Assessing Mortality Differences Across Acute Respiratory Failure Management Strategies in Covid-19

Authors: Jamuna K. Krishnan,[1] Mangala Rajan,[2] Benjamin R. Baer,[3] Katherine L. Hoffman,[4] Mark N. Alshak,[2] Kerri I. Aronson,[1] Parag Goyal,[2,5] Chiomah Ezeomah,[2] Shanna S. Hill,[6] Fernando J. Martinez,[1] Meredith L. Turetz,[1] Martin T. Wells,[3,7] Monika M. Safford,[2] Edward J. Schenck.[1]

Affiliations: [1]Divison of Pulmonary and Critical Care Medicine, Weill Cornell Department of Medicine, NY, NY. [2]Division of General Internal Medicine, Weill Cornell Department of Medicine, NY, NY. [3]Department of Statistics and Data Science, Cornell University, Ithaca, New York. [4]Division of Biostatistics and Epidemiology, Weill Cornell Medicine, NY, NY. [5]Division of Cardiology, Weill Cornell Department of Medicine, NY, NY. [6]Department of Anesthesiology, Weill Cornell Medicine, NY, NY. [7]Department of Population Health Sciences, Weill Cornell Medicine, NY, NY.

Funding Sources: Dr. Krishnan reports support from NIH T32 HL134629

Summary Conflict of Interest Statements: Dr. Krishnan reports support from NIH T32 HL134629 during the conduct of the study and non-financial support from GlaxoSmithKline, outside the submitted work. Dr. Hill discloses that her partner manages a financial fund that owns medical stocks including Johnson and Johnson, Merck, Medtronic, and Roche. These have been long standing holdings and are not relevant to the submitted work. Dr. Goyal reports receipt of fees for completion of medicolegal review in heart failure and receipt of honoraria for work with Akcea inc and Bionest inc not related to the contents of this manuscript. Dr. Martinez reports personal fees from GlaxoSmithKline, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Raziel, during the conduct of the study; personal fees

and non-financial support from AstraZeneca, personal fees and non-financial support from Boehringer Ingelheim, non-financial support from ProterrixBio, personal fees, non-financial support from Genentech, personal fees and non-financial support from GlaxoSmithKline, personal fees from MD Magazine, personal fees from Methodist Hospital Brooklyn, personal fees and non-financial support from Miller Communications, personal fees and non-financial support from National Society for Continuing Education, personal fees from New York University, personal fees and non-financial support from PeerView Communications, personal fees and non-financial support from Chiesi, personal fees and non-financial support from Sunovion, personal fees from UpToDate, personal fees from WebMD/MedScape, other from Afferent/Merck, non-financial support from Gilead, non-financial support from Nitto, personal fees from Patara/Respivant, other from Biogen, other from Veracyte, non-financial support from Zambon, personal fees from American Thoracic Society, grants from NIH, personal fees and non-financial support from Physicians Education Resource, personal fees from Rockpointe, other from Prometic, grants from Rare Disease Healthcare Communications, personal fees and other from Bayer, other from Bridge Biotherapeutics, personal fees and non-financial support from Canadian Respiratory Network, grants from ProMedior/Roche, personal fees and non-financial support from Teva, personal fees from CME Outfitters, personal fees and non-financial support from Csl Behring, personal fees from Dartmouth University, personal fees from DevPro, from Gala, personal fees from Integritas, personal fees from IQVIA, personal fees from Projects in Knowledge, personal fees and non-financial support from Sanofi/Regeneron, from twoXAR, personal fees from Vindico, other from AbbVie, personal fees from Academy for Continuing Healthcare Learning, outside the submitted work. Dr. Schenck reports personal fees from Axle

Informatics, outside the submitted work. The remaining authors have no conflicts of interest to report.

Corresponding Author and Contact:

Jamuna K. Krishnan

1305 York Ave

Box 96, Room Y-1059

New York, NY 10021

Phone: (646) 962-2738, Email: jkk9002@med.cornell.edu

ABSTRACT

Purpose

Prolonged observation could avoid invasive mechanical ventilation (IMV) and related risks in patients with Covid-19 acute respiratory failure (ARF) compared to initiating early IMV. We aimed to determine the association between ARF management strategy and in-hospital mortality.

Materials and Methods:

Patients in the Weill Cornell Covid-19 registry who developed ARF between March 5 – March 25, 2020 were exposed to an early IMV strategy; between March 26 – April 1, 2020 to an intermediate strategy; and after April 2 to prolonged observation. Cox proportional hazards regression was used to model in-hospital mortality and test an interaction between ARF management strategy and modified sequential organ failure assessment (mSOFA).

Results

Among 632 patients with ARF, 24% of patients in the early IMV strategy died versus 28% in prolonged observation. At lower mSOFA, prolonged observation was associated with lower mortality compared to early IMV (at mSOFA = 0, HR 0.16 [95% CI 0.04 – 0.57]). Mortality risk increased in the prolonged observation strategy group with each point increase in mSOFA score (HR 1.29 [95% CI 1.10–1.51], p=0.002).

Conclusion

In Covid-19 ARF, prolonged observation was associated with a mortality benefit at lower mSOFA scores, and increased mortality at higher mSOFA scores compared to early IMV.

INTRODUCTION:

Individuals with severe coronavirus disease 2019 (Covid-19) can develop acute hypoxic respiratory failure (ARF) and progress to acute respiratory distress syndrome (ARDS) [1]. The decision to initiate invasive mechanical ventilation (IMV) in patients with ARF requires physician judgment with repeated assessment and careful risk and benefit determination [1,2].

At New York Presbyterian-Weill Cornell Medical Center (WCM) and Lower Manhattan Hospital (LMH), we initially adopted an early IMV strategy whereby lower thresholds were employed and noninvasive methods such as high flow nasal cannula (HFNC) were not utilized. The rationale for an early IMV strategy included 1) avoiding emergent intubation and peri-intubation complications in patients with limited reserve, and 2) minimizing aerosolization from HFNC and subsequent risk of Covid-19 transmission to healthcare workers. Moreover, an early IMV strategy was supported by prior observational data in non-Covid-19 ARF showing that delaying invasive mechanical ventilation is associated with increased mortality[3].

On the other hand, delaying IMV in favor of prolonged observation has its theoretical benefits. While providing essential support, IMV is fraught with risks including ventilator-induced lung injury [4–6], ventilator associated pneumonia [7–9], deconditioning [10], and sedation related complications such as delirium [11]. IMV is resource intensive, requiring lower nurse to patient ratios and frequent respiratory therapy support. Given risks for IMV related complications and concerns about ventilator shortages, prolonged observation and higher thresholds for intubation were eventually adopted by many centers during the COVID-19 pandemic [12], including WCM and LMH. Higher thresholds for intubation included tolerating higher levels of hypoxia and the use of supportive devices such as HFNC. HFNC reduces the work of breathing and provides positive distending pressure, enabling lung recruitment and

potentially avoiding IMV [13]. Although some observational data suggest that HFNC can decrease the need for IMV, the safety of a policy that includes the use of HFNC and continuous positive airway pressure in Covid-19 associated ARF is unknown [14–16]

The optimal hospital-level strategy for timing of IMV in patients with COVID-19 related ARF has been an area of debate. Given that our institutions practiced both approaches at different times, there is an opportunity to study the potential impact of an early IMV versus prolonged observation strategy. The objective of this study was to compare in-hospital mortality in patients with Covid-19 related ARF managed with an early IMV strategy versus a prolonged observation strategy. Prior literature in non-COVID ARF has shown a mortality benefit for non-invasive ventilation prior to consideration of IMV in a carefully selected patient population with fewer organ failures [17,18]. We therefore hypothesized that the association of a prolonged observation strategy with mortality would vary based on the severity of illness at the time of developing ARF.

METHODS

Study Design:

This is a retrospective two-center observational cohort study using the Weill Cornell Covid-19 Registry; the registry includes patients older than 18 years admitted to WCM and LMH between March 5, 2020 – May 15, 2020 with confirmed Covid-19 [19]. Reverse-transcriptase polymerase chain reaction assays performed on nasopharyngeal swab specimens confirmed Covid-19 cases. Registry data were manually abstracted from electronic health records using a structured abstraction tool with a quality control protocol. The Weill Cornell Critical Care Database for Advanced Research (CEDAR) was linked to the Weill Cornell Covid-19 Registry, and used to extract daily vital signs, nursing flow sheet data, laboratory values and Sequential

Organ Failure Assessment (SOFA) scores from the electronic medical record [20]. This study was approved by the Weill Cornell Medicine Institutional Review Board (protocol 20-03021681).

Study Setting and Participants:

WCM is an 862-bed quaternary referral center and LMH is a 180-bed affiliated non-teaching hospital. Both are located in Manhattan. Patients from either WCM or LMH with ARF at any time during their hospitalization were included. ARF was defined as the receipt of the the following types of respiratory support due to hypoxia and/or work of breathing: ≥6L supplemental nasal cannula, venturi mask, noninvasive mechanical ventilation, high flow nasal cannula, and IMV. Exclusion criteria included 1) transfer from a hospital outside of WCM and LMH, and 2) do not intubate or do not resuscitate order (DNR/DNI) prior to developing ARF. Specific protocols adopted by our institution, such as approach to staffing and resource distribution, have been previously described [21].

Main Exposure:

The primary exposure was the strategy used to guide the intubation decision in patients with ARF. Patients who developed ARF between March 5, 2020 to March 25, 2020 were exposed to the early IMV strategy. Patients who developed ARF on or after April 2, 2020 – May 15, 2020 were exposed to a prolonged observation strategy. Those who developed ARF between March 26, 2020 and April 1, 2020 were in a transitional period. These patients experienced an "intermediate" strategy as the practice to adopt higher thresholds for intubation was being gradually adopted at both institutions.

As part of the early IMV strategy, IMV was the preferred intervention when patients required more than 6L nasal cannula support. This threshold was initially chosen as HFNC and

noninvasive positive pressure ventilation (NIPPV) were not permitted due to aerosolization concerns. In addition, this threshold was employed due to initial concerns about rapid patient deterioration, to minimize emergent intubation and reduce healthcare worker exposure. As the surge in New York City progressed during March of 2020 with ICU resource constraints, and increased acceptability of HFNC, we adopted a "prolonged observation strategy". In this strategy, patients were closely monitored by intensivists while tolerating increasing hypoxia. While there was no specific oxygen saturation threshold for intubation, the prior strategy of intubating all individuals requiring more than 6L of nasal cannula was no longer employed. Instead, a combination of nasal cannula, non-rebreather and HFNC were used to provide continued respiratory support, with clinician judgement based on level of respiratory distress guiding intubation decisions.

Throughout all strategies, volume-control ventilation was the preferred initial mode, with a target tidal volume between 6-8 cc/kg of ideal body weight (IBW) and a target plateau pressure of $\leq$30 cm H_20. Prone positioning was recommended for those in accordance with established guidelines [22,23].

Outcomes of Interest:

Our primary outcome was the time from development of ARF to in-hospital mortality ascertained through December 31, 2020. Secondary outcomes of interest included renal replacement therapy and length of stay among survivors. Among those who were intubated, we also examined the number of patients who had prolonged IMV defined by tracheostomy placement. All outcomes of interest were obtained by documentation of the event in the electronic medical record. Clinical documentation was abstracted from the electronic medical

record into the Weill Cornell Covid-19 registry using a uniform protocol with quality control [19].

Covariates:

In addition to demographic data (age, sex, race, and ethnicity), we also examined smoking history and comorbidities that were identified by the Centers for Disease Control to increase risk for severe illness in Covid-19 [24]. Comorbidities included obesity (defined as body mass index [BMI] greater than 30 kg/m^2), active malignancy, cardiovascular disease (coronary artery disease, heart failure), chronic kidney disease, obstructive airways disease (chronic obstructive pulmonary disease and asthma), stroke, and diabetes mellitus.

Severity of illness was captured using a modified sequential organ failure assessment (mSOFA) score, calculated by subtracting the pulmonary component of SOFA from the total SOFA score [25,26]. We examined CEDAR database records up to 48 hours prior to developing ARF to identify the closest recorded mSOFA score. If no mSOFA score was calculated in the database in the 48 hours prior to ARF, then we examined records in the 48 hours following ARF onset.

Due to the potential for hospital resource constraints as cases surged, we created a variable for daily hospital strain, calculated as total daily cumulative Covid-19 admissions minus cumulative Covid-19 discharges. Hospital strain was calculated for each subject in the study population on the day that ARF criteria were met. We also included receipt of corticosteroids during the hospitalization as a covariate due to studies demonstrating a mortality benefit associated with dexamethasone use [27,28].

Statistical methods:

Descriptive statistics were used to characterize demographics, underlying conditions, mSOFA scores, hospital strain, receipt of steroids, and intubation timing in the three exposure groups. Differences in proportion of deaths, receipt of renal replacement therapy, and progression to tracheostomy among intubated patients were tested using chi-square tests, or instead Fisher's exact test when an expected cell count was less than five. Length of stay among survivors was presented as a median with interquartile range and differences were compared using the Mann-Whitney test.

Time to in-hospital mortality was modelled in days using Cox proportional hazards regression, beginning when patients met criteria for ARF. Patients were censored at time of death, hospital discharge, or transfer to an institution outside of WCM or LMH. Sociodemographics, comorbidities, hospital strain, mSOFA, and receipt of in-hospital steroids were included in our multivariable model. We included an interaction term between mSOFA score and the ARF management strategy due to our *a priori* hypothesis. We estimated the parameters of the model using maximum partial likelihood [29]. Assumptions of proportionality of the hazard ratios were checked using a Score test for time varying coefficients. Multiple imputation using chained equations was used to impute missing data for our multivariable model. To visualize the interaction, we fit a smooth interaction via a Cox additive model [30].

A sensitivity analysis was conducted by only considering patients who developed ARF in the first three weeks that the prolonged observation strategy was in effect. While the early IMV strategy group and intermediate strategy group remained the same as in the main analysis, the prolonged observation strategy only included patients who developed ARF between April 2 – April 22 rather than up to May 15th. We compared this smaller prolonged observation strategy

group to the early IMV group to help understand the influence of unmeasured confounders that may have changed over time during New York City's spring surge.

All analyses were conducted using SAS Version 9.4 and R version 3.6.2 [31]. Plots were rendered using the R package ggplot2 [32]. An alpha level of 0.05 was identified as the threshold for significance.

RESULTS

Participants:

From March 5, 2020 through May 15, 2020, 1869 patients were hospitalized at either WCM or LMH with Covid-19. Of these patients, 773 met criteria for ARF. We excluded 5 patients who were transferred from outside hospitals and 136 patients who elected to be DNR/DNI prior to meeting criteria for ARF. Out of the 632 patients in our analytic sample with ARF, 101 patients were in the early IMV group, 131 were in the intermediate group, and 400 were in the prolonged observation group (**Figure 1).**

Baseline characteristics:

Characteristics of patients by ARF management strategy are summarized in **Table 1.** Patients in the early IMV group, intermediate group and prolonged observation group were of similar age (66 years [IQR 53-75] vs 64 [IQR 57-74] years vs 67 years [IQR 58-75]) with similar proportions of women. There was a higher proportion of individuals with prior smoking history (37% vs. 31% vs. 27%) and BMI $\geq$ 30 kg/m^2 (38% vs. 35% vs. 28%) in the early IMV versus the intermediate and prolonged observation group. Hospital strain was highest when patients met criteria for ARF in the prolonged observation strategy group, with an excess of 434 (IQR 401 – 484) cumulative admissions compared to an excess of only 118 admissions (IQR 73-190) in the early IMV strategy. The mSOFA score distribution at the time of developing ARF is presented

in **Figure 2** and **Figure E1**. Reflecting differences in ARF management strategies, 78.2% of patients in the early IMV group were intubated at the time of meeting criteria for ARF, this decreased to 49.5% in the prolonged observation group. In all three groups, non-invasive positive pressure ventilation was used sparingly at time of developing ARF (early IMV group 1%, intermediate group 2% and prolonged observation group 3%), with the remainder of patients managed with a combination of supplemental nasal cannula, non-rebreather, venti-mask and HFNC. The spO2:FIO2 (S:F) ratio at time of intubation in the early-IMV group was 206.4 ± 90.1 compared to 155.2 ± 110.0, reflecting increased hypoxia at time of intubation in the prolonged observation group. The P:F ratios corresponding to these S:F ratios are 170.6 ± 90.1 in the early IMV group and 105.7 ± 87.6 [33].

Outcomes:

Deaths occurred in 169 (27%) patients: 24 (24%) in the early IMV group, 34 (26%) in the intermediate strategy group and 111 (28%) in the prolonged observation strategy group (p = 0.7). The receipt of renal replacement therapy was more frequent in the early IMV group compared to the intermediate group and the prolonged observation group (28% vs 12% vs 14% p = .002). Among survivors, length of stay was longer in the early IMV versus intermediate and prolonged observation groups, though without a significant difference (p = 0.33). These outcomes are summarized in **Table 2.**

In a multivariable model adjusting for age, sex, race/ethnicity, comorbidities, hospital capacity, in-hospital receipt of steroids, and mSOFA score, the hazard ratio (HR) for the association between ARF management strategy and in-hospital mortality was 0.76 (95% CI 0.30 – 1.93, p=0.56). An expanded model which included an interaction term between mSOFA score and ARF management strategy (p = .003) demonstrated a heterogenous effect such that at at

lower mSOFA scores, prolonged observation was associated with mortality benefit. Specifically, at an mSOFA score of 0, the prolonged observation strategy is associated with a HR for mortality of 0.16 (95% CI 0.044 - 0.57, p=.005) compared to early IMV, **Table 3.** Each point increase in the mSOFA score was associated with an increased risk of mortality when comparing the prolonged observation strategy versus early-IMV strategy (HR 1.29 [95% CI 1.10 - 1.51], p=0.002), **Table 3.** The adjusted hazard ratio comparing prolonged observation versus early IMV at each mSOFA score is shown in **Figure 3**. The 95% pointwise confidence intervals are wide for high SOFA scores due to low patient counts. The test for whether the hazard ratios were proportional failed to reject the null hypothesis (p=0.09)

Sensitivity analyses:

A sensitivity analysis compared patients who developed ARF within the first three weeks of implementation of the prolonged observation strategy compared to the intermediate and early IMV strategy (**Table 4)**. The Cox proportional hazards model included the same covariates as our main model. Similar to our main analysis, as mSOFA score increased, there was increased mortality associated with the prolonged observation strategy compared to early IMV (HR 1.15 [95% CI 1.01 - 1.30, p = 0.003).

DISCUSSION:

In this retrospective observational study, the association of ARF management strategy with in-hospital mortality was dependent on mSOFA scores. Among patients with lower mSOFA scores, prolonged observation was associated with lower mortality compared with early IMV.

Our study builds on prior work in this area. Hernandez-Romieu *et al* [34] at Emory University and Hyman *et al* [35] at Mount Sinai Health System both compared timing of initiating IMV and mortality in severe Covid-19. The Emory study modelled time from intensive

care unit admission to intubation and in-hospital mortality— no difference in mortality was found in patients intubated within 8 hours, 8-24 hours, and greater than 24 hours. The Mount Sinai group studied the association between each additional day from time to hospital admission to intubation and in-hospital mortality. Their analysis revealed a very small increase in mortality with each additional day from admission to intubation (HR 1.03 [95% CI 1.01 - 1.05]). Limitations of both studies were that the study population only included patients who received IMV. Consequently, these studies could not account for the potential mortality impact among patients with ARF who avoided intubation altogether using non-invasive support. Our study addressed this limitation by including all patients who developed ARF and therefore were *at risk* for intubation—and now shows that the association of ARF management strategy with mortality is influenced by illness severity at the time of developing ARF.The increased mortality we describe associated with a prolonged observation strategy at higher illness severity scores has not been previously reported in severe Covid-19. In our study, the prolonged observation strategy was supported through the use of HFNC. An increased risk of HFNC failure with higher SOFA scores has been shown in populations with Covid-19 and mixed ARF [36,37]. We theorize that HFNC failure may subsequently put patients at increased risk for emergent intubation, which can increase the risk of complications. Prolonged observation exposes patients to both the detrimental effects of self-inflicted lung injury while on HFNC and ventilator associated complications once intubated [4]. Early mechanical ventilation may be more beneficial in patients with multi-system organ failure to assist work of breathing and increase perfusion. An alternative hypothesis is that clinical factors such as frailty may influence decision making on timing of intubation, leading to a bias in some individuals in the prolonged observation strategy being selected for a less invasive approach with HFNC. This bias would not have been present in

the early-IMV group where more concerted efforts may have been made about goals of care, leading to these patients being excluded from our analysis.

The availability of resources and skilled personnel should be considered when evaluating the generalizability of our findings. Under all strategies, intensivists performed serial reassessments of patients with ARF for further deterioration. Patients who were observed for longer periods of time tended to be more hypoxic at time of intubation. When intubation was deemed necessary, it was performed by a dedicated airway team consisting of a respiratory therapist and two experienced airway operators: an anesthesiologist and a certified registered nurse anesthetist (CRNA). Having multiple experienced airway operators with designated responsibilities allowed for difficult airway management and expedient intubations in situations where patients had low reserve and rapid desaturation. Specific protocols were developed to facilitate patient safety and speed, including pre-oxygenation coaching, use of video laryngoscope technology, and intubation in the more technically challenging semi-recumbent position to maximize functional residual capacity and avoid bag mask ventilation. An intensivist assisted with managing post-intubation ventilation and hemodynamic complications. At medical centers with less clinical staffing or overwhelming patient volume, this level of clinician support may not be available, and may increase the risk associated with a prolonged observation strategy.

Our finding of increased renal replacement therapy in the early IMV group could reflect the increased morbidity associated with this strategy. Invasive mechanical ventilation is associated with biotrauma leading to multi-organ dysfunction [38,39]. Alternatively, differences in proportion of renal replacement therapy were confounded by many additional factors including variations in fluid resuscitation and illness severity as reflected in higher SOFA scores in the early IMV group. Newer data pending peer review from the anticoagulation arm of the

REMAP-CAP, ATTACC ,and ACTIV4a indicate that therapeutic anticoagulation in the group of patients with moderate Covid-19 led to increased organ support-free days and could influence the proportion of patients needing renal replacement therapy over time [40].

A strength of our study is that our institutions used evidence-based practices for lung protective ventilation and prone positioning starting from the beginning of the pandemic. Therefore, injurious ventilation is unlikely to be a confounder in the early IMV group. A separate analysis was previously published describing important mechanical ventilation parameters among patients with Covid-19 who were intubated between March 1st 2020 to April 20,2020 at our institution. In this cohort, the mean day 3 (n = 252) tidal volume was 6.38 (6.00 – 6.97) cc/kg of ideal body weight (IBW), driving pressure was 12.0 cm H_20 (9.0 – 15.2), and mean plateau pressure was 12.0 cm H_20 [22].

Our results should be interpreting within the context of the following limitations. There were lower numbers of individuals at low mSOFA scores, therefore our estimates of the association between ARF management strategy and mortality may be less precise at these values. As more critically ill patients with severe Covid-19 were admitted, "pop-up intensive care units" were created on general medicine floors. Geographic dispersion of patients with primary pulmonary conditions to other medical units has previously been shown to negatively impact outcomes [41]. We adjusted our analysis for this potential confounder by including hospital strain as a covariate. We caution that mortality declined dramatically over the course of the spring outbreak for reasons that are not well understood. The decline in mortality over the course of the initial outbreak of Covid-19 has been reported across hospital systems in New York City as well as in other geographic areas [42–44]. It is possible that the unmeasured confounders leading to this decline complicate the association between ARF management strategy and in-

hospital mortality. In our second sensitivity analysis, we considered just the first three weeks that the prolonged observation strategy was in effect and compared mortality to the early-IMV group. This was an attempt to limit the influence of time-varying confounders as the entire study period was then shortened from March 2020 to early April 2020 rather than extending out to patients who developed ARF in May 2020. This analysis showed the same association between rising mSOFA scores, prolonged observation and mortality. Additional unmeasured confounders include frailty, performance status, differences in nursing staffing ratios, and differences in receipt of physical therapy.

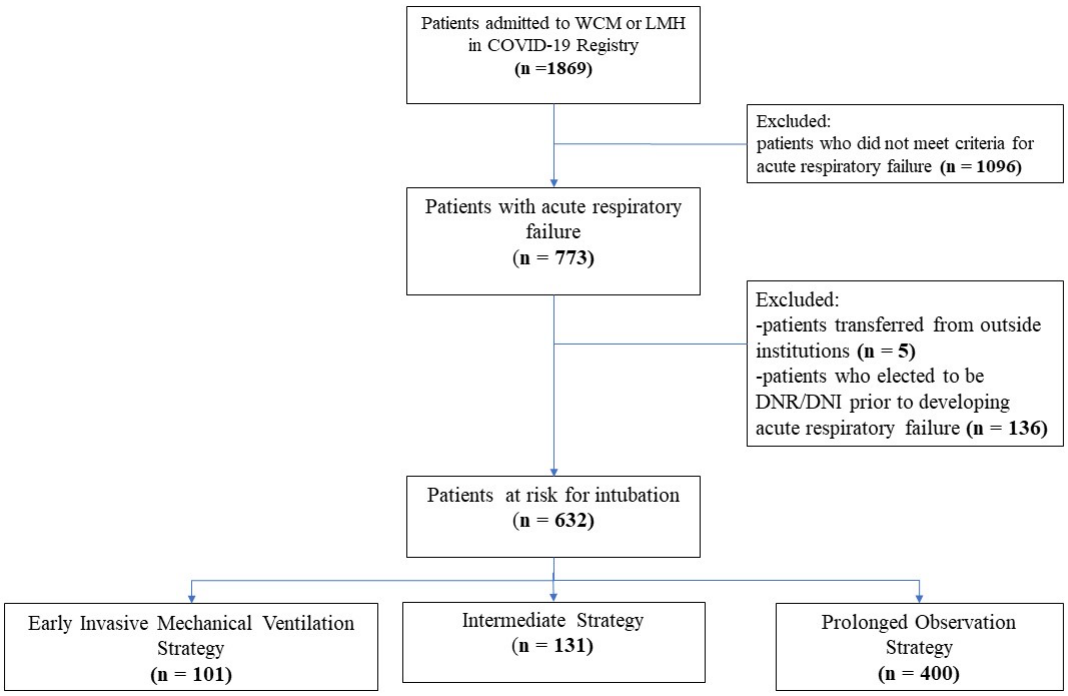
In conclusion, in patients with lower illness severity at the time of developing ARF, a prolonged observation strategy was associated with lower mortality. If our findings are confirmed, prolonged observation may be a reasonable strategy in patients with ARF and lower levels of multisystem organ failure when resources allow for safe levels of observation.

ACKNOWLEDGEMENTS

Dr. Krishnan takes responsibility for all aspects of the submitted work from inception to the manuscript, including the content of the manuscript, data and analysis.

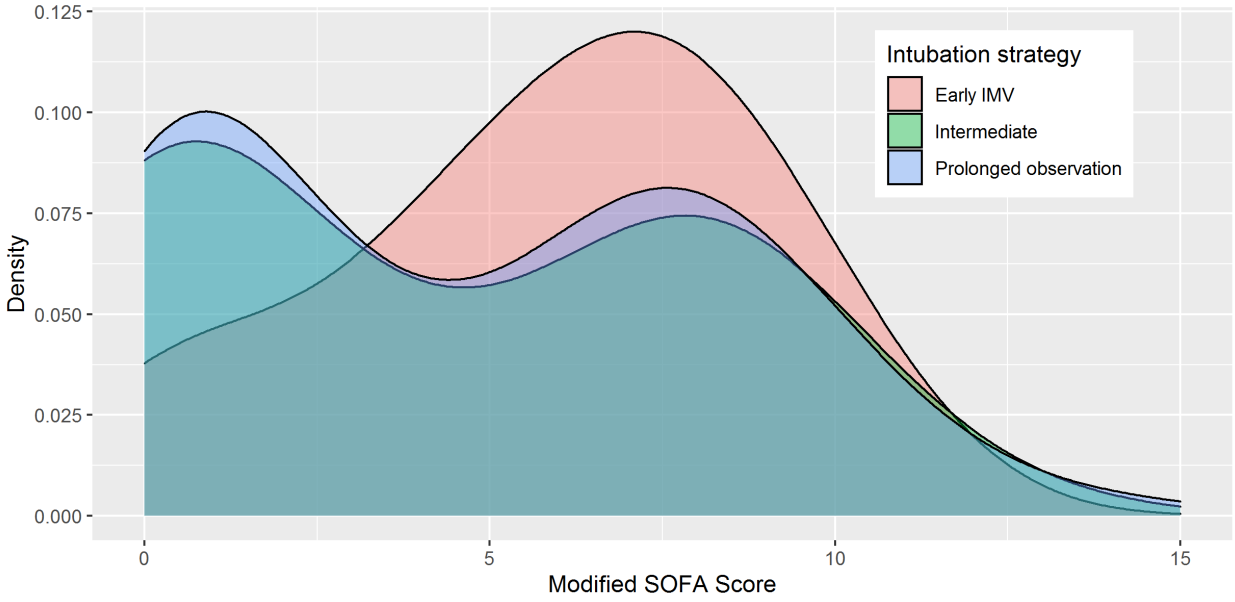
Author Contributions: Study conception and design: J.K.K., M.R., B.R.B, M.N.A., K.I.A., P.G., C.E., F.J.M., M.L.T., E.S., and M.M.S. Data acquisition: M.N.A and P.G. Data analysis and interpretation: J.K.K., M.R.R., B.R.B., K.L.H., M.N.A., C.E., M.T.W., E.S., and M.M.S. Drafting of the initial manuscript: J.K.K., C.E., and S.S.H. All authors contributed to revisions of the manuscript for critically important intellectual content. All of the authors approved this version of the manuscript to be published.

Figure 1.



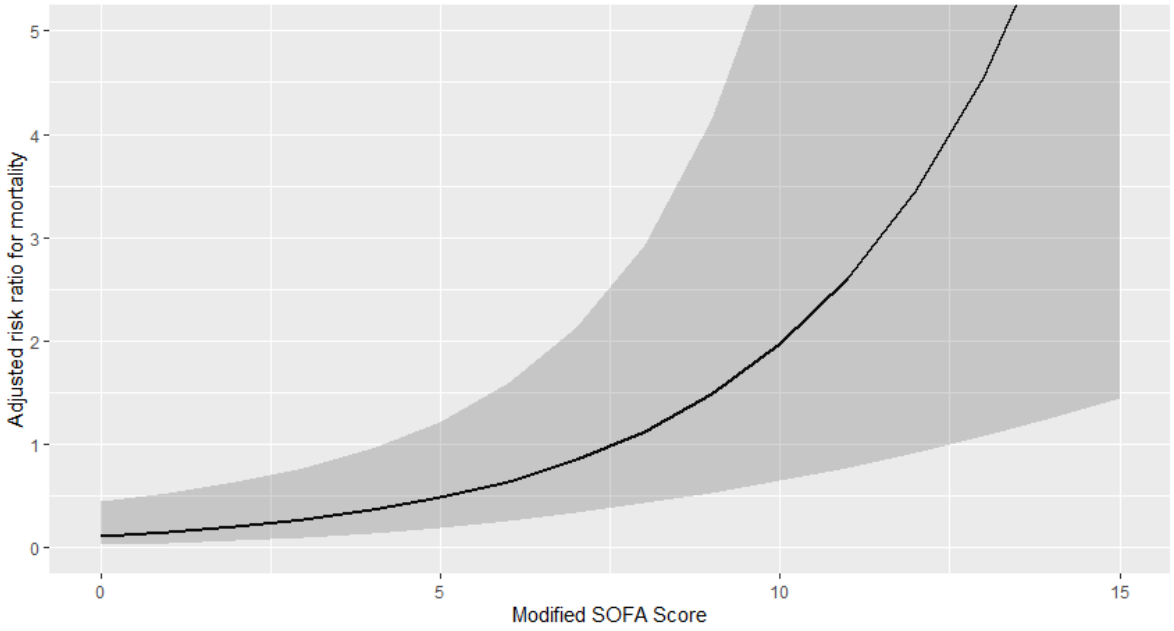
Legend: Exclusionary cascade. This figure illustrates the identification of our cohort at risk for intubation.

Figure 2.



Legend: SOFA score distribution by ARF management strategy. This figure illustrates the distribution of modified SOFA score by ARF management strategy (intubation strategy). The pink corresponds to patients in the early IMV group, green to the intermediate group, and light blue in the prolonged observation group. Overlapping distributions are presented by a mix of colors. For example, the turquoise color represents an overlap in the mSOFA distribution between the intermediate strategy and prolonged observation strategy.

Figure 3.



Legend: Hazard ratio for in-hospital mortality comparing the prolonged observation strategy to the early invasive mechanical ventilation strategy by modified SOFA score.

This figure plots the adjusted hazard ratio for mortality comparing the prolonged observation strategy versus the early IMV strategy as a function of the modified SOFA score. The shaded grey areas are the point-wise 95% confidence intervals.

Table 1: Cohort characteristics by acute respiratory failure (ARF) management strategy

	Management Strategy Employed for Acute Respiratory Failure		
Characteristic	**Early Invasive Mechanical Ventilation** *(n=101)*	**Intermediate** *(n=131)*	**Prolonged Observation** *(n=400)*
Baseline Demographics and Comorbidities			
Age, years, median (IQR)	66 (53 – 75)	64 (57- 74)	67 (58-75)
Female Sex, n (%)	33 (33)	39 (30)	139 (35)
BMI[1] ≥ 30 kg/m^2, n (%)	38 (38)	46(35)	109 (28)
Current or former smoker,[1] n(%)	37 (37)	40 (31)	108 (27)
Race and Ethnicity, n(%)			
Hispanic or Latinx	21 (21)	27 (21)	102 (26)
Asian	17 (17)	22 (17)	92 (23)
Non-hispanic Black	6 (5.9)	9 (6.9)	41 (10)
Non-hispanic White	35 (35)	53 (40)	104 (26)
Not specified	22 (22)	20 (15)	60 (15)
Comorbidities,[2] n(%)			
Coronary artery disease	24 (24)	17 (13)	67 (17)
Heart failure	6 (5.9)	6 (4.6)	30 (7.5)
Stroke	8 (7.9)	7 (5.3)	34 (8.5)
Diabetes mellitus	33 (33)	44 (34)	141 (35)
Chronic obstructive pulmonary disease and/or asthma	19 (19)	15 (11)	58 (14)
Renal Disease	12 (12)	9 (6.1)	46 (11)
Active Malignancy	6 (5.9)	4 (3.1)	30 (7.5)
Characteristics of Hospitalization			
Location of Initial Hospital Admission, n(%)			
NYP Cornell	73 (72)	98 (75)	301 (75)
NYP Lower Manhattan	28 (28)	33 (25)	99 (25)
Modified SOFA score,[1,3] median (IQR)	7 (4 – 8)	3 (0 – 8)	4 (1 – 8)

Receipt of steroids in-hospital, n(%)	32 (32)	48 (38)	201 (51)
Duration of steroid therapy, mean (SD), days			
Receipt of IL-6 inhibitors in-hospital, n(%)			
Duration of IL-6 inhibitor therapy, mean (SD), days			
Hospital strain,[4] median (IQR)	118 (73 – 190)	337 (281 – 374)	434 (401 – 483)
Intubation			
At time of ARF, n(%)	79 (78.2)	55 (42.0)	198 (49.5)
Anytime during hospitalization, n(%)	82 (81.2)	65 (49.6)	214 (53.5)
spO2/FIO2 ratio among intubated, mean (SD)	206.4 (90.1)	174.1 (78.3)	155.2 (110.0)

Abbreviations: BMI = Body mass index. SOFA = Sequential Organ Failure Assessment . IQR = interquartile range

[1]BMI was missing for 10 patients, 1 patient in the intermediate category and 9 in the prolonged observation category. Smoking status was missing for 2 patients, both in the prolonged observation category. Modified SOFA score was missing in 11 patients, 1 in the early IMV strategy, 2 in the intermediate strategy, and 9 in the prolonged observation strategy. Receipt of steroids was unknown in 8 patients, 3 in the intermediate strategy and 5 in the prolonged observation strategy.

[2]Comorbidities were present on admission

[3]Modified SOFA score was calculated by taking the total SOFA score and subtracting the pulmonary component on the day that the patient met ARF criteria

[4]Hospital strain was modelled as cumulative discharges minus admissions on day that each patient met criteria for ARF. Higher numbers represent increased strain.

Table 2. Outcomes of interest by management strategy for patients with ARF

Outcome	Early invasive mechanical ventilation *(n = 101)*	Intermediate *(n = 131)*	Prolonged observation *(n = 400)*	p-value
Progression to tracheostomy[1,2] n, (% of intubated)	28 (34)	31 (48)	48 (22)	<0.001
Secondary bacterial respiratory infection[2,3] n, (% of intubated)	35 (42)	36 (55)	08 (37)	
Renal Replacement Therapy n, (%)	28 (28)	16 (12)	57 (14)	0.002
Length of Stay Among Survivors, median days (IQR)	16 (8 - 24)	10 (6 - 18)	11 (6 - 22)	0.33
Death, n (%)	24 (24)	34 (26)	111 (28)	0.7

[1]Tracheostomies were placed in patients who were on prolonged mechanical ventilation.

[2]Denominator is based on the number of mechanically ventilated patients in each group (n=82 for early IMV, n=66 for intermediate, n=214 for prolonged observation)

[3]Secondary bacterial respiratory infection as confirmed by positive culture results

Table 3. Multivariable[1] Cox Proportional Hazards Model for Time to In-Hospital Mortality

Characteristic	HR	95% CI	p-value
Intubation strategy group, at mSOFA of 0			
Early IMV	--		
Intermediate	0.40	0.11, 1.44	0.16
Prolonged observation	0.16	0.04, 0.57	0.005
mSOFA * Intubation strategy group,interaction[2]			
mSOFA * Early IMV	--		
mSOFA * Intermediate	1.17	0.98, 1.39	0.08
mSOFA * Prolonged observation	1.29	1.10, 1.51	0.002

Abbreviations: mSOFA = modified Sequential Organ Failure Assessment score. IMV = invasive mechanical ventilation

[1]This model is additionally adjusted for age, race and ethnicity, hospital strain, in-hospital receipt of steroids, smoking history, body mass index, and comorbidities (coronary artery disease, heart failure, stroke, diabetes mellitus, chronic obstructive pulmonary disease and/or asthma, renal disease, and active malignancy).

[2]The hazard ratios presented here are the changing association of ARF management strategy with mortality with each point increase in mSOFA score.

Table 4. Multivariable[1] Cox Proportional Hazards Model for Time to In-Hospital Mortality,

Prolonged Observation Group Limited to First Three Weeks[2]

Characteristic	HR	95% CI	p-value
Management strategy group			
Early IMV	--		
Intermediate	0.80	0.30, 2.11	0.64
Prolonged observation	0.48	0.19, 1.20	0.12
mSOFA * management strategy group, interaction[3]			
mSOFA * Early IMV	--		
mSOFA * Intermediate	1.07	0.92, 1.23	0.39
mSOFA * Prolonged observation	1.15	1.01,1.30	0.029

Abbreviations: mSOFA = modified Sequential Organ Failure Assessment score. IMV = invasive mechanical ventilation

[1]This model is additionally adjusted for age, race and ethnicity, hospital strain, in-hospital receipt of steroids, smoking history, body mass index, comorbidities (coronary artery disease, heart failure, stroke, diabetes mellitus, chronic obstructive pulmonary disease and/or asthma, renal disease, and active malignancy), and DNR/DNI status.

[2]This model has the same early IMV group (patients with acute respiratory failure [ARF] between March 5, 2020 – March 25) and intermediate group (ARF between March 26 – April 1). The prolonged observation group however consists only of patients who developed ARF between April 2 – April 22 for this sensitivity analysis.

[3]The ratios presented here are the changing association of ARF management strategy with mortality with each point increase in mSOFA score.

References

[1] D.A. Berlin, R.M. Gulick, F.J. Martinez, Severe Covid-19., N. Engl. J. Med. 383 (2020) 2451–2460. https://doi.org/10.1056/NEJMcp2009575.

[2] M.J. Tobin, Basing Respiratory Management of COVID-19 on Physiological Principles., Am. J. Respir. Crit. Care Med. 201 (2020) 1319–1320. https://doi.org/10.1164/rccm.202004-1076ED.

[3] K.N. Kangelaris, L.B. Ware, C.Y. Wang, D.R. Janz, H. Zhuo, M.A. Matthay, C.S. Calfee, Timing of intubation and clinical outcomes in adults with acute respiratory distress syndrome., Crit. Care Med. 44 (2016) 120–129. https://doi.org/10.1097/CCM.0000000000001359.

[4] L. Brochard, A. Slutsky, A. Pesenti, Mechanical ventilation to minimize progression of lung injury in acute respiratory failure., Am. J. Respir. Crit. Care Med. 195 (2017) 438–442. https://doi.org/10.1164/rccm.201605-1081CP.

[5] J.R. Beitler, A. Malhotra, B.T. Thompson, Ventilator-induced Lung Injury., Clin. Chest Med. 37 (2016) 633–646. https://doi.org/10.1016/j.ccm.2016.07.004.

[6] L. Tremblay, F. Valenza, S.P. Ribeiro, J. Li, A.S. Slutsky, Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model., J. Clin. Invest. 99 (1997) 944–952. https://doi.org/10.1172/JCI119259.

[7] S. Chevret, M. Hemmer, J. Carlet, M. Langer, Incidence and risk factors of pneumonia acquired in intensive care units. Results from a multicenter prospective study on 996 patients. European Cooperative Group on Nosocomial Pneumonia., Intensive Care Med. 19 (1993) 256–264. https://doi.org/10.1007/BF01690545.

[8] L. Papazian, M. Klompas, C.-E. Luyt, Ventilator-associated pneumonia in adults: a narrative review., Intensive Care Med. 46 (2020) 888–906. https://doi.org/10.1007/s00134-020-05980-0.

[9] M.L. Metersky, Y. Wang, M. Klompas, S. Eckenrode, A. Bakullari, N. Eldridge, Trend in Ventilator-Associated Pneumonia Rates Between 2005 and 2013., JAMA. 316 (2016) 2427–2429. https://doi.org/10.1001/jama.2016.16226.

[10] B. De Jonghe, T. Sharshar, J.-P. Lefaucheur, F.-J. Authier, I. Durand-Zaleski, M. Boussarsar, C. Cerf, E. Renaud, F. Mesrati, J. Carlet, J.-C. Raphaël, H. Outin, S. Bastuji-Garin, Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation, Paresis acquired in the intensive care unit: a prospective multicenter study., JAMA. 288 (2002) 2859–2867. https://doi.org/10.1001/jama.288.22.2859.

[11] B.T. Pun, R. Badenes, Gabriel Heras La Calle, O.M. Orun, W. Chen, R. Raman, B.-G.K. Simpson, S. Wilson-Linville, B.H. Olmedillo, A.V. de la Cueva, M. van der Jagt, R.N. Casado, P.L. Sanz, G. Orhun, C.F. Gómez, K.N. Vázquez, P.P. Otero, F.S. Taccone, E.G. Curto, A. Caricato, et al., Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study, The Lancet Respiratory Medicine. (2021).

[12] J.C. Doidge, D.W. Gould, P. Ferrando-Vivas, P.R. Mouncey, K. Thomas, M. Shankar-Hari, D.A. Harrison, K.M. Rowan, Trends in Intensive Care for Patients with COVID-19 in England, Wales, and Northern Ireland., Am. J. Respir. Crit. Care Med. 203 (2021) 565–574. https://doi.org/10.1164/rccm.202008-3212OC.

[13] M. Nishimura, High-Flow Nasal Cannula Oxygen Therapy Devices., Respir. Care. 64 (2019) 735–742. https://doi.org/10.4187/respcare.06718.

[14] C. Brusasco, F. Corradi, A. Di Domenico, F. Raggi, G. Timossi, G. Santori, V. Brusasco, Galliera CPAP-Covid-19 study group, collaborators of the Galliera CPAP-COVID-19 study group are, Continuous positive airway pressure in COVID-19 patients with moderate-to-severe respiratory failure., Eur. Respir. J. 57 (2021). https://doi.org/10.1183/13993003.02524-2020.

[15] M. Oranger, J. Gonzalez-Bermejo, P. Dacosta-Noble, C. Llontop, A. Guerder, V. Trosini-Desert, M. Faure, M. Raux, M. Decavele, A. Demoule, C. Morélot-Panzini, T. Similowski, Continuous positive airway pressure to avoid intubation in SARS-CoV-2 pneumonia: a two-period retrospective case-control study., Eur. Respir. J. 56 (2020). https://doi.org/10.1183/13993003.01692-2020.

[16] A. Demoule, A. Vieillard Baron, M. Darmon, A. Beurton, G. Géri, G. Voiriot, T. Dupont, L. Zafrani, L. Girodias, V. Labbé, M. Dres, M. Fartoukh, E. Azoulay, High-Flow Nasal Cannula in Critically III Patients with Severe COVID-19., Am. J. Respir. Crit. Care Med. 202 (2020) 1039–1042. https://doi.org/10.1164/rccm.202005-2007LE.

[17] B. Rochwerg, L. Brochard, M.W. Elliott, D. Hess, N.S. Hill, S. Nava, P. Navalesi, M. Antonelli, J. Brozek, G. Conti, M. Ferrer, K. Guntupalli, S. Jaber, S. Keenan, J. Mancebo, S. Mehta, S. Raoof, Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure., Eur. Respir. J. 50 (2017). https://doi.org/10.1183/13993003.02426-2016.

[18] M. Antonelli, G. Conti, M. Bufi, M.G. Costa, A. Lappa, M. Rocco, A. Gasparetto, G.U. Meduri, Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial., JAMA. 283 (2000) 235–241. https://doi.org/10.1001/jama.283.2.235.

[19] P. Goyal, J.J. Choi, L.C. Pinheiro, E.J. Schenck, R. Chen, A. Jabri, M.J. Satlin, T.R. Campion, M. Nahid, J.B. Ringel, K.L. Hoffman, M.N. Alshak, H.A. Li, G.T. Wehmeyer, M. Rajan, E. Reshetnyak, N. Hupert, E.M. Horn, F.J. Martinez, R.M. Gulick, M.M.

Safford, Clinical Characteristics of Covid-19 in New York City., N. Engl. J. Med. 382 (2020) 2372–2374. https://doi.org/10.1056/NEJMc2010419.

[20] E.T. Sholle, J. Kabariti, S.B. Johnson, J.P. Leonard, J. Pathak, V.I. Varughese, C.L. Cole, T.R. Campion, Secondary use of patients' electronic records (SUPER): an approach for meeting specific data needs of clinical and translational researchers., AMIA Annu. Symp. Proc. 2017 (2017) 1581–1588.

[21] K.M. Griffin, M.G. Karas, N.S. Ivascu, L. Lief, Hospital Preparedness for COVID-19: A Practical Guide from a Critical Care Perspective., Am. J. Respir. Crit. Care Med. 201 (2020) 1337–1344. https://doi.org/10.1164/rccm.202004-1037CP.

[22] E.J. Schenck, K. Hoffman, P. Goyal, J. Choi, L. Torres, K. Rajwani, C.W. Tam, N. Ivascu, F.J. Martinez, D.A. Berlin, Respiratory Mechanics and Gas Exchange in COVID-19-associated Respiratory Failure., Ann. Am. Thorac. Soc. 17 (2020) 1158–1161. https://doi.org/10.1513/AnnalsATS.202005-427RL.

[23] C. Guérin, J. Reignier, J.-C. Richard, P. Beuret, A. Gacouin, T. Boulain, E. Mercier, M. Badet, A. Mercat, O. Baudin, M. Clavel, D. Chatellier, S. Jaber, S. Rosselli, J. Mancebo, M. Sirodot, G. Hilbert, C. Bengler, J. Richecoeur, M. Gainnier, PROSEVA Study Group, Prone positioning in severe acute respiratory distress syndrome., N. Engl. J. Med. 368 (2013) 2159–2168. https://doi.org/10.1056/NEJMoa1214103.

[24] Certain Medical Conditions and Risk for Severe COVID-19 Illness | CDC, (n.d.). https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html (accessed February 23, 2021).

[25] D.R. Price, K.L. Hoffman, C. Oromendia, L.K. Torres, E.J. Schenck, M.E. Choi, A.M.K. Choi, R.M. Baron, J.-W. Huh, I.I. Siempos, Effect of neutropenic critical illness on development and prognosis of acute respiratory distress syndrome., Am. J. Respir. Crit. Care Med. 203 (2021) 504–508. https://doi.org/10.1164/rccm.202003-0753LE.

[26] L.K. Torres, E.J. Finklesztein, C. Oromendia, E.J. Schenck, A. Higuera, R.M. Baron, L.E. Fredenburgh, J.W. Huh, A.M. Choi, I.I. Siempos, Attributable mortality of acute respiratory distress syndrome: a systematic review and meta-analysis, in: Critical Care, 2018.

[27] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, J.A.C. Sterne, S. Murthy, J.V. Diaz, A.S. Slutsky, J. Villar, D.C. Angus, D. Annane, L.C.P. Azevedo, O. Berwanger, A.B. Cavalcanti, P.-F. Dequin, B. Du, J. Emberson, D. Fisher, B. Giraudeau, A.C. Gordon, A. Granholm, C. Green, R. Haynes, J.C. Marshall, Association Between Administration of Systemic Corticosteroids and Mortality Among

Critically Ill Patients With COVID-19: A Meta-analysis., JAMA. 324 (2020) 1330–1341. https://doi.org/10.1001/jama.2020.17023.

[28] RECOVERY Collaborative Group, P. Horby, M. Mafham, L. Linsell, J.L. Bell, N. Staplin, J.R. Emberson, M. Wiselka, A. Ustianowski, E. Elmahi, B. Prudon, T. Whitehouse, T. Felton, J. Williams, J. Faccenda, J. Underwood, J.K. Baillie, L.C. Chappell, S.N. Faust, T. Jaki, M.J. Landray, Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19., N. Engl. J. Med. 383 (2020) 2030–2040. https://doi.org/10.1056/NEJMoa2022926.

[29] T.M. Thernau, P.M. Grambsch, Modeling Survival Data: Extending the Cox Model, Springer Nature, 2000.

[30] S.N. Wood, Generalized additive models: an introduction with R. , 2nd ed., Chapman and Hall/CRC, 2017.

[31] R Core Team., R: A language and environment for statistical computing. (Version 3.6.1), R Foundation for Statistical Computing, Vienna, Austria, 2019.

[32] H. Wickham, ggplot 2 Elegant Graphics for Data Analysis , Springer-Verlag New York, 2019.

[33] T.W. Rice, A.P. Wheeler, G.R. Bernard, D.L. Hayden, D.A. Schoenfeld, L.B. Ware, National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Network, Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS., Chest. 132 (2007) 410–417. https://doi.org/10.1378/chest.07-0617.

[34] A.C. Hernandez-Romieu, M.W. Adelman, M.A. Hockstein, C.J. Robichaux, J.A. Edwards, J.C. Fazio, J.M. Blum, C.S. Jabaley, M. Caridi-Scheible, G.S. Martin, D.J. Murphy, S.C. Auld, Emory COVID-19 Quality and Clinical Research Collaborative, Timing of Intubation and Mortality Among Critically Ill Coronavirus Disease 2019 Patients: A Single-Center Cohort Study., Crit. Care Med. 48 (2020) e1045–e1053. https://doi.org/10.1097/CCM.0000000000004600.

[35] J.B. Hyman, E.S. Leibner, P. Tandon, N.N. Egorova, A. Bassily-Marcus, R. Kohli-Seth, V. Arvind, H.L. Chang, H.-M. Lin, M.A. Levin, Timing of Intubation and In-Hospital Mortality in Patients With Coronavirus Disease 2019., Crit. Care Explor. 2 (2020) e0254. https://doi.org/10.1097/CCE.0000000000000254.

[36] G.L. Calligaro, U. Lalla, G. Audley, P. Gina, M.G. Miller, M. Mendelson, S. Dlamini, S. Wasserman, G. Meintjes, J. Peter, D. Levin, J.A. Dave, N. Ntusi, S. Meier, F. Little, D.L. Moodley, E.H. Louw, A. Nortje, A. Parker, J.J. Taljaard, C.F.N. Koegelenberg, The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: A multi-centre prospective observational study., EClinicalMedicine. 28 (2020) 100570. https://doi.org/10.1016/j.eclinm.2020.100570.

[37] K.J. Goh, H.Z. Chai, T.H. Ong, D.W. Sewa, G.C. Phua, Q.L. Tan, Early prediction of high flow nasal cannula therapy outcomes using a modified ROX index incorporating heart rate., J. Intensive Care. 8 (2020) 41. https://doi.org/10.1186/s40560-020-00458-z.

[38] V.M. Ranieri, P.M. Suter, C. Tortorella, R. De Tullio, J.M. Dayer, A. Brienza, F. Bruno, A.S. Slutsky, Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome, JAMA. 282 (1999) 54. https://doi.org/10.1001/jama.282.1.54.

[39] G.F. Curley, J.G. Laffey, H. Zhang, A.S. Slutsky, Biotrauma and Ventilator-Induced Lung Injury: Clinical Implications., Chest. 150 (2016) 1109–1117. https://doi.org/10.1016/j.chest.2016.07.019.

[40] ATTACC ACTIV-4a & REMAP-CAP multiplatform RCT- Results of interim analysis , (2021). https://www.attacc.org/presentations (accessed March 5, 2021).

[41] R. Kohn, M.O. Harhay, G.E. Weissman, G.L. Anesi, B. Bayes, H. Song, S.D. Halpern, S.R. Greysen, M.P. Kerlin, The Association of Geographic Dispersion with Outcomes among Hospitalized Pulmonary Service Patients., Ann. Am. Thorac. Soc. 17 (2020) 249–252. https://doi.org/10.1513/AnnalsATS.201906-471RL.

[42] D.A. Asch, N.E. Sheils, M.N. Islam, Y. Chen, R.M. Werner, J. Buresh, J.A. Doshi, Variation in US Hospital Mortality Rates for Patients Admitted With COVID-19 During the First 6 Months of the Pandemic., JAMA Intern. Med. 181 (2021) 471–478. https://doi.org/10.1001/jamainternmed.2020.8193.

[43] L.I. Horwitz, S.A. Jones, R.J. Cerfolio, F. Francois, J. Greco, B. Rudy, C.M. Petrilli, Trends in COVID-19 Risk-Adjusted Mortality Rates., J. Hosp. Med. 16 (2021) 90–92. https://doi.org/10.12788/jhm.3552.

[44] C. Garcia-Vidal, A. Cózar-Llistó, F. Meira, G. Dueñas, P. Puerta-Alcalde, C. Cilloniz, N. Garcia-Pouton, M. Chumbita, C. Cardozo, M. Hernández, V. Rico, M. Bodro, L. Morata, P. Castro, A. Almuedo-Riera, F. García, J. Mensa, J. Antonio Martínez, G. Sanjuan, A. Torres, COVID-19-researcher group, Trends in mortality of hospitalised COVID-19 patients: A single centre observational cohort study from Spain., Lancet Reg. Health Eur. 3 (2021) 100041. https://doi.org/10.1016/j.lanepe.2021.100041.

Supplementary Material

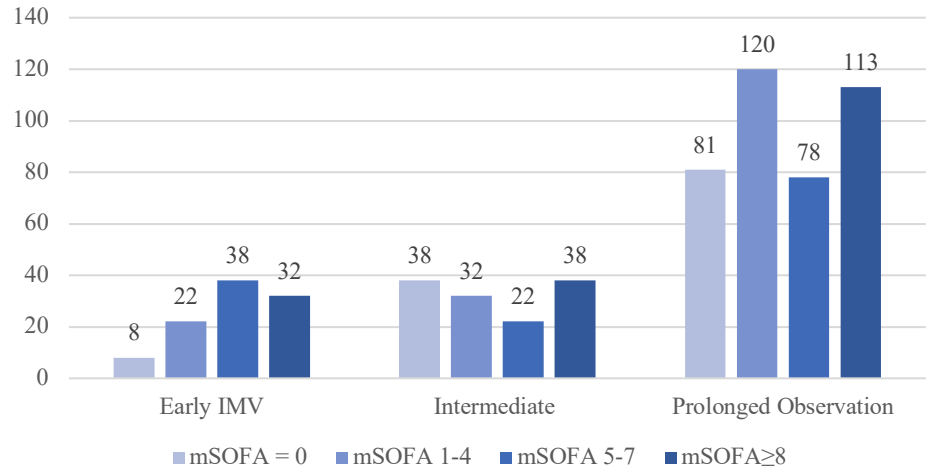


Figure 1. Distribution of modified SOFA (mSOFA) scores by ARF management strategy.

Abbreviations: mSOFA = modified Sequential Organ Failure Assessment (SOFA); ARF = acute respiratory failure; IMV = invasive mechanical ventilation.