RESEARCH

Early short course of neuromuscular blocking agents in patients with COVID-19 ARDS: a propensity score analysis

Gianluigi Li Bassi[1,2,3,4,5,6]*† , Kristen Gibbons[7]†, Jacky Y. Suen[1,2], Heidi J. Dalton[8], Nicole White[4], Amanda Corley[1,2], Sally Shrapnel[2,9], Samuel Hinton[2], Simon Forsyth[2], John G. Laffey[10], Eddy Fan[11], Jonathon P. Fanning[1,2,5,6], Mauro Panigada[12], Robert Bartlett[13], Daniel Brodie[14], Aidan Burrell[15], Davide Chiumello[16,17], Alyaa Elhazmi[18], Mariano Esperatti[19], Giacomo Grasselli[11,17], Carol Hodgson[15], Shingo Ichiba[20], Carlos Luna[21], Eva Marwali[22], Laura Merson[23], Srinivas Murthy[24,25], Alistair Nichol[15,26,27], Mark Ogino[28], Paolo Pelosi[29,30], Antoni Torres[3,31], Pauline Yeung Ng[32] and John F. Fraser[1,2,3,4,5,6] on behalf of The COVID-19 Critical Care Consortium

Abstract

Background: The role of neuromuscular blocking agents (NMBAs) in coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS) is not fully elucidated. Therefore, we aimed to investigate in COVID-19 patients with moderate-to-severe ARDS the impact of early use of NMBAs on 90-day mortality, through propensity score (PS) matching analysis.

Methods: We analyzed a convenience sample of patients with COVID-19 and moderate-to-severe ARDS, admitted to 244 intensive care units within the COVID-19 Critical Care Consortium, from February 1, 2020, through October 31, 2021. Patients undergoing at least 2 days and up to 3 consecutive days of NMBAs (NMBA treatment), within 48 h from commencement of IMV were compared with subjects who did not receive NMBAs or only upon commencement of IMV (control). The primary objective in the PS-matched cohort was comparison between groups in 90-day in-hospital mortality, assessed through Cox proportional hazard modeling. Secondary objectives were comparisons in the numbers of ventilator-free days (VFD) between day 1 and day 28 and between day 1 and 90 through competing risk regression.

Results: Data from 1953 patients were included. After propensity score matching, 210 cases from each group were well matched. In the PS-matched cohort, mean (± SD) age was 60.3 ± 13.2 years and 296 (70.5%) were male and the most common comorbidities were hypertension (56.9%), obesity (41.1%), and diabetes (30.0%). The unadjusted hazard ratio (HR) for death at 90 days in the NMBA treatment vs control group was 1.12 (95% CI 0.79, 1.59, $p = 0.534$). After adjustment for smoking habit and critical therapeutic covariates, the HR was 1.07 (95% CI 0.72, 1.61, $p = 0.729$). At 28 days, VFD were 16 (IQR 0–25) and 25 (IQR 7–26) in the NMBA treatment and control groups, respectively

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†Gianluigi Li Bassi and Kristen Gibbons equally contributed to this work

*Correspondence: g.libassi@uq.edu.au

[1] Critical Care Research Group, The Prince Charles Hospital, 627 Rode Rd, Chermside, Brisbane, QLD 4032, Australia
Full list of author information is available at the end of the article

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(sub-hazard ratio 0.82, 95% CI 0.67, 1.00, $p = 0.055$). At 90 days, VFD were 77 (IQR 0–87) and 87 (IQR 0–88) (sub-hazard ratio 0.86 (95% CI 0.69, 1.07; $p = 0.177$).

Conclusions: In patients with COVID-19 and moderate-to-severe ARDS, short course of NMBA treatment, applied early, did not significantly improve 90-day mortality and VFD. In the absence of definitive data from clinical trials, NMBAs should be indicated cautiously in this setting.

Keywords: SARS-CoV-2, COVID-19, Neuromuscular blocking agent, Mechanical ventilation, Intensive care unit

Background

Since early 2020, SARS-CoV-2 infections have placed tremendous burden on patients and international healthcare services [1]. A high proportion of diseased patients require hospitalization, and a small subset with severe coronavirus disease 2019 (COVID-19) become critically ill and require invasive mechanical ventilation (IMV) for life-threatening respiratory failure [2–5]. High mortality has been reported in this subpopulation [4, 6–9], irrespective of survival benefits from established treatments, such as corticosteroids and IL-6 receptor antagonists [10, 11].

Neuromuscular blocking agents (NMBAs) have been commonly used for acute respiratory distress syndrome (ARDS) [12, 13] to reduce patient–ventilator asynchrony and—in the context of severely damaged and poorly compliant lungs—to improve oxygenation, while minimizing the work of breathing and risks of barotrauma. International studies have confirmed the use of NMBAs in up to 26% of ARDS patients [14]. Yet, conflicting results were provided by large randomized clinical trials, such as the ACURASYS [15] and ROSE trials [16], and indication, efficacy, and safety on the use of NMBAs in such patients remain uncertain.

The severe respiratory failure associated with COVID-19 has been described as a form of ARDS, and the potential benefits of supportive treatments have largely been extrapolated from evidence in non-COVID-19-related ARDS. Thus, many COVID-19 patients have been treated with NMBAs [17, 18], and in some areas even shortage of these medications has been reported [19], especially during the early phase of the pandemic. To the best of our knowledge, no international studies have clearly elucidated the effects of NMBAs on mortality in COVID-19 patients. Interestingly, in a multicenter observational study, Courcelle et al. [20] reported that the duration of NMBA treatment in this population was often longer than 48 h and not associated with shorter duration of IMV.

To further delineate the role of NMBA in ventilated COVID-19 patients, data extracted from the multicenter registry of the international COVID-19 Critical Care Consortium incorporating the ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease (COVID-19–CCC/ECMOCARD) were examined. Our hypothesis was that in patients with microbiologically confirmed COVID-19 and moderate-to-severe ARDS, no significant difference in 90-day hospital mortality was to be found between populations who received or not early NMBAs. Thus, the primary goal of this study was to identify difference in 90-day mortality, through propensity score (PS)-adjusted analysis, between patients who received or not a short course of NMBAs, within 48 h from commencement of IMV.

Methods

Study design

This was a comparative study in which mechanically ventilated COVID-19 patients with moderate-to-severe ARDS, who received an early short course of NMBAs, were compared with patients who did not receive NMBA or underwent NMBA treatment only on the day of commencement of IMV to explore the impact on in-hospital mortality during a follow-up period up to 90 days. Of note, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were used to ensure the reporting of this observational study [21].

Study population and settings

Inclusion criteria

We studied a convenience sampling of patients (≥ 16 years old) with microbiologically confirmed *SARS-CoV-2* infection, via rapid nucleic acid amplification test (NAAT) or antigen tests, who were admitted to an intensive care unit (ICU) from February 1, 2020, through October, 31, 2021, at any of the COVID-19 Critical Care Consortiums participating hospitals. In addition, patients were selected if they presented with moderate-to-severe ARDS, defined by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of < 150 mm Hg [16], within 48 h from commencement of IMV.

Exclusion criteria

We excluded patients with unrecorded date of commencement of IMV or who were transferred from other institutions, after commencement of IMV. In addition, we excluded from the primary analysis all patients with

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continuous use of NMBA for periods longer than 3 days, and intermittent use of NMBA within a 3-day period of treatment.

Variables, data sources, and measurements

Data on demographics, comorbidities, clinical symptoms, and laboratory results were collected by clinical and research staff of the participating ICUs in an electronic case report form [22]. Details of respiratory and hemodynamic support, physiological variables, and laboratory results were collected daily, with worst daily values recorded preferentially. Duration of IMV, length of ICU and hospital stays, and hospital mortality were also recorded.

Study groups

In line with previous therapeutic protocols applied in patients with moderate-to-severe ARDS [15, 16], we aimed to appraise a short course of NMBAs, applied early during the course of IMV. Thus, patients were assigned to the following study groups.

NMBA treatment

Use of NMBA treatment for at least 48 h and up to 3 consecutive days, initiated early, within 48 h from commencement of IMV.

Control

No use of NMBAs or administration only on the day IMV was commenced.

Of note, the time of first NMBAs administration was not recorded on the case report form; thus, the treatment group was designed to include up to 3 consecutive days of NMBAs exposure to ensure that at least 2 days of full treatment were achieved in most of the patients, even if treatment commenced during the night or a single NMBA dose was given upon endotracheal intubation. In addition, patients who were tracheally intubated and transferred from institutions not collaborating with the COVID-19-CCC/ECMOCARD were excluded from the analysis to avoid enrolment of subjects who might have received NMBA prior to study monitoring. Recording of NMBA use was censored at 28 days from ICU admission, or upon discharge from the ICU or death, whichever occurred first.

Outcomes

The primary objective was comparison between groups in 90-day in-hospital mortality, through PS matching analysis. Secondary objectives were the numbers of ventilator-free days (days since successful weaning from mechanical ventilation) between day 1 and day 28 and between day 1 and day 90 in the PS-matched population.

VFD was calculated as follows: VFDs $=0$ if subject died in hospital within 28 or 90 days of mechanical ventilation; VFDs $=28$ or $90-x$ if successfully liberated from ventilation x days after initiation; VFDs $=0$ if the subject was mechanically ventilated for more than 28 or 90 days.

Data source

We analyzed the COVID-19-CCC/ECMOCARD study dataset. COVID-19-CCC/ECMOCARD is an international, multicenter, observational cohort study ongoing in 354 hospitals across 54 countries (Additional file 1: Appendix). The full study protocol has been published elsewhere [22]. The COVID-19-CCC/ECMOCARD observational study was reviewed under the National Mutual Acceptance scheme by the Alfred Health Human Research Ethics Committee on February 27, 2020. The ethics committee certified that the study protocol met the requirements of the National Statement on Ethical Conduct in Human Research (2007), granting approval on March 2, 2020. In addition, in accordance with the Office of the Health Services Commissioners Statutory Guidelines on Research issued for the purposes of Health Privacy Principles, the Alfred Health Human Research Ethics Committee granted a waiver of consent for the collection, use, and disclosure of participants health and personal information. Subsequently, the protocol was approved by all international participating hospitals prior to data collection and waiver of consent was granted in all centers.

Data management and quality

The COVID-19 Consortium collaborates with the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) group [23] and their Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection (SPRINT-SARI) [24] project. De-identified patient data are recorded by data collectors at each collaborating site via the REDCap (Vanderbilt/NIH/NCATS UL1 TR000445 v.10.0.23) electronic data capture tool, using instances hosted at the University of Oxford (UK), University College Dublin (Ireland), Monash University (Australia), and The University of Queensland (Australia). A detailed data dictionary was provided to all sites to assist in data collection. In addition, biweekly drop-in data sessions were scheduled to assist with all queries that data collectors might have. Importantly, the database quality audits of the COVID-19 Consortium dataset are a continuing and intensive process encompassing (1) data cleaning rules; (2) checks for outliers; (3) filtering rules setup during the initial development of the case report form, which was periodically monitored/adjusted; and (4) data completeness checks. Finally, in the case any issue was detected during monitoring of data quality, or

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statistical analysis, these matters were pursued to address any data collection/process limitation in a timely manner, often including follow-up with the site that entered the data for value verification and correction where appropriate.

Statistical analyses

Categorical data are presented as frequency and percentage, while continuous data as mean and standard deviation (SD; normally distributed) and median and interquartile range (IQR; non-normally distributed). Normality of continuous data was reviewed via visual inspection of histograms. Bivariate comparisons between patients receiving NMBA treatment and controls were compared using Fishers exact test, Students unpaired t test, or the Mann–Whitney U test for categorical, normally, and non-normally distributed continuous variables, respectively.

Analyses were performed to examine the relationship between the primary outcome—mortality censored at 90 days post-commencement of IMV—and NMBA treatment. Patients entered the study analysis once they commenced IMV. As an imbalance in several characteristics at ICU admission between the study groups was noted, propensity score (PS) matching analysis was undertaken to balance these patient characteristics. Matching was undertaken, in preference to other techniques involving propensity scores, to best mimic the results of a randomized controlled trial. Baseline features considered potential variables for inclusion in the PS calculation were demographic and clinical characteristics with either a documented relationship with mortality or a baseline imbalance. Variables with more than 5% missing data were not considered. Based on the available literature on risk factors associated with mortality in severe COVID-19, the following covariates were included during PS modeling: age, sex, region (reference group: North America), time from symptom onset to hospital admission and baseline comorbidities (PaO_2/FiO_2 within 48 h from commencement of IMV, hypertension, chronic cardiac disease, chronic kidney disease, obesity). Matched cohorts were constructed based on the logit of the PS using nearest-neighbor matching with a caliper width of 0.2 and replacement to promote better balance, and accounting for the estimation of the standard errors. Rubins *B* [25] (a summation measure of bias with value < 25% indicating adequate balance) and Rubins *R* (0.5–2.0 indicating appropriate balancing) statistics were initially calculated to assess the success of the matching (i.e., if the resulting matched cohort had balanced characteristics). Standardized mean differences for all covariates, before and after matching, were then estimated, with an absolute difference of 10% or greater considered indicative of imbalance [26, 27].

Following PS matching, survival curves were generated for the matched sample to compare patients undergoing NMBA treatment against control. Finally, multivariable Cox regression models were constructed to assess the effect of NMBA treatment on outcome—incorporating robust estimators of variance to account for matched observations—as well as investigating effect modification on the association between mortality and NMBA by concomitant use of corticosteroids and respiratory failure severity. Covariates considered for inclusion in the multivariable Cox regression were laboratory results upon admission, treatments received and ventilator settings; covariates with known relationship with mortality in COVID-19 patients available in this dataset with less than 5% missing data were included in the final model. Where potential covariates were correlated, the most relevant clinical variable was chosen for inclusion in the model to avoid multicollinearity and the violation of model assumptions. Continuous covariates were standardized by subtracting the mean and dividing by the standard deviation to facilitate meaningful interpretation of the hazard ratios. Multiple imputation was not undertaken, and complete case analysis was performed [28]. Assumptions of the Cox regression model, particularly the proportional hazards assumption, were evaluated using test of the Schoenfeld residuals, as well as graphical exploration of the log–log plot; the proportional hazards assumption was met. Competing risk regression was performed to assess the secondary outcomes of VFDs at 28 and 90 days post-starting of IMV [29].

Sensitivity analyses

Considering the observational nature of our report and potential limitations related to PS matching, we also balanced baseline patient characteristics by weighting each individual in the analysis, by the inverse probability of receiving exposure to NMBAs (inverse probability of treatment weighting [IPTW]) [30]. In addition, as the dataset did not report exact NMBA administration practice, the following sensitivity analyses were conducted to confirm the results of the primary analysis: (1) in patients with clinically suspected and microbiologically confirmed COVID-19, with the treatment group defined as per the primary analysis; and in the treatment group only including patients who received NMBAs (2) continuously for 2 days; (3) continuously for 3 days; and (4) continuously for more than 3 days.

Of note, a post hoc power calculation was undertaken, as a convenience sample was being used. In the unmatched cohort, assuming type I error of 0.05, as well as the rate of primary outcome and study group size as

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reported in the results, the analysis had 98% power, adequate to undertake and report on the analyses of interest. Data were analyzed using StataSE version 17.0 (StataCorp Pty Ltd., College Station, Texas). Any two-tailed *p* value less than 0.05 was considered significant. No correction was made for multiple comparisons.
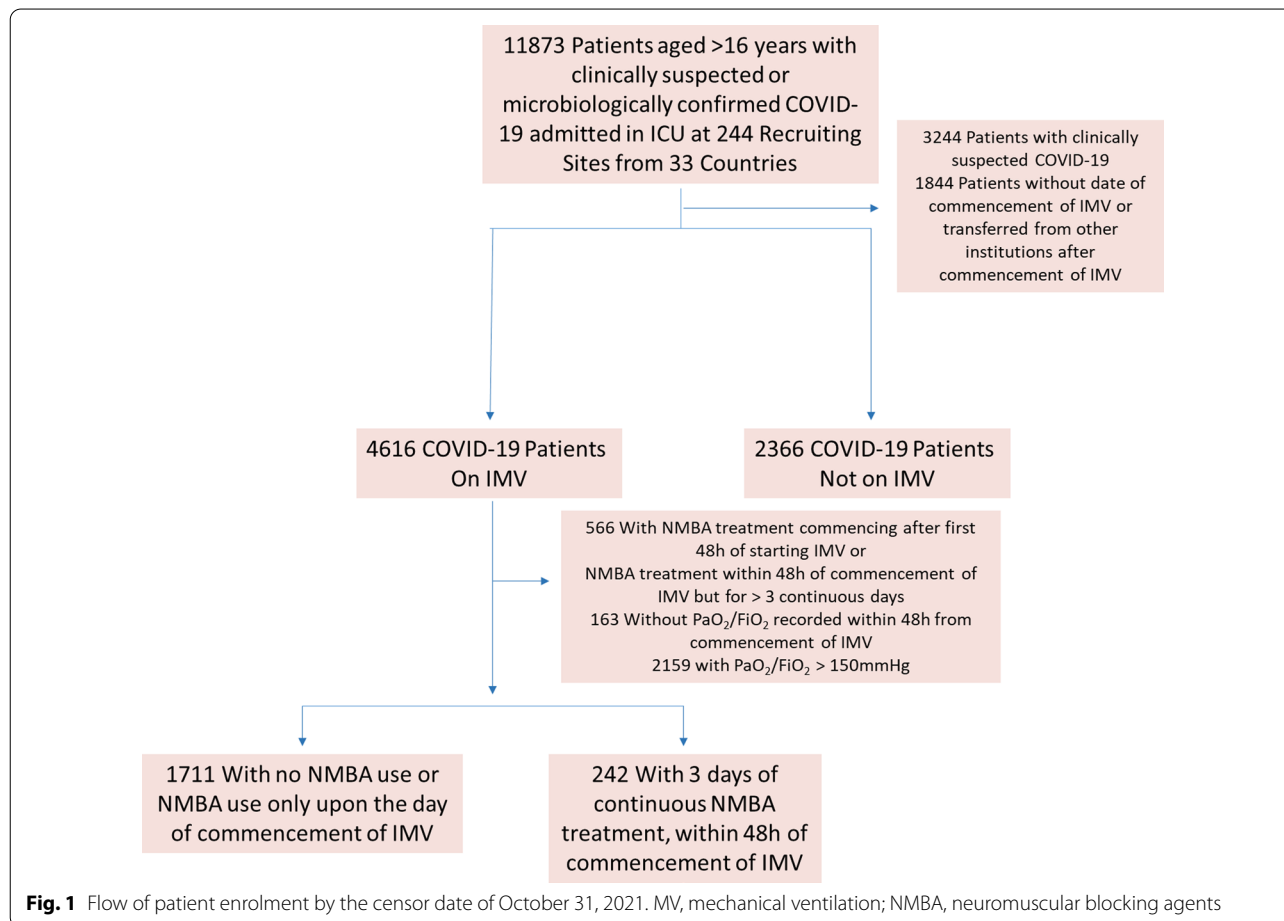
Results

Study population

There were 11,873 patients with microbiologically confirmed, or suspected, COVID-19 admitted to 244 hospitals between February 1, 2020, and October 31, 2021. After excluding 3244 patients because of lack of microbiological confirmation of SARS-CoV-2 infection and 1844 patients who were transferred from non-collaborating centers, or transferred out while still on mechanical ventilation, 4616 patients who were on IMV were included in the primary analysis (Fig. 1). Figure 2 shows enrolment rate of those mechanically ventilated patients by date of ICU admission. A matched cohort based on propensity scores was generated, with 210 patients who underwent NMBA treatment and 210 patients as control
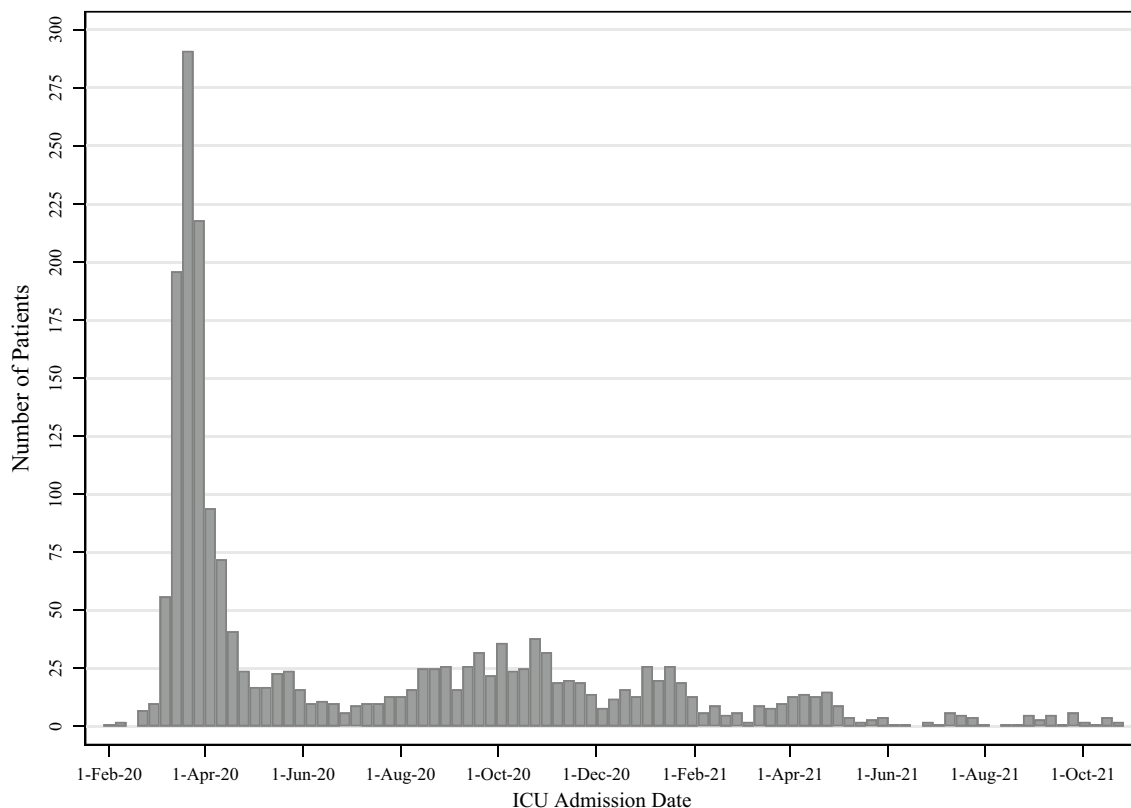
group. Overall, baseline characteristics were balanced in the propensity score-matched cohort. The mean age was 60.3 years (standard deviation [SD] 13.2 years) (Table 1) and 296 (70.5%) were male. The mean acute physiology and chronic health evaluation (APACHE) II score was 19.5 (SD 11.6; $N = 117$). In the NMBA treatment and control group, respiratory system compliance was 32.5 mL/cmH_2O (SD 12.6) and 33.9 (SD 12.2), respectively, and driving pressure was 22.7 cmH_2O (SD 7.5) and 22.4 (SD 8.6). The most common comorbidities among patients in the PS-matched cohort were hypertension (239, 56.9%), obesity (172, 41.1%), and diabetes (125, 30.0%).

NMBA therapy

In the full unmatched cohort, 180 (74.4%) patients received NMBAs for 48 h and 62 (25.6%) for 3 days, while in the control group, 1151 (67.3%) patients received NMBAs only on the day IMV started, and 560 (32.7%) never received NMBAs. In the PS-matched cohort, NMBA treatment was noted in 210 patients. Early use of NMBAs for 48 h was reported in 160 (76.2%) of the patients, while 50 (23.8%) patients received NMBAs for

Fig. 1 Flow of patient enrolment by the censor date of October 31, 2021. MV, mechanical ventilation; NMBA, neuromuscular blocking agents

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Fig. 2 Number of patients per week of intensive care unit (ICU) admission is depicted

3 days. In the matched control group, patients never received NMBAs, not even upon the day IMV started. NMBA was provided on average 1 day after ICU admission ($N = 207$; IQR 0–2 days). The median length from commencement of IMV to initiation of NMBA therapy was 0 days (IQR 0–0 days).

ICU management
In the PS-matched cohort, as summarized in Table 2, PaO_2/FiO_2 was 88.6 (SD 29.7) vs 86.0 (SD 30.7), in NMBA treatment and control group, respectively. Upon IMV commencement, patients who received NMBA treatment presented $PaCO_2$ of 51.0 mmHg (SD 13.7) vs 48.0 mmHg (SD 15.5) in those who did not. Positive end-expiratory pressure in those undergoing NMBA treatment or not was 12.8 cmH_2O (SD 3.3) vs 11.9 cmH_2O (SD 3.1), respectively. As for adjunctive therapies, extracorporeal membrane oxygenation, renal replacement therapy, and recruitment maneuvers were provided more frequently to patients who received NMBA treatment (Table 3). Pneumothorax occurred in 21 (10.4%) and 19 (9.6%) of the patients undergoing NMBA treatment or not, respectively.

Primary outcome: 90-day in-hospital mortality
The Kaplan–Meier (Fig. 3A) (log rank test $p < 0.001$) and the Cox regression model (unadjusted HR 1.78; 95% CI 1.38, 2.30; $p < 0.001$) confirmed that NMBA treatment was associated with increased mortality risk. The PS-matched cohort analysis comprised 210 patients in the NMBA treatment group vs 210 controls (using replacements). The summaries of balance for unmatched and matched critical parameters are depicted in Fig. 4. Kaplan–Meier curves (Fig. 3B) (log rank $p = 0.537$) showed no effect of NMBA treatment on mortality, which was also corroborated by the Cox regression model (unadjusted HR = 1.12, 95% CI 0.79, 1.59, $p = 0.534$). The lack of association with 90-day mortality was consistent after adjusting for smoking habit and critical therapeutic covariates (adjusted HR 1.07; 95% CI 0.72, 1.61, $p = 0.729$) (Table 4). In subgroup analyses, PaO_2/FiO_2 and the concomitant use of corticosteroids did not alter negative NMBA association with mortality.

Sensitivity analyses confirmed the lack of association between NMBA treatment and 90-day mortality, when inverse probability weighting analysis was applied (adjusted HR 1.28; 95% CI 0.89, 1.84; $p = 0.187$) and in

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Table 1 Demographic and clinical characteristics upon intensive care unit admission of patients who received or did not receive NMBA treatment

Parameter	Unmatched cohort (*N*=1953)		Propensity score-matched cohort (*N*=420)	
	Control (*N*=1711)	NMBA treatment (*N*=242)	Control (*N*=210)	NMBA treatment (*N*=210)
Age (years) mean (SD)	61.8 (12.3)	58.9 (12.2)	61.2 (14.2)	59.4 (12.1)
Age (years) n (%)				
< 50	268 (15.7%)	50 (20.7%)	42 (20.0%)	40 (19.0%)
50–59	366 (21.4%)	66 (27.3%)	45 (21.4%)	56 (26.7%)
60–69	578 (33.8%)	80 (33.1%)	57 (27.1%)	73 (34.8%)
70–79	448 (26.2%)	43 (17.8%)	59 (28.1%)	39 (18.6%)
≥ 80	51 (3.0%)	3 (1.2%)	7 (3.3%)	2 (1.0%)
Male *n* (%)	1,196 (70.0%)	175 (72.3%)	144 (68.6%)	152 (72.4%)
Duration of symptom onset to hospital admission (days) median (IQR)	6.0 (4.0–9.0)	7.0 (4.0–9.0)	6.0 (4.0–9.0)	7.0 (3.0–9.0)
Duration of symptom onset to ICU admission (days) median (IQR)	11.0 (8.0–15.0)	10.0 (7.0–13.0)	10.0 (8.0–15.0)	10.0 (7.0–13.0)
Duration of symptom onset to first use of mechanical ventilation (days) median (IQR)	11.0 (8.0–15.0)	10.0 (7.0–13.0)	10.0 (8.0–15.0)	10.0 (7.0–13.0)
Ethnicity				
Aboriginal	5 (0.3%)	0 (0.0%)	3 (1.4%)	0 (0%)
Arab	59 (3.4%)	6 (2.5%)	8 (3.8%)	4 (1.9%)
Black	53 (3.1%)	21 (8.7%)	11 (5.2%)	20 (9.5%)
East Asian	18 (1.1%)	5 (2.1%)	7 (3.3%)	5 (2.4%)
Latin American	108 (6.3%)	31 (12.8%)	25 (11.9%)	27 (12.9%)
South Asian	75 (4.4%)	9 (3.7%)	8 (3.8%)	9 (4.3%)
West Asian	5 (0.3%)	1 (0.4%)	1 (0.5%)	1 (0.5%)
White	163 (9.5%)	54 (22.3%)	18 (8.6%)	48 (22.9%)
Mixed	11 (0.6%)	8 (3.3%)	4 (1.9%)	5 (2.4%)
Other	22 (1.3%)	10 (4.1%)	1 (0.5%)	10 (4.8%)
Missing	1192 (69.7%)	97 (40.1%)	124 (59.0%)	81 (38.6%)
Continent				
Africa *n* (%)	19 (1.1%)	18 (7.4%)	14 (6.7%)	14 (6.7%)
Asia *n* (%)	148 (8.6%)	19 (7.9%)	12 (5.7%)	18 (8.6%)
Europe *n* (%)	1237 (72.3%)	135 (55.8%)	121 (57.6%)	114 (54.3%)
North America *n* (%)	175 (10.2%)	43 (17.8%)	42 (20.0%)	43 (20.5%)
Oceania *n* (%)	30 (1.8%)	7 (2.9%)	3 (1.4%)	5 (2.4%)
South/Central America *n* (%)	102 (6.0%)	20 (8.3%)	18 (8.6%)	16 (7.6%)
Healthcare or laboratory worker *n* (%)	42 (2.6%)	10 (4.5%)	8 (4.0%)	9 (4.7%)
Comorbidities				
Smoking *n* (%)	525 (31.0%)	76 (32.1%)	62 (29.5%)	65 (31.4%)
Obesity* *n* (%)	622 (36.7%)	97 (40.8%)	88 (41.9%)	84 (40.2%)
Hypertension *n* (%)	916 (53.9%)	125 (52.7%)	123 (58.6%)	116 (55.2%)
Chronic cardiac disease *n* (%)	227 (13.4%)	21 (8.9%)	17 (8.1%)	19 (9.0%)
Diabetes *n* (%)	502 (29.8%)	65 (27.9%)	65 (31.0%)	60 (29.1%)
Malignant neoplasm *n* (%)	66 (3.9%)	8 (3.4%)	9 (4.3%)	8 (3.8%)
Chronic pulmonary disease *n* (%)	171 (10.1%)	30 (12.6%)	32 (15.2%)	27 (12.9%)
Severe liver disease *n* (%)	30 (1.8%)	6 (2.5%)	4 (1.9%)	6 (2.9%)
Chronic kidney disease *n* (%)	152 (9.0%)	12 (5.0%)	12 (5.7%)	12 (5.7%)
BMI mean (SD)	30.2 (6.4)	30.9 (6.8)	30.3 (6.2)	30.6 (6.6)

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Table 1 (continued)

Parameter	Unmatched cohort (N=1953)		Propensity score-matched cohort (N=420)	
	Control (N=1711)	NMBA treatment (N=242)	Control (N=210)	NMBA treatment (N=210)
Severity of illness				
APACHE II mean (SD)	18.5 (10.5)	17.8 (11.0)	21.2 (12.3)	18.3 (11.0)
SOFA mean (SD)	6.0 (3.9)	5.3 (3.5)	6.1 (4.7)	5.4 (3.6)
Laboratory results upon ICU admission				
WBC count (10*3/µL) median (IQR)	9.6 (6.1–13.0)	8.8 (7.1–11.7)	10.0 (6.4–14.1)	8.7 (7.1–11.4)
Lymphocyte count (10*3/µL) median (IQR)	0.7 (0.5–1.1)	0.8 (0.5–1.0)	0.8 (0.5–1.2)	0.8 (0.5–1.0)
Neutrophils/lymphocyte ratio median (IQR)	9.9 (5.8–17.9)	10.6 (6.2–15.8)	9.8 (5.5–17.8)	10.4 (6.0–15.2)
Temperature (℃) mean (SD)	37.3 (1.1)	37.4 (1.1)	37.2 (1.0)	37.4 (1.0)
Creatinine (mg/dL) median (IQR)	0.9 (0.7–1.2)	0.8 (0.7–1.1)	1.0 (0.7–1.4)	0.8 (0.7–1.1)
C-reactive protein level (mg/dL) median (IQR)	104.8 (30.0–192.0)	86.3 (22.6–185.4)	126.3 (40.9–228.6)	82.8 (20.8–172.1)
D-dimer (mcg/mL) median (IQR)	0.9 (0.5–2.2)	1.0 (0.5–2.3)	1.0 (0.6–2.9)	1.1 (0.5–2.3)
Lactate (mmol/L) median (IQR)	1.5 (1.1–2.1)	1.6 (1.1–2.1)	1.6 (1.1–2.0)	1.5 (1.1–2.1)
Ferritin (ng/mL) median (IQR)	2.9 (1.4–4.8)	2.8 (1.7–5.6)	3.4 (1.7–5.9)	3.2 (1.7–5.6)
IL-6 (ng/L) median (IQR)	124.7 (51.2–268.0)	79.4 (28.9–108.2)	83.0 (47.8–173.3)	75.9 (26.3–100.1)

Demographic and clinical characteristics upon intensive care unit admission of patients who received or did not receive neuromuscular blocking agents (NMBA). NMBA treatment was defined as at least 2 days of continuous use of NMBAs or up to 3 days, within 48 h from commencement of IMV

IMV, invasive mechanical ventilation; BMI, body mass index; APACHE II, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; WBC, white blood cells; IL, interleukin

Table 2 Gas exchange and level of ventilatory support within 24 h of commencement of IMV in patients who received or did not receive neuromuscular blocking agents (NMBAs)

Parameter	Unmatched cohort (N=1953)		Propensity score-matched cohort (N=420)	
	Control (N=1711)	NMBA treatment (N=242)	Control (N=210)	NMBA treatment (N=210)
pH mean (SD)	7.4 (0.1)	7.3 (0.1)	7.3 (0.1)	7.3 (0.1)
FiO_2 (mmHg) mean (SD)	76.1 (21.9)	77.3 (21.9)	81.0 (20.8)	77.5 (22.0)
PaO_2/FiO_2 (mmHg) mean (SD)	98.1 (31.1)	88.5 (29.3)	86.0 (30.7)	88.6 (29.7)
$PaCO_2$ (mmHg) mean (SD)	48.7 (13.5)	50.9 (13.9)	48.0 (15.5)	51.0 (13.7)
Tidal volume (ml/PBW) mean (SD)	7.1 (1.4)	6.9 (1.4)	7.4 (1.6)	6.8 (1.4)
Respiratory system compliance (mL/cmH$_2$O) mean (SD)	33.8 (11.9)	32.9 (12.7)	33.9 (12.2)	32.5 (12.6)
Plateau pressure (cmH$_2$O) mean (SD)	25.4 (5.7)	26.1 (5.1)	25.0 (5.9)	26.2 (5.0)
Driving pressure (cmH$_2$O) mean (SD)	22.8 (7.4)	22.1 (7.6)	22.4 (8.6)	22.7 (7.5)
Respiratory rate (breaths/min) mean (SD)	23.8 (7.0)	24.5 (7.1)	24.7 (7.4)	24.8 (7.3)
PEEP level (cmH$_2$O) mean (SD)	12.0 (3.0)	12.8 (3.3)	11.9 (3.1)	12.8 (3.3)
Heart rate (beats/min) mean (SD)	89.1 (27.4)	93.9 (29.0)	90.9 (30.5)	95.5 (28.4)
Mean arterial pressure (mmHg) mean (SD)	80.9 (19.8)	77.3 (21.6)	80.2 (20.2)	76.7 (21.7)

NMBA treatment was defined as at least 2 days of continuous use of NMBAs or up to 3 days, within 48 h from commencement of IMV

IMV, invasive mechanical ventilation; FiO$_2$, inspiratory fraction of oxygen; PaO$_2$/FiO$_2$, ratio between arterial partial pressure of oxygen and inspiratory fraction of oxygen; PaCO$_2$, arterial partial pressure of carbon dioxide; PBW, predicted body weight; PEEP, positive end-expiratory pressure

the analysis of the cohort of patients with clinically suspected and microbiologically confirmed COVID-19 (adjusted HR 1.44; 95% CI 0.99, 2.09, $p=0.055$) (Table 5). In addition, when analyses were restricted to only 2 days (Table 6) or 3 days of NMBA treatment (Table 7), similar insignificant effect on 90-day mortality was found. Conversely, sensitivity analysis exploring continuous NMBA treatment beyond 3 days (Table 8) showed increased risk
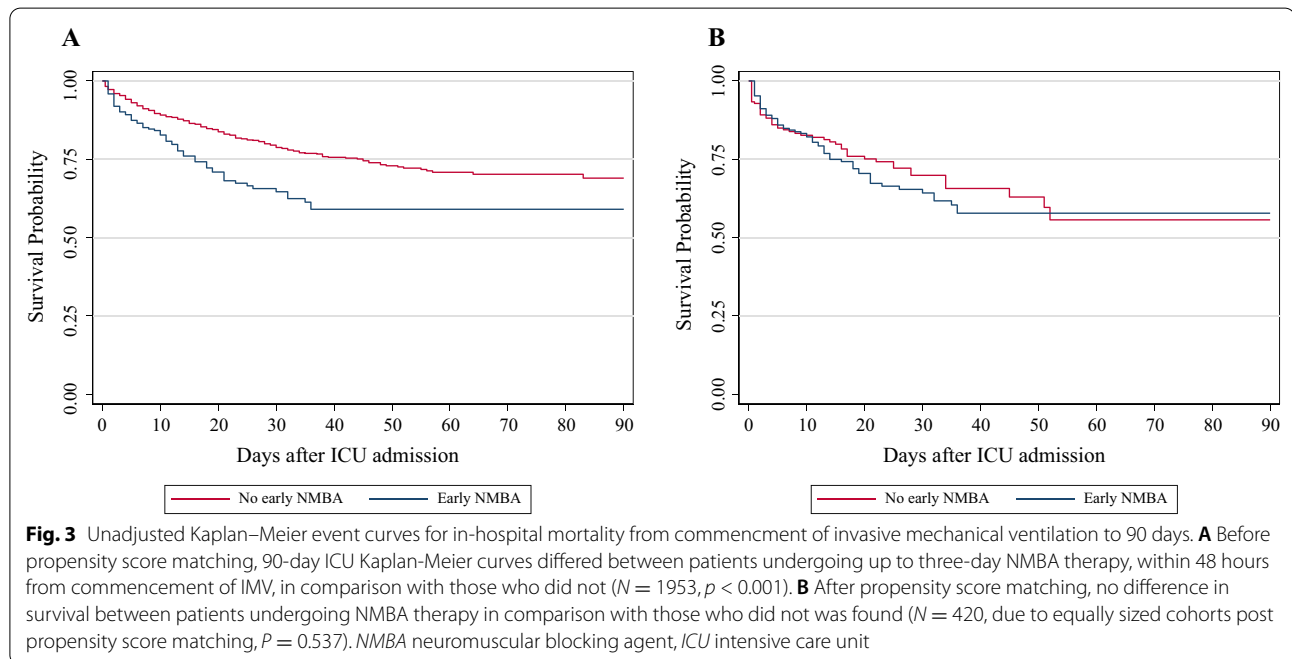
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Table 3 Intensive care unit clinical management in patients who received or did not receive neuromuscular blocking agents (NMBAs)

Parameter	Unmatched cohort (*N* = 1953)		Propensity score-matched cohort (*N* = 420)	
	Control (*N* = 1711)	NMBA treatment (*N* = 242)	Control (*N* = 210)	NMBA treatment (*N* = 210)
Vasopressor/Inotropic support *n* (%)	1556 (90.9%)	197 (81.4%)	180 (85.7%)	175 (83.3%)
Antibiotics *n* (%)	1629 (97.4%)	219 (96.5%)	194 (94.2%)	192 (96.5%)
Any antiviral *n* (%)	1399 (82.8%)	160 (70.5%)	154 (73.7%)	142 (71.7%)
Remdesivir *n* (%)	270 (16.1%)	38 (16.2%)	39 (18.8%)	34 (16.6%)
Use of corticosteroids (%)	364 (21.3%)	48 (19.8%)	48 (22.9%)	40 (19.0%)
Continuous renal replacement therapy *n* (%)	16 (0.9%)	11 (4.5%)	1 (0.5%)	10 (4.8%)
Vasoactive drugs *n* (%)	1483 (89.6%)	185 (81.1%)	178 (86.8%)	163 (81.5%)
Cardiac-assist devices *n* (%)	1 (0.1%)	4 (1.7%)	0 (0.0%)	3 (1.4%)
ECMO *n* (%)	132 (7.7%)	36 (14.9%)	14 (6.7%)	35 (16.7%)
Prone positioning *n* (%)	148 (8.6%)	52 (21.5%)	22 (10.5%)	46 (21.9%)
Use of iNO *n* (%)	2 (0.1%)	4 (1.7%)	1 (0.5%)	4 (1.9%)
Use of recruitment maneuvers *n* (%)	11 (0.6%)	20 (8.3%)	3 (1.4%)	19 (9.0%)
Pneumothorax *n* (%)	208 (12.4%)	22 (9.6%)	19 (9.6%)	21 (10.4%)
Duration of mechanical ventilation (days) median (IQR)	2 (2–4)	4 (3–13)	2 (2–10)	4 (3–13)
Duration of ICU stay (days) median (IQR)*	19 (10–34)	16 (8–27)	16 (8–29)	16 (8–27)
Time from ICU admission to death (days) median (IQR)	12 (6–23)	11 (5–18)	8 (2–22)	11 (4–19)
Time from commencement of MV to death (days) median (IQR)	9 (4–20)	10 (2–16)	5 (1–17)	9 (2–18)

NMBA treatment was defined as at least 2 days of continuous use of NMBAs or up to 3 days, within 48 h from commencement of IMV

IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide

Fig. 3 Unadjusted Kaplan–Meier event curves for in-hospital mortality from commencment of invasive mechanical ventilation to 90 days. **A** Before propensity score matching, 90-day ICU Kaplan-Meier curves differed between patients undergoing up to three-day NMBA therapy, within 48 hours from commencement of IMV, in comparison with those who did not (*N* = 1953, *p* < 0.001). **B** After propensity score matching, no difference in survival between patients undergoing NMBA therapy in comparison with those who did not was found (*N* = 420, due to equally sized cohorts post propensity score matching, *P* = 0.537). *NMBA* neuromuscular blocking agent, *ICU* intensive care unit

of 90-day mortality (adjusted HR 1.73, 95% CI 1.22, 2.37, *p* = 0.001). In this context, the reported median duration of NMBA treatment was 6 days (IQR 5–10).

Secondary outcome: ventilator-free days

In the PS-matched cohort at 28 days after

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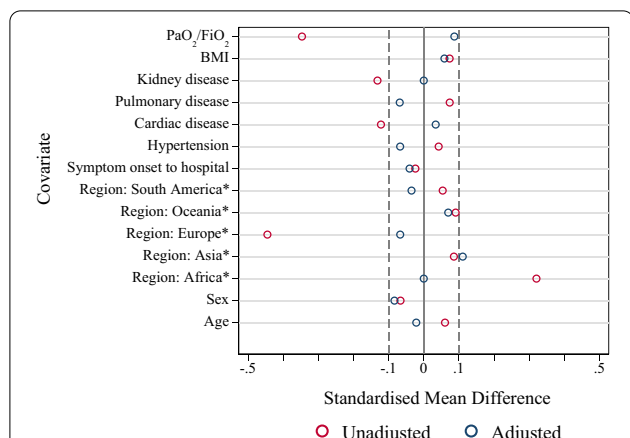
Fig. 4 Standard mean difference of key parameters before and after propensity score matching. *Compared with North America

commencement of IMV, VFD were 16 (IQR 0–25) in patients undergoing NMBA treatment and 25 (IQR 7–26) in the control group, and the sub-hazard ratio is 0.82 (95% CI 0.67, 1.00, $p = 0.055$). However, at 90 days after commencement of IMV, VFD were 77 (IQR 0–87) in patients undergoing NMBA treatment and 87 (IQR 0–88) in the control group; HR 0.86 (95% CI 0.69, 1.07; $p = 0.177$).

Discussion

To the best of our knowledge, this is the largest, international observational study of patients with COVID-19 requiring mechanical ventilation to assess the impact of short-course NMBA treatment, commenced early during IMV, on 90-day in-hospital mortality. We found that NMBA use was common, specifically

Table 5 NMBA treatment versus controls in patients with clinically suspected and microbiologically confirmed COVID-19 on 90-day in-hospital mortality

90-day mortality from ICU admission	Propensity score-matched cohort (N = 792)		
	Control (N = 396)	NMBA treatment (N = 396)	Total (N = 792)
Survived	334 (84.3%)	314 (79.3%)	648 (81.8%)
Died	62 (15.7%)	82 (20.7%)	144 (18.2%)
Total	396	396	792

Prior to propensity score matching, neuromuscular blocking agent (NMBA) treatment, defined as at least 2 days of continuous use of NMBAs or up to 3 days, within 48 h from commencement of invasive mechanical ventilation, was associated with mortality (unadjusted Cox regression; HR 1.33, 95% CI 1.06, 1.66, $p = 0.015$). After propensity score matching, 396 patients who received NMBA treatment were matched with 396 controls (using replacement). Using the propensity score-matched cohort and adjusting for covariates listed in Table 4, NMBA therapy was not associated with 90-day mortality (adjusted HR 1.44, 95% CI 0.99, 2.09, $p = 0.055$)

at European sites, and frequently applied in patients who presented hypercapnic and required higher levels of PEEP upon commencement of IMV. PS-matching analysis confirmed that early NMBA treatment did not result in lower mortality, while post hoc sensitivity analysis found increased mortality risk when NMBAs use was extended beyond 3 days. In addition, at 28 and 90 days, there were no between-group differences in days free of mechanical ventilation.

NMBAs are commonly used in critically ill patients who require IMV, but this practice has considerably changed throughout the years. In the 1980s, a survey from Great Britain reported NMBA administered in 90% of the patients on IMV [13], while in 2005 data from an international large cohort of mechanically

Table 4 90-day mortality in patients with coronavirus disease 2019 identified by Cox proportional hazards regression model, considering neuromuscular blocking agents (NMBAs) treatment as at least 2 days of continuous use of NMBAs and up to 3 days, within 48 h from commencement of IMV

Variable	Propensity score-matched cohort[a] (N = 420)		
	Adjusted hazard ratio for 90-day mortality^	95% CI	p value
NMBA treatment	1.07	0.72, 1.61	0.729
NMBA treatment and corticosteroids	1.09	0.39, 3.05	0.872
NMBA treatment per PaO$_2$/FiO$_2$ Strata within 24 h from Commencement of IMV			
< 100	0.70	0.28, 1.74	0.445
100–149	(Reference)	–	–

[a] Post-propensity score matching, also adjusting for smoking, use of antibiotics, antivirals, corticosteroids, renal replacement therapy, ECMO, and prone positioning. N = 420, due to equally sized cohorts post-propensity score matching

IMV, invasive mechanical ventilation; NMBA, neuromuscular blocking agents; PaO$_2$/FiO$_2$, ratio between arterial partial pressure of oxygen and inspiratory fraction of oxygen

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Table 6 Impact of NMBA treatment (defined by 2 days of continuous use of NMBAs within 48 h from commencement of mechanical ventilation) vs controls on 90-day in-hospital mortality

90-day mortality from ICU admission	Propensity score-matched cohort (*N* = 320)		
	Control (*N* = 160)	NMBA treatment (*N* = 160)	Total (*N* = 320)
Survived	117 (73.1%)	112 (70.0%)	229 (72.6%)
Died	43 (26.9%)	48 (30.0%)	91 (28.4%)
Total	160	160	320

Prior to propensity score matching, neuromuscular blocking agent (NMBA) treatment, defined as 2 days of continuous use of NMBAs, within 48 h from commencement of invasive mechanical ventilation, was associated with 90-day mortality (unadjusted Cox regression; HR 1.65, 95% CI 1.22, 2.23, *p* = 0.001). After propensity score matching, 160 patients who received NMBA treatment were matched with 160 controls (using replacement). Using the propensity score-matched cohort and adjusting for covariates as per Table 4, NMBA therapy was not associated with 90-day mortality (adjusted HR 1.15, 95% CI 0.74, 1.78, *p* = 0.524)

Table 7 Prior to propensity score matching, neuromuscular blocking agent (NMBA) treatment, defined as 3 days of continuous use of NMBAs, within 48 h from commencement of invasive mechanical ventilation, was associated with 90-day mortality (unadjusted Cox regression; HR 2.13, 95% CI 1.40, 3.24, *P* < 0.001). After propensity-score matching, 50 patients who received NMBA treatment were matched with 50 controls (using replacement). Using the propensity score-matched cohort (and adjusting for covariates as per Table 4, NMBA therapy was not associated with 90-day mortality (adjusted HR 1.56 95% CI 0.55, 4.32, *P* = 0.392)

90-day mortality from ICU admission	Propensity score-matched cohort (*N* = 100)		
	Control (*N* = 50)	NMBA treatment (*N* = 50)	Total (*N* = 100)
Survived	38 (76%)	33 (66%)	71 (71%)
Died	12 (24%)	17 (34%)	29 (29%)
Total	50	50	100

Table 8 NMBA treatment (defined by > 3 days within 48 h from commencement of mechanical ventilation) vscontrols on 90-dayin-hospital mortality

90-day mortality from ICU admission	Propensity score-matched cohort (*N* = 324)		
	Control (*N* = 162)	NMBA treatment (*N* = 162)	Total (*N* = 362)
Survived	130 (80.3%)	81 (50.0%)	211 (65.1%)
Died	32 (19.8%)	81 (50.0%)	113 (34.9%)
Total	162	162	324

Prior to propensity score matching, neuromuscular blocking agent (NMBA) treatment, defined as more than 3 days of continuous use of NMBAs, within 48 h from commencement of invasive mechanical ventilation, was associated with 90-day mortality (unadjusted Cox regression; HR 2.57, 95% CI 2.02, 2.71, *p* < 0.001). After propensity score matching, 372 patients who received NMBA treatment were matched with 372 controls (using replacement). Using the propensity score-matched cohort and adjusting for covariates as per Table 4, NMBA therapy was associated with 90-day mortality (adjusted HR 1.73, 95% CI 1.27, 2.37, *p* = 0.001)

Early Neuromuscular Blockade (ROSE) trial failed to show reductions in mortality [16]. Meta-analyses emphasized potential limitations of those previous trials, i.e., heterogeneity in the use of sedation and prone positioning, selection bias, and crossover between treatment groups. Thus, to date, available evidence supports the use of NMBAs to reduce risks of barotrauma and to improve oxygenation [34–36], but without clear advantage in survival rate. ARDS caused by COVID-19 has broad similarities with historic ARDS caused by other etiologies [18, 37–39], although pulmonary blood flow derangement and resulting pulmonary shunt seem to play a primary role in COVID-19 ARDS [40]. As a result, various interventions previously employed for ARDS, such as prone position [41], ECMO [42], and NMBAs [20], were extensively applied in the COVID-19 population.

In the current study, we describe COVID-19 patients who required mechanical ventilation and who presented with moderate-to-severe hypoxemia. Various small case reports have demonstrated substantial ventilatory asynchrony in these patients [43–45] and adverse sequelae, such as pneumothorax or pneumomediastinum [46–48]. Patients receiving NMBA also frequently required adjunctive therapies for ARDS, suggesting that the severity of disease was a main driver in the use of these drugs. The COVID-19 population subset investigated in our analyses provides further value to our study; indeed, we identified patients with moderate-to-severe ARDS who received, early, a short course of NMBAs. This is in line with protocols applied in previous large randomized trials [15, 16]. Furthermore, in comparison with the ACURASYS and ROSE trials, we found that the COVID-19 population presented similar baseline impairment in

ventilated patients reported NMBAs use merely in 13% of the patients [31]. The most recent clinical practice guidelines by the Society of Critical Care Medicine specified various indications for the use of NMBA in critically ill adult patients [32], among those patients with ARDS and $PaO_2/FiO_2 < 150$. In line with the original findings by Gainnier et al. demonstrating consistent oxygenation improvement in ARDS patients undergoing a 48-h course of NMBA [33], the confirmatory ACURASYS trial found that early administration of continuous cisatracurium for 48 h improved 90-day survival [15] and reduced risk of barotrauma. However, subsequent results from the Reevaluation of Systemic

respiratory function, and as in the ROSE trial, low tidal volume and high PEEP were applied and resulted in comparable airway plateau pressure. However, prone position was used much more frequently in the COVID-19 population and the improvements associated with its use [49, 50] might have offset any additional benefit related to NMBAs.

Courcelle and collaborators specifically investigated the effects of NMBAs in COVID-19 patients enrolled in French/Belgian ICUs. After PS matching, they did not find a significant difference in 28-day mortality [20]. Similar to these preliminary findings, our international, larger multicenter investigation also found no improvement in 90-day mortality in patients receiving a short course of NMBAs. Moreover, Courcelle found a median duration of NMBA use of 5 days; conversely, our study appraised only patients who received continuous NMBAs up to 3 days, and interestingly, we found higher hazard ratio of 90-day mortality when the use of NMBAs was extended more than 3 days. This finding provides further evidence on the risks associated with NMBAs in COVID-19 patients. Relative to Courcelles PS-matched cohort, our matched population was similar in age, gender proportion, and BMI and initial ventilatory settings. Yet, in the French/Belgian study, prone positioning was applied in over 90% and ECMO in 15% of the patients, in line with French expert consensus guidelines recommendations [51] and evidence in favor of the aforementioned interventions in COVID-19 patients [42, 50, 52]. Conversely, our dataset encompassed a global population of critically ill COVID-19 patients, including ICU centers both with and without access to modalities such as prone position and ECMO, which were applied in up to 69.6% and 16.7%, respectively. In the early waves of the pandemic, centers with the highest patient numbers acknowledged that treatments, such as prone positioning, could sometimes not be accomplished, due to staffing limitations and patient safety concerns [11]. Similarly, NMBA use at centers with overwhelming ICU surge may also be greater than in less resource-constrained environments.

Non-depolarizing NMBAs inhibit the acetylcholine (Ach) receptor on the motor endplate and are available as aminosteroid or benzylisoquinolinium compound, the latter being the first choice for ARDS patients [53]. Renal and hepatic disease can drastically prolong the clearance of aminosteroid NMBAs, and in these conditions benzylisoquinolinium agents are preferred, since they undergo spontaneous degradation via Hofmann elimination. The NMBA class used was not recorded in our dataset, but severe liver and chronic kidney diseases were present in only 2.9 and 5.7% of the patients treated with NMBAs, respectively. Of note, COVID-19 can cause a broad variety of neurological symptoms and sequelae [54] and has been associated with the development of anti-Ach receptors antibodies [55] and myasthenia gravis [56]. Hence, comprehensive research is needed in this field to elucidate whether underlying neurological mechanisms associated with COVID-19 lead to an increased risk of death when NMBA are administered, and caution should be applied.

Strengths and limitations

To date, this is the first international report of a large group of mechanically ventilated COVID-19 patients with severe disease to investigate the effects of NMBA. Employing comprehensive PS matching analysis, we demonstrated no improvement in mortality with NMBA use. These findings were consistently corroborated in sensitivity analysis applying inverse probability of treatment weighting. In addition, we provided inferences not limited by clinical practice specific to single-country studies. Nonetheless, certain limitations must be highlighted. First, although we conducted a comprehensive comparative PS-matched analysis that resulted in significant homogeneity in the evaluated sub-cohorts, the observational nature of our study and risks of drawing causal inferences should be highlighted. While immortal time bias could be considered as a potential limitation of this study design, given the short duration between cohort entry and exposure to NMBA therapy, the magnitude of the bias is expected to be limited [57]. In addition, similar times from ICU admission to death were found in both groups. Yet, the risk of immortal time bias should also be considered for several interventions potentially associated with survival—such as prone positioning, ECMO, and corticosteroids—since only patients who survived long enough to receive these interventions were analyzed. Second, the analyzed dataset did not provide any information on the type of NMBA, doses, or adequacy of the block achieved; hence, we were unable to extrapolate the appropriateness of their clinical use. In addition, the time of commencement of NMBA treatment was not recorded; thus, although we included patients who received NMBAs up to 3 days, and we explored different treatment regimens in sensitivity analyses, potential discrepancy in the clinically indicated 2-day full course of NMBA treatment [15, 16] should be considered when interpreting the results. Third, a proportion of the studied population was admitted to the ICU early during the pandemic. Consequently, potential logistical limitations related to managing critically ill patients treated in newly developed and understaffed ICUs, due to shortages in ICU beds or healthcare providers, must be considered. Fourth, as shown in Fig. 4, residual discrepancy for Asia likely persisted post-matching. Further assessment on

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the potential reasons for this divergence suggested possible increased mortality in control patients from Asia. This could be related to the specific regional differences in ventilatory practice or application of adjunctive therapies, which should be further explored in future studies. Irrespective, potential random effect related to heterogenous practice among collaborating hospitals should be considered while interpreting our results. Fifth, the voluntary nature of site participation in the study must be emphasized, especially during a pandemic, as data may be skewed toward centers with enough resources to enter data. Lastly, as our observational study acquired data from routine clinical records, missing data could have biased our estimates.

Conclusions

Our results derived by PS-matching analysis suggest that among patients with COVID-19 and moderate-to-severe ARDS, early administration of a short course of NMBAs did not result in improved 90-day in-hospital mortality. In addition, NMBA treatment did not impact ventilator-free days. Thus, the use of NMBAs should be cautiously assessed in this population, pending further studies that could elucidate specific indications for NMBAs in COVID-19.

Abbreviations

ARDS: Acute respiratory distress syndrome; $PaCO_2$: Arterial partial pressure of carbon dioxide; CI: Confidence interval; COVID-19: Coronavirus disease 2019; COVID-19–CCC/ECMOCARD: COVID-19 Critical Care Consortium incorporating the ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease; HR: Hazard ratio; ISARIC: International Severe Acute Respiratory and Emerging Infection Consortium; IMV: Invasive mechanical ventilation; IQR: Interquartile range; MAP: Mean arterial pressure; NMBAs: Neuromuscular blocking agents; PEEP: Positive end-expiratory pressure; PS: Propensity score; PaO_2/FiO_2: Ratio between arterial partial pressure of oxygen and inspiratory fraction of oxygen; SD: Standard deviation; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SPRINT-SARI: Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-022-03983-5.

Additional file 1. Appendix.

Availability of data materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Participating hospitals obtained local ethics committee approval, and a waiver of informed consent was granted in all cases.

Consent for publication

Not applicable.

Competing interests

A/Prof Li Bassi received research support from Fisher & Paykel outside the submitted work. Prof. Dalton consults with Innovative ECMO Concepts, Abiomed and Instrumentation Labs, which does not affect the current work. Prof. Brodie receives research support from ALung Technologies, and he has been on the medical advisory boards for Baxter, Abiomed, Xenios, and Hemovent. A/Prof Fan reports personal fees from ALung Technologies, Baxter, Fresenius Medical Care, Getinge, and MC3 Cardiopulmonary outside the submitted work. Prof. Laffey reports consulting fees from Baxter and Cala Medical, both outside the submitted work. Prof. Nichol is supported by a Health Research Board of Ireland Award (CTN-2014-012). Prof. Fraser receives research support from Fisher & Paykel outside the submitted work. Prof. Grasselli reports personal fees from Draeger Medical, Biotest, Getinge, Fisher & Paykel, and MSD outside the submitted work.

Author details

[1] Critical Care Research Group, The Prince Charles Hospital, 627 Rode Rd, Chermside, Brisbane, QLD 4032, Australia. [2] University of Queensland, Brisbane, Australia. [3] Institut dInvestigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain. [4] Queensland University of Technology, Brisbane, Australia. [5] UnitingCare Hospitals, Brisbane, Australia. [6] Wesley Medical Research, Brisbane, Australia. [7] Child Health Research Centre, The University of Queensland, Brisbane, QLD, Australia. [8] INOVA Fairfax Medical Center, Heart and Vascular Institute, Falls Church, VA, USA. [9] The Australian Research Council Centre of Excellence for Engineered Quantum Systems (EQUS, CE170100009), Brisbane, Australia. [10] Anaesthesia and Intensive Care Medicine, School of Medicine, National University of Ireland, and Galway University Hospitals, Galway, Ireland. [11] Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada. [12] Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy. [13] University of Michigan Medical Center, Ann

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Arbor, MI, USA. [14]Department of Medicine, Columbia College of Physicians and Surgeons, and Center for Acute Respiratory Failure, New-York-Presbyterian Hospital, New York, NY, USA. [15]Australian and New Zealand Intensive Care Research Centre, School of Public Health, Monash University, Melbourne, Australia. [16]Ospedale San Paolo, Milan, Italy. [17]University of Milan, Milan, Italy. [18]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. [19]Hospital Privado de Comunidad, Escuela de Medicina, Universidad Nacional de Mar del Plata, Mar del Plata, Argentina. [20]Nippon Medical School Hospital, Tokyo, Japan. [21]Neumología, Hospital de Clínicas, UBA, Buenos Aires, Argentina. [22]National Cardiovascular Center Harapan Kita, Jakarta, Indonesia. [23]ISARIC, Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, UK. [24]Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, Canada. [25]BC Childrens Hospital Research Institute, Vancouver, Canada. [26]University College Dublin-Clinical Research Centre at St Vincents University Hospital, Dublin, Ireland. [27]Department of Intensive Care, The Alfred Hospital, Melbourne, Australia. [28]Nemours Alfred I duPont Hospital for Children, Wilmington, DE, USA. [29]Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy. [30]Anesthesia and Critical Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy. [31]Hospital Clinic of Barcelona, Barcelona, Spain. [32]Department of Medicine, The University of Hong Kong, Pok Fu Lam, Hong Kong. [33]Al Adan Hospital, Hadiya, Kuwait. [34]Allegheny General Hospital, Pittsburgh, USA. [35]Avera McKennan Hospital & University Health Centre, Sioux Falls, USA. [36]Barmherzige Bruder Regansburg, Regensburg, Germany. [37]Baylor Scott & White Health, Dallas, USA. [38]Baylor University Medical Centre, Dallas, USA. [39]Bergamo Hospital, Bergamo, Italy. [40]Beth Israel Deaconess Medical Centre, Boston, USA. [41]Box Hill Hospital, Box Hill, Australia. [42]Caboolture Hospital, Caboolture, Australia. [43]Canberra Hospital, Canberra, Australia. [44]Carilion Clinic, Roanoke, USA. [45]Chiba University Graduate School of Medicine, Chiba, Japan. [46]Chonnam National University Hospital, Gwangju, South Korea. [47]Cleveland Clinic - Abu Dhabi, Abu Dhabi, UAE. [48]Cleveland Clinic - Florida, Weston, USA. [49]Cleveland Clinic - Ohio, Cleveland, USA. [50]Clinica Alemana de Santiago, Santiago, Chile. [51]Clinica Las Condez, Las Condes, Chile. [52]Clinica Pasteur National- University of Comahue, Neuquén, Argentina. [53]Linica Valle de Lilli, Cali, Colombia. [54]Medical ICU, Columbia College of Physicians and Surgeons, New-York-Presbyterian Hospital, New York, NY, USA. [55]Dr Sulaiman Alhabib Medical Group – Research Center, Riyadh, Saudi Arabia. [56]Emory University Healthcare System, Atlanta, USA. [57]Fatmawati Hospital, Fatmawati, Indonesia. [58]Fondazione IRCCS Policlinico of Milan (Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico), Milan, Italy. [59]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy. [60]Fujieda Municipal General Hospital, Fujieda, Japan. [61]Fukuoka University, Fukuoka, Japan. [62]Fundación Cardiovascular de Colombia, Bogota, Colombia. [63]Galway University Hospitals, Galway, Ireland. [64]Geelong Hospital, Geelong, Australia. [65]Glenfield Hospital, Leicester, UK. [66]Gold Coast University Hospital, Gold Coast, Australia. [67]Groote Schuur Hospital, Cape Town, South Africa. [68]Hamad General Hospital - Weill Cornell Medical College in Qatar, Ar-Rayyan, Qatar. [69]Hartford HealthCare, Hartford, USA. [70]Hasan Sadikin Hospital (Adult), Jawa Barat, Indonesia. [71]Hiroshima University, Hiroshima, Japan. [72]Hokkaido University Hospital, Sapporo, Japan. [73]Hospital Alemán, Buenos Aires, Argentina. [74]Hospital Civil Marie Curie, Charleroi, Belgium. [75]Hospital Clinic, Barcelona, Spain. [76]Hospital de Clínicas, Buenos Aires, Argentina. [77]Hospital del Tórax, Barcelona, Spain. [78]Hospital du Sacre Coeur (Universite de Montreal), Montréal, Canada. [79]Hospital Emergencia Ate Vitarte, Ate, Peru. [80]Hospital for Tropical Diseases, London, UK. [81]Hospital Mater Dei, Msida, Malta. [82]Hospital Nuestra Señora de Gracia, Zaragoza, Spain. [83]Hospital Puerta de Hierro, Zapopan, Mexico. [84]Hospital Universitari Sagrat Cor, Barcelona, Spain. [85]Hospital Universitario Sant Joan dAlacant, Alicante, Spain. [86]Hospital Universitario Virgen de Valme, Sevilla, Spain. [87]Hospital Verge de La Cinta de Tortosa, Tortosa, Spain. [88]Houston Methodist Hospital, Houston, USA. [89]INCOR (Universidade de São Paulo), São Paulo, Brazil. [90]INOVA Fairfax Hospital, Falls Church, USA. [91]ISMETT, Palermo, Italy. [92]Johns Hopkins, Baltimore, USA. 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