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Assessing mortality differences across acute respiratory failure management strategies in Covid-19

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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.

1. 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

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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 in the initial surge of the pandemic, 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.

2. Methods

2.1. 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).

2.2. 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 following types of respiratory support due to hypoxia and/or work of breathing: ≥6 L 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. There were two senior physicians (attendings) for every 20 ICU patients, one of whom was an intensivist. Nursing staff were added to pre-existing critical care nursing teams and provided extensive training in ICU skills [21].

2.3. 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 6 L 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 6 L 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 judgment 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 and 8 cc/kg of ideal body weight (IBW) and a target plateau pressure of ≤30 cm H_20. Prone positioning was recommended for intubated patients in accordance with established guidelines [22,23].

2.4. 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 developed secondary bacterial respiratory infections and 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].

2.5. 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 h prior to developing ARF to identify the closest recorded mSOFA score. If no mSOFA score was calculated in the database in the 48 h prior to ARF, then we examined records in the 48 h 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 later studies demonstrating a mortality benefit associated with

dexamethasone use [27,28] Of note, these studies were not published during the time period considered in this analysis.

2.6. 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, secondary bacterial infection, and progression to tracheostomy among intubated patients were tested using chi-square tests, or alternatively 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.

3. Results

3.1. 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 (Fig. 1).

3.2. 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 ≥ 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 Fig. 2 and Fig. E1. Reflecting differences in ARF management strategies, 78.2% of patients in the early IMV group were intubated at the

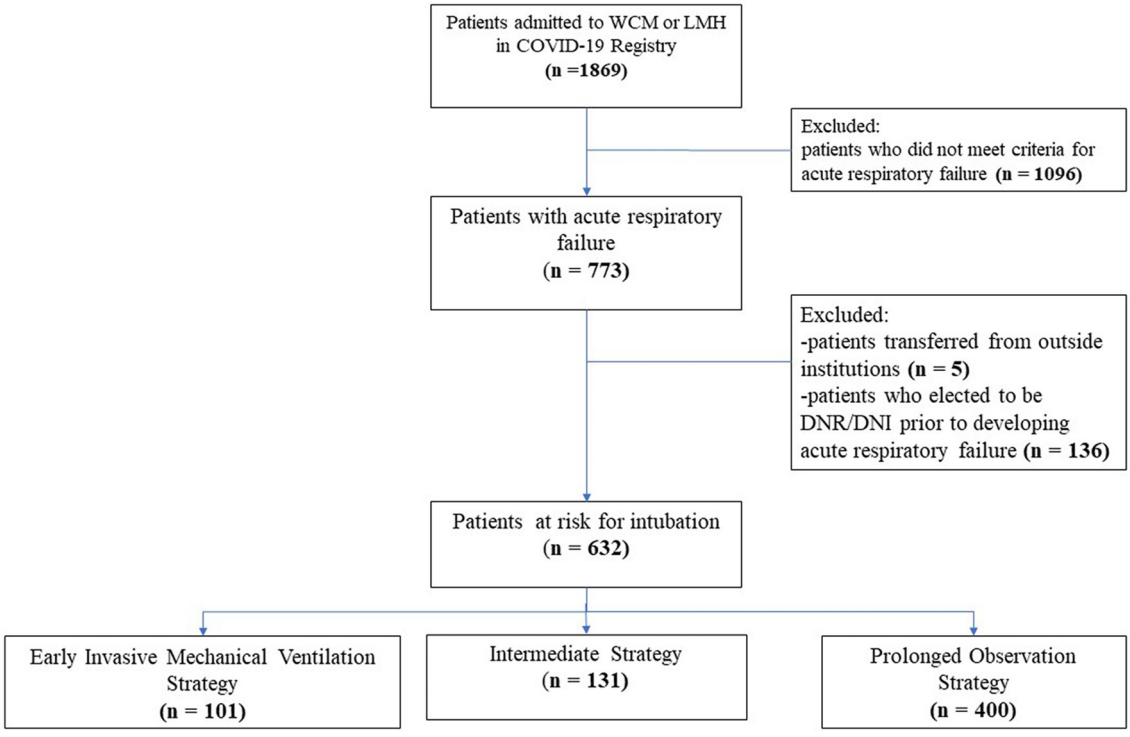

Fig. 1. Exclusionary cascade. This figure illustrates the identification of our cohort at risk for intubation.

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	2.1 (5.1)	5.5 (14.9)	6.5 (12.9)
Receipt of IL-6 inhibitors in-hospital, n(%)	13 (13)	11 (8)	55 (14)
Duration of IL-6 inhibitor therapy, mean (SD), days	0.4 (2.9)	0.2 (1.9)	0.5 (2.5)
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.

time of meeting criteria for ARF, decreasing 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 in the prolonged observation group [33].

3.3. 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% $p = 0.002$). 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, $p = 0.56$) comparing prolonged observation to early-IMV. An expanded model which included an interaction term between mSOFA score and ARF management strategy ($p = 0.003$) demonstrated a heterogenous effect such that 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, $p = 0.005$) 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 Fig. 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 ($p = 0.09$).

3.4. 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, $p = 0.003$).

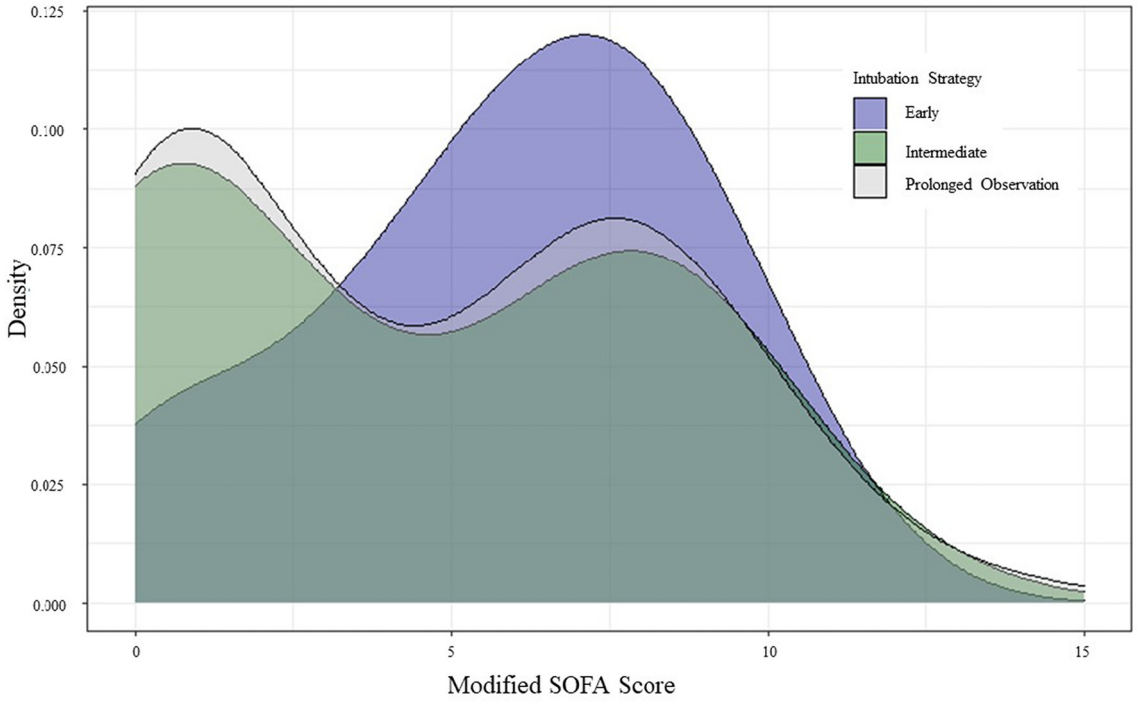

Fig. 2. SOFA score distribution by ARF management strategy. This figure illustrates the distribution of modified SOFA score by ARF management strategy (intubation strategy). The purple corresponds to patients in the early IMV group, green to the intermediate group, and grey to the prolonged observation group. Overlapping distributions are presented by a mix of colors.

4. 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 h, 8–24 h, and greater than 24 h. 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.

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)	33 (40)	35 (53)	74 (35)	0.02
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.

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.

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

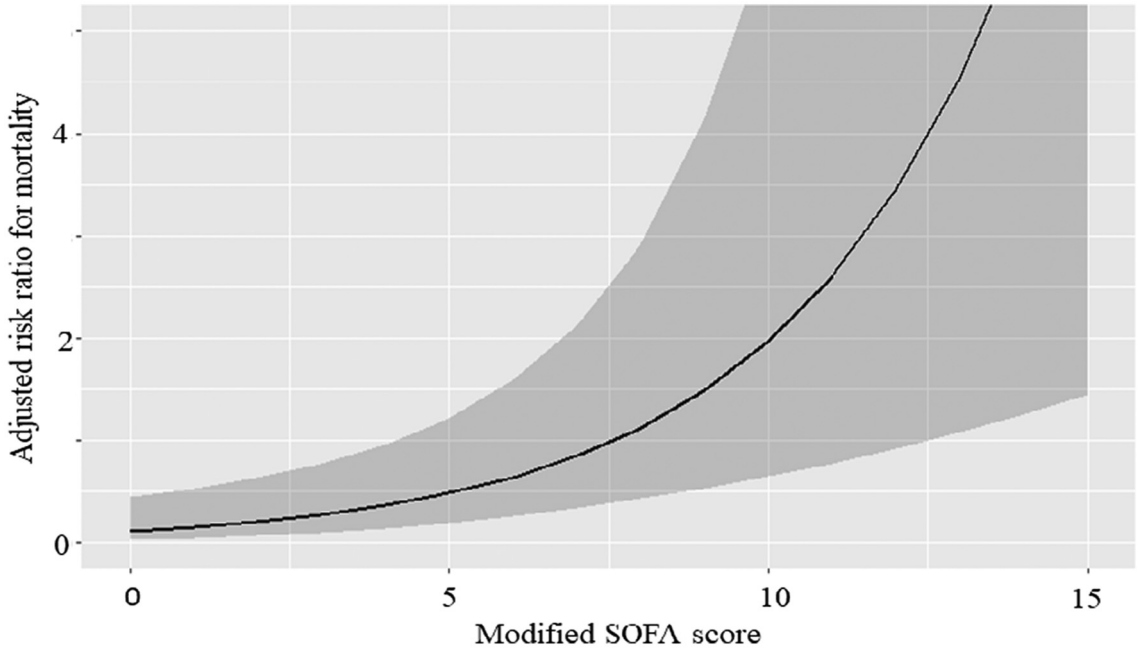

Fig. 3. Hazard ratio for in-hospital mortality comparing the prolonged observation strategy to the early invasive mechanical ventilation strategy by modified SOFA score. This figure plots the adjusted hazard ratio for mortality comparing the prolonged observation strategy versus the early IMV strategy as a function of the modified SOFA score. The shaded grey areas are the point-wise 95% confidence intervals.

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 median 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 median plateau pressure was 24.0 cm H_20 (20.0–28.0) [22].

Our results should be interpreted 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 [40]. 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 [41-43]. It is possible that the unmeasured confounders leading to this decline complicate the association between ARF management strategy and in-hospital mortality. Additional unmeasured confounders include differences in frailty, performance status, nurse staffing ratios, and receipt of physical therapy which may have led to differences in mortality over time, independent of the ARF management strategy. 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.

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.

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.

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Summary conflict of interest statements

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Appendix A. Supplementary data

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