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Intubation Timing in COVID-19 Patients Based on ROX Index and Association with Patient Outcomes

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Abstract

Background: Timing of intubation in COVID-19 is controversial. We sought to determine the association of ROX index defined as oxygen saturation divided by fraction of inspired oxygen divided by breathing frequency at time of intubation with clinical outcomes.

Methods: We conducted a retrospective cohort study of intubated COVID-19 patients using Cerner Real World-Data™. Multivariable logistic regression was used to evaluate the impact of ROX on mortality. We analyzed ROX as a continuous variable as well as a categorical variable using cutoffs previously described as predicting success with high flow nasal cannula.

Results: Of 1087 subjects in the analysis group, the median age was 64 years, and more than half had diabetes; 55.2% died, 1.8% were discharged to hospice, 7.8% were discharged home, 27.3% were discharged to another institution and 7.8% had another disposition. Increasing age and longer time from admission to intubation were associated with mortality. After adjusting for sex, race, age, comorbidities, and days from admission to intubation, increasing ROX score at time of intubation was associated with lower risk of death. In a logistic regression model, each increase in ROX by 1 at time of intubation was associated with an 8% reduction in odds of mortality (Odds Ratio (OR) 0.92, 95% CI 0.88-0.95). We also found an OR for death of 0.62 (95% CI 0.47-0.81) for subjects with ROX ≥ 4.88 at time of intubation.

Conclusions: Among a cohort of COVID-19 subjects who were ultimately intubated, higher ROX at time of intubation was positively associated with survival.

Background

Timing of intubation is an important and controversial decision in Coronavirus Disease 2019 (COVID-19) patients with respiratory failure. If patients are intubated too early then patients who otherwise would not have required mechanical ventilation are exposed to complications such as sedation, delirium, and ventilator associated pneumonia[1, 2]. Clinicians often use noninvasive positive pressure ventilation in an effort to avoid these complications. However, non-invasive positive pressure ventilation is known to cause ventilator induced lung injury thru many of the same mechanisms such as volutrauma and biotrauma which are seen in invasively ventilated patients[3]. In biotrauma, cytokines released from injured lung not only cause worsening of lung injury but can promote dysfunction in other organs such as the kidneys[4, 5]. Patients receiving non-invasive positive pressure ventilation may experience elevated transpulmonary pressures, high tidal volumes, pendelluft, increased intravascular pressure and asynchrony resulting in patient induced lung injury[3, 6, 7]. Patient induced lung injury has also been postulated to occur in patients with severe lung injury breathing spontaneously without positive pressure[7]. The optimal oxygenation target among intensive care unit patients also remains controversial[8]. Finally, patients on prolonged non-invasive positive pressure ventilation may not receive adequate nutritional support and may develop facial skin breakdown[9-11]. Expert clinicians have advocated approaches ranging from extremely late to very early intubation[12-14]. The popularity of the different recommendations varies from institution to institution and has evolved throughout the pandemic.

In addition to respiratory management, other patient and treatment related factors influence outcomes. Cardiovascular disease, diabetes, obesity, and older age have been

associated with higher risk of death from COVID-19 in multiple studies[15-18]. Acute kidney injury is both common in hospitalized patients with COVID-19 and associated with higher mortality[19]. Pharmacological treatments such as the antiviral Remdesivir and anti-inflammatory treatments such as steroids have been shown to improve outcomes in COVID-19 patients with respiratory failure[20, 21]

Evidence regarding the timing of intubation in COVID-19 is mostly based on observational cohort studies, which not surprisingly have reached different conclusions. A retrospective cohort study of 755 intubated patients at 5 New York City hospitals reported that increasing time from hospital admission to intubation was associated with a small but statistically significant increased risk of death[22]. In contrast, a prospective cohort study from France of 245 invasively ventilated patients found that intubation later than 2 days after admission was associated with improved survival[23]. A single center study of 75 mechanically ventilated patients reported that late intubation (>1.27 days) was associated with longer duration of mechanical ventilation, lower lung compliance, and worse survival[24]. A meta-analysis of 12 studies of 8944 patients with COVID-19 reported there was no difference in survival with early versus late intubation[25]. An analysis of 231 patients at 4 US hospitals, found that mortality was approximately 38% among patients intubated within 8 hours of admission and was the same for patients intubated more than 24 hours after admission[26]. Investigators in Greece are currently recruiting patients for a randomized trial to address the question of early versus late intubation in COVID-19 (NCT04632043).

Early and late intubation exist on a continuum of respiratory distress. The degree of respiratory distress can be approximated by ROX index ((oxygen saturation/fraction of inspired oxygen)/ breathing frequency)). The ROX index was first validated by Rocca et al. in a cohort of 191 patients on HFNC with bacterial pneumonia. They examined ROX scores at 2, 6, and 12 hours after initiation of high flow nasal cannula (HFNC); and reported that scores ≥ 4.88 were associated with lower risk of intubation[27]. Early in the pandemic, this same group examined use of ROX for COVID-19 patients on HFNC and found that a slightly higher cutoff of ≥ 5.37 within 4 hours of HFNC initiation was associated with lower risk of intubation[28]. Subsequently, various investigators have studied the use of ROX in COVID-19 in different cohorts at varying times in the disease course resulting in slightly different proposed cutoffs. In a cohort of 113 patients treated HFNC with or without, Colaianni-Alfonso et al. report ROX cutoff of ≤ 6.28 after 12 hours of treatment predicted failure of non-invasive therapy with sensitivity of 97.6% and specificity of 51.8%[29]. In a cohort of 120 patients, Vega et al. reported that after 12 hours of HFNC therapy the optimal ROX cutoff was 5.99[30]. Myers et al suggested a ROX cutoff at 12 hours of 3.85 for predicting need for mechanical ventilation in COVID-19[31]. Chandel et al. focused on using ROX predicting success of HFNC, rather than failure, in COVID-19 patients, and found that among patients not intubated or weaned from HFNC after 12 hours, ROX greater than 3.0 had a sensitivity of 85.3% and specificity of 51.1% for successful treatment (i.e., not needing intubation). In studies of COVID-19 patients, the range of suggested ROX cutoff values varies from 1.4 in an ED cohort to 25.6 in hospitalized patients[32, 33]. A meta-analysis of studies examining use of ROX for COVID-19 patients on HFNC concluded that “the optimal cut off value may fall close to 5”[34]. These data demonstrate the utility of ROX in COVID-19 respiratory failure;

however, for the clinician at the bedside, applying this finding still involves a substantial amount of art given the variability in populations studied, timing in the illness course, suggested ROX cutoff values and the relatively low specificity.

While ROX was initially reported as a method for determining if bacterial pneumonia patients treated with HFNC were likely to need intubation, its components make it an intuitive measure of severity of respiratory distress in general. The components of ROX are degrees of hypoxemia and tachypnea, which have historically been used subjectively by clinicians to make decisions regarding need for intubation. We hypothesized that: If high ROX index (low respiratory distress) at time of intubation is associated with better outcomes, then this would favor early intubation. If not, it would suggest that early intubation may needlessly subject patients to complications of invasive mechanical ventilation.

Therefore, we sought to determine the association of ROX index at time of intubation with clinical outcomes using Cerner Real-World Data™, a large database built from electronic health records organized into a common data model and managed by Cerner. Given that acute kidney injury is known to increase risk of mortality, we also sought to determine the impact of acute kidney injury on the relationship between ROX and mortality.

Methods

This retrospective cohort study was approved by the Christiana Care Institutional Review Board (CCC#: 40097) on June 17, 2020.

Study population

We created a dataset using the Cerner COVID Data Lab database (Q2JUN) released on September 2, 2020. This database contains deidentified electronic health record data on COVID-19 subjects from 62 institutions and has previously been described in detail[35]. Criteria for inclusion were an inpatient hospital encounter that had a diagnosis of COVID during which the patient was intubated. We defined diagnosis of COVID-19 as a positive COVID-19 test during the encounter or within 2 weeks prior to the encounter. We excluded subjects intubated in the emergency department. We excluded subjects with missing data which did not allow for the calculation of ROX or who did not have a ROX score within 4 hours of intubation. Encounters prior to the diagnosis of COVID-19 were also included from January 1, 2015, onward for all subjects meeting the inclusion criteria. Most of the subjects in this dataset were hospitalized in the first 6 months of 2020. However, because the dates were shifted to protect confidentiality, we cannot verify the exact hospitalization dates. Figure 1 is a consort diagram showing the creation of the analysis dataset.

Intubation and Intubation Time

The following International Classification of Disease, 10th Revision, Procedure Coding System (ICD10-PCS) procedure codes were used to identify subjects who underwent intubation and mechanical ventilation: 5A1945Z, 5A1955Z, and OBH17EZ. The time of intubation was designated as the earliest of the service date/time for the above procedure or earliest date/time for ventilator settings whichever was earliest. Appendix 1 shows the codes used to identify ventilator settings in the Cerner database.

Oxygen Source and ROX calculation

From the database, we obtained oxygen source (i.e., nasal cannula, non-breather mask, etc.), breathing frequency, oxygen saturation, and oxygen flow rates as well as fraction of inspired oxygen (FiO2) when available. When FiO2 was available, ROX was calculated as reported oxygen saturation divided by reported FiO2 divided by breathing frequency. When an FiO2 was not reported but nasal cannula oxygen flow rates were between 1 and 6 liters per minute (L/min), FiO2 was calculated according to the estimates provided by Fuentes et al [15] (see appendix 2) and was used to calculate ROX[36]. Appendix 3 shows examples of ROX calculation. We defined high flow oxygen as greater than or equal to 30 L/min. For our analysis, we used the ROX score closest to but preceding time of intubation.

Kidney Function

We used serum creatinine values to evaluate acute changes in kidney function during hospitalization. We defined acute kidney injury as an increase in serum creatinine greater than 0.3 mg/dl[37]. We then examined the relationship between ROX and mortality for patients with and without acute kidney injury.

Severity of Illness

We calculated a modified sequential organ failure assessment (SOFA) score by excluding the respiratory system component because the respiratory component is part of ROX calculation. We calculated modified SOFA using the worst values within 24 hours of intubation of all non-respiratory components (coagulation, liver, cardiovascular, central nervous system and renal). We used previously described numerical scores for each of the components[38, 39]. While modifying the SOFA score makes the total score not comparable to other studies reporting an unmodified SOFA score, our goal in using the modified SOFA score was to control

for non-respiratory severity illness, not to predict mortality overall. This method of removing respiratory component of SOFA score has been previously used by investigators seeking to look separate at respiratory and non-respiratory severity of illness[40].

Statistical Analysis

Bivariate comparisons of subjects included versus excluded from analyses were conducted using Wilcoxon rank sum or chi-squared tests. The estimated probability of in hospital death from logistic regression was plotted against polynomial ROX to investigate the relationship between ROX and mortality and the effect of acute kidney injury on this relationship after examining the interaction between ROX and acute kidney injury. The patients' probability of mortality was graphed along with the 95% confidence interval. A multivariable logistic regression model evaluated the impact of ROX on in hospital mortality, adjusting for sex, race, age, comorbidities, and days from admission to intubation. Additional multivariable logistic regression models were constructed to examine the effect of ROX on mortality after adjusting for modified SOFA score and for Glasgow Coma Scale (GCS). All models using mortality used inpatient mortality alone and do not include subjects who may have died after discharge. Statistical analyses were conducted using R Version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The dataset contained 2102 subjects. Due to missing data, ROX prior to intubation could only be calculated on 1690 subjects. An additional 603 subjects were excluded because the last

ROX available before intubation was more than 4 hours before intubation resulting in an analysis cohort of 1087 subjects. The median time between calculated ROX score and time of intubation was 0.95 hours (Inter Quartile Range (IQR) 0.5-1.0) and the median number of days from admission to intubation was 1.37 (IQR 0.15-3.50). Characteristics of those included and excluded from the analysis were similar as shown in Table 1. Diabetes and hypertension were extremely common comorbidities in this population. The term "high flow nasal cannula" does not appear in the dataset and subjects on nasal cannula predominately had flow rates less than 6 L/min. Only 33 patients had flow rate ≥ 30 L/min. Appendix 4 shows the last recorded oxygen source before intubation.

Table 2 shows the discharge dispositions of subjects included and those excluded. In our final study population of 1087 intubated subjects, 85 subjects (7.8%) were discharged home, 287 (27.3%) were discharged to a facility such as rehab or nursing home, 600 (55.2%) died, 20 (1.8%) were discharged to hospice, and 85 (7.8%) had another discharge disposition. Creatinine values were available for 976 (89.8%) subjects. The median creatinine at time of intubation was 1.40 mg/dl (IQR 0.9 mg/dl-2.5 mg/dl).

The majority of subjects (74%) were on at least one vasopressor at some point during their hospital stay. The median ROX before intubation was 4.0 with an IQR of 3.0-5.9. The median number of ventilator days was 9 with an IQR of 5-17. There were 15 subjects (1.4%) treated with extracorporeal membrane oxygenation.

After adjusting for sex, race, age, comorbidities, days from admission to intubation, increasing ROX score at time of intubation was associated with lower risk of death (Table 3). We found that each increase in ROX of 1.0 prior to intubation was associated with an 8%

reduction in odds of death in the hospital (OR 0.92, 95% CI 0.88-0.95, p <0.001). Figure 2 shows the linear relationship between ROX prior to intubation and estimated probability of death. We also examined odds of death for ROX values greater than 4.88 and 5.36, which have been reported to predict successful management without intubation in pneumonia patient treated with high flow nasal cannula without and with COVID-19 respectively[27, 28, 41]. We found a 38% reduction in the odds of death for subjects with a ROX ≥4.88 (OR 0.62 (95% CI 0.47-0.81, p < 0.001) and a 42% reduction in the odds of death for subjects with a ROX ≥5.36 (OR 0.58 (95% CI 0.44-0.77, p<0.001). Increasing age and each day from admission to intubation were associated with increase mortality (Table 3).

Of 976 subjects with creatinine values, 409 (41.9%) had a maximum increase in creatinine at any time after intubation ≤ 0.3 mg/dl, 181 (18.5%) had increase of >0.3 mg/dl and ≤ 1.0 mg/dl, 256 (26.2%) had an increase >1-≤4 mg/dl, and 130 (13.3%) had an increase in creatinine > 4 mg/dl. ROX at time of intubation was not associated with increase in creatinine but acute kidney injury (defined as increase in creatinine of ≥ 0.3 mg/dl) developing after intubation was associated with increased mortality (OR 4.34 (95% CI 3.24-5.84, p < 0.001). Figure 3 shows that the association between ROX and mortality is similar for patients with and without acute kidney injury. The subgroup of subjects with an increase in creatinine of > 4 mg/dl (n=130) had a survival of 27.5% compared to a 64.1% survival for subjects with increase in creatinine ≤0.3 mg/dl (n=409).

We conducted a sensitivity analysis excluding subjects with missing values for creatinine, Glasgow Coma Score (GCS), platelets, or bilirubin, resulting in 569 subjects available

for analysis. Because of this important decrease in sample size, we opted not to include the modified SOFA in the multivariable logistic regression model reported above. However, we did analyze this subset for association between ROX and mortality after controlling for sex, age, race, modified SOFA, days to intubation as covariates. As shown in Table 4, the odds ratio for mortality with increasing ROX was similar at 0.95 (95% CI 0.90-1.01, p value =0.09). Modified SOFA was associated with mortality (OR 1.14, 95% CI 1.06-1.22 for each point increase). We also created a model including 943 patients with GCS available to examine the impact of neurologic status on the association of ROX and mortality. As shown in Table 5, the odds ratio for ROX in this model was 0.92 (95% CI 0.87-0.96).

Discussion

Higher ROX at time of intubation is associated with improved survival to hospital discharge. This may reflect high respiratory severity illness in subjects with lower ROX. However, this finding remained consistent even when adjusting for multiple variables and comorbidities suggesting that delaying intubation until a higher respiratory severity of illness as measured by decreased ROX may be associated with higher mortality. The association between increasing days from admission to intubation and increasing mortality also raises concerns about the risks of delaying intubation. It also provides some reassurance that earlier intubation is not associated with harm. While ROX at time of intubation was not associated with development of acute kidney injury, we did confirm prior work suggesting that acute kidney injury in COVID-19 results in substantially worse prognosis suggesting that every effort should be made to avoid this complication.

The developers of the ROX index validated it in patients with respiratory failure due to pneumonia being treated with high flow nasal cannula[41]. Therefore, the cutoff values predicting success or failure of conservative management without intubation are not necessarily valid in the predominantly lower flow supplemental oxygen subjects in our study. Nonetheless, it is worth noting that when subjects were intubated at or above ROX scores previously reported to predict success with high flow nasal cannula, outcomes were better.

The ROX score captures numerically what many clinicians use in considering when to intubate a patient (i.e., oxygenation and work of breathing). Therefore, high ROX suggests low threshold (decision for early intubation) and lower ROX suggests high threshold (decision for late intubation). In both the lay press and medical literature there has been discussion of so called "happy hypoxemia" in COVID-19[42-44]. Some critical care physicians have hypothesized that ARDS from COVID19 is different and should be treated differently than ARDS from other respiratory viruses such as influenza. In our experience, the absence of symptoms combined with the high volume of COVID-19 patients has caused some clinicians to use 100% oxygen delivered by non-invasive devices for longer and tolerate lower oxygen saturations than they would in other disease such as influenza.

Our multicenter retrospective study confirms the result from a prior single center study which suggested worse clinical outcomes with lower ROX scores[45]. Patients with higher ROX may do better because they have a lower respiratory specific severity illness and would not have progressed to worse ROX score had they not been intubated. However, a recent prospective cohort study of 84 ICU patients with ARDS due to COVID-19 found that respiratory

distress defined as breathing frequency >25 and PaO2/FiO2<100 prior to intubation, was strongly associated with inability to achieve driving pressure less than 14 during the first 24 hours of lung protective ventilation[46]. This study suggests that at least in patients who eventually require intubation, delaying intubation beyond thresholds typically used for other causes of respiratory failure may result in worse respiratory mechanics, as assessed by driving pressure. Driving pressure is known to be associated with mortality[47].Our study adds to these findings by demonstrating that delayed intubation may be associated with worse clinical outcomes. Further prospective randomized controlled trials are needed to determine the optimal timing of intubation.

Strengths to this analysis include the large data set of Cerner based electronic health records (EHR). While treatments may vary across institutions the multi-center design should eliminate bias from one individual health system. Additionally, our findings remained consistent after including a marker of severity of disease (mSOFA) in a sensitivity analysis.

Several limitations can be found in this retrospective cohort study. The Cerner COVID Data Lab database is composed of data collected for patient care, not research. Therefore, the data dictionary explaining what each of the entries mean is limited. Different institutions may describe the same intervention differently in their EHRs and document events or interventions based on varied local policies. Of note very few subjects received high flow nasal cannula prior to intubation. This could be due to misclassification of oxygen delivery devices (ventilator used for high flow for example) or missing data, but it may reflect the timing of when subjects were treated during the pandemic, as early in the pandemic there were fears that high flow nasal

cannula might increase infection transmission. The dataset we used was released in September of 2020, and while we are not able to determine when during the pandemic the subjects were hospitalized, most were probably treated during the first 6 months of 2020. Additionally, due to date shifting to protect confidentiality we cannot examine trends over time. We used an accepted conversion from liters per minute on nasal cannula to fraction of inspired oxygen; however, the actual concentration of inspired oxygen inhaled by subjects breathing on nasal cannula is known to vary slightly[48]. Furthermore, we did not collect data on pharmacologic treatments that subjects may have received such as steroids. However, the RECOVERY trial which first showed benefit of steroids in this population was not released on a pre-print server until June 22, 2020, so it may not have had a large impact on clinicians caring for our cohort during the first have half 2020[20]. Similarly, it was May 2020 before data on the benefits of Remdesivir became available[21]. We postulate that clinician or institutional preference for early or late intubation is likely to be independent of how rapidly they adopted use of new pharmacologic treatments. We are also limited by missing data. For example,due missing data we were only able to calculate modified SOFA for a subset of patients. We acknowledge the potential for residual differences in non-respiratory severity of illness. However, the consistency of our results in the subset of subjects with modified SOFA score are somewhat reassuring. Additionally, we do not have data on death or disability that occurred after hospital discharge. Finally, all subjects in our cohort were eventually intubated. While it would be interesting to compare outcomes of subjects with similar ROX scores who were intubated versus managed conservatively, we did not design our study to do this because we felt it would

not be possible to adequately match subjects to control for clinical factors influencing the decision to intubate.

Conclusion

In conclusion this multicenter study of COVID-19 subjects receiving mechanical ventilation found a high mortality rate. Higher ROX scores prior to intubation were positively associated with survival. Older age and increasing days from admission to intubation were associated with mortality.

References

1. Klompas M. Potential Strategies to Prevent Ventilator-associated Events. Am J Respir Crit Care Med 2015;192(12):1420-1430.
2. Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018;46(9):e825-e873.
3. Katira BH. Ventilator-Induced Lung Injury: Classic and Novel Concepts. Respir Care 2019;64(6):629-637.
4. Goodman RB, Pugin J, Lee JS, Matthay MA. Cytokine-mediated inflammation in acute lung injury. Cytokine Growth Factor Rev 2003;14(6):523-535.
5. Husain-Syed F, Slutsky AS, Ronco C. Lung-Kidney Cross-Talk in the Critically Ill Patient. Am J Respir Crit Care Med 2016;194(4):402-414.
6. Brochard L, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. Am J Respir Crit Care Med 2017;195(4):438-442.
7. Cruces P, Retamal J, Hurtado DE, Erranz B, Iturrieta P, Gonzalez C, et al. A physiological approach to understand the role of respiratory effort in the progression of lung injury in SARS-CoV-2 infection. Crit Care 2020;24(1):494.
8. Hochberg CH, Semler MW, Brower RG. Oxygen Toxicity in Critically Ill Adults. Am J Respir Crit Care Med 2021;204(6):632-641.
9. Kelly CR, Higgins AR, Chandra S. Noninvasive Positive-Pressure Ventilation. N Engl J Med 2015;373(13):1279.
10. Kelly CR, Higgins AR, Chandra S. Videos in clinical medicine. Noninvasive positive-pressure ventilation. N Engl J Med 2015;372(23):e30.
11. Mahmoodpoor A, Golzari SE. Noninvasive Positive-Pressure Ventilation. N Engl J Med 2015;373(13):1279.
12. Brown CA, 3rd, Mosier JM, Carlson JN, Gibbs MA. Pragmatic recommendations for intubating critically ill patients with suspected COVID-19. J Am Coll Emerg Physicians Open 2020.
13. Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. Ann Intensive Care 2020;10(1):78.
14. Voshaar T, Stais P, Kohler D, Dellweg D. Conservative management of COVID-19 associated hypoxaemia. ERJ Open Res 2021;7(1).
15. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.
16. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054-1062.
17. Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: A federated electronic medical record analysis. PLoS Med 2020;17(9):e1003321.
18. Kompaniyets L, Goodman AB, Belay B, Freedman DS, Sucosky MS, Lange SJ, et al. Body Mass Index and Risk for COVID-19-Related Hospitalization, Intensive Care Unit Admission, Invasive

Mechanical Ventilation, and Death - United States, March-December 2020. MMWR Morb Mortal Wkly Rep 2021;70(10):355-361.
19. Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, et al. AKI in Hospitalized Patients with COVID-19. J Am Soc Nephrol 2021;32(1):151-160.
20. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021;384(8):693-704.
21. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020;383(19):1813-1826.
22. Hyman JB, Leibner ES, Tandon P, Egorova NN, Bassily-Marcus A, Kohli-Seth R, et al. Timing of Intubation and In-Hospital Mortality in Patients With Coronavirus Disease 2019. Crit Care Explor 2020;2(10):e0254.
23. Dupuis C, Bouadma L, de Montmollin E, Goldgran-Toledano D, Schwebel C, Reignier J, et al. Association Between Early Invasive Mechanical Ventilation and Day-60 Mortality in Acute Hypoxemic Respiratory Failure Related to Coronavirus Disease-2019 Pneumonia. Crit Care Explor 2021;3(1):e0329.
24. Pandya A, Kaur NA, Sacher D, O'Corragain O, Salerno D, Desai P, et al. Ventilatory Mechanics in Early vs Late Intubation in a Cohort of Coronavirus Disease 2019 Patients With ARDS: A Single Center's Experience. Chest 2021;159(2):653-656.
25. Papoutsi E, Giannakoulis VG, Xourgia E, Routsi C, Kotanidou A, Siempos, II. Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies. Crit Care 2021;25(1):121.
26. Hernandez-Romieu AC, Adelman MW, Hockstein MA, Robichaux CJ, Edwards JA, Fazio JC, et al. Timing of Intubation and Mortality Among Critically Ill Coronavirus Disease 2019 Patients: A Single-Center Cohort Study. Crit Care Med 2020;48(11):e1045-e1053.
27. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernandez G, et al. An Index Combining Respiratory Rate and Oxygenation to Predict Outcome of Nasal High-Flow Therapy. Am J Respir Crit Care Med 2019;199(11):1368-1376.
28. Zucman N, Mullaert J, Roux D, Roca O, Ricard JD, Contributors. Prediction of outcome of nasal high flow use during COVID-19-related acute hypoxemic respiratory failure. Intensive Care Med 2020;46(10):1924-1926.
29. Colaianni-Alfonso N, Montiel G, Castro-Sayat M, Siroti C, Laura Vega M, Toledo A, et al. Combined Noninvasive Respiratory Support Therapies to Treat COVID-19. Respir Care 2021;66(12):1831-1839.
30. Vega ML, Dongilli R, Olaizola G, Colaianni N, Sayat MC, Pisani L, et al. COVID-19 Pneumonia and ROX index: Time to set a new threshold for patients admitted outside the ICU. Pulmonology 2022;28(1):13-17.
31. Myers LC, Mark D, Ley B, Guarnieri M, Hofmeister M, Paulson S, et al. Validation of Respiratory Rate-Oxygenation Index in Patients With COVID-19-Related Respiratory Failure. Crit Care Med 2022.
32. Mukhtar A, Rady A, Hasanin A, Lotfy A, El Adawy A, Hussein A, et al. Admission SpO2 and ROX index predict outcome in patients with COVID-19. Am J Emerg Med 2021;50:106-110.
33. Suliman LA, Abdelgawad TT, Farrag NS, Abdelwahab HW. Validity of ROX index in prediction of risk of intubation in patients with COVID-19 pneumonia. Adv Respir Med 2021;89(1):1-7.
34. Prakash J, Bhattacharya PK, Yadav AK, Kumar A, Tudu LC, Prasad K. ROX index as a good predictor of high flow nasal cannula failure in COVID-19 patients with acute hypoxemic respiratory failure: A systematic review and meta-analysis. J Crit Care 2021;66:102-108.
35. Adnan I Qureshi WIB, Wei Huang, Daniel Shyu, Danny Myers, Murugesan Raju, Iryna Lobanova, M Fareed K Suri, Hasan Naqvi, Chi-Ren Shyu. Facilitating the Study of Relationships between

COVID-19 and Cardiovascular Health Outcomes Using Cerner Real-World COVID-19 Deidentified Dataset. Health Care Research Journal 2020;1(1):17-28.
36. Fuentes S CY. StatPearls
37. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11(2):R31.
38. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001;286(14):1754-1758.
39. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score-development, utility and challenges of accurate assessment in clinical trials. Crit Care 2019;23(1):374.
40. Torres LK, Hoffman KL, Oromendia C, Diaz I, Harrington JS, Schenck EJ, et al. Attributable mortality of acute respiratory distress syndrome: a systematic review, meta-analysis and survival analysis using targeted minimum loss-based estimation. Thorax 2021;76(12):1176-1185.
41. Roca O, Messika J, Caralt B, Garcia-de-Acilu M, Sztrymf B, Ricard JD, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: The utility of the ROX index. J Crit Care 2016;35:200-205.
42. Tobin MJ, Jubran A, Laghi F. Misconceptions of pathophysiology of happy hypoxemia and implications for management of COVID-19. Respir Res 2020;21(1):249.
43. Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. Conceptions of the pathophysiology of happy hypoxemia in COVID-19. Respir Res 2021;22(1):12.
44. Safe IP, Lacerda MVG, Almeida Val FF, Sampaio VS, Hajjar LA, Brito-Sousa JD, et al. Severe Hypoxemia With Normal Heart and Respiratory Rate in Early-stage Coronavirus Disease 2019 Patients: The "Happy Hypoxemia Phenomenon". Clin Infect Dis 2021;73(3):e856-e858.
45. Fink DL, Goldman NR, Cai J, El-Shakankery KH, Sismey GE, Gupta-Wright A, et al. Ratio of Oxygen Saturation Index to Guide Management of COVID-19 Pneumonia. Ann Am Thorac Soc 2021;18(8):1426-1428.
46. Tsolaki VS, Zakynthinos GE, Mantzarlis KD, Deskata KV, Papadonta ME, Gerovasileiou ES, et al. Driving Pressure in COVID-19 Acute Respiratory Distress Syndrome Is Associated with Respiratory Distress Duration before Intubation. Am J Respir Crit Care Med 2021;204(4):478-481.
47. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372(8):747-755.
48. Wettstein RB, Shelledy DC, Peters JI. Delivered oxygen concentrations using low-flow and high-flow nasal cannulas. Respir Care 2005;50(5):604-609.

Quick Look

Current Knowledge

The timing of intubation in COVID-19 patients is controversial. While some clinicians use similar criteria and oxygenation cutoffs as in other causes of respiratory failure, others have argued that COVID-19 should be managed differently.

What this paper contributes to our knowledge

We found that among subjects who ultimately underwent endotracheal intubation, those intubated at lower respiratory severity illness as measured by ROX scores had better outcomes. This remained true in sensitivity analyses accounting for non-respiratory severity of illness.

Figure 1: Consort Diagram showing creation of analysis dataset

Figure 2

Relationship between ROX prior to intubation and hospital mortality

The y-axis shows the estimated probability of death in the hospital. The x-axis shows the ROX index score prior to intubation. The solid line shows the line of best fit generated by multivariable model for association between ROX index score and mortality. The higher the ROX, the lower the estimated probability of death. The shaded area shows the 95% confidence interval around the line. Because fewer patients were intubated at ROX values >5, the 95% confidence interval widens as the ROX index scores increases.

Figure 3

Impact of Acute Kidney Injury on relationship between ROX and mortality

The y-axis shows the probability of in-hospital death. The x-axis shows the ROX index scores. The dotted line shows the line of best fit generated by multivariable model for association between ROX index score and mortality for patients with acute kidney injury. The solid line shows the line of best fit generated by model for patients without acute kidney injury. While risk of mortality is higher in patients with acute kidney injury at all ROX values, the relationship between ROX index score prior to intubation and mortality remains similar.

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Table 1
Population Characteristics of patients included and excluded from analysis

Characteristic	Excluded N=1015	Analysis Cohort N=1087	p-value
Male, N (%)	602 (59)	674 (62)	0.27
Race			<0.001
White N (%)	455 (45)	387 (36)	
Black, N (%)	193 (19)	252 (23)	
Other, N (%)	367 (36)	448 (41)	
Age in Years, Median (IQR)	65 (55, 74)	64 (54, 73)	0.24
Body Mass Index, Median (IQR)	29 (26, 35)	30 (26, 35)	0.28
Comorbidities, N (%)			
Hypertension	724 (71)	805 (74)	0.16
Diabetes	550 (54)	588 (54)	0.97
Peripheral Vascular Disease	119 (12)	135 (12)	0.63
Myocardial Infarction	203 (20)	205 (19)	0.51
Congestive Heart Failure	245 (24)	284 (26)	0.29

IQR – Interquartile range, N- number

Patients were excluded if ROX could not be calculated or if the last ROX was more than 4 hours before intubation time

Table 2
Discharge disposition of included and excluded patients

Discharge Disposition N (%)	Excluded n=1015	Included n=1087
Home	136 (13.4)	85 (7.8)
Dead	523 (51.5)	600 (55.2)
Hospice	18 (1.8)	20 (1.8)
Other	59 (5.8)	85 (7.8)
Facility	279 (27.5)	297 (27.3)

Table 3
Adjusted Association of ROX prior to intubation with mortality (n=1087)

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
ROX index score	0.92	0.88-0.95	<0.001
Male	1.28	0.97-1.68	0.07
Black vs. white	1.37	0.96-1.96	0.08
Other Race vs. white	0.81	0.59-1.10	0.18
Age	1.04	1.03-1.06	<0.001
Peripheral Vascular Disease	1.26	0.83-1.93	0.29
Myocardial Infarction	1.34	0.95-1.91	0.10
Congestive Heart Failure	1.04	0.75-1.44	0.83
Diabetes	1.21	0.92-1.58	0.18
Hypertension	0.85	0.61-1.18	0.34
Days from Admission to Intubation	1.08	1.04-1.13	<0.001

Table 4
Adjusted Association of ROX prior to intubation with mortality for patients with mSOFA available (n=569)

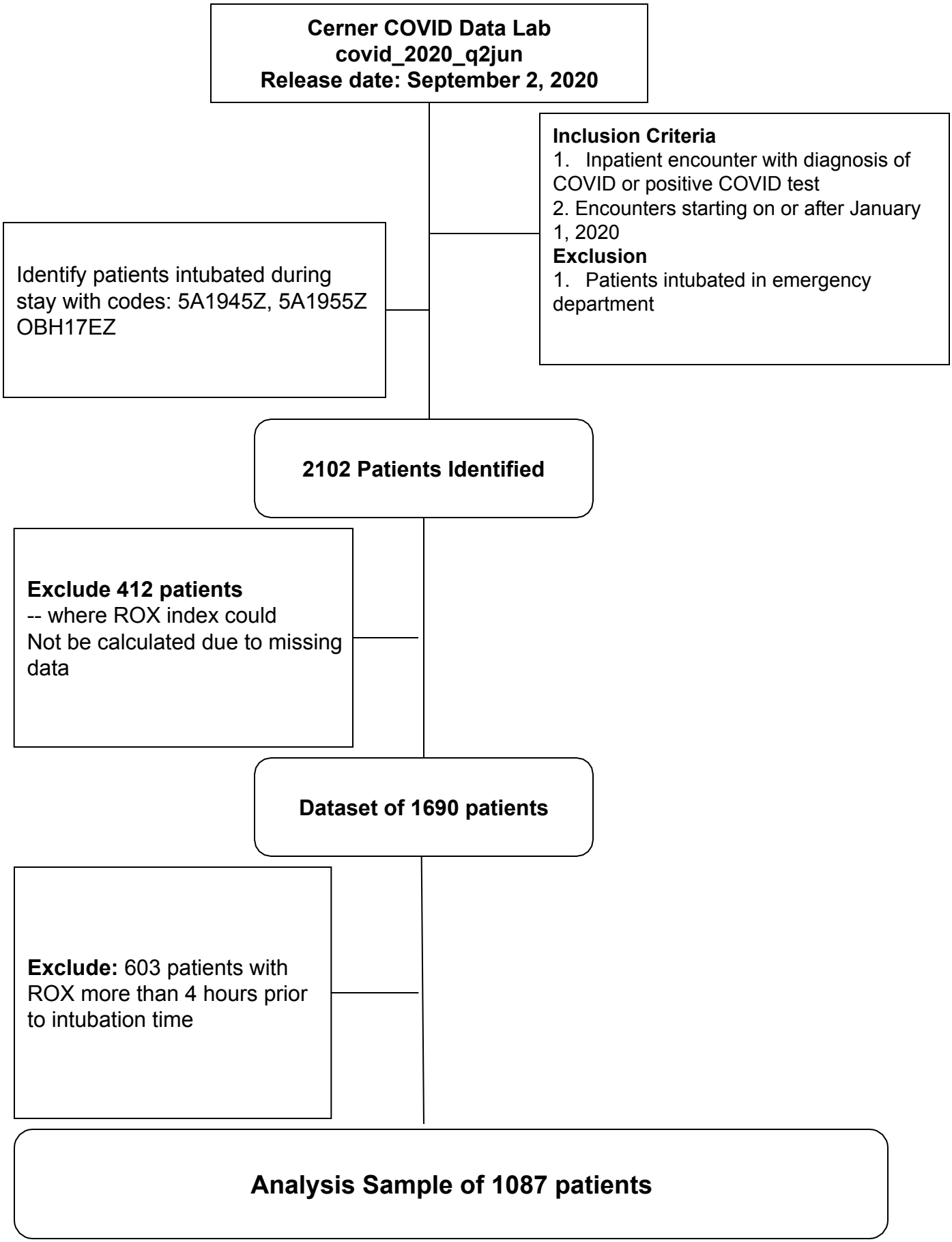
Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
ROX index score	0.95	0.90-1.01	0.09
Male	1.0	0.69-1.46	1.00
Black vs. white	1.69	1.05-2.73	0.03
Other Race vs. white	0.97	0.63-1.51	0.90
Age	1.04	1.03-1.06	<0.001
mSOFA	1.14	1.06-1.22	0.001
Peripheral Vascular Disease	1.33	0.75-2.40	0.33
Myocardial Infarction	1.71	1.01-2.96	0.05
Congestive Heart Failure	1.00	0.64-1.58	0.99
Diabetes	0.91	0.62-1.33	0.63
Hypertension	0.86	0.54-1.36	0.52
Days from Admission to Intubation	1.08	1.02-1.14	0.02

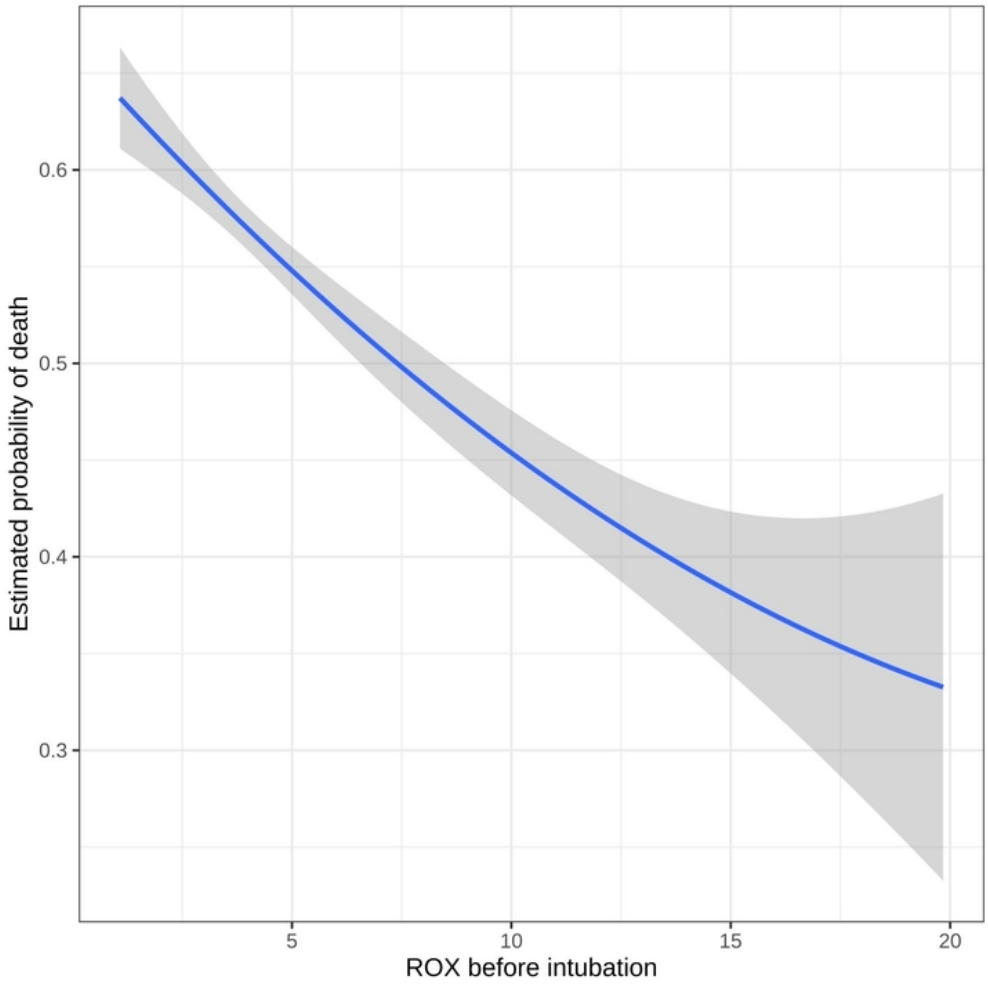
Table 5

Model for Outcome of Mortality Including Glasgow Coma Score (GCS)

N- 943 (excludes patients with missing GCS)

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
ROX index score	0.92	0.87-0.96	<0.0001
Male	1.19	0.90-1.59	0.23
Black v White Race	1.22	0.84-1.76	0.30
Other Race v White	0.71	0.51-0.98	0.04
Age	1.04	1.03-1.05	<0.0001
Peripheral Vascular Disease	1.40	0.90-2.21	0.14
Myocardial Infarction	1.50	1.00-2.13	0.05
Congestive Heart Failure	1.00	0.70-1.41	0.98
Diabetes	1.29	0.96-1.73	0.09
Hypertension	0.75	0.52-1.07	0.11
Days from Admission to Intubation	1.10	1.05-1.15	<0.0001
Glasgow Coma Scale Score	1.01	0.97-1.04	0.65


Cerner COVID Data Lab
covid_2020_q2jun
Release date: September 2, 2020
Inclusion Criteria
1. Inpatient encounter with diagnosis of COVID or positive COVID test
2. Encounters starting on or after January 1, 2020
Exclusion
1. Patients intubated in emergency department
Identify patients intubated during stay with codes: 5A1945Z, 5A1955Z OBH17EZ
2102 Patients Identified
Exclude 412 patients
-- where ROX index could Not be calculated due to missing data
Dataset of 1690 patients
Exclude: 603 patients with ROX more than 4 hours prior to intubation time
Analysis Sample of 1087 patients



The y-axis shows the estimated probability of death in the hospital. The x-axis shows the ROX index score prior to intubation. The solid line shows the line of best fit generated by multivariable model for association between ROX index score and mortality. The higher the ROX, the lower the estimated probability of death. The shaded area shows the 95% confidence interval around the line. Because fewer patients were intubated at ROX values >5, the 95% confidence interval widens as the ROX index scores increases.

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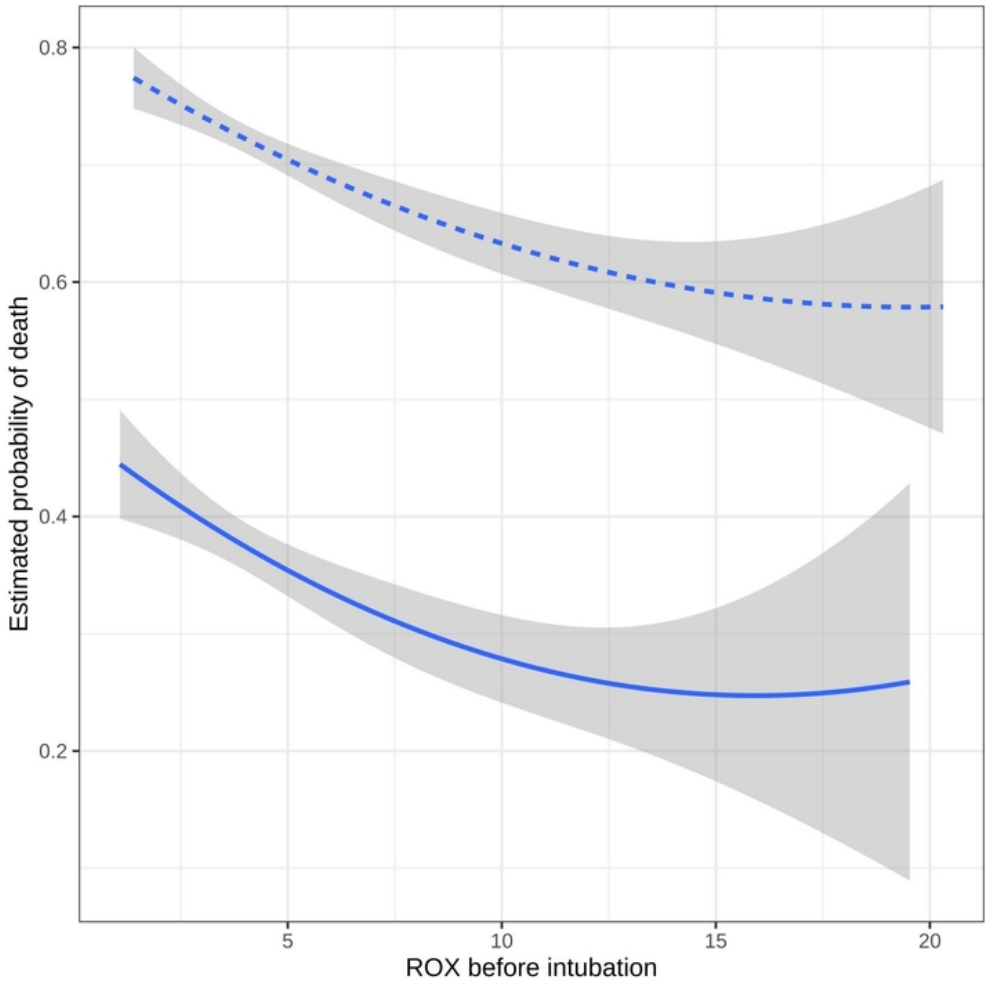

The y-axis shows the probability of in-hospital death. The x-axis shows the ROX index scores. The dotted line shows the line of best fit generated by multivariable model for association between ROX index score and mortality for patients with acute kidney injury. The solid line shows the line of best fit generated by model for patients without acute kidney injury. While risk of mortality is higher in patients with acute kidney injury at all ROX values, the relationship between ROX index score prior to intubation and mortality remains similar.

30x30mm (600 x 600 DPI)