290)	10.2% (1649)	8.4% (678)	0.051	0.9
Asthma	8.7% (4777)	9.1% (2293)	8.7% (1652)	7.5% (678)	0.7	0.2
Malignant neoplasm	5.5% (4715)	5.6% (2270)	6.1% (1636)	4.1% (659)	0.5	0.13
Chronic kidney disease	7.1% (4772)	6.9% (2294)	7.8% (1646)	6.9% (679)	0.3	0.9
Diabetes	2.9% (3352)	2.2% (1649)	3.5% (1152)	4.3% (442)	0.039	0.014
HIV	0.4% (4407)	0.5% (2121)	0.3% (1537)	0.3% (626)	0.5	0.9
Immunosuppression	5.1% (4720)	5.4% (2279)	5% (1635)	4.6% (654)	0.6	0.4
Chronic medications						
ACE-inhibitor	19.5% (4551)	19.1% (2216)	20.3% (1560)	18% (634)	0.4	0.5
Angiotensin II receptor antagonist	15.2% (4543)	15.5% (2216)	15.3% (1556)	14.7% (631)	0.9	0.6
Anticoagulation	6.9% (4593)	5.3% (2220)	7.4% (1579)	9.4% (648)	0.008	< 0.001
Antiplatelet therapy	16.7% (4580)	15.9% (2215)	17% (1578)	20.5% (643)	0.3	0.006
Clinical status at ICU admission						
Referral from another ICU	7.7% (4823)	11.2% (2324)	2.6% (1667)	1.6% (682)	< 0.001	< 0.001
ICU admission due to respiratory failure	88% (4823)	86.3% (2324)	93.1% (1667)	87.4% (682)		
ICU admission due to other complication of COVID-19	2.2% (4823)	1% (2324)	2.2% (1667)	6.6% (682)		
ICU admission due to other diagnosis	2.1% (4823)	1.5% (2324)	2.6% (1667)	4.4% (682)		
Time between symptoms and hospital admission (days)	7 [4–9] (4251)	7 [5–10] (1987)	7 [4–9] (1496)	6 [3–9] (592)	0.025	< 0.001
LoS in hospital before ICU admission (days)	1 [0–4] (4693)	1 [0–4] (1258)	2 [0–4] (1628)	1 [0–5] (624)	0.2	0.039
Respiratory support before ICU admission (any)	72.7% (4505)	72.5% (2132)	74.6% (1610)	66.6% (655)	0.2	0.003
HFNC	7.9% (3230)	7.3% (1524)	8.1% (1198)	9.4% (435)	< 0.001	< 0.001
CPAP	10.7% (3230)	14.6% (1524)	7.4% (1198)	4.4% (435)		
NIV	5.2% (3230)	5.2% (1524)	5.3% (1198)	3% (435)		

Table 1 (continued)

Characteristic	All patients (*N* = 4994)[1]	Patients intubated at admission (*N* = 2325) [1]	Patients intubated during ICU stay (*N* = 1677)[1]	Not invasively ventilated during ICU stay (*N* = 682)	*p* values[2]	*p* values[2]
		A	B	C	A vs B	A vs C
standard oxygen	76.3% (3228)	72.9% (1524)	79.2% (1198)	83.2% (435)		
Total duration of support before ICU admission (days)	1 [1–3] (713)	1 [1–3] (368)	1 [1–2.75] (246)	1 [1–3] (72)	0.2	0.9
Thromboembolic complication at admission (any)	7.4% (4994)	4% (2325)	3.2% (1677)	6.2% (682)	0.2	0.014
DVT	0.8% (4994)	0.9% (2325)	0.8% (1677)	0.7% (682)	0.8	0.7
PE	1.9% (4994)	2% (2325)	1.4% (1677)	2.2% (682)	0.2	0.7
other	1.4% (4994)	1.2% (2325)	1.1% (1677)	3.1% (682)	0.6	0.001
Highest temperature (°C)	37.95 [37–38.7] (4651)	37.9 [37–38.7] (2227)	38 [37.1–38.8] (1631)	37.8 [37–38.5] (662)	0.2	0.01
Highest white cell count (10^9/L)	9.9 [7–13.8] (4766)	10.2 [7.5–14.1] (2295)	9.6 [6.9–13.3] (1661)	8.5 [6.33–12] (677)	< 0.001	< 0.001
Lowest lymphocyte count (10^9/L)	0.7 [0.5–1.01] (4442)	0.7 [0.46–1] (2097)	0.7 [0.5–1] (1570)	0.88 [0.57–1.3] (650)	0.035	< 0.001
Highest CRP (mg/L)	165 [77–259.5] (4316)	186 [94–285] (2125)	161 [86–247] (1509)	98 [38.5–175.5] (592)	< 0.001	< 0.001
Highest procalcitonin (ng/mL)	0.42 [0.18–1.30] (2539)	0.52 [0.21–1.67] (1200)	0.41 [0.18–1.2] (919)	0.22 [0.1–0.54] (372)	< 0.001	< 0.001
Highest ferritin (mg/L)	135.5 [1.4–1095.6] (2704)	222.5 [1.48–1325] (1178)	7.17 [1.39–892] (993)	221 [1.1–891.6] (475)	< 0.001	0.003
Highest D-dimers (ng/mL)	999 [356–2900] (3093)	1176 [495–4077] (1409)	910 [352–2450] (1109)	700 [116–1540] (506)	< 0.001	< 0.001
Admission to surge capacity beds	43.1% (4605)	45.6% (2191)	40.4% (1567)	44.3% (645)	0.002	0.6
Admission to standard ICU beds	56.8% (4605)	54.4% (2191)	59.6% (1567)	55.7% (645)		

Tests are reported without correction for multiple comparisons

BMI Body Mass Index, *HNFC* high-flow nasal cannula, *CPAP* continuous positive airway pressure, *LoS* length of hospital stay, *NIV* non-invasive ventilation, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *CRP* C-reactive protein

[1] *n* (%); median (IQR)

[2] Pearson's chi-squared test; Wilcoxon rank sum test; Fisher's exact test

(IQR 7–13.8) and the median lymphocyte count was low (0.7×10^9/L, IQR 0.5–1.01).

Supportive care and pharmacological therapy in the ICU

In total 4129 patients (85.8%) were mechanically ventilated; 2325 patients were intubated at the time of admission to ICU, and another 1677 were intubated during their ICU stay. Table 2 reports the supportive care received during ICU admission for each of these categories.

Most patients (84.7%, IQR across units 75–100%) were sedated during their ICU stay, for a median of 14 (8–21) days. Vasoactive drugs were used in 75.4% for a median of 8 (4–14) days. Renal replacement therapy (RRT) was required in 24.3% (IQR across centers 15.5–41.2%) of the patients, with continuous RRT (CRRT) used most frequently (69.5%). In 12.9% of patients, RRT modalities not routinely used outside of the COVID-19 pandemic were applied. RRT was used for a median of 9 (4–18) days. In 4.5% of patients, extra-corporeal membrane oxygenation (ECMO) was used for a duration of 17 (11–30) days. Most of the other types of ICU support were similar in patients on IMV at ICU admission and patients who required IMV later, except for tracheostomy, which was more common in the former (38.2% vs 33.9%, $p = 0.006$). Patients who never needed IMV had a lower need for any form of organ support.

Pharmacological therapy in ICU is reported in Supplemental material Table 2. Antiviral treatment was prescribed to 43.1% of patients, with lopinavir/ritonavir used most frequently (24.8%); others included remdesivir (3.6%), neuroaminidase inhibitors (4%), and ribavirin (1.2%). Just over half of the patients were treated with corticosteroids (51.6%) for a median of 7 days (IQR

Table 2 Supportive care received during ICU stay

Characteristic	All patients (*N* = 4994)[1]	Patients intubated at admission (*N* = 2325)[1]	Patients intubated during ICU stay (*N* = 1677)[1]	Not invasively ventilated during ICU stay (*N* = 682)	*p* values[2]	*p* values[2]
		A	B	C	A vs B	A vs C
Duration of IMV	16 [10–27] (3984)	18 [11–27] (2251)	15 [8–26] (1609)	NA	< 0.001	NA
Prone position	61.7% (4717)	65.2% (2276)	67.4% (1646)	36.4% (668)	0.14	< 0.001
Prone positioning during IMV duration (days)	4 [2–7] (2622)	4 [2–7] (1452)	4 [2–7] (1101)	NA	0.031	NA
Neuromuscular blockers used	67.6% (4761)	79.2% (2309)	77.8% (1653)	NA	0.3	NA
Duration of neuromuscular blocker use (days)	6 [3–10] (3160)	6 [3–11] (1791)	5 [3–10] (1268)	NA	< 0.001	NA
Sedation during ICU stay	84.7% (4811)	98.7% (2325)	95.9% (1676)	7.5% (682)	< 0.001	< 0.001
Duration of sedation (days)	14 [8–21] (4018)	15 [9–22] (2265)	13 [7–21] (1581)	2 [1–3] (50)	< 0.001	< 0.001
Need for inotropes/vasopressors	75.4% (4812)	88.9% (2325)	84.4% (1677)	6.2% (682)	< 0.001	< 0.001
Duration of inotropes/vasopressors (days)	8 [4–14] (3565)	8 [4–14] (2025)	8 [4–14] (1400)	2 [1–4] (39)	0.08	< 0.001
Tracheostomy during ICU admission	31.3% (4802)	38.2% (2323)	33.9% (1677)	NA	0.006	NA
Timing of tracheostomy after intubation (days)	16 [11–21] (1454)	16 [11–21.5] (860)	15 [10–21] (550)	NA	0.016	NA
Need for RRT	24.3% (4808)	28% (2321)	27% (1677)	4.4% (682)	0.5	< 0.001
CRRT	69.5% (1149)	72.2% (641)	67.8% (444)	34.5% (29)	0.13	< 0.001
Intermittent	20.7% (1149)	17.3% (641)	23% (444)	62.1% (29)		
Peritoneal dialysis	0.4% (1149)	0.5% (641)	0.5% (444)	0% (29)		
Mixture	9.3% (1149)	10% (641)	8.8% (444)	3.4% (29)		
RRT modality not routinely used outside COVID-19 pandemic	12.9% (1151)	13.1% (642)	11.5% (445)	20.7% (29)	0.4	0.2
Duration of RRT (days)	9 [4–18] (1142)	10 [5–19] (636)	7 [3–17] (442)	5 [2–12] (29)	0.002	0.003
ECMO therapy	4.5% (4795)	5.5% (2315)	3.9% (1674)	0% (680)	0.022	< 0.001
Duration of ECMO therapy (days)	17 [11–30] (214)	17 [11.5–29] (124)	15 [10–29] (65)	NA	0.7	NA

Tests are reported without correction for multiple comparisons

IMV invasive mechanical ventilation, *ICU* intensive care unit, *RRT* renal replacement therapy, *CRRT* continuous RRT, *ECMO* extra-corporeal membrane oxygenation

[1] *n* (%); median (IQR)

[2] Pearson's chi-squared test; Wilcoxon rank sum test; Fisher's exact test

4–11). Steroids were initiated within 2 days (IQR 0–8) after admission. Antivirals were more commonly administered to patients on IMV at a later stage than in patients on IMV at admission (46.7% vs 40.3%, $p < 0.001$), while the use of corticosteroids was far less common in patients never needing mechanical ventilation ($p < 0.001$).

Other therapies were used in 22.9% of patients, including tocilizumab (13.9%), interferon-beta (4.1%), convalescent plasma (2.8%), anakinra (1.3%), and interferon-alpha (0.7%). Antimalarial drugs were used in 57.3% of the whole population, for a median of 6 days (5–10). Fourteen percent of patients were included in a clinical trial.

Complications during ICU stay and patient outcomes

Complications during ICU stay were common (Table 3). Cardiac arrhythmias requiring therapy occurred in more than a quarter of patients and were slightly more common in those on IMV at ICU admission compared to patients requiring IMV later (29.9% vs 27.0%, $p = 0.044$). Respiratory complications included atelectasis (24.1%), endotracheal tube obstruction (10.5%), pneumothorax

(8.4%) and accidental extubation (3.5%). Acute kidney injury (AKI) developed in 42.6% of patients, with higher rates in patients on IMV at admission compared to patients requiring IMV later (49.7% vs 45.9%, $p=0.019$). Facial pressure sores occurred in 23.6% of patients who needed proning. Patients who never needed IMV had less complications.

Surge capacity bed patients

A large proportion of patients ($n=1986$; 39.8%) were admitted to a surge capacity bed. The medical history of patients admitted to a surge capacity bed was comparable to those admitted to a standard ICU bed, except for a lower prevalence of chronic obstructive pulmonary disease (COPD) and immunosuppression in patients admitted to surge beds (Supplemental Table 3). IMV at admission was more frequent in patients admitted to standard ICU beds than in patients admitted to surge beds (51.2% vs 46.7%, $p=0.003$). Patients admitted to standard ICU beds also more frequently suffered from other organ failures such as sepsis-induced cardiomyopathy (8.2% in standard vs 3.9% in surge capacity beds, $p<0.001$), cardiac arrhythmias (27% vs 24.2%, $p=0.03$), and more frequently developed AKI (44.8% vs 39.6%, $p<0.001$). Correspondingly, advanced organ support such as RRT and ECMO was more frequently applied to patients in non-surge capacity beds (25.9% vs 21.7%, $p=0.001$ for CRRT, 6.1% vs 1.7% $p<0.001$ for ECMO).

There was some difference in the type of therapies used in surge vs standard beds: antivirals and corticosteroids were more commonly administered in surge beds vs standard ICU beds (48.8% vs 40.6%, $p<0.001$; 58.3% vs 48.0%, $p<0.001$, respectively) (Supplemental material Table 3). The unadjusted survival of patients admitted to surge beds was similar to patients admitted to standard ICU beds (ICU mortality 32.1% vs 32.4%, $p=0.8$ and hospital mortality 33.2% vs 33.7%, $p=0.6$).

Unadjusted mortality

Overall, 33.9% (IQR across units 20–50%) of patients died by day 60 after ICU admission. Most died in the ICU (32.7%), and a small number died after being discharged for palliative care outside of the ICU. At day 60 after ICU admission, 2.8% of the patients were still in the ICU, 8.0% were transferred to another institution, 5% were still hospitalized on a non-ICU ward and 50% were discharged alive from the hospital (Table 4). The median length of stay in the ICU was 17 days (10–24) and the median length of stay in hospital was 28 (18–44) days.

Patients on IMV at ICU admission had a lower risk of mortality compared to patients who did not receive IMV at ICU admission but subsequently needed IMV (35.6% vs 42.0%, $p<0.001$), while length of ICU and hospital stay

Table 3 Complications during ICU stay

Characteristic	All patients ($N=4994$)[1]	Patients intubated at admission ($N=2325$)[1]	Patients intubated during ICU stay ($N=1677$)[1]	Not invasively ventilated during ICU stay ($N=682$)	*p* values[2]	*p* values[2]
		A	B	C	A vs B	A vs C
Cardiac arrhythmia requiring therapy	26.2% (4747)	29.9% (2294)	27% (1644)	11.2% (678)	0.044	< 0.001
Sepsis induced cardiomyopathy	6.2% (4495)	6.6% (2178)	8% (1531)	1.2% (670)	0.088	< 0.001
Stress myocardiopathy	3.4% (4483)	3.6% (2177)	4.4% (1526)	1.2% (666)	0.2	0.002
Myocarditis	3% (4526)	3.6% (2200)	3% (1530)	1% (670)	0.3	< 0.001
Pericardial effusion	4.6% (4619)	5% (2239)	4.9% (1588)	1.5% (663)	0.9	< 0.001
Pneumothorax	8.4% (4780)	10.1% (2307)	9.3% (1662)	0.7% (680)	0.4	< 0.001
Atelectasis	24.1% (4615)	26.1% (2224)	26.4% (1595)	10.4% (670)	0.8	< 0.001
Prolonged delirium	25.9% (4690)	31.5% (2250)	27.1% (1634)	5.7% (682)	0.003	< 0.001
Seizure	2.4% (4765)	3% (2296)	2.1% (1657)	0.4% (681)	0.083	< 0.001
Pressure sores–facial (prone)	15.6% (4644)	18.2% (2231)	17% (1610)	2.4% (674)	0.4	< 0.001
Pressure sores–other	21.6% (4597)	25.6% (2211)	22.4% (1589)	4.3% (673)	0.22	< 0.001
Developed infection during ICU stay	56.7% (4792)	65.2% (2314)	62.1% (1672)	12.4% (680)	0.046	< 0.001
Acute kidney injury	42.6% (4770)	49.7% (2308)	45.9% (1655)	10% (677)	0.019	< 0.001

Tests are reported without correction for multiple comparisons

[1] *n* (%); median (IQR)

[2] Pearson's chi-squared test; Wilcoxon rank sum test; Fisher's exact test

were similar ($p=0.08$ and $p=0.6$, respectively). Patients who never needed IMV had by far significant lower mortality (6.4%, $p<0.001$), shorter ICU stay (7.0 [4–12] vs 20 [12–31] days, $p<0.001$), and shorter hospital stay (16.0 [10–22] vs 34 [22–49] days, $p<0.001$) when compared with patients needing IMV at admission.

Adjusted mortality

A forest plot summarizing the results of the mixed-effect multivariable analysis for mortality in the overall population after multiple imputation is displayed in Fig. 1, while Supplemental Table 4 reports model results and overall model performance. Invasive mechanical ventilation (OR 14.94%, 95% CI 9.94–22.47), age (OR progressively increasing to 4.67 [95% CI 3.12–6.98] for patients aged 70–80 years and to 13.65 [95% CI 7.59–24.54] for patients over 80 years of age compared to patients aged 40 or less), AKI (OR 3.63, 95% CI 3.0–4.39) and pneumothorax (OR 2.55, 95% CI 1.9–3.43) were the main variables associated with mortality. Admission to surge capacity beds was not associated with mortality when controlling for other factors (OR 1.01, 95% CI 0.82–1.25, $p=0.9$).

The variables primarily associated with survival were prolonged delirium (OR 0.22 [95% CI 0.18–0.28) and tracheostomy (OR 0.35 [95% CI 0.27–0.45]). Controlling for random variation related to different centers improved model performance, even if the variance related to site ID was relatively low (ICC 0.23). Baseline random effects intercepts for each center are reported in Supplemental Fig. 2.

We performed a sensitivity analysis including 2006 patients admitted to ICU for COVID-19 related respiratory failure and on IMV at ICU admission and report the results in Supplemental Fig. 3 and Supplemental table 5. The sensitivity analysis confirms the absence of association of admission to surge beds with mortality when controlling for other factors (OR 1.12, 95% CI 0.82–1.54, $p=0.5$). In addition, it confirms AKI and age to be the variables most strongly associated with mortality.

Discussion

In this point prevalence study of critically ill COVID-19 patients admitted to 280 centers around the world, the largest study in its kind, we found a mortality rate of almost 34% (IQR from 20 to 50% across centers). Invasive ventilation, AKI, pneumothorax, and age were associated with mortality. While ICU capacity was increased in two thirds of hospitals, and staffing decreased, admission to a surge capacity bed was not associated with increased mortality.

Table 4 Outcomes

Characteristic	All patients ($N=4994$)[1]	Patients intubated at admission ($N=2325$)[1]	Patients intubated during ICU stay ($N=1677$)[1]	Not invasively ventilated during ICU stay ($N=682$)	*p* values[2]	*p* values[2]
		A	B	C	A vs B	A vs C
Deceased	33.9% (4724)	35.6% (2272)	42% (1649)	6.4% (659)	< 0.001	< 0.001
Deceased in ICU	32.7% (4723)	34.6% (2271)	40.3% (1648)	5.5% (659)	< 0.001	< 0.001
Palliative discharge	0.3% (4724)	0.3% (2272)	0.4% (1649)	0.3% (659)	0.02	< 0.001
Still in ICU (at day 60)	2.8% (4724)	2.7% (2272)	3.7% (1649)	0.3% (659)		
Transfer to other facility	8% (4724)	9.6% (2272)	7.2% (1649)	5.9% (659)		
Hospitalized (at day 60)	5% (4724)	4.7% (2272)	5.2% (1649)	3.5% (659)		
Discharged alive	50% (4724)	47.2% (2272)	41.5% (1649)	83.6% 659)		
Duration of stay in ICU before ICU discharge (including death) (days)	17 [10–28] (4535)	20 [12–31] (2183)	19 [12–30] (1568)	7 [4–12] (649)	0.08	< 0.001
Duration of stay in hospital before discharge alive or transfer (days)	28 [18–44] (2664)	33.5 [22–49] (1258)	34 [23–48] (781)	16 [10–22] (569)	0.6	< 0.001
Ongoing RRT requirement after ICU discharge	12.7% (300)	14.4% (174)	7.9% (101)	29.4% (17)	0.11	0.1

Tests are reported without correction for multiple comparisons

RRT renal replacement therapy, *ICU* intensive care unit

[1] *n* (%); median (IQR)

[2] Pearson's chi-squared test; Wilcoxon rank sum test; Fisher's exact test

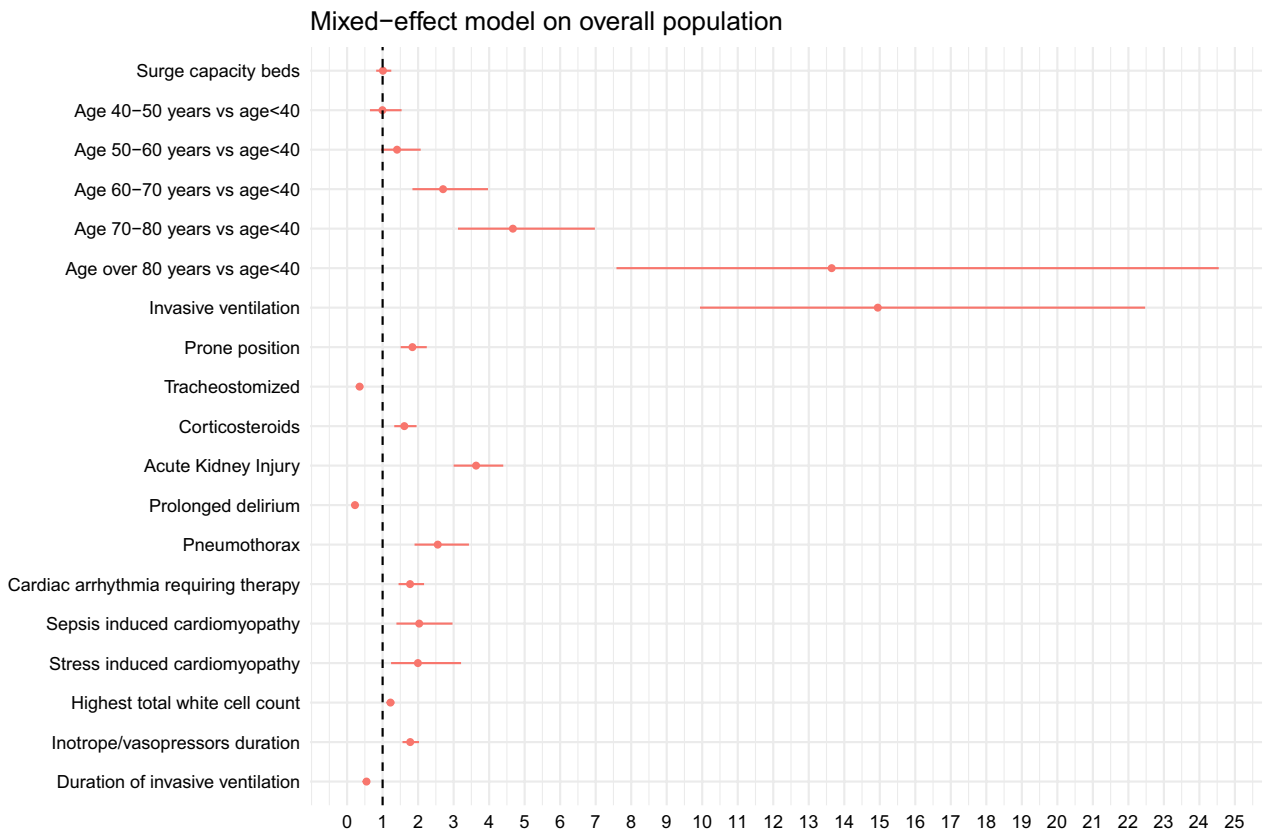

Fig. 1 Forest-plot results from multivariable mixed-effect model for mortality in the overall population, after multiple imputation (OR with 95% CI)

In most hospitals, standard capacity was insufficient for the number of patients requiring intensive care. Capacity was increased up to 155% in total for all participating hospitals. These separate crisis units reached the size of a medium to large ICU. Our findings are in line with previous reports. Kurtz et al. described a 133% increase in ICU available beds before and after the first COVID-19 wave [11]. Surge ICU beds were increased disproportionally compared to the lower-than-expected increase in the number of healthcare workers, with 2.5 (SD 1.1) patients per nurse during the surge vs 2 (SD 0.85) before the COVID pandemic. The patient-to-nurse ratios show that hospitals faced higher workload than their personnel capacity, a finding previously reported in other studies, with significant variations according to time and country [12, 13]. While a study from the Netherlands reported only a 10% increase in patients-per-nurse ratio, our data show an increase by about 25%, even though the large majority of ICUs employed non-ICU nurses to manage the workload (85% of units) [12]. ICUs increased the number of intensivists by 20% and residents by 44% compared to baseline, as well as allocating non-ICU clinicians to care for ICU patients in 58% of units.

In our study, 39.8% of the total number of patients were admitted to surge capacity beds. While overall the patient characteristics were not very different from those admitted to standard ICU beds, we found some differences: there was a slightly higher prevalence of IMV at ICU admission in surge beds. Extra-corporeal techniques of organ support such as CRRT and ECMO were more commonly used in standard ICU beds than in surge capacity beds, suggesting that patients with higher level of organ failure were more commonly admitted to standard ICU location, while single-organ failure patients were commonly treated in surge areas. The latter may also have influenced the type of drugs administered, as antivirals and corticosteroids were administered more commonly to patients in surge beds than in standard ICU beds. Another explanation may be the sequence of admissions of patients, with surge capacity beds progressively becoming occupied later during the course of the pandemic, as we can hypothesize that standard ICU beds were occupied first. As therapies evolved quickly during the first wave, patients who were admitted later may have been treated differently. Despite a higher prevalence of other organ failures in standard ICU beds on one

side and the huge pressure on hospitals and ICU teams on the other, mortality did not vary between surge vs standard ICUs in univariable analysis, nor in multivariable analysis when controlling for other factors. This is somehow surprising, considering that surge capacity beds were in most cases outside standard ICU locations, and that logistic and organizational factors including patient-to-nurse ratio are an important factor determining quality of care and outcomes for ICU patients [14, 15]. Our results suggest that ICU teams may have reallocated expert ICU resources evenly among surge and standard capacity beds, and selected more stable patients for surge capacity beds to balance for reduced organizational resources. From our data, we are only able to demonstrate the even distribution of resources between surge-capacity and standard ICU beds, implying that critical care teams were able to fairly allocate both expert personnel and multi-organ failure patients in the most appropriate areas. We cannot assess how the extreme operating conditions could have increased mortality, as intensified workload was a systemic issue in the large majority of involved ICUs. ICU teams apparently managed to limit the increase in patient-to-nurse ratio to 2.5, despite the significant increase in the total number of beds available. While this is a very significant increase in workload for the nurses, also considering the mandatory use of PPE that slowed down routine processes of care, it also suggests that ICU units were trying to preserve a pre-COVID patient-to-nurse ratio and were redistributing resources evenly to preserve patient safety. While the patient-to-nurse ratio was only slightly increased, we have no data on the nurses' level of expertise in caring for critically ill patients.

A similar conclusion can be reached regarding the impact of different centers on mortality, which we included as a random factor in the multivariable model and contributed relatively low to the variance of the model (adjusted ICC 0.23, Supplemental Fig. 2). Low contribution suggests that, when controlling for other factors, patient outcomes were explained mainly by the severity of COVID-19 disease and patient characteristics, rather than by organizational factors and differences in disease management among centers.

Not surprisingly, respiratory failure was the main reason for ICU admission, while admission for other COVID-19 related complications or reasons not directly related to COVID-19 were relatively uncommon, confirming previous findings from other studies on COVID-19 ICU admission [16, 17]. Invasive mechanical ventilation was required in 85% of patients during ICU stay, with 48% of patients already on IMV at ICU admission. Mortality in patients on IMV at ICU admission was 35.6%, while 72% of patients not on IMV at admission needed IMV later. These patients had higher mortality than patients requiring IMV at ICU admission (42.0% vs 35.6%, p value for difference < 0.001). Several studies have previously analyzed the best timing for initiation of IMV in COVID-19 patients, investigating whether early or delayed intubation was the best option, considering the specific characteristics of COVID-19 acute respiratory distress syndrome (ARDS) and possible risk of patient self-induced lung injury (P-SILI) [18, 19]. Our results confirm an association between intubation at a later stage and increased mortality. However, we cannot conclude from our data whether this is related to worsening of COVID-19 or the development of new complications, including infection, nor can we demonstrate a causal link.

Similar to previous findings, mortality of patients who never needed IMV was low [20]. These patients suffered from diabetes, chronic cardiac or chronic liver disease more often and were more frequently admitted to ICU for reasons other than respiratory failure, suggesting that they may represent a different category of patients who were admitted earlier to the ICU due to baseline comorbidities and at lower risk of mortality—a hypothesis also reflected by the high proportion of pregnant patients and healthcare workers in this group.

Respiratory support before ICU admission was common, with CPAP and NIV employed, respectively, in 10.7% and 5.2% of patients, although hospital stay before ICU admission was relatively short (IQR 1–4 days), indicative of the severity of illness in these patients.

Our population consisted mostly of male patients (71.4%), with half of the population having a history of hypertension and more than a third of patients suffering from obesity, well described risk factors for developing severe or critical COVID-19 [21, 22].

In multivariable analysis, IMV was the strongest predictor of mortality, increasing 14 times the odds for mortality. Age was strongly associated with mortality, a constant finding in the COVID-19 literature, with OR doubling to 2.7 at 60–70 years and doubling again between 70 and 80 years [14, 21].

The incidence of AKI was high in our population (42.6%), and AKI and need for RRT were strong predictors of mortality in multivariable analysis. AKI has been associated with unfavorable outcomes in COVID-19 since the first studies [23, 24]. It is commonly multifactorial, including potentially direct viral damage [25]. Silver et al. performed a systematic review on AKI prevalence in COVID-19 patients and reported a prevalence of 46% for AKI and 19% for RRT, comparable to our findings [26]. Similarly, a study by Gupta and colleagues reported a 20% incidence of RRT in COVID-19 ICU patients [20]. Lumlertgul and colleagues reported that 76% of critically

ill COVID-19 patients had AKI during the first wave of whom one-third needed RRT [27].

Pneumothorax doubled the mortality risk in this population (OR 2.5, 95% CI 1.8–3.4). Several studies have previously described an increased prevalence of barotrauma in COVID-19 patients, primarily pneumothorax and pneumomediastinum with reported incidences in the range of 7–20% [28, 29]. The occurrence of pneumothorax reflects both severity of underlying ARDS and direct lung damage as well as reduced lung compliance, and is a complication that can directly affect patient survival [30].

Both tracheostomy and prolonged delirium were associated with patient survival. Prolonged delirium can be interpreted as either a marker of a favorable evolution, or as the positive effect of strategies that minimize prolonged sedation on patient outcomes, such as daily sedation interruptions [31]. The incidence of delirium in this population was 25%, which is lower than what is reported in other COVID-19 studies [32]. While we did not record these data, we are aware of the many difficulties in adhering to delirium prevention strategies during the peaks of ICU admissions, such as daily sedation holds and reorientation through interactions with family members [31, 33]. Tracheostomy was used in 38.2% of patients on IMV at admission, at a median interval of 16 days after the start of IMV. Similarly, the association of tracheostomy and survival is not unexpected as tracheostomy is unlikely to be used in the early stage in patients who are unstable or more likely to die.

This study has the limitations of observational studies, including the impossibility of inferring causation between variables. We could not include all variables and related details including exact indications for organ support which could have improved the analysis, due to the difficulties in completing data collection at the end of the first wave of COVID-19 patients. We relied on the data entered in the clinical notes, and it is possible that not all events were recorded, and the prevalence of adverse events may even be higher. Finally, our data refer to the first wave, and conclusions may not apply to subsequent waves. However, our data represent one of the largest populations of critically ill COVID-19 patients, with data collected on the peak day of COVID-19 admissions when the strain was the highest. Also, we focused not only on the clinical effects and management of COVID-19, but also on organizational changes in response to the steep increase of critically ill patients.

Most of our centers were teaching hospitals that could allocate in-training staff such as residents to data collection, which may limit the applicability of these results to smaller centers that did not have the same staff available.

Conclusions

The first wave of the COVID-19 pandemic had a huge impact on ICUs globally, which responded by creating new ICU beds in non-ICU locations and reallocating staff from other areas, while trying to maintain pre-pandemic standards. Even distribution of resources among areas helped to ensure similar survival chances for patients admitted to surge capacity beds compared to standard ICU beds, implying equal stress on ICU workload between the two areas. The authors recognize that increased ICU workload could have reduced patient survival, but this systemic factor cannot be measured from our data due to the burdensome operating conditions in all the included ICU. Accordingly, overall mortality of this population remained high, with roughly 1 of 3 patients admitted to the ICU because of COVID-19 not surviving, similar to findings of previous studies. Invasive mechanical ventilation, AKI, and older age were strongest predictors of mortality in this population.

Supplementary Information
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