Neuromuscular Blocking Agent Use in Acute Respiratory Distress Syndrome: Which Variable is Important?

Farshid Rahimibashar¹, Mahmood Salesi², Amir Vahedian-Azimi³, Masoum Khosh Fetrat⁴*

¹Department of Anesthesiology and Critical Care, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
²Chemical Injuries Research Center, Life Style Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
³Trauma Research Center, Nursing Faculty, Baqiyatallah University of Medical Sciences, Tehran, Iran
⁴Department of Anesthesiology and Critical Care, Khatamalanbia Hospital, Zahedan University of Medical Sciences, Zahedan, Iran

*Corresponding Author: Masoum Khosh Fetrat, M.D., Associate Professor, Departments of Anesthesiology and Critical Care, Khatamalanbia Hospital, Zahedan University of Medical Sciences, Zahedan, Iran. Tel: +98-9196017138, Email: drkhoshfetrat@yahoo.com

1. Background
Acute respiratory distress syndrome (ARDS) is an acute inflammatory process that impairs the capacity of the lungs to oxygenate, resulting in respiratory failure.¹ In spite of advanced therapeutic techniques, ARDS is still associated with poor prognosis.² The estimated incidence of ARDS globally ranges from 10 to 86 cases per 100,000 patients and hospital mortality related to ARDS is high, with rates reported ranging from 35% to 46%, depending on the severity of initial hypoxemia.³,⁴ ARDS evolved within one week of exposure to a risk factor for ARDS.³ Pneumonia, aspiration, inhalation injury, near drowning, and pulmonary contusion are risk factors which cause ARDS through direct lung injury. For the majority of ARDS cases, pneumonia and aspiration events are responsible.⁵,⁶ In addition, other risk factors for ARDS that cause indirect lung injury are sepsis, pancreatitis, cardiopulmonary bypass, burns, injuries, hemorrhagic shock, transfusions, and an overdose of medication.⁵,⁹

Treatment of ARDS is also a multimodal strategy, which used both non-pharmacological and pharmacological treatment methods, in ARDS patients.¹⁰,¹¹ Non-pharmacologic mechanical ventilation (MV) strategies include low tidal volumes ventilation, open lung ventilation, low inspiratory pressures, high positive end-expiratory pressure (PEEP) and recruitment maneuvers.
in patients with moderate to severe ARDS and prone positioning in patients with severe ARDS.21-24 On the other hand, neuromuscular blocking agents (NMBAs) have been prescribed as a pharmacological treatment method for patients with ARDS to minimize inflammation, oxygen intake, and cardiac output, help to facilitate ventilation synchronization and thus reducing ARDS-related mortality.16-19

A meta-analysis by Tao et al20 indicated that a 48 hours NMB infusion might reduce intensive care unit (ICU) mortality in patients with moderate-to-severe ARDS. Furthermore, a recent systematic and meta-analysis by Chang et al21 showed that the use of NMBAs could significantly decrease mortality in moderate-to-severe ARDS patients and reduce the incidence of barotrauma during MV. However, Honor et al22 pointed out that the conclusions of Chang et al,21 are not the recommendations of the experts focusing upon the most hypoxemic patients and this message seems crucial to considering the numerous side effects of NMBAs. However, the benefit of NMBA was not confirmed by a recently published randomized controlled trial (RCT), the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial,23 leaving the use of NMBA in ARDS patients unclear and controversial. Therefore, it seems that the therapeutic role of NMBA in patients with ARDS is still an open field to explore. Accordingly, we conducted this observational retrospective secondary analysis on the database of the 4200 patients with ARDS from the mixed medical–surgical ICUs of two academic medical centers in Iran, to assess mortality in ARDS patients who underwent NMBA.

2. Objectives
The main purpose of this study was to evaluate mortality in ARDS patients who underwent NMBA.

3. Methods
3.1. Study Design and Participants
This study was a retrospective secondary analysis of an original project that was prospective longitudinal cohort study.24 In brief, the original study was a prospective longitudinal cohort study was conducted of 4200 mixed medical–surgical ICUs patients with ARDS on MV from of two academic teaching hospitals in Tehran, Iran between June 1, 2007 and October 31, 2015.24 This secondary analysis study was performed to assess the impact of NMBAs use in ARDS patients with different subgroups including mild and moderate-to-severe ARDS, age more and less than 65 years, having medical turnover vs. not-having, and high acute nursing care vs. moderate to low nursing care. The patients, or their relatives, were informed about participation in the study by the physician at the time of admission with consent in all cases. All study parts were reviewed according to the “Strengthening the Reporting of Observational Studies in Epidemiology for respondent-driven sampling studies” (STROBE-RDS) statement.25

3.2. Eligible Criteria
The inclusion criteria were: (a) age ≥ 18 years, (b) intubated and mechanically ventilated patients with ARDS, (c) PaO/FiO less than 150 with PEEP at least 5 within the first 48 hours of the onset of ARDS (d) full-code status, and (e) informed consent obtained from the patient, legal guardian, or healthcare surrogate. Exclusion criteria included pregnancy, patient receiving continuous infusion of NMBA, known NMBA allergy, contraindication to introduction of nasogastric tube, undrained pneumothorax, treatment with extracorporeal membrane oxygenation or extracorporeal CO removal, increased intracranial pressure, respiratory chronic insufficiency, body mass index greater than 40 kg/m², severe chronic liver disease (Child–Pugh class C), bone marrow transplantation or chemotherapy-induced neutropenia, burn lesions greater than 30% of body surface, Simplified Acute Physiology Score (SAPS) II of 70 or greater.

Moderate-to-severe ARDS patients diagnosed according to the Berlin criteria,26 or American-European Consensus Conference (AECC) criteria27; which were characterized by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO/FiO) of less than 150 mm Hg with a PEEP at least 5 cm of water within the first 48 hours of the onset of ARDS. In addition, NMBAs doses (determined in accordance with published recommendations in three levels high, moderate, and low.28 The NMBAs dose is cumulative one.

3.3. Data Collection and Outcome
Demographic and clinical characteristics were recorded for all participants, including age, gender, acute nursing care determined by requiring >8 hours nursing care in an 8-hour shift, staff burnout and anticipated turnover measured with the Anticipated Turnover Scale questionnaire,29 ICU length of stay (LOS), free-ICU days, sedative dose which determined in accordance with published recommendations.30 Additionally, illness severity was measured by the Simplified Acute Physiology Score (SAPS) II at the day of ICU admission.31 The main outcome variable was ICU mortality, following ICU admission.

3.4. Statistical Analysis
Data are presented as mean ± standard deviation (SD) or percentages. Categorical data were compared using the χ² test (or Fisher exact test when appropriate); and continuous data, using the Student t test. In addition, both unadjusted and adjusted logistic regressions were used to estimate the odds ratio (OR) to determine the association of demographic and clinical characteristics with mortality. All data were analyzed using the Statistical Package for the Social Sciences (SPSS) 21.0 (Chicago, IL, USA) and GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA),32 and two-side P < 0.05 indicated a statistically significant difference.
4. Results

4.1. Demographic and Clinical Characteristics
A total of 4200 subjects were included in the second analysis. The mean ± SD age of total participants was 67.25 ± 11.5 years and near to half of the patients were over 65 years (n = 2051, 48.8%) and 58.1% of the included patients were female. According to the Berlin criteria, more than half of the participants were recognized with moderate-to-severe ARDS (n = 3031, 72.16%) and the other patients (n = 1169, 27.84%), with mild ARDS. The mean ± SD age of patients with moderate-to-severe ARDS was 67.29 ± 11.59 years, more than half of the patients were over 65 years (51%), and 1770 (58.4%) patients were female, which was not significantly different from patients with mild ARDS (P > 0.05). In addition, in the patients with mild and moderate-to-severe ARDS did not differ significantly in terms of having medical turnover vs. not-having, and high acute nursing care vs. moderate to low nursing care (P > 0.05).

4.2. NMBA Doses in Two Groups of Study
A total of 2254 (53.75) subject received moderate dose of NMBA, and the other patients received low 1055 (25.1%) and high 891 (21.2%) dose of NMBA, respectively. In mild ARDS patients group low, moderate and high doses of NMBA were used in 287 (24.5%), 609 (52.5%), and 273 (23.3%) patients, respectively. In patients with moderate-to-severe ARDS, 768 (25.3%), 1645 (54.3%), and 618 (20.4%) patients received low, moderate and high doses of NMBA, respectively. The results show that not only was there no statistically significant difference between the two groups (P > 0.05), but also there was no statistically significant difference even within group (P > 0.05).

4.3. Outcome
ICU mortality has occurred in 1169 (27.8%) participants. The mortality rate was 28.6% and 27.5% in patients with mild and moderate-to-severe ARDS, respectively. Mortality was not significant between the two groups of study. Effect of different doses of NMBAs on mortality according to demographic and clinical characteristics of participants are presented in Table 1. According to Table 1, the increasing NMBAs doses had no effect on patients’ mortality with mild and moderate to severe ARDS. High doses of NMBA significantly increased mortality in patients over 65 years (P = 0.036). In the subjects without medical turnover, the moderate dose of NMBAs significantly reduces the mortality of patients (P = 0.044). In patients who need high acute nursing care, increasing the NMBAs dose significantly reduces patients’ mortality (P = 0.010). In addition, increasing the NMBAs doses significantly reduces ICU LOS (P < 0.001). However, it had no effect on the free-ICU days (P = 0.168). Logistic regression (Figure 1) revealed that the high dose vs. low dose of NMBAs was increased the risk of mortality among patients between 80 to 84 years old (odds ratio [OR]: 3.142, 95% CI: 1.461-6.756, P = 0.003). However, higher doses of NMBA than low doses reduce the risk of death in patients between 50 and 54 years of age (OR: 0.432, 95% CI: 0.267-0.798, P = 0.006). Accordingly, the effect of moderate and low dose of NMBAs was similar on mortality according to the age groups.

5. Discussion
In this secondary analysis study, we evaluated the administration of different doses of NMBA (low to high doses) in patients with mild and moderate-to-severe ARDS and its effect on patient mortality. The results indicated that the increasing NMBAs doses had no effect on patients’ mortality with mild and moderate-to-severe ARDS. However, increasing the NMBAs doses significantly reduces ICU LOS. In addition, the high dose vs. low dose of NMBA was significantly increased the risk of mortality among patients between 80 to 84 years old (odds ratio [OR]: 3.142, 95% CI: 1.461-6.756, P = 0.003). However, higher doses of NMBA than low doses reduce the risk of death in patients between 50 and 54 years of age (OR: 0.432, 95% CI: 0.267-0.798, P = 0.006). Accordingly, the effect of moderate and low dose of NMBAs was similar on mortality according to the age groups.

Figure 1. Logistic Regression Analysis of the Effect of NMBAs Doses on Mortality According to age Groups.
NMBAs was increased the risk of mortality among patients between 80 to 84 years old. However, higher dose of NMBA than low doses reduce the risk of death in patients between 50 and 54 years of age.

Gainnier et al\(^3\) conducted a multi-center, prospective controlled randomized trial and found that the use of NMBAs during a 48-hour period in ARDS patients was associated with a sustained improvement in oxygenation. In the ACURASYS trial, Papazian et al\(^1\) found that in patients with severe ARDS, early administration of

| Variables | Outcomes | Total | P-value |
|-----------|----------|-------|---------|
|          | Death    | Alive |         |
| Patients with Mild ARDS | | | |
| High dose of NMBAs | 82 (30.0) | 191 (70.0) | 273 (100) | 0.513 |
| Moderate dose of NMBAs | 165 (27.1) | 444 (72.9) | 609 (100) | |
| Low dose of NMBAs | 87 (30.3) | 200 (69.7) | 287 (100) | |
| Total | 334 (28.6) | 815 (71.4) | 1169 (100) | |
| Patients with moderate to severe ARDS\(^\text{c}\) | | | |
| High dose of NMBAs | 172 (27.8) | 446 (72.2) | 618 (100) | 0.981 |
| Moderate dose of NMBAs | 451 (27.4) | 119 (72.6) | 1645 (100) | |
| Low dose of NMBAs | 212 (27.6) | 556 (72.4) | 768 (100) | |
| Total | 835 (27.5) | 2196 (72.5) | 3031 (100) | |
| Age <65 years | | | |
| High dose of NMBAs | 117 (25.0) | 351 (75.0) | 468 (100) | 0.258 |
| Moderate dose of NMBAs | 340 (28.7) | 843 (71.3) | 1183 (100) | |
| Low dose of NMBAs | 145 (29.1) | 353 (70.9) | 498 (100) | |
| Total | 602 (28.0) | 1547 (72.0) | 2149 (100) | |
| Age >65 years | | | |
| High dose of NMBAs | 137 (32.4) | 286 (67.6) | 423 (100) | 0.036* |
| Moderate dose of NMBAs | 276 (25.8) | 795 (74.2) | 1071 (100) | |
| Low dose of NMBAs | 154 (27.6) | 403 (72.4) | 557 (100) | |
| Total | 567 (27.6) | 1484 (72.4) | 2051 (100) | |
| Patients with medical turnover\(^b\) | | | |
| High dose of NMBAs | 150 (27.7) | 391 (72.3) | 541 (100) | 0.631 |
| Moderate dose of NMBAs | 407 (29.3) | 984 (70.7) | 1391 (100) | |
| Low dose of NMBAs | 162 (27.4) | 430 (72.6) | 592 (100) | |
| Total | 719 (28.5) | 1805 (71.5) | 2524 (100) | |
| Patients without medical turnover\(^b\) | | | |
| High dose of NMBAs | 104 (29.7) | 246 (70.3) | 350 (100) | 0.044* |
| Moderate dose of NMBAs | 209 (24.2) | 654 (75.8) | 863 (100) | |
| Low dose of NMBAs | 137 (29.6) | 326 (70.4) | 463 (100) | |
| Total | 450 (26.8) | 1226 (73.2) | 1676 (100) | |
| Patients who need moderate to low nursing care\(^c\) | | | |
| High dose of NMBAs | 214 (29.3) | 516 (70.7) | 730 (100) | 0.288 |
| Moderate dose of NMBAs | 487 (27.2) | 1306 (72.8) | 1793 (100) | |
| Low dose of NMBAs | 212 (25.8) | 611 (74.2) | 823 (100) | |
| Total | 913 (27.3) | 2433 (72.4) | 3346 (100) | |
| Patients who need high nursing care\(^c\) | | | |
| High dose of NMBAs | 40 (24.8) | 121 (75.2) | 191 (100) | 0.010* |
| Moderate dose of NMBAs | 129 (28.0) | 332 (72) | 461 (100) | |
| Low dose of NMBAs | 87 (37.5) | 145 (65.5) | 232 (100) | |
| Total | 256 (30.0) | 598 (70.0) | 854 (100) | |

\(^a\) As determined by a ratio of PaO2/FiO2 <150 mm Hg with a PEEP at least 5 cm of water within the first 48 h of the onset of ARDS

\(^b\) As determined by the anticipated turnover scale (ATS)

\(^c\) As determined by requiring >8 hours nursing care in an 8 hour shift

NMBAs was increased the risk of mortality among patients between 80 to 84 years old. However, higher dose of NMBA than low doses reduce the risk of death in patients between 50 and 54 years of age.

Gainnier et al\(^3\) conducted a multi-center, prospective controlled randomized trial and found that the use of NMBAs during a 48-hour period in ARDS patients was associated with a sustained improvement in oxygenation. In the ACURASYS trial, Papazian et al\(^1\) found that in patients with severe ARDS, early administration of
cisatracurium continuously for 48 hours improved the adjusted 90-day survival, decreased the risk of barotrauma, and increased the time off the ventilator without increasing muscle weakness. However, more recent results from the ROSE trial failed to show reductions in mortality when NMBAs were administered in moderate-severe ARDS. While cisatracurium has been shown to have anti-inflammatory properties in animal models, its clinically applicable advantage is likely to include the avoidance of ventilator dysynchrony and lung compliance improvements. The results of three recent meta-analyses have all demonstrated that NMBA administration in ARDS patients is associated with reduced barotrauma and improved oxygenation; however, the impact on mortality remains controversial.

On the other hand, data regarding the compare of different doses of NMBAs in critically ill patients with ARDS is limited. Two studies have used cisatracurium 15 (mg) as a continuous infusion NMBA at a set rate of 37.5 mg/h × 48 h to demonstrate a mortality benefit with NMBA for ARDS patients. A study by Papazian et al showed the positive effects of cisatracurium on 28- and 90-day mortality rates compared to patients did not receive NMBA. However, they reported significant adverse effects in the control group compared with the NMBA group. The high set rate of NMBA is a criticism of this research, possibly contributing to overexposure and adverse effects.

In the present study, high doses of NMBA increased the risk of mortality in patients between the ages of 80 and 84 years, while higher doses of NMBA reduced the risk of death in patients between 50 and 54 years of age. This could be related to the risk associated with high doses of NMBA in very old intensive care patients (≥80 years). The use of NMBAs in critically ill patients can be further complicated by drug interactions, alterations in pH and electrolytes, venous thromboembolisms, myopathy and prolonged recovery. In addition, in patients with ARDS, the rate of acquired ICU weakness is reported to be between 30 and 60%, which can increase with older age, female gender, multi-organ failure, administration of corticosteroids, and prolonged durations of vasopressor support, MV, and ICU length of stay. Therefore, high doses of NMBA in older ICU patients with ARDS can increase patients’ risk and ultimately increase mortality in these individuals.

The strengths of our study included the large sample size and its multi-center design. However, our study has a several limitations. First, data were collected prospectively in the original study, but data analysis on NMBA was performed retrospectively. Second, due to the retrospective nature of the study, we were not able to evaluate adverse effects associated NMBA in ICU patients. However, our results provide insights into abusers of high dose of NMBA in older age patients that need further reflection and study.

6. Conclusion
This multicenter retrospective observational study provides evidence that the administration of different doses of NMBAs had no effect on patients’ mortality with mild or moderate-to-severe ARDS. However, higher doses of NMBAs than low doses increased the risk of mortality in patients over 80 years and can reduce the risk of death in patients less than 55 years. So, patients should be carefully monitored while receiving NMBAs and only short durations of use should be prescribed to prevent further complications, especially in older patients.

Research Highlights

What Is Already Known?
• Treatment of ARDS is also a multimodal strategy, which used both non-pharmacological and pharmacological treatment methods, in ARDS patients.
• NMBAs have been prescribed as a pharmacological treatment method for patients with ARDS to minimize inflammation, oxygen intake, and cardiac output, help to facilitate ventilation synchronization and thus reducing ARDS-related mortality.

What Does This Study Add?
• The increasing NMBAs doses had no effect on patients’ mortality with mild and moderate-to-severe ARDS.
• Increasing the NMBAs doses significantly reduces ICU LOS.
• The high dose vs. low dose of NMBAs was increased the risk of mortality among patients between 80 to 84 years old. However, higher dose of NMBA than low doses reduce the risk of death in patients between 50 and 54 years of age.
• Patients should be carefully monitored while receiving NMBAs and only short durations of use should be prescribed to prevent further complications, especially in older patients.

Authors’ Contributions
FR, MS, MKH, and AV-A designed the study and were responsible for the data acquisition, data analysis, and interpretation, and both authors substantively revised and approved the submitted version of the manuscript

Conflict of Interest Disclosures
The authors declare that they have no conflict of interests.

Ethical Approval
Current study was approved by the Investigative Review Board at Baqiyatallah University of Medical Sciences, Tehran, Iran (IR. BMSU.REC.1394.451) and Shariati Hospital of Tehran University of Medical Sciences, Tehran, Iran.

Acknowledgements
Thanks to guidance and advice from the “Clinical Research
References

1. Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. Nat Rev Dis Primers. 2019;5(1):18. doi:10.1038/s41572-019-0069-0
2. Ma K, Patel K, Naddour M, et al. Acute respiratory distress syndrome novel therapies. Crit Care Nurs Q. 2019;42(4):411-416. doi:10.1097/CNQ.0000000000000281
3. Villar J, Blanco J, Kacmarek RM. Current incidence and outcome of the acute respiratory distress syndrome. Curr Opin Crit Care. 2016;22(1):1-6. doi:10.1097/MCC.0000000000000266
4. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291
5. Fanelli V, Vlachou A, Ghannadian S, Simonetti U, Slutsky AS, Zhang H. Acute respiratory distress syndrome: new definition, current and future therapeutic options. J Thorac Dis. 2013;5(3):326-334. doi:10.3978/j.issn.2072-1439.2013.04.05
6. Tenhoor T, Mannino DM, Moss M. Risk factors for ARDS in the United States: analysis of the 1993 National Mortality Followback Study. Chest. 2001;119(4):1179-1184. doi:10.1378/chest.119.4.1179
7. Dai Q, Wang S, Liu R, Wang H, Zheng J, Yu K. Risk factors for outcomes of acute respiratory distress syndrome patients: a retrospective study. J Thorac Dis. 2019;11(3):673-685. doi:10.21037/jtd.2019.02.84
8. Robinson BRH, Cohen MJ, Holcomb JB, et al. Risk factors for the development of acute respiratory distress syndrome following hemorrhage. Shock. 2018;50(3):258-264. doi:10.1097/shk.0000000000010773
9. Torbic H, Duggal A. Neuromuscular blocking agents for acute respiratory distress syndrome. J Crit Care. 2019;49:179-184. doi:10.1016/j.jcrc.2018.10.019
10. Araz O. Current pharmacological approach to ARDS: the place of boseantin. Eurasian J Med. 2020;52(1):81-85. doi:10.5152/eurasianmed.2020.19218
11. Peck TJ, Hibbert KA. Recent advances in the understanding and management of ARDS. F1000Res. 2019;8. doi:10.12688/f1000research.20411.3
12. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;195(9):1253-1263. doi:10.1164/rccm.201703-0548ST
13. Patel BK, Wolfe KS, Polhman AS, Hall JB, Kress JP. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA. 2016;315(22):2435-2441. doi:10.1001/jama.2016.6338
14. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2159-2168. doi:10.1056/NEJMoa1214103
15. Sud S, Friedrich JO, Tiaccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med. 2010;36(4):585-599. doi:10.1007/s00134-009-1748-1
16. Zheng Z, Jiang L, Zhang S, et al. Neuromuscular blocking agents for acute respiratory distress syndrome: an updated meta-analysis of randomized controlled trials. Respir Res. 2020;21(1):23. doi:10.1186/s12931-020-1287-4
17. Tarazan N, Alshehri M, Sharif S, et al. Neuromuscular blocking agents in acute respiratory distress syndrome: updated systematic review and meta-analysis of randomized trials. Intensive Care Med Exp. 2020;8(1):61. doi:10.1186/s40635-020-00348-6
18. Alhazzani W, Alshahrani M, Jaeschke R, et al. Neuromuscular blocking agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. Crit Care. 2013;17(2):R43. doi:10.1186/cc12557
19. Papazian L, Ford JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010;363(12):1107-1116. doi:10.1056/NEJMoa1005372
20. Tao W, Yang LQ, Gao J, Shao J. Neuromuscular blocking agents for adult patients with acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. J Trauma Acute Care Surg. 2018;85(6):1102-1109. doi:10.1097/ta.0000000000002057
21. Chang W, Sun Q, Peng F, Xie J, Qiu H, Yang Y. Validation of neuromuscular blocking agent use in acute respiratory distress syndrome: a meta-analysis of randomized trials. Crit Care. 2020;24(1):54. doi:10.1186/s13054-020-2765-2
22. Honore PM, Mugisha A, Kugener L, et al. The use of a neuromuscular blocking agent could significantly decrease mortality in moderate-to-severe ARDS patients: is moderate ARDS the best indication for neuromuscular blocking agents. Crit Care. 2020;24(1):217. doi:10.1186/s13054-020-02947-x
23. Moss M, Huang DT, Brower RG, et al. Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med. 2019;380(21):1997-2008. doi:10.1056/NEJMoa1901686
24. Bashar FR, Vahedian-Azimi A, Hajiesmaeili M, et al. Post-ICU psychological morbidity in very long ICU stay patients with ARDS and delirium. J Crit Care. 2018;43:88-94. doi:10.1016/j.jcrc.2017.08.034
25. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-349. doi:10.1016/j.jclinepi.2007.11.008
26. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669
27. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149(3 Pt 1):818-824. doi:10.1164/ajrccm.149.3.7509706
28. Nagaraj SB, McClain LM, Zhou DW, et al. Automatic classification of sedation levels in ICU patients using heart rate variability. Crit Care Med. 2016;44(9):c782-789. doi:10.1097/CCM.0000000000001708
29. Barlow KM, Zangaro GA. Meta-analysis of the reliability and validity of the anticipated turnover scale across studies of registered nurses in the United States. J Nurs Manag. 2010;18(7):862-873. doi:10.1111/j.1365-2834.2010.01171.x

30. Nagaraj SB, Biswal S, Boyle EJ, et al. Patient-specific classification of ICU sedation levels from heart rate variability. Crit Care Med. 2017;45(7):e683-e690. doi:10.1097/CCM.0000000000002364

31. Rapsang AG, Shyam DC. Scoring systems in the intensive care unit: a compendium. Indian J Crit Care Med. 2014;18(4):220-228. doi:10.4103/0972-5229.130573

32. Kline RB. Software review: software programs for structural equation modeling: Amos, EQS, and LISREL. J Psychoeduc Assess. 1998;16(4):343-364. doi:10.1177/07342829801600407

33. Gainnier M, Roch A, Forel JM, et al. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit Care Med. 2004;32(1):113-119. doi:10.1097/01.ccm.0000104114.72614.bc

34. Fanelli V, Morita Y, Cappello P, et al. Neuromuscular blocking agent cisatracurium attenuates lung injury by inhibition of nicotinic acetylcholine receptor-a1. Anesthesiology. 2016;124(1):132-140. doi:10.1097/ALN.0000000000001097

35. Murray MJ, DeBlock H, Erstad B, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med. 2016;44(11):2079-2103. doi:10.1097/CCM.0000000000002027

36. Ho ATN, Patolia S, Guervilly C. Neuromuscular blockade in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. J Intensive Care. 2020;8:12. doi:10.1186/s40560-020-0431-z

37. Hua Y, Ou X, Li Q, Zhu T. Neuromuscular blockers in the acute respiratory distress syndrome: a meta-analysis. PLoS One. 2020;15(1):e0227664. doi:10.1371/journal.pone.0227664

38. Huang DT, Angus DC, Moss M, et al. Design and rationale of the Reevaluation of Systemic Early Neuromuscular Blockade trial for acute respiratory distress syndrome. Ann Am Thorac Soc. 2017;14(1):124-133. doi:10.1513/AnnalsATS.201608-629OT

39. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol. 2011;10(10):931-941. doi:10.1016/s1474-4422(11)70178-8

40. Hraiech S, Dizier S, Papazian L. The use of paralytics in patients with acute respiratory distress syndrome. Clin Chest Med. 2014;35(4):753-763. doi:10.1016/j.ccm.2014.08.012