Original Article

Critical COVID-19 patients through first, second, and third wave: retrospective observational study comparing outcomes in intensive care unit

Irene Coloretti[1]^, Carlotta Farinelli[1], Emanuela Biagioni[1], Ilenia Gatto[1], Elena Munari[1], Lorenzo Dall'Ara[1], Stefano Busani[1], Marianna Meschiari[2], Roberto Tonelli[3], Cristina Mussini[2], Giovanni Guaraldi[2], Andrea Cossarizza[4], Enrico Clini[3], Massimo Girardis[1]; the MO-COVID19 Working Group

[1]Intensive Care Unit, University Hospital of Modena, Modena, Italy; [2]Infectious Disease Unit, University Hospital of Modena, Modena, Italy; [3]Respiratory Disease Unit, University Hospital of Modena, Modena, Italy; [4]Immunology Laboratory, University of Modena and Reggio Emilia, Modena, Italy

Contributions: (I) Conception and design: I Coloretti, C Farinelli, S Busani, M Girardis; (II) Administrative support: M Girardis; (III) Provision of study materials or patients: M Girardis; (IV) Collection and assembly of data: I Coloretti, C Farinelli, M Girardis; (V) Data analysis and interpretation: I Coloretti, C Farinelli, S Busani, M Girardis; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Irene Coloretti, MD. Intensive Care Unit, University Hospital of Modena, L.go del Pozzo, 71, 41100 Modena, Italy.
Email: irene.coloretti@gmail.com.

Background: The time-course of the coronavirus disease 2019 (COVID-19) pandemic was characterized by subsequent waves identified by peaks of intensive care unit (ICU) admission rates. During these periods, progressive knowledge of the disease led to the development of specific therapeutic strategies. This retrospective study investigates whether this led to improvement in outcomes of COVID-19 patients admitted to ICU.

Methods: Outcomes were evaluated in consecutive adult COVID-19 patients admitted to our ICU, divided into three waves based on the admission period: the first wave from February 25th, 2020, to July 6th, 2020; the second wave from September 20th, 2020, to February 13th, 2021; the third wave from February 14th, 2021 to April 30th, 2021. Differences were assessed comparing outcomes and by using different multivariable Cox models adjusted for variables related to outcome. Further sensitivity analysis was performed in patients undergoing invasive mechanical ventilation (IMV).

Results: Overall, 428 patients were included in the analysis: 102, 169, and 157 patients in the first, second, and third wave. The ICU and in-hospital crude mortalities were lower by 7% and 10% in the third wave compared to the other two waves (P>0.05). A higher number of ICU- and hospital-free days at day 90 was found in the third wave when compared to the other two waves (P=0.001). Overall, 62.6% underwent invasive ventilation, with decreasing requirement during the waves (P=0.002). The adjusted Cox model showed no difference in the hazard ratio (HR) for mortality among the waves. In the propensity-matched analysis the hospital mortality rate was reduced by 11% in the third wave (P=0.044).

Conclusions: With application of best practice as known by the time of the first three waves of the pandemic, our study failed to identify a significant improvement in mortality rate when comparing the different waves of the COVID-19 pandemic, notwithstanding, the sub-analyses showed a trend in mortality reduction in the third wave. Rather, our study identified a possible positive effect of dexamethasone on mortality rate reduction and the increased risk of death related to bacterial infections in the three waves.

Keywords: Coronavirus disease 2019 (COVID-19); acute respiratory distress syndrome (ARDS); intensive care unit (ICU); mechanical ventilation; treatment

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^ ORCID: 0000-0002-9022-1768.

Introduction

Despite the advanced status of the vaccination campaign in high-income countries, coronavirus disease 2019 (COVID-19) remains a major health problem, continuing to burden the healthcare system worldwide. Intensive care units (ICUs) have played a pivotal role in the management of this pandemic, with impressive admission rates (1). Mortality rates of COVID-19 patients admitted to ICU remains high, ranging from 30% to 80% (2-8). Some meta-analyses identified a trend of reduction in mortality rates as the pandemic progressed (9,10), but the latest cohort retrospective observational study performed on 3,795 ICU patients in Spain, demonstrated no substantial differences in mortality through subsequent waves of the pandemic, although a trend in reduction of mortality was present (11).

The time-course of the pandemic has been characterized worldwide by subsequent waves identified based on hospital admission rates: periods of high admission rates and phases of defervescence. The reasons to be addressed to explain this trend are the lockdown policies and social distancing measures facilitated to partially control the initial surge, therefore varying in different countries. Each wave was characterized by progressive awareness of the nature of this complex disease, carrying different hypotheses on the treatments to be adopted in these patients and gaining expertise by physicians. In fact, at the beginning of the outbreak of the COVID-19 pandemic, no validated therapies existed yet, and no former recommendation was available to guide physicians in decision making. Along with supportive therapy, several studies started to indagate both pathophysiology and evaluate specific treatments and the first to be investigated were antiviral agents, hydroxychloroquine, convalescent plasma, specific and non-specific immunosuppressive agents, and others (12-14).

Our retrospective study aimed to identify whether the progressive knowledge of this disease, the introduction of evidence-based treatments and the enhancement in the general management led to improvement in the outcome of COVID-19 patients admitted to ICU. We present this article in accordance with the TREND reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-764/rc).

Highlight box

Key findings

- With application of best practice no significant mortality reduction was achieved during the three waves of COVID-19 pandemic in critically ill patients.

What is known and what is new?

- This study highlighted possible positive effect of dexamethasone in critical COVID-19 patients.
- Secondary bacterial infections were associated with increased mortality risk.

What is the implication, and what should change now?

- Dexamethasone should be a first-line therapy in COVID-19. As it has immunosoppresant properties, early recognition and treatment of secondary sepsis appears of paramount importance in order to keep the benefits of dexamethasone among critically ill COVID-19 patients.

Methods

Study design

This observational, retrospective cohort study was conducted in the ICUs dedicated to COVID-19 patients of Modena University Hospital. In our hospital, due to a rise in the need for intensive care support, the 12-bed ICU raised its capacity up to 35 beds, divided into three ICUs. This retrospective study included consecutively admitted adult patients (≥18 years) with moderate to severe acute respiratory distress syndrome (ARDS) requiring invasive or non-invasive mechanical ventilation (NIMV), laboratory-confirmed COVID-19 infection and ICU stay > 24 hours, from February 25th, 2020, to April 30th, 2021 (Figure S1). Patients with missing data on outcomes and patients with the decision to withhold life-sustaining treatments because too sick to benefit were excluded. The decision to withhold life-sustaining treatments was taken after a briefing between the ICU physicians, and the same criteria for decision-making regarding this issue were applied through the three waves (15,16). Moreover, we never experienced a shortage of ICU beds during the first wave and the admission criteria did not vary among the three waves. Anyway, we adjusted our analysis for these confounders. Moderate to severe ARDS was defined according to Berlin criteria as new or worsening respiratory failure with bilateral opacities and partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤200 mmHg with positive end-expiratory pressure (PEEP) ≥5 cmH_2O not fully explained by cardiac failure, fluid overload, pleural effusions and lobar or lung collapse (17). COVID-19 infection was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasopharyngeal swabs or

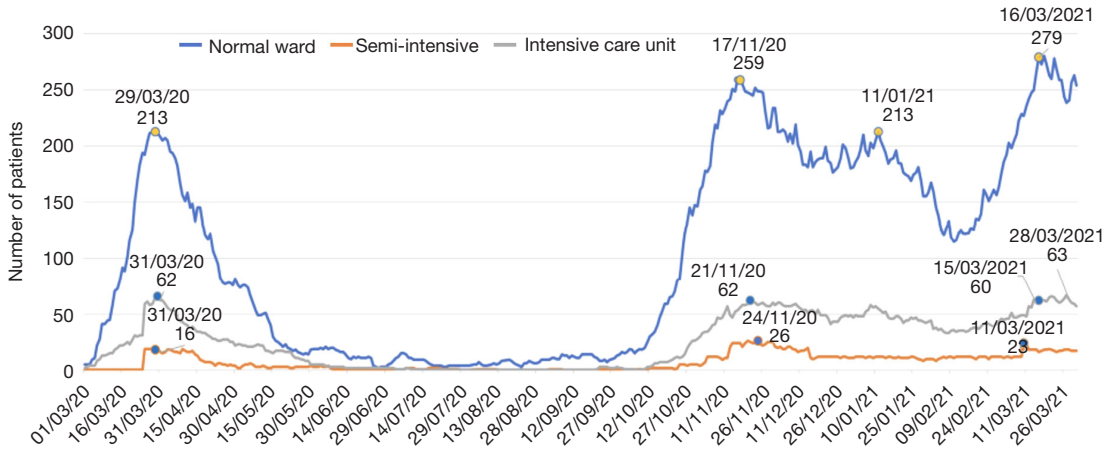

Figure 1 Hospitalised patients from March 1 2020 to March 31 2021 at AOU Policlinico Di Modena (Filippo Franchini-Controllo di Gestione AOU di Modena). Admissions were divided in normal wards, semi-intensive units and ICU. AOU, Azienda Ospedaliero-Universitaria; ICU, intensive care unit.

lower respiratory tract specimens.

The study population was divided into three waves, based on the peaks of admission rates to ICU, as described in *Figure 1*. The first wave included patients admitted to ICU from February 25th, 2020, to July 6th, 2020; the second wave from September 20th, 2020, to February 13th, 2021; the third wave from February 14th, 2021, to April 30th, 2021.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Area Vasta Nord Emilia Romagna who deemed informed consent unnecessary because of the retrospective design (approval code: 0029747/20, approval date: 21/10/2020).

Process of care

All patients received standard ICU monitoring and supportive care according to disease-severity, comprehensive protective mechanical ventilation, according to World Health Organization (WHO) (18) guidelines and specific therapies following national (19,20) and local protocol for the management of severe COVID-19. Pharmacological therapy was in agreement with the Italian Society of Infectious Diseases' Guidelines (SIMIT) (19) and according to the evolving recommendations provided by the WHO on COVID-19 pandemic (18).

Among these treatments, our internal protocol for the management of COVID-19 patients is included as follows.

Ventilation

Respiratory support was adopted according to local standardized protocols. Settings were adjusted by the attending physician based on the continuous monitoring of the cardiorespiratory parameters.

NIMV, with patients connected via a conventional circuit with an appropriately sized oronasal facemask equipped with a dedicated output for probes (Bluestar^{TM}, KOO Medical Equipment, Shanghai, China) to a high-performance ventilator (GE Healthcare Engstrom Carestation^{TM}, GE Healthcare, Finland) in pressure support (PS) pre-set mode. PEEP was initially set at 5–7 cmH_2O and subsequently fine-tuned to target a peripheral oxygen saturation (SpO_2) >92% with a delivered FiO_2 less than 0.7. PS was set at 10 cmH_2O, and then progressively modified, according to tidal volume [Vte/kg of predicted body weight (PBW)], to target a Vte/kg of PBW <9.5 mL/kg of PBW and a respiratory rate (RR) <30 breaths/min. The inspiratory trigger was set at 3 L/min and expiratory cycling was set at 25% of the inspiratory peak flow. The delivered FiO_2 was increased to target a SpO_2 of 88–94%. The oronasal facemask was tightened to target a leak flow lower than 2 L/min.

Invasive mechanical ventilation (IMV) need was decided according to the best clinical practice by the attending staff. Criteria for endotracheal intubation (ETI) included: (I) PaO_2/FiO_2 ratio unchanged or worsened despite the use of non-invasive respiratory support (NRS); (II) need to protect airways due to neurological deterioration or

massive secretions; (III) hemodynamic instability or major electrocardiographic abnormalities; (IV) unchanged or worsened dyspnea and persistence of respiratory distress despite NRS (i.e., RR >35 bpm, gasping for air, psychomotor agitation requiring sedation, abdominal paradox).

Steroids

Methylprednisolone 2 mg/kg/day to prevent the onset of pulmonary fibrosis in patients who maintained a PaO_2/FiO_2 ratio <150 for at least 7 days of mechanical ventilation.

From the second wave steroid therapy consisted of dexamethasone 6 mg intravenous (iv) per day for 7 to 10 days, with the eventuality to shift to methylprednisolone 0.5 mg/kg iv every 6 hours in case of lack of response to previous glucocorticoid therapy in terms of clinical worsening and persistence of hyperinflammatory state.

Cytokine-blocking agents

The use of Tocilizumab was introduced on March 5th, 2020. During the first wave was adopted as off-label treatment, based on the results of upcoming clinical trials, whereas during the second and third wave Tocilizumab became the standard of care. Tocilizumab was administered iv at the dosage of 8 mg/kg with an optional second dose. Patients were treated when at least two of the following conditions were fulfilled: lymphocyte count below 1,000 cells/mcL, C-reactive protein (CRP) above 7 mg/mL or PaO_2/FiO_2 ratio <250 mmHg.

Anticoagulants

Enoxaparin 4,000 U subcutaneously every 12 hours, with adjustments based on individual body weight was used as prophylaxis. The use of unfractionated heparin was considered in case of pulmonary embolism documented by computed tomography (CT)-scan or strong clinical suspicion.

Antiviral agents

Lopinavir/ritonavir o darunavir/cobicistat and hydroxychloroquine during the first wave (discontinued on March 22nd, 2020).

None of patients admitted to ICU until 30t April 2021 was vaccinated. In Italy, with exception of health-care personnel, the vaccination started at the end of February 2021 with population aged >80 years.

Management of supportive therapy was not modified during the study period.

Data collection and statistical analysis

Demographics, co-morbidities, medications, and laboratory tests were collected by reviewing electronic medical records. We defined immunosuppression as chronic immunotherapy recipients, presence of active hematologic malignancies, neoplastic disease, autoimmune disease, and transplant recipients (19). The primary endpoint was the in-hospital mortality rate after ICU admission. Secondary endpoints were ICU mortality, ICU-free days censored at day 90, the need for IMV, invasive ventilator-free days (VFDs) at day 90, tracheostomy and the incidence of secondary bacterial infections within ICU stay. Infections were identified and recorded considering all microbiological isolates obtained during the ICU course, independently reviewed and classified in light of the available clinical, laboratory, and radiographic data by dedicated intensivists and infectious disease specialists, following international guidelines (21,22). The timeframe for diagnosing healthcare-associated infections (HAIs) was limited to the ICU stay, without follow-up after ICU discharge. All enrolled patients achieved the follow-up period.

In the analysis, categorical variables were expressed as absolute numbers and percentages, continuous variables as the median and interquartile range (IQR). For the comparison were performed chi-squared or Fisher's exact test for categorical variables, Mann-Whitney U-test for continuous variables. The association between different variables and in-hospital mortality censored at day 90 was estimated by multivariable Cox proportional hazards regression model, including all variables resulting associated with P value <0.2 at the unadjusted analysis, and forcing in the model the variable expressing the different waves. Patients discharged from the hospital before day 90 were considered survived.

Additional sensitivity analysis included the same set of analyses was performed only in the population undergoing IMV. Propensity matching was then performed to minimize the influence of selection bias and potential confounding. This was performed by using the demographic and clinical variables as covariates with a one-to-one nearest neighbor matching algorithm at a caliper of 0.2. The standardized difference in means and distribution of propensity scores were used in assessing the improvement of covariate balance after propensity score matching.

SPSS version 22.0 package (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.

Table 1 Baseline characteristics and process-of-care of study population with the comparison between waves for all ICU study population

Baseline	All population (n=428)	First wave (n=102)	Second wave (n=169)	Third wave (n=157)	P value
Age (years), median [IQR]	64 [56–72]	63 [56–70]	67 [61–73]	63 [53–72]	0.002
Sex (male), n (%)	322 (75.2)	81 (79.4)	134 (79.2)	107 (68.1)	0.036
SAPS II, median [IQR]	35 [29–40]	32 [27–38]	37 [33–43]	35 [28–38]	<0.001
BMI (kg/m^2), median [IQR]	29.0 [26.0–33.0]	27.8 [25.9–30.9]	29.7 [26.0–33.0]	29.0 [26.0–35.0]	0.035
Comorbidities, n (%)	239 (55.8)	59 (57.8)	81 (47.9)	99 (63.1)	0.021
Hypertension, n (%)	162 (37.9)	44 (43.1)	55 (32.5)	63 (40.1)	0.167
Diabetes, n (%)	71 (16.6)	16 (15.7)	22 (13.0)	33 (21.0)	0.146
Chronic renal failure, n (%)	12 (2.8)	2 (2.0)	5 (3.0)	5 (3.2)	0.833
Chronic respiratory disease, n (%)	38 (8.9)	10 (9.8)	10 (5.9)	18 (11.5)	0.198
Immunesuppression, n (%)	61 (14.3)	14 (13.7)	25 (14.8)	22 (14.0)	0.965
Patients excluded from analysis because limitation of care, n (%)	31 (7.2)	7 (6.9)	13 (7.7)	11 (7.0)	0.958
PaO_2/FiO_2 (mmHg), median [IQR]	106 [84–140]	100 [80–121]	109 [89–142]	110 [81–145]	0.039
D-dimer (ng/mL), median [IQR]	1,440 [820–2,840]	1,775 [860–3,240]	1,390 [785–2,805]	1,390 [840–2,620]	0.279
Lymphocyte count (cells/mcL), median [IQR]	0.65 [0.46–0.9]	0.64 [0.43–0.9]	0.65 [0.47–0.93]	0.12 [0.10–0.40]	0.648
Platelet count (1,000/mm^3), median [IQR]	219 [169–286]	220 [169–296]	212 [164–273]	220 [171–289]	0.510
LDH (U/L), median [IQR]	803 [624–1,076]	766 [601–1,048]	756 [613–1,047]	859 [660–1,097]	0.102
CRP (mg/dL), median [IQR]	7.45 [2.4–18.2]	15.0 [5.8–22.7]	7.7 [2.2–17.9]	4.6 [1.1–14.3]	<0.001
PCT (ng/mL), median [IQR]	0.2 [0.1–0.6]	0.3 [0.1–1.1]	0.2 [0.1–0.6]	0.1 [0.1–0.4]	0.037
Steroids administration, n (%)	381 (89.0)	60 (58.8)	166 (98.2)	155 (98.7)	<0.001
Methylprednisolone, n (%)	205 (47.9)	60 (58.8)	89 (52.7)	56 (35.7)	<0.001
Dexamethasone, n (%)	176 (41.1)	0 (0.0)	77 (45.6)	99 (63.1)	<0.001
Tocilizumab, n (%)	333 (77.8)	56 (54.9)	130 (76.9)	147 (93.6)	<0.001

P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. ICU, intensive care unit; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; BMI, body mass index; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin.

Results

Between February 25th, 2020, to April 30th, 2021, a total of 428 patients with confirmed COVID-19 pneumonia were included in the analysis: 102, 169, and 157 patients in the first, second and third wave, respectively. The proportion of patients excluded from analysis because "too sick to benefit" was 6.9%, 7.7%, and 7.0% in the first, second and third wawe (P>0.05) (*Table 1*). Demographic and baseline characteristics of included patients are shown in *Table 1*. In the second wave, age, Simplified Acute Physiology Score II (SAPS II) score, and body mass index (BMI) were significantly higher compared to the first and third waves. Laboratory test analysis values were well balanced among the three waves, with exception of CRP and procalcitonin (PCT) levels, significantly higher in the first wave. Steroid therapy use was significantly more frequent in the second and third waves. Similarly, the proportion of patients receiving Tocilizumab increased during the waves.

The ICU and in-hospital mortalities were lower by about 7% and 10% in the third wave compared to the other two waves (P>0.05) (*Table 2*). A higher number of ICU and hospital-free days censored at day 90 was found

Table 2 Main outcomes in the study population in the comparison between different waves for all ICU study population

Outcomes	All population (n=428)	First wave (n=102)	Second wave (n=169)	Third wave (n=157)	P value
ICU mortality, n (%)	103 (24.1)	28 (27.5)	45 (26.6)	30 (19.1)	0.187
ICU-free days at day 90, median [IQR]	82 [9–86]	78 [0–85]	81 [0–86]	84 [53–87]	0.001
Hospital mortality, n (%)	136 (31.8)	35 (34.3)	62 (36.7)	39 (24.8)	0.059
Hospital-free days at day 90, median [IQR]	59 [0–74]	53 [0–69]	48 [0–73]	68 [27–79]	<0.001
IMV, n (%)	268 (62.6)	78 (76.5)	104 (61.5)	86 (54.8)	0.002
Invasive VFDs at day 30, median [IQR]	25 [0–30]	22 [0–28]	23 [0–30]	28 [9–30]	<0.001
Tracheostomy, n (%)	89 (20.8)	16 (15.7)	43 (25.4)	30 (19.1)	0.128
Bacterial infection, n (%)	165 (38.6)	34 (33.3)	69 (40.8)	62 (39.5)	0.449
Bloodstream infection, n (%)	38 (23.0)	8 (23.5)	16 (23.1)	14 (22.5)	–
Pneumonia, n (%)	100 (60.6)	20 (58.8)	43 (62.3)	37 (59.6)	–
Hospital-acquired pneumonia, n (%)	26 (26.0)	5 (25.0)	11 (25.6)	10 (27.0)	–
Ventilator-associated pneumonia, n (%)	74 (74.0)	15 (75.0)	32 (74.4)	27 (73.0)	–
Urinary-tract infection, n (%)	17 (10.3)	4 (11.7)	6 (8.6)	7 (11.3)	–
Abdominal infection, n (%)	2 (1.2)	0 (0.0)	1 (1.4)	1 (1.6)	–
Other site, n (%)	8 (4.8)	2 (5.9)	3 (4.3)	3 (4.8)	–

P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. ICU, intensive care unit; IQR, interquartile range; IMV, invasive mechanical ventilation; VFD, ventilation-free day.

in the third wave when compared to the other two waves (P<0.001). Overall, 268 patients (62.6%) underwent IMV, with a progressive decrease of patients requiring mechanical ventilation during the waves (P=0.002) with a consequent increase of invasive VFDs at day 30 (P<0.001) (*Table 2*).

The Cox regression multivariable analysis for all the study population admitted to ICU indicated that SAPS II score, decreasing platelet count at ICU admission, IMV and documented bacterial infection during ICU stay increased the risk of in-hospital mortality censored at day 90 (P<0.05). Therapy with dexamethasone reduced the adjusted risk for hospital mortality to hazard ratio (HR) =0.63 [95% confidence interval (CI): 0.40–1.00; P=0.052]. No difference was observed in the HR for mortality among the waves (*Table 3*).

The sensitivity analysis conducted in the subgroup of patients undergoing IMV during ICU stay (268 patients to 78 patients in the first wave, 104 patients in the second wave and 86 patients in the third) confirmed the association between lactate dehydrogenase (LDH) and platelet count at ICU admission, the dexamethasone therapy and documented bacterial infection during ICU stay and hospital mortality censored at day 90, with no difference of risk among waves (Tables S1-S3).

We further performed a propensity-matched analysis of patients in first and second waves with patients of the third wave matched for age, sex, SAPS II score, comorbidities, CRP and PCT (Tables S4-S6). In the 290 matched patients (145 patients in the first and second waves group and 145 in the third wave group) the hospital mortality rate was reduced by 11% in the third wave (P=0.044) (Table S5). Univariate analysis showed that the third wave was significantly associated with lower mortality risk (HR =0.64; 95% CI: 0.42–0.97; P=0.034), but the effect was lost in the adjusted analysis (P=0.148) (Table S6).

Discussion

Key findings from our cohort study showed a difference in crude mortality during the three pandemic waves, with the third wave having a lower mortality rate than the first. In detail, the third wave had a lower death rate than the first. However, after adjusting for confounding

Table 3 HRs and CI obtained by unadjusted univariate and adjusted Cox regression analysis for in-hospital mortality censored at day 90 for all ICU study population

Variables included in regression analysis	Survived (n=292)	Not survived (n=136)	Unadjusted HR (95% CI), P value	Adjusted HR (95% CI), P value
Age (years), median [IQR]	63 [53–71]	69 [62–75]	1.04 (1.03–1.06), <0.001	1.01 (0.99–1.03), 0.322
SAPS II score, median [IQR]	29 [25–37]	38 [34–44]	1.04 (1.03–1.05), <0.001	1.02 (1.00–1.04), 0.045
Comorbidities, n (%)	153 (52.4)	86 (63.2)	1.45 (1.02–2.05), 0.038	1.06 (0.73–1.54), 0.769
LDH (U/L), median [IQR]	768 [611–1,030]	906 [672–1,257]	1.00 (1.00–1.00), <0.001	1.00 (1.00–1.01), 0.029
Platelet count (1,000/mm^3), median [IQR]	232 [184–296]	187 [137–247]	0.99 (0.99–1.00), <0.001	0.99 (0.99–0.99), 0.001
CRP (mg/dL), median [IQR]	7 [2–17]	8 [3–20]	1.01 (1.00–1.03), <0.001	1.01 (0.99–1.03), 0.169
Dexamethasone, n (%)	147 (50.3)	29 (21.3)	0.33 (0.22–0.50), <0.001	0.63 (0.40–1.00), 0.052
IMV, n (%)	142 (48.6)	126 (92.6)	9.86 (5.17–18.78), 0.001	4.19 (2.10–8.33), <0.001
Bacterial infection, n (%)	69 (23.6)	96 (70.6)	4.67 (3.22–6.77), <0.001	2.46 (1.63–3.72), <0.001
Waves, n (%)				
1st wave	67 (22.9)	35 (25.7)	1	1
2nd wave	107 (36.6)	62 (45.6)	1.00 (0.66–1.51), 0.983	1.00 (0.60–1.67), 0.983
3rd wave	118 (40.4)	39 (28.7)	0.64 (0.40–1.01), 0.053	0.78 (0.46–1.67), 0.369

P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; LDH, lactate dehydrogenase; CRP, C-reactive protein; IMV, invasive mechanical ventilation.

factors, this difference became insignificant despite a slight decrease in the risk of death in the third wave in both the overall population and the IMV subgroup. Variables influencing this analysis were related to COVID-19 disease severity (SAPS II score, LDH, and platelet values), bacterial superinfection occurrence, and dexamethasone administration. In the propensity-matched population, univariate analysis showed a reduction in mortality rate in patients admitted in the third wave. This finding may be explained by the reduction of potential selection bias provided by matching patients of the three waves with a propensity score based on demographic and clinical variables at ICU admission and by the differences in steroids and tocilizumab use in the three periods (*Table 1*).

Our data differed from several previous reports, which showed improved survival as the pandemic progressed (23-27). Among these reports, many included mixed populations (23-25,27). A Brazilian multicentre observational study (28) of over 13,000 critically-ill patients identified temporal changes in death during the first two waves, but overall hospital mortality at day 60 was only 13%, so maybe this population was of different severity with respect to our data. Of note, our population was characterised by moderate to severe ARDS, excluding the evaluation in patients with mild ARDS. Like our results, a large European multicentre retrospective study found a significant decrease in mortality overtime during the study period at crude analysis with a similar rate of IMV. But the decrease found in this study in the unadjusted analysis was not confirmed in the adjusted one. The same analytic trend occurred in a large multicentre observational study involving ICUs from Spain, Andorra, and Ireland (13): the unadjusted mortality showed a significant decrease, but these differences were not further confirmed after adjusting for confounding factors.

As stated, the risk of death during the different waves was strongly affected by the severity of patients admitted to the ICU with low platelets count, as described in pathophysiological reports (29). Furthermore, bacterial superinfection and the administration of dexamethasone seem to play a role, even if the p-value of the latter appears to the limit of significance (P=0.055). The protective role of dexamethasone has been elucidated since June 2020 by the release of the RECOVERY trial (30) which demonstrated reduced mortality at day 28 among patients with acute respiratory failure related to COVID-19 infection receiving oxygen therapy. So, from the second wave onwards,

dexamethasone has become the standard of care in this patient setting (31,32). In contrast to dexamethasone, which appeared protective in mortality-rate reduction, consistently with recently published meta-analysis (32), the development of bacterial infection during ICU stay in our patients was associated with an increased risk of death throughout the pandemic.

As the pandemic developed, in our centre we had a progressive increase in the number of patients who underwent tocilizumab therapy, up to a rate of 93.6% in the third wave. However, such use did not have an impact in terms of risk of death reduction; contrary to a recent RECOVERY randomized controlled trial (RCT) that reported improvement in survival in hospitalized COVID-19 patients with hypoxia and systemic inflammation regardless of the amount of respiratory support (30).

In the sensitivity analysis, we observed a significant absolute reduction in the rate of invasively ventilated patients of 21.7% resulting in a significant improvement in days without mechanical ventilation between the three waves. This may be attributable to the change in the use of respiratory support during the pandemic due to increased use of NIMV even in more severe patients, as elsewhere described (23,25,28,33,34).

The strengths of our study refer to a well-controlled design because it was performed in a single centre with three ICUs, with pre- and post-ICU hospital general management protocols and pathways shared between the professionals and unchanged throughout the pandemic. In addition, medical and nursing teams were stable in the three waves with no shortage of staff and ICU beds. As for weaknesses, we must emphasize the observational and single-centre nature of the study which may involve possible unmeasured confounding factors. Further limitation may be the lack of information regarding the characterisation of specific COVID-19 variants and the days of symptoms before hospital admission that may have influenced mortality. Moreover, our study was underpowered for mortality detection, as the available sample size allows to detect as significant (alpha 0.05, power 0.8) an absolute difference in mortality rate of ±15% among the waves considering the mean mortality rate of the study population 24.1% (*Table 2*). In addition, we have focused on ICU mortality from all causes and to be able to better interpret mortality rates, the latter should be examined in detail for the specific causes of death. To better interpret our rsults, is important to consider the timings of treatment administration as a major issue that could have resulted in better survival.

Conclusions

Our study failed to demonstrate a significant improvement in survival rate when comparing the different waves in both the whole population and in invasively ventilated patients, however, a trend in mortality reduction in the third wave was identified when propensity score-matched population was considered. We intercepted the possible protective effect of dexamethasone on mortality and the increased risk of death related to bacterial infections in the three waves. From this perspective, a major factor that our study could underline is that dexamethasone as a first-line therapy in COVID-19, is also a strong immune-suppressant, predisposing to potentially life-threatening breakthrough infections. Early recognition and abrupt empiric treatment of secondary bacterial sepsis appears of paramount importance in order to keep the benefits of dexamethasone among critically ill patients recovering from COVID-19.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-764/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Area Vasta Nord Emilia Romagna who deemed informed consent unnecessary because of the retrospective design (approval code: 0029747/20, approval date: 21/10/2020).

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Supplementary

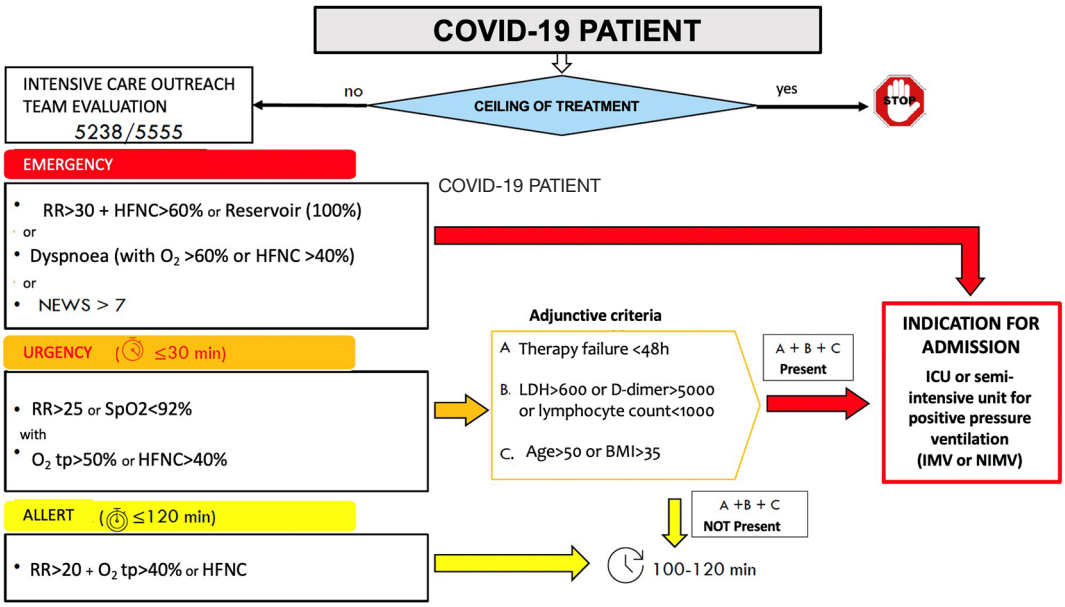

Figure S1 Internal protocol indicating criteria used for triggering the evaluation for ICU admission. COVID-19, coronavirus disease 2019; RR, respiratory rate; HFNC, high-flow nasal cannulae; NEWS, National Early Warning Score; SpO_2, oxygen peripheral saturation; tp, therapy; LDH, lactate dehydrogenase; BMI, body mass index; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIMV, non-invasive mechanical ventilation.

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Table S1 Baseline characteristics and process-of-care of the patients undergoing IMV during the study period with the comparison between waves

Baseline	All population (n=268)	First wave (n=78)	Second wave (n=104)	Third wave (n=86)	P value
Age (years), median [IQR]	67 [61–73]	65 [60–72]	69 [63–74]	66 [56–74]	0.116
Sex (male), n (%)	207 (77.2)	63 (80.8)	84 (80.8)	60 (69.8)	0.134
SOFA, median [IQR]	4 [4–6]	4 [3–6]	5 [4–7]	4 [4–5]	<0.001
SAPS II, median [IQR]	36 [32–43]	34 [27–40]	39 [35–46]	35 [30–39]	<0.001
BMI (kg/m^2), median [IQR]	29 [26–33]	27.8 [24.7–0.5]	29.4 [26.0–34.0]	30.5 [26–35]	0.011
D-dimer (ng/mL), median [IQR]	1,620 [890–3,180]	1,915 [965–3,525]	1,580 [840–3,565]	1,345 [840–2,590]	0.149
Lymphocyte count (cells/mcL), median [IQR]	0.61 [0.43–0.89]	0.59 [0.40–0.85]	0.64 [0.46–0.90]	0.64 [0.41–0.85]	0.535
Platelet count (1,000/mm^3), median [IQR]	209 [160–284]	216 [160–286]	203 [160–264]	221 [157–294]	0.618
LDH (U/L), median [IQR]	837 [657–1,126]	803 [662–1,096]	823 [655–1,144]	915 [658–1,135]	0.595
CRP (mg/dL), median [IQR]	11.2 [3.0–19.9]	16.2 [7.6–23.8]	7.9 [1.3–18.4]	5.8 [2.2–15.1]	<0.001
PCT (ng/mL), median [IQR]	0.3 [0.1–0.9]	0.42 [0.20–1.30]	0.30 [0.12–0.80]	0.2 [0.1–0.5]	0.009
Steroids administration, n (%)	237 (88.4)	51 (65.4)	102 (98.1)	84 (97.7)	<0.001
Methylprednisolone, n (%)	154 (57.5)	51 (65.4)	61 (58.7)	42 (48.8)	0.096
Dexamethasone, n (%)	83 (31)	0 (0.0)	41 (39.4)	42 (48.8)	<0.001
Tocilizumab, n (%)	204 (76.1)	39 (50)	82 (78.8)	83 (96.5)	<0.001

P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. IMV, invasive mechanical ventilation; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; BMI, body mass index; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin.

Table S2 Main outcomes in patients undergoing IMV and the comparison between different waves

Outcomes	All population (n=268)	First wave (n=78)	Second wave (n=104)	Third wave (n=86)	P value
ICU mortality, n (%)	102 (38.9)	28 (35.9)	45 (43.3)	29 (33.7)	0.361
ICU-free days at day 90, median [IQR]	69.5 [0–81]	74 [0–81]	45 [0–80]	79 [0–84]	0.022
Hospital mortality, n (%)	126 (47.0)	35 (44.9)	58 (55.8)	33 (38.4)	0.052
Hospital-free days at day 90, median [IQR]	26 [0–66]	37 [0–62]	0 [0–56]	59 [0–79]	0.001
Invasive VFDs at day 30, median [IQR]	3 [0–25]	9.5 [0–25]	1 [0–21]	11 [0–26]	0.004
Tracheostomy, n (%)	84 (31.3)	15 (19.2)	40 (38.5)	29 (33.7)	0.018
Bacterial infection, n (%)	143 (53.4)	31 (39.7)	58 (55.8)	54 (62.8)	0.010

P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. IMV, invasive mechanical ventilation; ICU, intensive care unit; IQR, interquartile range; VFD, ventilation-free day.

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Table S3 HRs and CI obtained by unadjusted univariate and adjusted Cox regression analysis for in-hospital mortality censored at day 90 in patients undergoing IMV

Variables included in regression analysis	Survived (n=142)	Not survived (n=126)	Unadjusted HR (95% CI), P value	Adjusted HR (95% CI), P value
Age (years), median [IQR]	65 [55–72]	69 [63–75]	1.03 (1.02–1.05), <0.001	1.01 (0.99–1.03), 0.257
SAPS II score, median [IQR]	35 [30–40]	38 [35–44]	1.02 (1.01–1.04), 0.001	1.02 (0.99–1.04), 0.094
LDH (U/L), median [IQR]	803 [656–1,701]	935 [671–1,271]	1.00 (1.00–1.00), 0.008	1.00 (1.00–1.00), 0.028
Platelet count (1,000/mm^3), median [IQR]	232 [182–294]	189 [140–249]	0.99 (0.99–0.99), 0.001	0.99 (0.99–1.00), 0.015
Dexamethasone, n (%)	59 (41.5)	24 (19.0)	0.45 (0.29–0.70), <0.001	0.63 (0.38–1.02), 0.061
Tocilizumab, n (%)	120 (84.5)	99 (78.6)	0.74 (0.48–1.13), 0.157	–
Bacterial infection, n (%)	54 (38.0)	89 (70.6)	2.35 (1.60–3.45), <0.001	2.08 (1.36–3.17), 0.001
Wave, n (%)				
1st wave (February 25th, 2020–July 6th, 2020)	43 (30.3)	35 (27.8)	1	1
2nd wave (September 20th, 2020–February 13th, 2021)	46 (32.4)	58 (46.0)	1.19 (0.79–1.82), 0.404	0.98 (0.59–1.61), 0.928
3rd wave (February 14th, 2021–April 30th, 2021)	53 (37.3)	33 (26.2)	0.74 (0.46–1.19), 0.215	0.68 (0.40–1.15), 0.149

Data for survived and not survived during hospital stay are also reported. P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. HR, hazard ratio; CI, confidence interval; IMV, invasive mechanical ventilation; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; LDH, lactate dehydrogenase.

Table S4 Baseline characteristics and process-of-care of the patients in the propensity matched analysis with the comparison between waves

Baseline	All population (n=290)	First-second wave matched (n=145)	Third wave matched (n=145)	P value
Age (years), median [IQR]	64 [56–72]	65 [59–72]	63 [53–72]	0.122
Sex (male), n (%)	215 (74.1)	115 (79.3)	100 (69.0)	0.044
SAPS II, median [IQR]	35 [28–39]	34 [28–39]	35 [28–39]	0.840
Comorbidities, n (%)	176 (60.7)	86 (59.3)	90 (62.1)	0.631
CRP (mg/dL), median [IQR]	5.4 [1.5–15.1]	5.8 [2.0–15.3]	47 [1.3–14.6]	0.310
PCT (ng/mL), median [IQR]	0.2 [0.1–0.5]	0.2 [0.1–0.5]	0.1 [0.1–0.4]	0.970
Steroids administration, n (%)	265 (91.4)	122 (84.1)	143 (98.6)	<0.001
Dexamethasone, n (%)	128 (44.1)	39 (26.9)	89 (61.4)	<0.001
Tocilizumab, n (%)	248 (85.5)	110 (75.9)	138 (95.2)	<0.001

P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; CRP, C-reactive protein; PCT, procalcitonin.

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Table S5 Main outcomes of the patients in the propensity matched analysis and the comparison between different waves

Outcomes	All population (n=290)	First-second wave matched (n=145)	Third wave (n=145)	P value
Hospital mortality, n (%)	92 (31.7)	54 (37.2)	38 (26.2)	0.044
IMV, n (%)	178 (61.4)	95 (65.5)	83 (57.2)	0.148
Invasive VFDs at day 30, median [IQR]	25 [0–30]	20 [0–30]	27 [7–30]	<0.001
Tracheostomy, n (%)	59 (20.3)	30 (20.7)	29 (20.0)	0.884
Bacterial infection, n (%)	116 (40.0)	58 (40.0)	58 (40.0)	1.000

P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. IMV, invasive mechanical ventilation; VFD, ventilation-free day; IQR, interquartile range.

Table S6 HRs and CI obtained by unadjusted univariate and adjusted Cox regression analysis for in-hospital mortality censored at day 90 of the patients in the propensity matched analysis

Variables included in regression analysis	Survived (n=198)	Not survived (n=92)	Unadjusted HR (95% CI), P value	Adjusted HR (95% CI), P value
Age (years), median [IQR]	63 [53–71]	69 [62–74]	1.04 (1.02–1.06), <0.001	1.00 (0.98–1.03), 0.929
SAPS II score, median [IQR]	33 [28–38]	36 [34–43]	1.05 (1.03–1.07), <0.001	1.03 (0.99–1.05), 0.076
Comorbidities, n (%)	112 (56.6)	64 (69.6)	1.55 (1.00–2.42), 0.053	–
CRP (mg/dL), median [IQR]	4.9 [1.5–14.4]	6.2 [1.7–17.2]	1.02 (0.99–1.04), 0.120	1.02 (0.99–1.04), 0.170
Dexamethasone, n (%)	108 (54.5)	20 (21.7)	0.31 (0.19–0.50), <0.001	0.56 (0.33–0.95), 0.033
IMV, n (%)	94 (47.5)	84 (91.3)	8.60 (4.16–17.78), <0.001	4.29 (1.99–9.25), <0.001
Bacterial infection, n (%)	47 (23.7)	69 (75.0)	5.64 (3.51–9.07), <0.001	2.69 (1.59–4.56), <0.001
Waves, n (%)				
1st and 2nd wave matched	91 (46.0)	54 (58.7)	1	1
3rd wave matched	107 (54.0)	38 (41.3)	0.64 (0.42–0.97), 0.034	0.72 (0.47–1.12), 0.148

Data for survived and not survived during hospital stay are also reported. P value: probability value, i.e., how likely it is that there is no difference in the given parameter between the indicated waves (null hypothesis). Considered significant: P<0.05. HR, hazard ratio; CI, confidence interval; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; CRP, C-reactive protein; IMV, invasive mechanical ventilation.

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