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CHEST

Critically Ill Adults With Coronavirus Disease 2019 in New Orleans and Care With an Evidence-Based Protocol

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BACKGROUND: Characteristics of critically ill adults with coronavirus disease 2019 (COVID-19) in an academic safety net hospital and the effect of evidence-based practices in these patients are unknown.

RESEARCH QUESTION: What are the outcomes of critically ill adults with COVID-19 admitted to a network of hospitals in New Orleans, Louisiana, and what is an evidence-based protocol for care associated with improved outcomes?

STUDY DESIGN AND METHODS: In this multi-center, retrospective, observational cohort study of ICUs in four hospitals in New Orleans, Louisiana, we collected data on adults admitted to an ICU and tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between March 9, 2020 and April 14, 2020. The exposure of interest was admission to an ICU that implemented an evidence-based protocol for COVID-19 care. The primary outcome was ventilator-free days.

RESULTS: The initial 147 patients admitted to any ICU and tested positive for SARS-CoV-2 constituted the cohort for this study. In the entire network, exposure to an evidence-based protocol was associated with more ventilator-free days (25 days; 0-28) compared with non-protocolized ICUs (0 days; 0-23, $P = .005$), including in adjusted analyses ($P = .02$). Twenty patients (37%) admitted to protocolized ICUs died compared with 51 (56%; $P = .02$) in non-protocolized ICUs. Among 82 patients admitted to the academic safety net hospital's ICUs, the median number of ventilator-free days was 22 (interquartile range, 0-27) and mortality rate was 39%.

INTERPRETATION: Care of critically ill COVID-19 patients with an evidence-based protocol is associated with increased time alive and free of invasive mechanical ventilation. In-hospital survival occurred in most critically ill adults with COVID-19 admitted to an academic safety net hospital's ICUs despite a high rate of comorbidities. CHEST 2021; 159(1):196-204

KEY WORDS: ARDS; COVID-19; critical care

FOR EDITORIAL COMMENT, SEE PAGE 7

ABBREVIATIONS: COVID-19 = coronavirus disease 2019; NIPPV = noninvasive positive-pressure ventilation; PEEP = positive end-expiratory pressure; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VFD = ventilator-free day

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected millions worldwide and caused coronavirus disease 2019 (COVID-19) in hundreds of thousands.[1] COVID-19 is associated with a high rate of critical illness, morbidity, and mortality.[2]Click or tap here to enter text. Specifically, acute respiratory failure requiring respiratory support, the development of ARDS, acute kidney injury, and shock are common in critically ill adults with COVID-19.[3,4] Outcomes of critically ill adults with COVID-19 admitted to an academic safety net hospital are unknown.

The syndromes caused by COVID-19, specifically acute respiratory failure and ARDS, have evidence- and guideline-based management recommendations. First, in some patient populations the use of certain respiratory support devices, such as noninvasive positive-pressure ventilation (NIPPV), decrease the need for tracheal intubation[5-8] and is recommended for consideration in patients with COVID-19.[9] Second, if patients do require endotracheal intubation and develop ARDS, the provision of low tidal volume ventilation,[10] and a conservative fluid management strategy[11] improve the number days alive and free of invasive mechanical ventilation. If ARDS is moderate to severe, treatment with prone positioning[12,13] and higher amounts of positive end-expiratory pressure (PEEP)[12,14] may improve survival. When patients with respiratory failure have improved, liberation from sedatives[15] and invasive ventilation by providing support with NIPPV may decrease the need for reintubation.[16] However, some have argued against using these interventions in critically ill adults with COVID-19 because of unknown effectiveness and potential harm.[17,18]

We conducted a retrospective, cohort, observational study of critically ill adults with COVID-19 admitted to a network of four hospitals. Some ICUs in this network implemented an evidence-based pilot protocol that provided guidance on the management of the patient with acute respiratory failure and ARDS. We hypothesized that protocol implementation would be associated with increased ventilator-free days in critically ill adults with COVID-19.

Methods

Study Design and Oversight

We conducted a retrospective cohort study of all initial patients admitted to a group of four hospitals in New Orleans, Louisiana, who were critically ill and tested positive for SARS-CoV-2 between March 9, 2020 and April 14, 2020. The study was approved with a waiver of informed consent by the institutional review board at Louisiana State University School of Medicine New Orleans.

Study Sites and Patient Population

The retrospective study was conducted using quality improvement data collected by a network of four hospitals located in New Orleans, Louisiana. The study population consisted of the first 147 critically ill adults who were admitted to any ICU in the network of hospitals and had a positive nasopharyngeal swab for SARS-CoV-2. The current observational study was conducted with data entered into the database at the time of analysis and consisted of patients admitted to any ICU from March 9, 2020 through April 14, 2020. At the time of submission, 28-day hospital vital status or discharge status was known on all patients. Seven patients remain alive and hospitalized beyond 28 days. Data included demographics, co-morbidities, laboratory values, ventilator parameters, medication administration, and in-hospital clinical outcomes.

As a potential quality improvement initiative and during the observational period, two ICUs located in an academic, safety-net hospital within the network implemented an evidence-based pilot protocol to guide the care of the critically ill adult with COVID-19 (e-Appendix 1). The feasibility, effectiveness, and resource availability aspects of this protocol were unknown, specifically related to the use of noninvasive positive-pressure ventilation; therefore, implementation occurred in two ICUs during the observational period before expanding to all ICUs. This protocol consisted of guidance on the management of all phases of acute respiratory failure, including the prevention of tracheal intubation, applying evidence-based ARDS care to intubated patients, and guidance on extubation. Protocol development occurred via an iterative process of literature review regarding the care of the ARDS patient, protocol development meetings with stakeholders, and development of bedside algorithms. Implementation of this protocol occurred via dissemination of these algorithms to bedside providers in the pilot ICUs, teaching of the evidence supporting recommendations, multiple daily checks by protocol champions to ensure adherence, and institutional oversight. The pilot protocol was available to all ICUs in the network; however, the implementation described here only occurred in selected ICUs. None of the ICUs in the network had specific criteria for ICU admission. All ICUs in the network of hospitals had daytime staffing by board-certified intensivists; however, few ICUs had house staff or advanced-practice practitioners, and none had electronic ICU coverage.

Study Outcomes and Statistical Analysis

The primary comparison in this cohort study was between patients admitted to an ICU that implemented the pilot care protocol vs patients admitted to an ICU that did not undergo implementation during the observation period. The primary analysis in this cohort was ventilator-free days, calculated by 28 minus the number of days the patient was tracheally intubated, with a value of zero assigned to patients who died in the hospital. Ventilator-free days (VFDs) was chosen as the primary outcome, because this is a well-validated, patient-centered outcome commonly chosen in studies of acute respiratory failure.[10,11,19,20] Secondary outcomes included 28-day in-hospital mortality, need for tracheal intubation, and need for renal replacement therapy. We also analyzed the primary outcome of VFDs and processes of care over the course of the observational period to see whether this outcome improved over time. Finally, given we only had access to data that were already entered into this

database and could not exclude the possibility of patients not yet entered into the database late in the observation period, we performed a sensitivity analysis for the primary outcome of VFDs restricted to patients admitted in the first calendar month since the diagnosis of the index ICU patient.

Most data were not normally distributed and, therefore, were reported as median values with interquartile range for continuous variables and frequencies for categorical variables. Univariate analyses of continuous variables were conducted with Mann-Whitney *U* tests and χ^2 tests for categorical variables. A linear regression model was also used to analyze the dependent variable of VFDs with the independent variables of pilot protocol implementation, APACHE II score, age, and the ratio of Pao_2/Fio_2 on ICU admission. One-way repeated measures analysis of variance was used to compare groups regarding repeated measures over time. IBM SPSS Statistics (version 25) was used for statistical analysis. A two-sided significance value of .05 was used for statistical significance. The STROBE Guidelines for Reporting Observational Studies were followed in drafting this manuscript.[21]

Results

Baseline Characteristics

Of 214 critically ill adults who were admitted to a network ICU and tested for SARS-CoV-2 during the observation period, 147 patients tested positive and constituted the primary cohort for the current analysis (Fig 1). Regarding patients exposed to protocol implementation or not, there were statistically significant imbalances in location before ICU admission, asthma, and end-stage renal disease. Laboratory values on ICU admission were not statistically significantly different other than a lower Pao_2/Fio_2 ratio in patients not exposed to protocol implementation (Table 1).

Management in ICUs with Pilot Protocol Implementation

A total of 14 (25%) patients in the pilot protocol group never required intubation compared with 16 (17%, $P = .15$) patients admitted to ICUs without pilot protocol implementation. In patients never requiring intubation and in pilot protocol ICUs, 57% were supported with noninvasive positive pressure ventilation (e-Table 1). In intubated patients, there was no statistically significant difference in tidal volumes provided, Fio_2 to PEEP ratio, or receipt of prone positioning over the first 5 days of ICU care (e-Figs 1, 2, 3). Patients cared for in ICUs undergoing protocol implementation received higher mean daily doses of furosemide over the first 5 days of ICU care ($P = .005$) (e-Fig 4). At the time of extubation, 57% of patients were extubated to noninvasive positive pressure ventilation (Table 2).

Primary Outcome

The median number of VFDs in patients exposed to pilot protocol implementation was 25 days (0-28) compared with 0 days (0-23, $P = .005$) in patients not exposed to pilot protocol implementation (Table 2). Pilot protocol

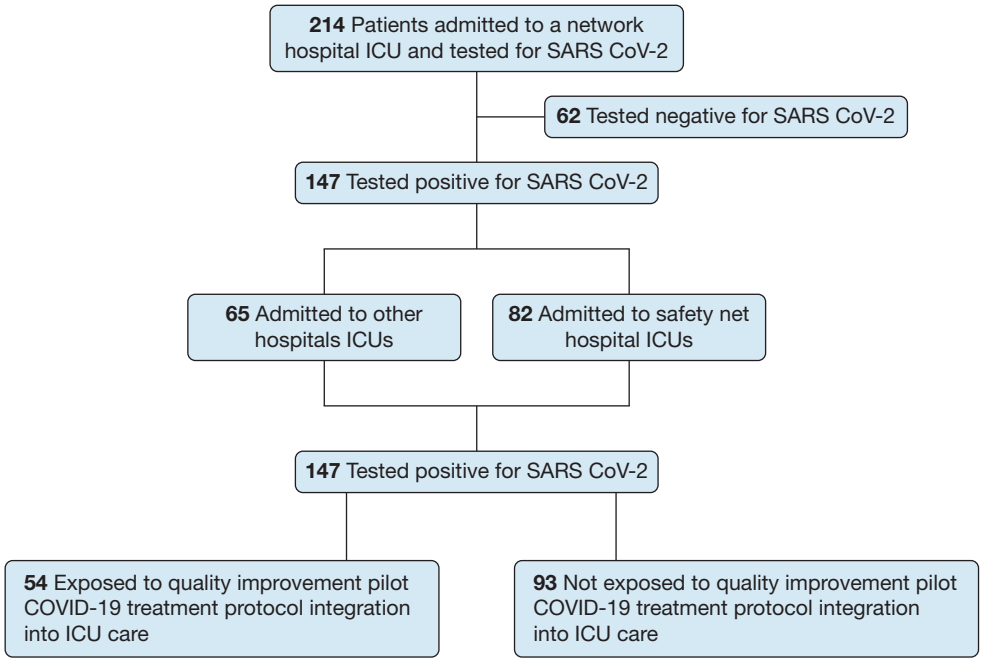

Figure 1 – *Study flow diagram.*

TABLE 1] Baseline Characteristics

Characteristic	Safety Net Hospital SARS CoV-2 + ICU Patients (n = 82)	Network ICUs with Quality Improvement Pilot Protocol Implementation (n = 54)	Network ICUs without Quality Improvement Pilot Protocol Implementation (n = 93)	*P* (Comparison Between Pilot Protocol Groups)
Age, y	61 (50-71)	62 (50-74)	65 (54-76)	.25
Men, No. (%)	38 (46%)	25 (46%)	46 (49%)	.71
African American, No. (%)	77 (93%)	51 (94%)	75 (80%)	.12
BMI	35 (30-43)	35 (29-41)	32 (28-38)	.24
APACHE II Score	13 (10-18)	12 (9-16)	15 (9-20)	.09
SOFA Score	4 (2-6)	4 (3-5)	4 (3-6)	.43
Location Before ICU Admission, No. (%)				.003
ED	44 (53%)	32 (59%)	38 (40%)	
Hospital floor	35 (42%)	19 (35%)	55 (59%)	
Outside-of-network hospital	3 (3%)	3 (5%)	0	
Comorbidities, No. (%)				
Hypertension	71 (86%)	45 (83%)	70 (75%)	.25
Diabetes mellitus	47 (57%)	29 (53%)	43 (46%)	.45
Cardiovascular disease	29 (35%)	16 (29%)	30 (32%)	.76
Heart failure	16 (19%)	9 (16%)	14 (15%)	.81
Solid malignancy	7 (8%)	4 (7%)	14 (15%)	.16
COPD	15 (18%)	11 (20%)	9 (9%)	.08
Asthma	19 (23%)	14 (25%)	9 (9%)	.01
Chronic kidney disease	22 (26%)	14 (25%)	28 (30%)	.56
End-stage renal disease	3 (3%)	0	9 (9%)	.01
Chronic liver disease	2 (2%)	2 (3%)	2 (2%)	.58
Laboratory data on ICU admission				
D-dimer (n = 67)	483 (250-948)	469 (278-867)	332 (4-1330)	.32
Ferritin (n = 81)	678 (345-1524)	556 (220-1359)	695 (408-2108)	.06
C-reactive protein (n = 86)	15.8 (11.4-22.2)	15.4 (12.1-22.2)	16.1 (11.1-24.6)	.92
WBC count (n = 136)	9.3 (7.3-12)	8.9 (7.2-12.3)	9.05 (6.25-12.47)	.79
Absolute neutrophil count (n = 116)	7,500 (5,500-9,840)	7,550 (5,375-10,600)	7,235 (5,277-10,225)	.76
Absolute lymphocyte count (n = 116)	915 (700-1,325)	940 (700-1,410)	920 (670-1,400)	.6

(Continued)

TABLE 1] *(Continued)*

Characteristic	Safety Net Hospital SARS CoV-2 + ICU Patients (n = 82)	Network ICUs with Quality Improvement Pilot Protocol Implementation (n = 54)	Network ICUs without Quality Improvement Pilot Protocol Implementation (n = 93)	*P* (Comparison Between Pilot Protocol Groups)
Neutrophil to lymphyocyte ratio (n = 113)	7.1 (4.6-11.4)	6.8 (4.4-10.5)	8 (4.6-12.6)	.3
Creatinine kinase (n = 67)	181 (89-564)	164 (88-403)	342 (91-896)	.28
BUN (n = 136)	20 (14-42)	19 (13-39)	26 (13-42)	.46
Creatinine (n = 136)	1.26 (0.93-1.88)	1.25 (0.83-1.71)	1.31 (0.95-2.25)	.29
Lactate dehydrogenase (n = 69)	416 (315-513)	428 (307-520)	451 (372-634)	.1
Triglyceride (n = 17)	138 (84-327)	138 (84-327)	134 (93-250)	.84
Fibrinogen (n = 10)	700 (700-700)	700 (700-700)	666 (412-700)	.23
Pao_2/Fio_2 (n = 99)	112 (78-199)	116 (94-265)	101 (55-154)	.02

Data given as median (25th percentile-75th percentile) or number (percentage) of patients. *P* value = Mann-Whitney *U* test for continuous variables, χ^2 test for categorical variables, and χ^2 test for a trend for categorical variables with more than two groups.
APACHE = acute physiology and chronic health evaluation; SOFA = Sequential Organ Failure Assessment.

implementation remained associated with increased VFDs after adjustment for APACHE II score alone (P = .007; Fig 2) and after adjustment for APACHE II score, age, and Pao_2/Fio_2 on ICU admission (P = .02) (e-Table 2). In a sensitivity analysis restricted to the first calendar month of ICU admissions for COVID-19, pilot protocol implementation remained associated with increased VFDs (23 days, 0-27) compared with no pilot protocol implementation (0 days, 0-22) in both unadjusted (P = .03) and adjusted analyses for APACHE II score, age, and Pao_2/Fio_2 ratio on ICU admission (beta, 5.28; 95% CI, 0.1-10.4; P = .04).

TABLE 2] Clinical Outcomes

Outcome	Safety Net Hospital SARS CoV-2 + ICU Patients (n = 82)	Network ICUs With Quality Improvement Pilot Protocol Implementation (n = 54)	Network ICUs Without Quality Improvement Pilot Protocol Implementation (n = 93)	Relative Risk (95% Confidence Interval)	*P* (Comparing Protocol Implementation Groups)
Ventilator-free days	22 (0-27)	25 (0-28)	0 (0-23)		.005
In-hospital mortality, No. (%)	32 (39%)	20 (37%)	51 (56%)	0.67 (0.48-0.94)	.02
In-hospital mortality in only patients ever tracheally intubated (n = 111), No. (%)	30 (50%)	18 (47%)	50 (68%)	0.68 (0.47-0.99)	.03
Need for renal replacement therapy, No. (%)	22 (26%)	8 (14%)	36 (38%)	0.38 (0.19-0.76)	.002

Data given as median (25th percentile-75th percentile) or number (percentage) of patients.
P = Mann-Whitney *U* test for continuous variables and χ^2 test for categorical variables.

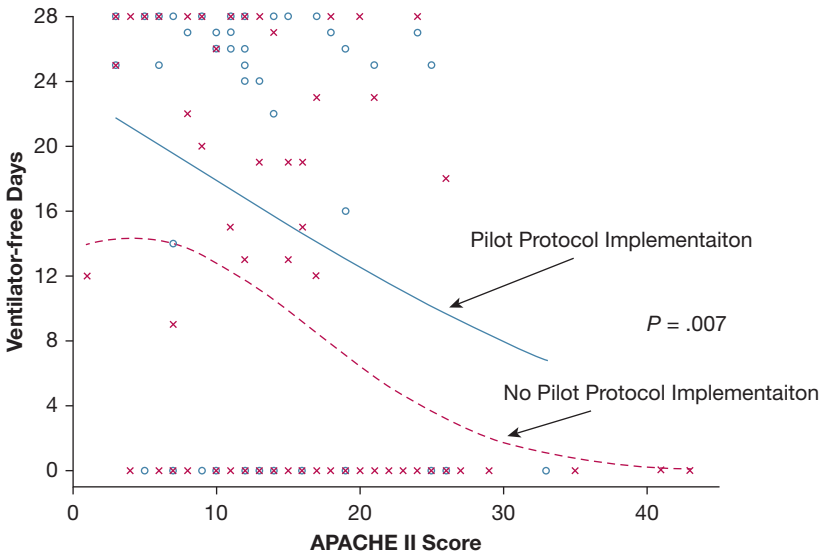

Figure 2 – *Ventilator-free days adjusted for APACHE II score on ICU admission. For every increase in APACHE II score, pilot protocol implementation was always associated with increased ventilator-free days.* P-*value represents result of a linear regression analysis with the dependent variable as ventilator-free days and the independent variables of pilot protocol implementation* (P = .007) *and APACHE II score.*

Secondary Outcomes

Exposure to pilot protocol implementation was associated with a decreased 28-day in-hospital mortality for all comers (37% vs 56%; $P = .02$) as well as for those who required invasive mechanical ventilation (47% vs 68%; $P = .03$). Pilot protocol implementation was also associated with a reduction in need for any type of renal replacement therapy (14% vs 38%; $P = .002$) (Table 2).

Regarding the entire cohort of the initial 147 patients admitted to any network ICU, VFD increased over time from the date of the first SARS-CoV-2 positive diagnosis until the end of the observation period (e-Fig 5). Over this same period, severity of illness on ICU admission did not significantly decrease (e-Fig 6). Process of care measures that improved over this period include increasing amounts of PEEP for respective Fio_2 provision (e-Fig 7), decrease in tracheal intubations, and an increase in use of NIPPV before intubation or if never intubated in pilot protocol implementation ICUs (Fig 3). There was no significant change in the provision of tidal volumes nor in mean cumulative furosemide dosing over this period (e-Fig 8). In pilot protocol implementation ICUs with the highest rates of NIPPV use, only one nurse is known to have tested positive for SARS-CoV-2.

Characteristics of Patients Admitted to the Network Safety-Net Hospital

A total of 82 patients were admitted to ICUs in the Network's academic safety net hospital. Patients admitted to this academic safety net hospital had a median age of 61 years (50-71) with a BMI of 35 (30-43), and 93% were African American. Additionally, patients admitted to this academic safety net hospital had high rates of hypertension (86%) and diabetes mellitus (57%) (Table 1). In these 82 patients, the median number of ventilator-free days was 22 (interquartile range, 0-27), and the mortality rate was 39% (Table 2).

Discussion

Most critically ill adults with COVID-19 admitted to an academic safety net hospital survived to hospital discharge, and 21% never required tracheal intubation. Implementation of a pilot patient care protocol was associated with significantly more ventilator-free days and higher survival. Ventilator-free days increased over the duration of the observation, along with an increase in NIPPV use, higher PEEP, and decreased tracheal intubation rates. To our knowledge, this is the first description of the outcomes of patients with COVID-19 patients in an academic safety net hospital and of the associated treatment effect of evidence- and guideline-based interventions for patients with ARDS in a population with COVID-19.

Safety net hospitals, defined as those that by obligation or mission provide health care to patients regardless of insurance status or ability to pay, are commonly also academic hospitals and frequently care for a patient population with high rates of co-morbidities.[22,23] We observed these same high rates of co-morbidities in the patient population admitted to the academic safety net hospital during this study. However, most of these critically ill patients with COVID-19 had good clinical

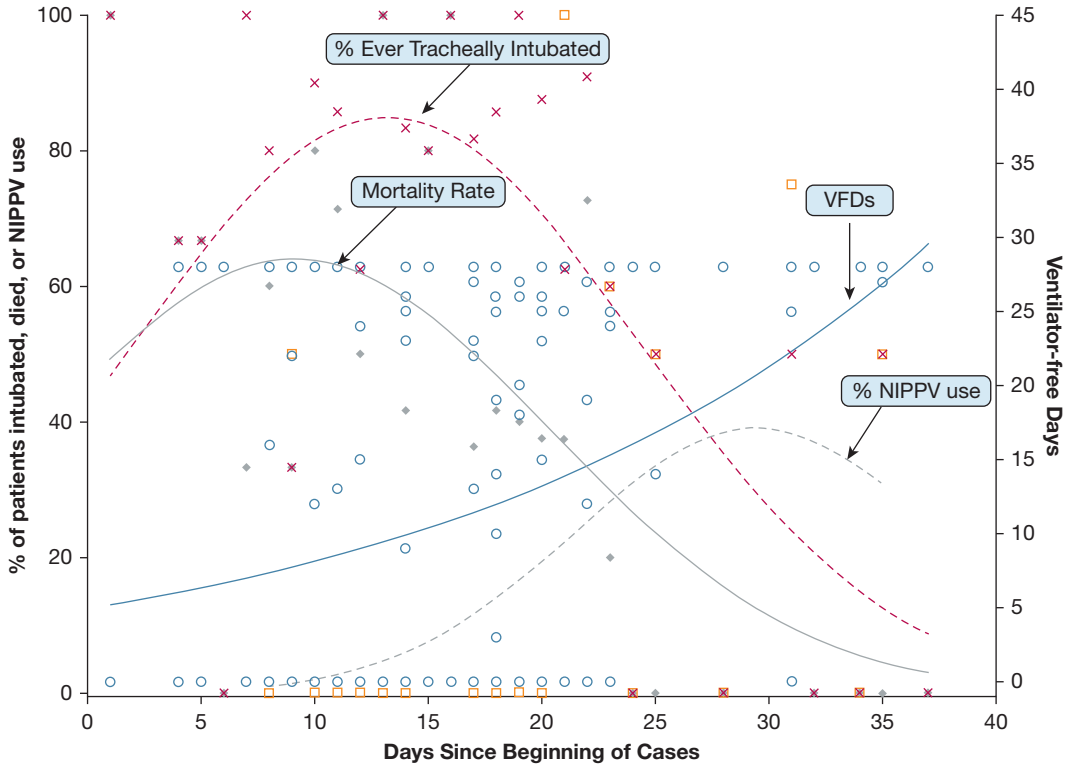

Figure 3 – *Number of ventilator-free days along with incidence of tracheal intubation, mortality, and non-invasive ventilation use to prevent intubation over time. Day of admission to an ICU is displayed on the x-axis. Ventilator-free days are displayed on the right y-axis. Incidence of tracheal intubation, death, and noninvasive positive pressure use to prevent intubation is displayed on the left y-axis. The solid and dashed lines represent Gaussian distribution lines. Over the course of the observation period, rates of intubation based on day of ICU admission rose initially and then decreased in the latter half of the observation period. Rates of NIPPV use were low in patients admitted to the ICU at the outset of the observation and increased in patients admitted over time. Mortality rates were highest in patients admitted to the ICU early in the observation and decreased in patients admitted to the ICU later in the observational period. NIPPV = noninvasive positive-pressure ventilation in pilot protocol group; VFDs = ventilator-free days.*

outcomes such as survival to hospital discharge. The cause of the improved outcomes in this patient population is unknown. Mortality rates from the current study are not directly comparable to reported mortality rates in other studies of COVID-19, because the number of measured and unmeasured differences between geographically separate hospitals are numerous.

At the time of this observational study, there were no treatments of SARS-CoV-2 known to cause an improvement in patient-centered outcomes. However, there were numerous evidence- and guideline-based interventions that have been used for decades in critical care to improve outcomes in patients with the syndrome caused by COVID-19, such as acute respiratory failure and ARDS. Support of respiratory failure with NIPPV has been shown to prevent intubation in a number of patient populations.[5,6,8,24] Decreased mortality and ventilator utilization have occurred in past trials of low tidal volume ventilation, a conservative fluid management strategy, prone positioning, application of higher amounts of PEEP, spontaneous awakening and breathing trials, and use of NIPPV at the time of extubation. As part of a quality improvement initiative to increase our surge capacity of ventilators and ICU rooms and improve outcomes of patients with COVID-19, guidance was created based on this evidence and implemented as a pilot protocol in a subgroup of ICUs. As previously noted, the pilot protocol was available to all ICUs in the network but only underwent implementation in selected ICUs. The availability of the protocol to all ICUs should have biased our results toward the null; however, a statistically significant associated effect remained despite this bias.

The current study describes the association between pilot protocol implementation and increased VFDs in patients with COVID-19, whether this protocol caused improved outcomes is unknown. Which aspects of the protocol may have provided benefit to patients and which aspects had little effect are also unknown. We observed an increase in the number of VFDs over time

in all network ICUs since the index case, despite no apparent decrease in measures of severity of illness over the same period. Regarding protocol items based on the evidence listed, provision of low tidal volume ventilation did not improve over time. However, low tidal volume ventilation was provided to most of the patients regardless of protocol guidance. Cumulative daily furosemide dose also seems unlikely to explain the effect of increasing VFDs over time. Protocol-recommended items that did increase over the observation period included the level of PEEP, avoidance of tracheal intubation, and use of NIPPV before intubation or if never intubated.

Although some have recommended avoidance of respiratory support devices such as NIPPV because of potential risk of aerosolization of SARS-CoV-2,[17] the risk of transmission of SARS-CoV-2 to health-care providers caring for patients receiving NIPPV is unknown.[9]Click or tap here to enter text. In the current study, only one nurse and no respiratory therapists in the ICUs with the highest rate of NIPPV use are known to have tested positive for SARS-CoV-2.

The current study has a number of limitations. First, the observational nature of the study may introduce selection and other biases into the analyses that were incompletely controlled for in adjusted analyses. Second, there may have been unmeasured differences between groups other than pilot protocol implementation, because this observation occurred across a network of hospitals serving different patient populations, albeit in a geographic region experiencing rapid increases in patients presenting with COVID-19. The analyses of changes of processes of care and outcomes over time were not comparative, but rather descriptive, and we are unable to make inferences of the effect of higher amounts of NIPPV use and PEEP on improved outcomes. The observational nature of the study limits our ability to say with confidence that the protocol is effective and which aspects of the protocol provided the greatest benefit. The limited number of regression analyses performed in this study raises the possibility of a type I error. Finally, the analysis was conducted using existing data in the database and cannot account for the possibility of patients not yet entered into the database late in the observation period. In a sensitivity analysis to attempt to account for this limitation, we eliminated approximately the last third of the observation period, which has a lower density of patients and encompasses a new calendar month. In this sensitivity analysis, the statistically significant association between pilot protocol implementation and VFDs remained in both unadjusted and adjusted analyses.

Conclusions

An academic safety net hospital caring for critically ill adults with COVID-19 and high rates of co-morbidities achieved in-hospital survival in most patients. Additionally, a care strategy of using NIPPV to avoid intubation and evidence-based ARDS management strategies applied, if intubated, may be safe for health-care workers and is associated with improved patient-centered outcomes. Future study is needed to confirm that this associated effect is consistent in a larger cohort over time.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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