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The Lancet Regional Health - Europe

journal homepage: www.elsevier.com/lanepe

Research paper

Mortality comparison between the first and second/third waves among 3,795 critical COVID-19 patients with pneumonia admitted to the ICU: A multicentre retrospective cohort study

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ARTICLE INFO

Article History:

Received 15 August 2021

Revised 10 September 2021

Accepted 22 September 2021

Available online 4 November 2021

ABSTRACT

Background: It is unclear whether the changes in critical care throughout the pandemic have improved the outcomes in coronavirus disease 2019 (COVID-19) patients admitted to the intensive care units (ICUs).

Methods: We conducted a retrospective cohort study in adults with COVID-19 pneumonia admitted to 73 ICUs from Spain, Andorra and Ireland between February 2020 and March 2021. The first wave corresponded with the period from February 2020 to June 2020, whereas the second/third waves occurred from July 2020 to March 2021. The primary outcome was ICU mortality between study periods. Mortality predictors and differences in mortality between COVID-19 waves were identified using logistic regression.

Findings: As of March 2021, the participating ICUs had included 3795 COVID-19 pneumonia patients, 2479 (65.3%) and 1316 (34.7%) belonging to the first and second/third waves, respectively. Illness severity scores predicting mortality were lower in the second/third waves compared with the first wave according with the Acute

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Physiology and Chronic Health Evaluation system (median APACHE II score 12 [IQR 9–16] vs 14 [IQR 10–19]) and the organ failure assessment score (median SOFA 4 [3–6] vs 5 [3–7], $p < 0.001$). The need of invasive mechanical ventilation was high (76.1%) during the whole study period. However, a significant increase in the use of high flow nasal cannula (48.7% vs 18.2%, $p < 0.001$) was found in the second/third waves compared with the first surge. Significant changes on treatments prescribed were also observed, highlighting the remarkable increase on the use of corticosteroids to up to 95.9% in the second/third waves. A significant reduction on the use of tocilizumab was found during the study (first wave 28.9% vs second/third waves 6.2%, $p < 0.001$), and a negligible administration of lopinavir/ritonavir, hydroxychloroquine, and interferon during the second/third waves compared with the first wave. Overall ICU mortality was 30.7% ($n = 1166$), without significant differences between study periods (first wave 31.7% vs second/third waves 28.8%, $p = 0.06$). No significant differences were found in ICU mortality between waves according to age subsets except for the subgroup of 61–75 years of age, in whom a reduced unadjusted ICU mortality was observed in the second/third waves (first 38.7% vs second/third 34.0%, $p = 0.048$). Non-survivors were older, with higher severity of the disease, had more comorbidities, and developed more complications. After adjusting for confounding factors through a multivariable analysis, no significant association was found between the COVID-19 waves and mortality (OR 0.81, 95% CI 0.64–1.03; $p = 0.09$). Ventilator-associated pneumonia rate increased significantly during the second/third waves and it was independently associated with ICU mortality (OR 1.48, 95% CI 1.19–1.85, $p < 0.001$). Nevertheless, a significant reduction both in the ICU and hospital length of stay in survivors was observed during the second/third waves.

Interpretation: Despite substantial changes on supportive care and management, we did not find significant improvement on case-fatality rates among critical COVID-19 pneumonia patients.

Funding: Ricardo Barri Casanovas Foundation (RBCF2020) and SEMICYUC.

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Research in context

Evidence before this study

We searched PubMed for original peer-reviewed studies (from February 2020 and June 2021) investigating the trends in mortality and changes in critical care practices between pandemic waves in COVID-19 patients admitted to the intensive care unit (ICU), using the terms ‘coronavirus disease 2019’, ‘covid-19’, ‘mortality changes’, ‘wave comparison’, and ‘critically ill’. Data about trends in mortality throughout the COVID-19 pandemic among critically ill patients is scarce. Most available data describe trends in mortality during short study timeframes. We found no large-scale studies involving COVID-19 patients admitted to the ICU during the entire first year of the pandemic, evaluating the differences in outcomes between different waves.

Added value of this study

In a multicentre cohort study conducted in three countries in Europe among critically ill COVID-19 patients with pneumonia over the first year of the pandemic, we did not find significant differences in ICU mortality between the first wave and the second/third waves, despite the improvement in clinical experience along with changes in treatment approaches and respiratory support measures such as the remarkable increase in the use of non-invasive respiratory support during the second and third waves. Mortality predictors were the age, SOFA score, ischemic heart disease, immunosuppression, D-dimer, C-reactive protein, number of pulmonary infiltrates on chest radiograph, mild and moderate ARDS, HFNC failure, invasive mechanical ventilation, VAP, acute kidney injury, and myocardial dysfunction. Case-fatality rates during the second and third waves seemed to be higher in months with higher incidence of patients admitted to the participant ICUs, suggesting that the ICU demand and ICU bed capacity may be associated with outcomes.

Implications of all available evidence

No substantial reduction in mortality rates has been observed between the first and second/third waves of the pandemic among severely ill patients. These findings have major implications for the

fields of critical care and public health, because most of previous scientific research observing a decline in case-fatality rates were conducted within shorter study periods with different peaks of admissions rather than between waves, where lower ICU overload may affect the observed outcomes. Further research is needed to improve survival in critical care patients with COVID-19 and it is imperative to investigate how ICU demand may affect negatively the outcomes and to identify strategies to prevent healthcare system overload in the following waves.

Introduction

The coronavirus disease 2019 (COVID-19) continues to be a major health problem causing thousands of deaths daily worldwide [1], despite the fact that it has been over a year struggling with the disease and the understanding of its pathophysiology continues to grow exponentially to date [2]. The first wave hit health systems firmly leading hospital and intensive care units (ICUs) to collapse, resulting in large uncertainty regarding the nature of the new disease and the prognosis. This global burden of pandemic revealed that countries had scarce preparedness and resource shortage to confront a pandemic such as insufficient ICU beds, ventilators, and personal protective equipment for health workers [3].

The World Health Organization warned that the pandemic was unfolding in “one big wave” with no evidence that it followed seasonal variations common to other viruses. However, the lockdown policies and social distancing measures facilitated to partially control the initial surge. With the subsequent easing in isolation measures, the spread of the virus increased triggering the rise in infection rates and the pandemic was back with the second and third waves [4]. Unlike in the first wave, where evidence about the COVID-19 was limited, in the second and third waves scientific understanding of the disease heightened and consequently, healthcare systems engaged in delivering a better medical response. The experience from the first months of the pandemic along with the overwhelming amount of scientific evidence to identify mortality risk factors and to test respiratory support measures and drug’s effectiveness, allowed the physicians to face the following waves of the pandemic with greater expertise. Notwithstanding, the mortality among critical COVID-19

patients remains unacceptably high [5], and it is unclear if the aforementioned improvements in critical care have truly changed outcomes.

We aimed to compare trends in mortality between the first and the second/third waves of the pandemic among critically ill patients with COVID-19 pneumonia.

Methods

Study design

This was an observational and retrospective cohort study with prospectively collected data of COVID-19 patients involving 73 ICUs (seventy-one from Spain, one from Andorra, and one from Ireland). Between February 22, 2020 and March 11, 2021, consecutive critical COVID-19 patients were included in a large-scale patient database supported by the SEMICYUC (Spanish Society of Intensive Care Medicine and Coronary Units). The pandemic in Spain initiated with the first cases in February, peaked in March and lasted until June 2020, when infection rates steadily decreased. Subsequently, on July, the cumulative incidence of COVID-19 raised progressively up to 50 cases per 100,000 inhabitants (week 32) [6]. Therefore, the timepoint that separated the end of the first wave and the beginning of the second wave was established on July 1, 2020. The persistent incidence of cases admitted to the ICU between the second and third waves, contributed to a lack of clear time gap between them, hence the study was divided into two timeframes: the first wave (from February 2020 to June 31, 2020) and the second/third waves (from July 1, 2020 to March 31, 2021). The follow-up time was defined from ICU admission to hospital discharge or death.

The inclusion criteria were adults admitted to any of the participating ICU and who met the criteria of COVID-19 pneumonia and acute respiratory failure. For the current study, we only excluded subjects with missing data on outcomes. The referral Ethics Committee of Joan XXIII Hospital approved the study (IRB# CEIM/066/2020) and the Committee board at each participating center approved the inclusion of patients. The informed consent was waived because all data were de-identified by removing patient's name and medical record number. The study was registered in ClinicalTrials.gov (NCT04948242) and followed the Strobe guidelines ([Supplementary material](#)).

Data collection

Demographic and clinical data of the patients participating in the study were recorded into a case report form. After anonymizing the data, the forms were sent to the Study Coordinator and all the information was entered in the COVID-19 SEMICYUC registry by two different Data Entry Investigators and validated after data accuracy confirmation. Collected data included demographic characteristics (age, gender, and body mass index), comorbidities, time course of the illness (dates of the symptoms onset, diagnosis, hospital admission, and ICU admission), laboratory test, microbiologic results, radiological findings, respiratory support (non-invasive and invasive) at ICU admission and at day one, complications and organ support measures, treatments used, and outcomes ([Supplementary Table 1](#)). Data on the use of antithrombotic prophylaxis and anticoagulation were not collected, even though the recommendations of the SEMICYUC were followed [7]. Disease severity was evaluated at 24 h of ICU admission using the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score. Patients with acute respiratory distress syndrome (ARDS) were classified in mild, moderate and severe according to the oxygenation impairment if all the criteria of the Berlin definition were met [8]. Clinical practice decisions such as the indication for intubation, the use of specific respiratory support devices

and treatments were left to the discretion of the attending physician.

COVID-19 diagnosis was confirmed with a positive reverse transcription-polymerase chain reaction for SARS-CoV-2 of collected specimens from the upper (naso/oropharyngeal swabs) or lower respiratory tract (tracheal aspirate or bronchoalveolar lavage). COVID-19 pneumonia was diagnosed when individuals developed clinical signs of pneumonia with acute respiratory failure and pulmonary involvement with lung infiltrates on chest imaging [9]. Ventilator-associated pneumonia (VAP) was diagnosed as a microbiologically confirmed pneumonia developed in patients under invasive mechanical ventilation for at least 48 h [10].

Outcomes

Primary outcome was to compare all-cause ICU mortality between the first and second/third waves. Secondary outcomes were to compare risk factors associated with ICU mortality, ICU and hospital length of stay in survivors, mechanical ventilation days, ventilator-free days at 28 days, incidence density of ventilator associated pneumonia, and in-hospital mortality in the first versus second/third waves.

Statistical analysis

No statistical sample size calculation was made and sample size was equal to the number of patients admitted to the participating ICUs during the study period. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as medians (interquartile ranges [IQR]). For baselines characteristics, differences between groups were assessed using chi-squared or Fisher's exact tests for categorical variables and the Mann-Whitney U test for continuous variables. Significant differences were considered if P values were < 0.05 for a two-tailed test. There were missing data because of the challenges on data collection during the pandemic and proportions of missing data are reported in the [Supplementary Figure 1](#). Missing data were not imputed as most of explanatory variables had very low rate of missing values (lower than 10%). Primary endpoint was investigated through a binary logistic regression to evaluate the risk factors associated with ICU mortality including the variable of interest (wave) to assess differences in mortality between study waves. Factors included in the model were those with statistical significance in the univariable analysis. The results of the multivariable analysis were reported as odds ratios (OR) with the 95% confidence intervals (CI).

To evaluate whether a center effect could alter observed mortality, a multilevel logistic regression analysis through a conditional random intercept model was performed to investigate hospital level or inter-hospital (as random-effects) variation of ICU mortality [11]. center level variation was assessed classifying hospital according the total number of beds (< 200 , $200-500$, and >500). The regression coefficients were summarized as the variance with standard deviation (SD) and the interclass correlation coefficient (ICC).

Ventilator-free days at 28 days were calculated as the number of days with successful cessation (alive and free) from invasive mechanical ventilation (IMV) for at least 48 h without reintubation in patients who survived 28 days after ICU admission, whereas for patients ventilated 28 days or more, or who died within 28 days (irrespective of IMV status), ventilator-free days were zero [12]. Results were presented as means with SD.

The incidence density of ventilator-associated pneumonia (VAP) for each study period was calculated as follows: number of episodes of VAP/number of ventilator days) $\times 1000$ = VAP rate per 1000 ventilator days. Data analysis were done with SPSS version 24 (IBM Corp. Armonk, NY, USA) and R software (cran.r-project.org).

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, interpretation of data, the writing of the report, or in the decision to submit the paper for publication.

Results

Between February 22, 2020 to March 11, 2021 a total of 4011 patients with confirmed COVID-19 pneumonia were recruited. Two hundred and sixteen patients were excluded because of missing data on study outcomes. In total, 3795 patients met the inclusion criteria, of whom 2479 ($n = 65.3\%$) were admitted during the first wave and 1316 ($n = 34.7\%$) during the second/third waves (Fig. 1). Clinical characteristics of the cohort and differences between waves are shown in Table 1. Most patients were men (70.8%, $n = 2686$) and the median age was 64 years (IQR 55–71), with a median APACHE II and SOFA scores of 14 (IQR 10–18) and 4 (IQR 3–7), respectively. Hypertension was the most common comorbidity (46%, $n = 1751$), closely followed by obesity (35.7%, $n = 1356$), and diabetes (22.9%, $n = 868$). High rate of patients fulfilled the ARDS criteria ($n = 2987$, 78.7%) and the median arterial oxygen partial pressure to fractional inspired oxygen ratio was 122 (IQR 85–177) mmHg.

Comparison of clinical characteristics and management between waves

Subjects in the second/third waves had lower illness severity scores compared with those in the first wave according to the APACHE II (12 [9–16] vs 14 [IQR 10–19] $p < 0.001$) and SOFA (4 [3–6] vs 5 [IQR 3–7] $p < 0.001$). During the second/third waves, there was higher incidence of chronic cardiovascular diseases such as hypertension (49.4% vs 44%, $p = 0.04$), diabetes (26.7 vs 20.9%, $p < 0.001$), and obesity (42.3% vs 32.2%, $p < 0.001$). Patients in the second/third waves were diagnosed with COVID-19 earlier (4 days [2–6] vs 7 days [4–9] $p < 0.001$) than those in the first wave, however, the time from symptom onset to either the hospital or ICU admission did not differ between periods.

Respiratory support with high flow nasal cannula (HFNC) significantly increased through the pandemic, used as the first line of oxygen therapy on admission in almost half of the patients in the second/third waves unlike the first wave (48.7% vs 18.2%, $p < 0.001$).

HFNC failure was more frequently observed during the second period (29.2% vs 11.7%, $p < 0.001$), and the time to failure with HFNC was also longer (48 [13–102] vs 24 [12–72] hours, $p = 0.008$). The use of non-invasive mechanical ventilation was low during the first and the second/third waves, as well (5.2% vs 6.8%, $p = 0.09$). The need of IMV was high during the whole pandemic ($n = 2888$, 76.1%) without significant differences between periods. More than half of the patients ($n = 2269$, 59.8%) needed prone position due to ARDS, with a slight reduction in the prone therapy during the second/third waves (62.4% vs 54.8%, $p = 0.001$). The rate of extracorporeal membrane oxygenation remained low during the study period ($n = 81$, 2.1%).

Treatments prescribed between study waves were completely different. There was a large decrease in the second/third waves in the use of lopinavir/ritonavir, hydroxychloroquine and interferon (81.2% vs 2.4%, 93.3 vs 0.4%, and 37.1% vs 0.2%, respectively; $p < 0.001$) compared with the first wave. A significant reduction was also found with tocilizumab therapy during the second/third phase of the pandemic. Conversely, corticosteroid treatment was widely used in both study periods, although in the second/third wave almost all patients received corticosteroids.

The use of vasopressors (42.3% vs 23.3%, $p < 0.001$), acute kidney injury (29.2% vs 22.6%, $p = 0.008$), and community-acquired respiratory coinfection (9.6% vs 7.6%, $p = 0.03$) was more frequent in the first wave, whereas the development of VAP was significantly higher (24.9% vs 18%, $p < 0.001$) in the second/third waves. We observed many similarities in the clinical management among countries (Supplementary Tables 2–3).

Mortality analysis

Overall ICU mortality was 30.7% ($n = 1166$), without significant differences between waves (Table 2). Monthly un-adjusted mortality varied over time with a trend towards an increase when higher incidence of cases admitted to ICU was observed during second/third waves, despite that illness severity scores remained unchanged (Fig. 2). Stratified age-related ICU mortality showed higher case-fatality rates among adults aged more than 75 years (Supplementary figure 2). No significant differences were found in mortality between waves according to age subsets except for the subgroup of 61–75 years of age, in whom a reduced unadjusted ICU mortality was observed in the second/third waves. Non-survivors were older,

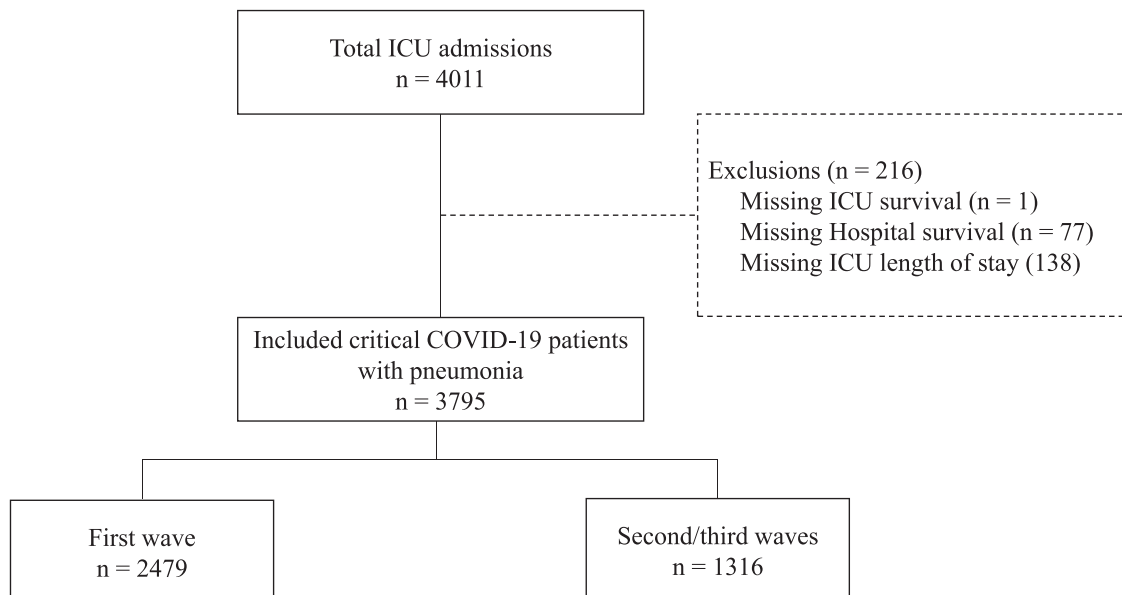


Fig. 1. Flowchart of the study.

Table 1

Baseline characteristics and comparison between the first and second/third waves of COVID-19 patients with pneumonia admitted in ICU. Data are expressed as numbers (%) or medians (IQR). Diagnosis gap is the time between the symptom onset and confirmed diagnosis. Hospital gap is the time between the symptom onset and hospital admission. ICU gap is the time between hospital admission and ICU admission.

	All patients (n = 3795)	First wave (n = 2479)	Second/third waves (n = 1316)	P value
General characteristics				
Age (years)	64 (55–71)	64 (55–71)	63 (53–71)	0.05
Gender (male)	2686 (70.8%)	1744 (70.4%)	942 (71.6%)	0.42
BMI (kg/m ²)	28 (26–32)	28 (25–31)	29 (26–32)	<0.001
Comorbidities				
Hypertension	1751 (46.1%)	1101 (44.4%)	650 (49.4%)	0.04
Obesity (>30 Kg/m ²)	1356 (35.7%)	799 (32.2%)	557 (42.3%)	<0.001
Diabetes mellitus	868 (22.9%)	517 (20.9%)	351 (26.7%)	<0.001
Dyslipidaemia	305 (8%)	227 (9.2%)	78 (5.9%)	<0.001
COPD	269 (7.1%)	172 (6.9%)	97 (7.4%)	0.62
Asthma	245 (6.5%)	161 (6.5%)	84 (6.4%)	0.69
Ischemic heart disease	248 (6.5%)	165 (6.7%)	83 (6.3%)	0.68
Immunosuppression	213 (5.6%)	104 (4.2%)	109 (8.3%)	<0.001
Chronic kidney disease	203 (5.3%)	114 (4.6%)	89 (6.8%)	0.005
chronic heart failure	132 (3.5%)	74 (3%)	58 (4.4%)	0.02
Hematological disease	121 (3.2%)	86 (3.5%)	35 (2.7%)	0.12
Chronic liver disease	25 (0.7%)	17 (0.7%)	8 (0.6%)	0.77
Course of illness (days)				
Diagnosis gap	6 (3–8)	7 (4–9)	4 (2–6)	<0.001
Hospital gap	7 (4–9)	7 (4–9)	7 (4–9)	0.28
ICU gap	2 (0–4)	2 (0–4)	2 (0–4)	0.77
Severity of illness				
APACHE II score ^a	14 (10–18)	14 (10–19)	12 (9–16)	<0.001
SOFA score ^b	4 (3–7)	5 (3–7)	4 (3–6)	<0.001
Pulmonary infiltrates (quadrants) [*]	3 (2–4)	3 (2–4)	3 (2–4)	0.02
PaO ₂ /FiO ₂ (mmHg) [*]	122 (85–177)	128 (87–186)	125 (90–180)	0.32
No ARDS	173 (4.6%)	125 (5%)	48 (3.6%)	0.54
ARDS [*]	2987 (78.7%)	1889 (76.2%)	1098 (83.4%)	<0.001
Mild	476 (12.5%)	310 (12.5%)	166 (12.6%)	0.92
Moderate	1470 (38.7%)	912 (36.8%)	558 (42.4%)	0.001
Severe	1041 (27.4%)	667 (26.9%)	374 (28.4%)	0.32
Unknown ARDS severity [#]	635 (16.7%)	465 (18.8%)	170 (13%)	<0.001
Laboratory data[*]				
White blood cells count (10 ⁹ /ml)	8.7 (6.2–12.4)	8.4 (6.0–12.2)	9.3 (6.6–13.0)	<0.001
C-reactive protein (mg/dl)	14 (7.3–22.9)	15 (8.3–24.2)	11 (6.4–19.2)	<0.001
Procalcitonin (ng/ml)	0.21 (0.1–0.56)	0.26 (0.12–0.63)	0.15 (0.08–0.40)	<0.001
D-dimer (ng/ml)	1008 (584–2275)	1100 (608–2781)	891 (549–1744)	<0.001
Respiratory support and oxygenation				
COT [*]	576 (15.2%)	418 (16.9%)	158 (12%)	<0.001
PaO ₂ /FiO ₂ (mmHg)	115 (77–175)	113 (75–177)	118 (90–171)	0.53
HFNC [*]	1091 (28.7%)	450 (18.2%)	641 (48.7%)	<0.001
PaO ₂ /FiO ₂ (mmHg)	107 (78–148)	100 (74–138)	113 (83–160)	<0.001
NIV [*]	219 (5.8%)	130 (5.2%)	89 (6.8%)	0.09
PaO ₂ /FiO ₂ (mmHg)	115 (85–152)	113 (78–159)	116 (91–151)	0.60
IMV [*]	1788 (47.1%)	1367 (55.1%)	421 (32%)	<0.001
PaO ₂ /FiO ₂ (mmHg)	138 (92–196)	142 (94–200)	125 (90–186)	0.02
IMV at 24 h	2486 (65.5%)	1701 (69.6%)	785 (59.7%)	<0.001
PaO ₂ /FiO ₂ (mmHg)	184 (136–245)	185 (136–246)	178 (136–236)	0.19
HFNC failure	675 (17.8%)	291 (11.7%)	384 (29.2%)	<0.001
Hours of failure	36 (12–96)	24 (12–72)	48 (13–102)	0.008
Unknown support at admission	121 (3.2%)	111 (4.4%)	7 (0.5%)	<0.001
Prone position	2269 (59.8%)	1548 (62.4%)	721 (54.8%)	<0.001
ECMO	81 (2.1%)	51 (2.1%)	30 (2.3%)	0.64
Organ failure and complications				
Invasive mechanical ventilation	2888 (76.1%)	1958 (79%)	930 (70.7%)	0.23
Shock [*]	1355 (35.7%)	1049 (42.3%)	306 (23.3%)	<0.001
Acute kidney injury [*]	1021 (26.8%)	723 (29.2%)	298 (22.6%)	0.008
Myocardial dysfunction [*]	358 (9.4%)	245 (9.9%)	113 (8.6%)	0.23
CARC [*]	339 (8.9%)	239 (9.6%)	100 (7.6%)	0.03
Ventilator-associated pneumonia	775 (20.4%)	446 (18%)	328 (24.9%)	<0.001
Treatments[*]				
Antibiotics	3114 (82.1%)	2308 (93.1%)	806 (61.2%)	<0.001
Corticosteroids	2706 (71.3%)	1444 (58.2%)	1262 (95.9%)	<0.001
Tocilizumab	798 (21%)	716 (28.9%)	82 (6.2%)	<0.001
Remdesivir	254 (6.7%)	42 (1.7%)	212 (16.1%)	<0.001
Lopinavir/ritonavir	2044 (53.9%)	2013 (81.2%)	31 (2.4%)	<0.001
Hydroxychloroquine	2317 (61.1%)	2312 (93.3%)	5 (0.4%)	<0.001
Interferon beta	922 (24.3%)	920 (37.1%)	2 (0.2%)	<0.001

ICU, intensive care unit; BMI, body mass index; COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Assessment Failure; PaO₂/FiO₂, arterial oxygen partial pressure to fractional inspired oxygen ratio; ARDS, acute respiratory distress syndrome; COT, conventional oxygen therapy; HFNC, high flow nasal cannula; NIV, non-invasive ventilation; IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation; CARC, community-acquired respiratory coinfection.

^a Calculated as the worst value within the first 24 h of ICU admission.

^b Calculated within the first 24 h of ICU admission.

^{*} At admission.

[#] The severity is unknown due to missing data on PaO₂/FiO₂ values.

Table 2

Comparison of clinical outcomes between the first and second/third waves among COVID-19 patients with pneumonia admitted to the ICU. Data are expressed as numbers (%) or medians (IQR).

	All patients (n = 3795)	First wave (n = 2479)	Second/third waves (n = 1316)	P value
Outcomes				
ICU LOS (days)				
Survivors	14 (7–9)	15 (8–29)	12 (7–27)	<0.001
Non-survivors	16 (8–26)	15 (8–25)	19 (12–29)	<0.001
Hospital LOS (days)				
Survivors	28 (18–46)	31 (20–48)	24 (15–41)	<0.001
Non-survivors	19 (11–30)	18 (9–29)	23 (14–32)	<0.001
Hospital LOS (days)	19 (11–30)	18 (9–29)	23 (14–32)	<0.001
Duration of MV (days) ^a	15 (9–27)	15 (9–27)	15 (8–32)	0.02
VFD-28 (days)	7.3 (±8.9)	7.3 (±8.8)	7 (±9.1)	0.48
ICU mortality	1166 (30.7%)	787 (31.7%)	379 (28.8%)	0.06
Hospital mortality	1234 (32.5%)	834 (33.6%)	400 (30.4%)	0.04

ICU, Intensive Care Unit; LOS, length of stay; MV, mechanical ventilation; VFD, Ventilator-free at 28 days.

^a In patients under invasive mechanical ventilation.

with higher severity of the disease, had more comorbidities, and developed more complications (Supplementary Table 4) compared with survivors. After multilevel modeling, no center effect was found on ICU mortality according to hospital variation (variance 0.39, SD 0.63; ICC 0.10) neither to the hospital size level (variance 0.001, SD 0.04; ICC 0.0004). A sensitivity analysis focused only on Spanish hospitals showed consistency of the results, since no center effect was found.

In the multivariate analysis (Fig. 3), the factors independently associated with ICU mortality were the age (OR 1.06, 95% CI 1.05–1.07, $p < 0.001$), immunosuppression (OR 2.05, 95% CI 1.39–2.99; $p < 0.001$), ischemic heart disease (OR 1.65, 95% CI 1.14–2.37, $p = 0.007$), SOFA score (OR 1.06, 95% CI 1.02–1.11; $p = 0.004$), number of pulmonary infiltrates on the chest radiograph (OR 1.13, 95% CI 1.02–1.26; $p = 0.02$), mild ARDS (OR 0.59, 95% CI 0.40–0.87; $p = 0.009$), moderate ARDS (OR 0.65, 95% CI 0.47–0.88, $p = 0.006$), D-dimer (OR 1.00, 95% CI 1.00–1.00; $p = 0.03$), C-reactive protein (OR 1.01, 95% CI 1.01–1.02; $p = 0.002$), invasive mechanical ventilation (OR 2.24, 95% CI 1.71–2.89; $p < 0.001$), acute kidney injury (OR 2.69, 95% CI 2.17–3.34, $p < 0.001$), myocardial dysfunction (OR 2.70, 95% CI 2.01–3.64, $p < 0.001$), ventilator-associated pneumonia (OR 1.48, 95% CI 1.19–1.85, $p < 0.001$), and HFNC failure (OR 1.74, 95% CI 1.29–2.34; $p < 0.001$). After confounding adjustment, no significant association

was found between ICU mortality and COVID-19 waves (OR 0.81, 95% CI 0.64–1.03; $p = 0.09$, Fig. 3).

Secondary outcomes

An increase in the incidence density of VAP was observed from 12.0 in the first wave to 16.5 episodes per 1000 days of mechanical ventilation in the second/third waves. The causative microorganisms of VAP are shown in Supplementary Table 5. *Pseudomonas aeruginosa* was the most common pathogen isolated from the respiratory samples, almost in one third of the patients with VAP during the study period. *Aspergillus* spp. was responsible of the infection etiology in 50 (6.5%) patients diagnosed with VAP, with a significant increase of this isolation during the second/third waves (3.8% vs 10%, $p < 0.001$).

There was a reduction in the LOS in the second/third waves compared to the first wave among survivors (median ICU LOS 12 [IQR 7–27] vs 15 [IQR 8–29], $p < 0.001$; hospital LOS 24 [IQR 15–41] vs 31 [IQR 20–48], $p < 0.001$). Unadjusted in-hospital mortality was lower in the second/third waves but, after adjusting for confounding factors these differences were no longer observed (COVID-19 wave OR 0.83, 95% CI 0.67–1.04; $p = 0.10$ in the Supplementary Table 6–7). The remaining secondary outcomes are shown in Table 2.

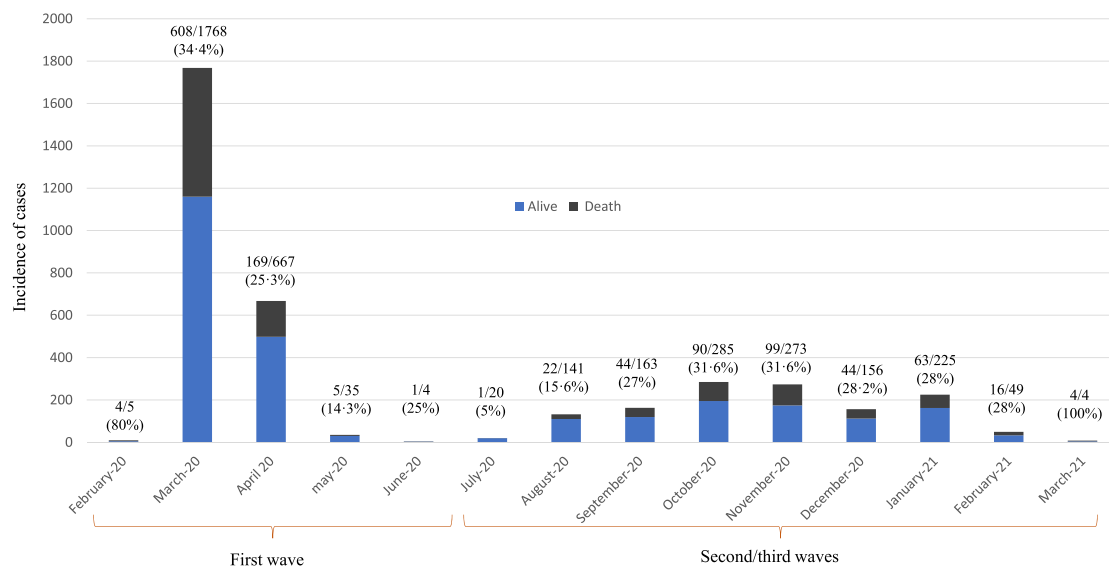


Fig. 2. Monthly incidence of ICU case-fatality rates throughout the pandemic between waves. Data represents N° deaths/Total N° admitted cases. Observed mortality increased during the first months in the second/third waves (August to November) when the incidence of cases admitted to the ICU raised up, despite that severity scores (APACHE II and SOFA scores) remained unchanged. ICU, Intensive Care Unit; APACHE, Acute Physiology And Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

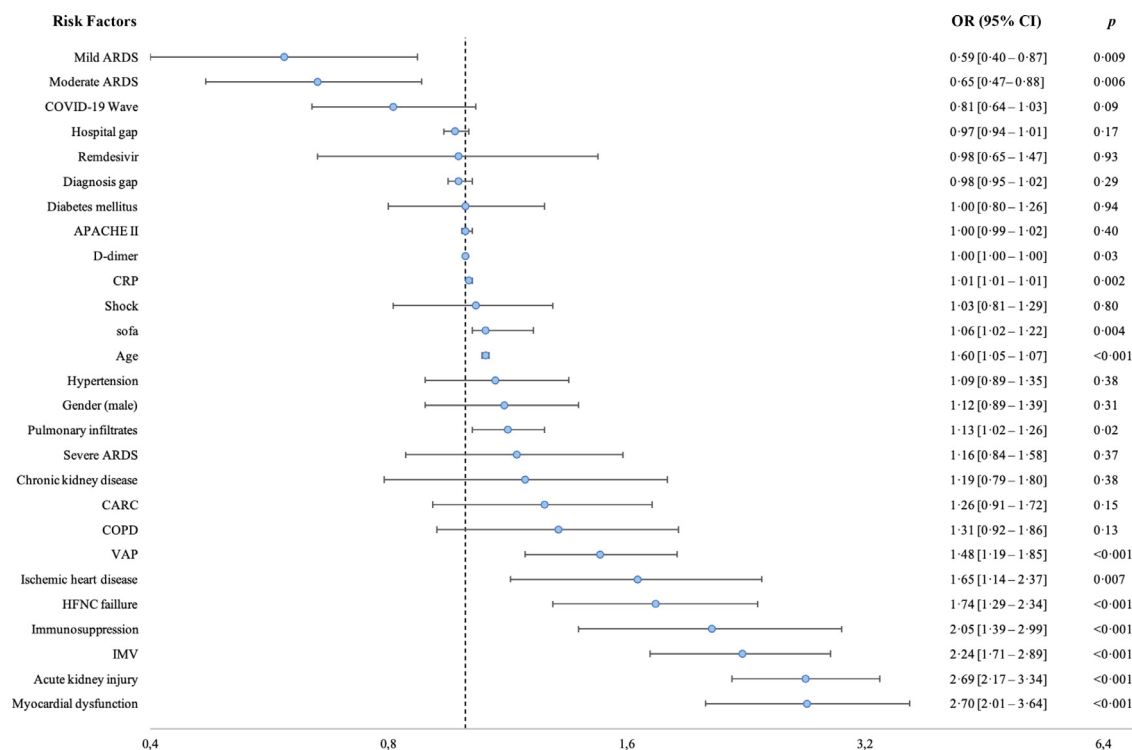


Fig. 3. Forest plot of the logistic regression analysis with ICU mortality predictors. Hospital gap was the time between the symptom onset and hospital admission. Diagnosis gap was the time between the symptom onset and the confirmation of COVID-19 diagnoses. OR, Odds ratio; ARDS, acute respiratory distress syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; sofa, Sequential Organ Failure Assessment; CARC, Community-acquired respiratory co-infection, COPD, chronic obstructive pulmonary disease; VAP, ventilator-associated pneumonia; HFNC, high flow nasal cannula; IMV, invasive mechanical ventilation.

Discussion

In this multicentre cohort study of critical COVID-19 patients with pneumonia, we did not find differences in the mortality rates between the first and second/third waves during the first year of the pandemic. These results have been observed after adjusting for several confounding factors. Although critical care practices have substantially changed during the study period, case-fatality rates among patients admitted to the ICU remain unaltered and high.

Our findings differ from those reported previously, in which a decline in mortality was observed over time using different outcomes and time periods [13–18]. Potential explanations of mortality reduction have been suggested, such as better healthcare organization avoiding the ICU overload, improvements in critical care management with changes in respiratory support and treatment approaches, presence of less virulence circulating virus strains, and changes in patient's characteristics with different predictors of mortality. Most of these studies include case-mixes from the ward and critical care units, where the range of fatality rates is considerably different and thereby potential selection bias could be present. Contrary, other authors did not find differences in inpatient mortality after propensity score matching, remaining as high in the first as in the second wave [19].

Two large multicentre cohort studies focused on critically ill patients with COVID-19 also reported a decrease of the mortality over time. The study reported by Kurtz and colleagues [20] conducted in Brazil, found a reduction in 60-day in-hospital mortality in the last two periods of the eight-month study. However, the overall 60-day mortality was surprisingly low compared with ICU patients in our study suggesting that those patients were clearly distinct populations. Notably, 60-day mortality among invasive mechanically ventilated patients remained above 50% during the four periods of the study with no apparent decrease. In fact, in our cohort, where three out of four patients received IMV, the ICU mortality rate was not different between waves. A reduction in the 90-day mortality has also

been observed over time in critically ill COVID-19 patients in a multicentre study conducted in three European countries with a more similar population to our study [21]. Nevertheless, these findings were based on the unadjusted 90-day mortality within a four-month study period. Actually, we found a decrease in the unadjusted in-hospital mortality during the second/third waves compared with the first wave, differences that no longer were observed after adjusting for numerous confounding factors. In spite of the fact that no significant differences on mortality were found after adjusting for confounding, the trend toward a decrease both in the un-adjusted hospital mortality and ICU mortality in the subset of age between 61 and 75 years, suggest that some clinical/practical changes in the case-fatality rates could be present.

The changes in the mortality rates during the course of the pandemic around the world could be difficult to interpret due to the fact that COVID-19 waves occurred in different stages, periods of time, and among patients with diverse underlying medical conditions [22]. For instance, African continent countries had experienced more severe second wave than the first [23]. Moreover, recent studies have reported association of increased mortality with hospital load [24] and strains on critical care capacity.[25] Likewise, our data showed oscillations on the mortality rates over time with a trend toward higher ICU-mortality rates when higher incidence of cases admitted to the ICU was observed during the pandemic. These findings could affect the observed rebound of ICU mortality around 30% during the second/third waves in months when the ICU bed capacity peaked above 25% in Spain indicating extreme risk level (in late October to the end of November 2020 and January to February 2021) [26]. Better understanding on how ICU demand in periods with health-care system overload may be associated with increased mortality among critically ill patients warrants further clinical research. Therefore, investigating the changes of mortality over time should also be evaluated between waves, when the rapid surge of patients could affect negatively patient's outcomes. The cornerstone to control the

pandemic and mortality rates are the widespread administration of vaccines. The start of the vaccination program in Spain was on December 27, 2020, hence at the end of the study follow up the rate of national immunization still was extremely low. To explore the consequences of vaccination on mortality rates is mandatory in the near future.

We further identified case-fatality independent predictors such as the age, SOFA score, ischemic heart disease, immunosuppression, D-dimer, C-reactive protein, number of pulmonary infiltrates on chest radiograph, mild and moderate ARDS, HFNC failure, invasive mechanical ventilation, VAP, acute kidney injury, and myocardial dysfunction. These results coincide with those mortality risk factors observed in other studies of critical COVID-19 patients [20,21,27]. Our analysis showed some differences in patient's characteristics during the second/third waves such as lower illness severity scores and higher rates of underlying cardiovascular disease, but these factors were not found as independent predictors of mortality. Nevertheless, the appearance of immunosuppression, community-acquired respiratory co-infection and longer timeframe from hospital to ICU admission, definitely contributed to higher mortality in the second/third waves.

A notable increase of the use of non-invasive respiratory support (NIRS) as the first line therapy has been recognized throughout the pandemic, similar to previous data [13,20,28]. Specifically, the HFNC was used upon admission almost in half of subjects in the second/third waves compared with the 18% during the first. Observational data suggested benefit from the use of HFNC with an increase in ventilator-free days and reduction in ICU length of stay compared to early initiation of invasive mechanical ventilation [29]. However, among the users of such respiratory support, the rate of HFNC failure was around 60% of cases over the pandemic and the time to failure was 24 h longer during the second/third compared with the first wave. While the increasing use of NIRS appears to be evident and potential impact on outcomes are currently under investigation through ongoing trials (NCT04424836, NCT04668196), whether the HFNC failure could affect negatively in clinically relevant outcomes warrant further research and to identify concrete predictors of NIRS failure might help clinicians in daily practice [30].

Not only significant changes on the respiratory support were found between the study periods but also substantial changes on treatment used to combat the virus. Important increase on the use of corticosteroids to up to 95% of patients in the second/third waves was observed since the release on July 2020, of the results of the RECOVERY trial in which a reduction in 28-day mortality was found in patients with acute respiratory failure among those who were receiving either invasive mechanical ventilation or oxygen alone [31]. Lower use of tocilizumab and remdesivir was found due to lack of benefit on survival from RCTs among severe COVID-19 patients [32,33]. Notwithstanding, a recent RCT also conducted by the RECOVERY Collaborative group [34] have reported that tocilizumab improved survival in hospitalized patients with COVID-19 with hypoxia and systemic inflammation regardless of the amount of respiratory support. Future changes beyond these results could yield an upturn of the use of tocilizumab in the following months.

Possible explanations for the lack of improvement in survival in our study may be the insufficient knowledge of the disease (for instance the better respiratory support management), the shortage of some effective antiviral treatment, and the alleged inability of the health systems to control the ICU capacity strain resulting from increased patient volume during the peaks of the waves. Moreover, the significant reduction on the use of tocilizumab during the second/third could be an additional reason for the incessant mortality, since the results of the RECOVERY trial [34] were released in May 2021, beyond the end of the third wave of the pandemic in Spain.

It is worth mentioning that the administration of antibiotics on ICU admission was markedly high despite the viral etiology of the disease besides the lower incidence of CARC. The overuse and wrong

consumption of antibiotics could lead to catastrophic effects on antimicrobial resistance hence, even during a pandemic, antibiotics should be reasonably used. As one of the biggest threats to global health which yields a major concern, current control policies to handle multidrug resistant microorganisms and prioritization of antibiotic stewardship programs are mandatory [35]. A further important finding of the study was that the incidence density of VAP significantly raised up to 16.5 episodes per 1000 days of mechanical ventilation during the second/third waves, an issue that could impact on outcomes as it has been associated with increased 28-day mortality rates and longer mechanical ventilation duration and ICU length of stay in SARS-CoV-2 patients [36]. These results coincide with ours since VAP was independently associated with increased ICU mortality (OR 1.48, 95% CI 1.19–1.85; $p < 0.001$). The observed increase on the incidence of VAP during the second/third wave could be explained by the higher incidence of immunosuppression, higher rate of ARDS with a trend toward longer duration of mechanical ventilation along with common use of corticosteroids.

Strengths of this study are the large number of critically ill COVID-19 patients included, the multicentre design and the comparison of the adjusted mortality rates between pandemic waves within a one year-study period. Nevertheless, some limitations should be acknowledged. First, the observational nature of the study implies that possible unmeasured confounders could affect the outcomes. Second, the study was conducted in three countries in Europe (mostly in Spain), therefore, the results may not be extrapolated to other world regions. Moreover, only one ICU from Ireland contributed in the inclusion of patients, which implies that clinical management might not reflect the critical care practices across the entire country. Nevertheless, we observed many comparable medical attitudes in the management of patients among the three countries. Third, the study evolved in 73 different ICUs which might entail different criteria for the respiratory support management and therapeutic attitudes. However, we found similarities of these management approaches and medical skills in other studies, which entails that routinary critical care practices have been carried out. Further, we assessed the possible center effect on ICU mortality, accounting for chance imbalances between centres and providing firmer results. Fourth, we could not assess the association of the ICU overload and mortality due to lack of data regarding the ICU bed capacity and expansion. However, we observed variations in ICU mortality depending on the monthly cumulative incidence of admitted cases. Fifth, longer follow up such as 60 or 90-day mortality were not evaluated. Reporting short-term end-points is not enough and the investigation of long-term outcomes can be highly important in critical care setting. Sixth, the study period has been conducted before the broad implementation of vaccination programs and global immunization may contribute to substantial reduction in case-fatality rates. Seventh, we focused on all-cause ICU mortality. To be able to better interpret mortality rates, more data of the specific causes of death in COVID-19 are needed. Eighth, missing data in our study is acknowledged. The impact of missing data on clinical research can be serious, leading to biased results and decreased statistical power. However, there were no missing data on the primary or secondary end-points, and missing values were low for the most of explanatory variables. Finally, we did not collect data from the current circulating virus strains which also could alter the results.

In conclusion, despite the improvement in clinical experience and growing knowledge for the management of this challenging infectious disease along with changes in therapy approaches and respiratory support measures, we did not find significant differences between waves neither in the ICU nor in-hospital mortality after accounting for several confounding factors. It is imperative to continue striving to develop more effective treatments, apart from investigating the optimal

supportive care measures to enhance outcomes among critically ill COVID-19 patients during the following waves.

Author contributions

GM, RC, SU, and AR conceptualised the study and curated the data. GM, RC, SU, and AR accessed and verified the underlying data. GM, SU, RC, and AR did the formal analysis. GM, SU, RC, AR, IML, JSV, ED, JG, and ST contributed to the methodology. MB, JSV, IML, and AR acquired funding and resources. GM, RC, and SU developed the first draft of the manuscript. RC, SU, AR, MB, IML, JSV, ED, JG, ST, MV, JM, AA, AL, LSC, JCB, EP, LV, SS, MN, MCL, OB, VF, FA, AE, LS, IS, AM, and GM made substantial contributions to the conception of the work, reviewed critically the data and contributed with important intellectual content, agreed the responsibility for the accuracy and integrity of the data of the work and approved the final version of the manuscript to be published.

Data sharing statement

The data that support the findings of this study are available from the corresponding author [GM] upon reasonable request.

Declaration of interests

The authors have nothing to disclose.

Acknowledgements

This study was partially supported by a grant from Ricardo Barri Casanovas Foundation and the Spanish Society of Intensive Care Medicine and Coronary Units (SEMICYUC). The funding source had no role in the study design, data collection, data analysis, interpretation of data, the writing of the report, or in the decision to submit the paper for publication. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication. We wish to thank to Valeria Herrera-Lasso for reviewing the English. We would like to thank all the COVID-19 SEMICYUC members for the effort to collect patient data during the challenging situation of the pandemic.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.lanep.2021.100243](https://doi.org/10.1016/j.lanep.2021.100243).

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