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Comparative Evaluation of Risk of Death in Mechanically Ventilated Patients With COVID-19 and Influenza: A Population-Based Cohort Study

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Abstract

Background: Reports on the comparative mortality among mechanically ventilated patients with coronavirus disease 2019 (COVID-19) and influenza show conflicting findings, but studies focused largely on the early phase of the pandemic, using historical influenza comparators. We sought to examine the population-level comparative mortality among mechanically ventilated patients with COVID-19 during the latter pandemic years using contemporaneous influenza comparators.

Methods: We used a statewide dataset to identify mechanically ventilated hospitalizations aged ≥ 18 years with COVID-19 or influenza in Texas between October 2021 and March 2023. Their comparative short-term mortality (in-hospital death or discharge to hospice) was estimated using overlap propensity score weighting (primary model), entropy balance, and hierarchical logistic models.

Results: Among 22,195 mechanically ventilated hospitalizations, 19,659 (88.6%) had COVID-19 and 2,536 (11.4%) had influenza. Compared to mechanically ventilated hospitalizations with influenza, those with COVID-19 were more commonly racial or ethnic minority (49.3% vs. 48.4%) and had lower mean (standard deviation (SD)) Deyo comorbidity index (2.04 (2.03) vs. 2.53 (1.91)), but higher number of organ dysfunctions (2.60 (1.37) vs. 2.13 (1.27)), respectively. Short-term mortality among mechanically ventilated hospitalizations with COVID-19 and influenza was 49.1% vs. 20.7%. The risk of short-term mortality was attenuated but remained higher among hospitalizations with COVID-19 in the primary model (adjusted risk ratio: 1.24 (95% confidence interval (CI): 1.18 - 1.30); adjusted risk difference 8.8% (95% CI: 6.7 - 10.4)), with consistent findings in alternative models, subgroups, and sensitivity analyses.

Conclusions: Population-level short-term mortality among mechanically ventilated hospitalizations with COVID-19 has been higher than that among those with influenza during the latter years of the pandemic.

Keywords: COVID-19; Influenza; Mechanical ventilation; Mortality

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has resulted in a tremendous global morbidity and mortality toll [1]. In the United States (USA), by the time of the official declaration of the end of the public health emergency phase of the pandemic in May 2023 [2], the national mortality toll of COVID-19 infections was over 1 million deaths [3]. Nevertheless, there has been substantial decline in mortality of patients with COVID-19 during the pandemic years [4], including among hospitalized patients [5, 6].

Prior to the COVID-19 pandemic, influenza was the most common cause of hospitalization and mortality due to respiratory viral infections in the USA [7], with annual estimates of hospitalizations and deaths up to 700,000 and 51,000, respectively, during the prepandemic decade [8]. However, there has been dramatic decrease in influenza activity worldwide during the 2020 - 2021 influenza season [9], precluding even national estimates of the number of influenza-related hospitalizations and deaths in the USA during that period [8]. Because both infections share common risk factors and clinical, predominantly respiratory, manifestations [10], numerous studies sought to examine their comparative mortality burden, generally showing higher mortality rates among hospitalized patients with COVID-19 compared to those with influenza [11, 12], including during the latter years of the pandemic [5, 13].

Hospitalized patients with COVID-19 and influenza can present with or subsequently develop severe respiratory failure requiring mechanical ventilation, which has been associated with exceedingly high mortality among the former [14]. Thus, not unexpectedly, mortality among patients with COVID-19 was reported to be driven by those requiring mechanical ven-

tilation [15, 16]. However, the evidence on the comparative outcomes of mechanically ventilated patients with COVID-19 and influenza shows conflicting findings, with COVID-19 patients reported to have higher [17, 18], lower [19, 20], or similar [21, 22] mortality rates compared to those with influenza. Comparisons across these studies and their generalizability are hampered by common monocentric design, small cohort size, limitations of analytical approach and, importantly, by use of historical rather than contemporaneous influenza comparators, as well as predominant focus on the early phase of the pandemic. Thus, these studies may not be representative of the more contemporaneous comparative outcomes of mechanically ventilated patients with COVID-19 vs. influenza, given the substantial decrease in mortality among patients with COVID-19 [4-6], reflecting the interplay between evolving intrinsic viral virulence, growing infection- and vaccine-related population immunity, availability of antiviral and immunomodulatory agents, and advances in the care of severely ill patients over time.

Although COVID-19 is no longer considered a public health emergency in the USA [2], it remains a leading cause of respiratory viral hospitalizations [23], and nearly 77,000 COVID-19-related deaths were reported in 2023 [24]. It is, however, unknown whether the short-term outcomes of mechanically ventilated patients with COVID-19 have become comparable to those with other common respiratory viral infections, such as influenza. These data can inform health policy and resource allocation, clinician decision-making, and serve as benchmarks for preventive and interventional efforts to mitigate the toll of COVID-19 in this population subset. We sought to examine the population-level short-term mortality among mechanically ventilated patients with COVID-19 compared to contemporaneous counterparts with influenza.

Materials and Methods

Study design and data sources

This was a retrospective, population-based cohort study. Because we used a publicly available, deidentified dataset, the study was determined to be exempt from formal review by the Texas Tech Health Sciences Center Institutional Review Board. The reporting of the study findings follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines on reporting observational studies in epidemiology [25].

We used the Texas Inpatient Public Use Data File (TIPUDF) to identify the target population. In brief, the TIPUDF is an administrative dataset maintained by the Texas Department of State Health Services [26] and includes inpatient discharge data from state-licensed, non-federal hospitals, and captures approximately 97% of all hospital discharges in the state.

The information on diseases and procedures in the dataset is based on International Classification of Diseases codes. Thus, the TIPUDF does not contain clinical information, such as patients' clinical condition at the time of initiation of mechanical ventilation, indications for mechanical ventilation, ventilation strategies and settings, or physiological data.

Study population

We have identified hospitalizations aged 18 years or older requiring mechanical ventilation in acute care hospitals with a diagnosis of COVID-19 or influenza between October 1, 2021, and March 31, 2023. Mechanical ventilation was defined by the International Classification of Diseases, 10th Revision (ICD-10) procedure codes 5A1935Z, 5A1945Z, and 5A1955Z. Hospitalizations with COVID-19 were identified by ICD-10 code U071 [17, 27, 28] and those with influenza by ICD-10 codes J09x, J10x, and J11x [22, 27, 29, 30]. We have excluded hospitalizations related to pregnancy (n = 86) and those with diagnosis codes for both COVID-19 and influenza (n = 279). In addition, we excluded hospitalizations transferred from or discharged to another acute care hospital (n = 2,997) because these lacked data on complete hospital course [17, 18].

Outcome

The primary outcome was short-term mortality among mechanically ventilated hospitalizations. Short-term mortality was defined as the combination of in-hospital mortality or discharge to hospice. We selected this composite outcome because in-hospital mortality rates in the USA are known to be influenced by nonclinical variables, including hospital transfer practices [31, 32]. Specifically, discharges to hospice among hospitalized patients have progressively increased in the USA over the past decades and were associated with corresponding decrease in in-hospital mortality across broad categories of patients [33], which shifts attribution of death from index hospitalization to hospice [34]. These data suggest that in-hospital mortality rates can bias estimates across groups [35]. As a result, this composite outcome has been increasingly used in epidemiological studies [36, 37].

Risk-adjustment covariates

Risk-adjustment covariates were selected *a priori* based on biological and clinical plausibility and existing literature [38-43] and included patients' sociodemographic variables (age, gender, race/ethnicity, primary health insurance), coexisting conditions (conditions included in the Deyo modification of the Charlson comorbidity index [44, 45], obesity, tobacco use, alcohol use and substance use disorders), measures of illness severity, organ support interventions (hemodialysis and extracorporeal membrane oxygenation (ECMO)), do-not-resuscitate status (ICD-10 code Z66), palliative care (ICD-10 code Z515), and hospitals' teaching status. In addition, we abstracted the year and calendar quarter of hospitalization. A calendar quarter represents the shortest time period reported in TIPUDF.

We used the Clinical Classifications Software Refined (CCSR) tool [46] to identify ICD-10 codes for obesity (CCSR

category END009), tobacco use (category MBD024), alcohol use (category MBD017), and substance use disorders (categories MBD018 - MBD023, MBD025, and MBD028 - MBD033). Severity of illness was characterized using ICD-10 codes for organ dysfunction [47, 48]. ICD-10 procedure codes were used to identify hospitalizations with hemodialysis (5A1D00Z, 5A1D60Z, 5A1D70Z, 5A1D80Z, 5A1D90Z) and ECMO (5A15223, 5A1522F, 5A1522G, 5A1522H).

Statistical analysis

We summarized categorical variables as frequencies and percentages, while continuous variables were reported as mean (standard deviation (SD)). The Chi-square test was used for group comparison involving categorical variables, while *t*-test was used for comparison of continuous variables.

Because the TIPUDF dataset provides discharge-level, rather than patient-level information, which precludes accounting for repeated admissions, we report the number of hospitalizations as units of analysis, rather than number of patients.

We used three distinct models to adjust for confounding: 1) overlap propensity score weighting (primary model); 2) entropy balance; and 3) hierarchical multivariable logistic regression. The primary model was also used for subgroup analyses and sensitivity analyses.

Overlap propensity score weighting

Overlap weighting is a technique that assigns weight to each patient equal to the probability of being assigned to the opposite exposure group [49]. The method assigns less weight to those with outlier propensity scores (and more weight to those with propensity score close to 0.5). Thus, overlap weights prevent subjects with extreme propensity scores from dominating results and worsen precision, as can occur with inverse probability treatment weighting. Overlap weighting for the two groups will always lead to an exact balance in the means and proportions of all measured covariates leading to an absolute standardized difference of 0 when propensity score is estimated by logistic regression, does not exclude any study participants, and was shown to optimize precision of estimates compared with other types of propensity score-based methods [49]. Thus, overlap weighting has been considered as effective as randomization if no adjustment was needed [50]. We calculated overlap weights using all the covariates listed earlier under risk-adjustment. Because healthcare data are often hierarchical, we have accounted for the spatial (outcomes affected by facility of hospitalization) and temporal (potential outcome differences in groups among hospitalizations during different time periods) clustering of our data in creating overlap weights for individual hospitals and the quarter of hospitalization, as recommended by Li et al [51]. We used weighted logistic regression with robust standard error to estimate the risk of short-term mortality among mechanically ventilated hospitalizations with COVID-19 compared to those with influenza.

Entropy balance

Entropy balancing is a data processing method that assigns scalar weight to each patient, incorporating covariate balance into the weight function, so that covariate distribution in the reweighted data achieves exact balance, capturing the average difference in outcomes across the full population studied [52]. Balance improvement with entropy balancing reduces model dependence for effect estimates. All the covariates listed earlier under risk-adjustment were included in estimating entropy balancing weights. Similar to overlap weighting, we have accounted for the spatial and temporal clustering of our data, using the approach reported by Xu et al [53]. Weighted logistic regression with robust standard error was used to estimate the risk of short-term mortality among mechanically ventilated hospitalizations with COVID-19 compared to those with influenza.

Hierarchical multivariable logistic regression

We fit a hierarchical logistic regression model, adjusted for all the covariates listed in the risk-adjustment section. We nested mechanically ventilated hospitalizations within individual hospitals and treated hospitals as a random effect. Multicollinearity was excluded by examination of variance inflation factors.

The estimates of comparative short-term mortality of mechanically ventilated hospitalizations with COVID-19 vs. those with influenza in the weighted logistic regressions of the overlap propensity score weighting, the entropy balance model, and in the hierarchical multivariable logistic regression model were expressed as adjusted risk ratio (aRR) and adjusted risk difference (aRD), using the approach described by Austin [54]. The aRD represents the absolute difference in short-term mortality, expressed as percentage, between mechanically ventilated hospitalizations with COVID-19 compared to those with influenza. Non-parametric bootstrap 95% confidence intervals (CIs) were determined using 10,000 bootstrap samples and the percentile method, as described by Austin [54].

The State of Texas suppresses gender data of hospitalizations with a diagnosis of infection with the human immunodeficiency virus, and of those with alcohol or drug use to protect patients' identity. Gender data were missing nonrandomly in 7.8% of hospitalizations in our cohort, precluding imputation of missing values. We used an indicator variable to model gender data for hospitalizations with suppressed gender information. Randomly missing data (1% of health insurance) were modelled as indicator variable.

Subgroup analyses

We performed pre-specified subgroup analyses within the overlap propensity score weighted cohort, including: 1) age; 2) gender; 3) race and ethnicity; 4) Deyo comorbidity index; and 5) the number of organ dysfunctions. Age, gender, race and ethnicity, Deyo comorbidity index, and the number of organ dysfunctions, were excluded from models 1 - 5, respectively.

Sensitivity analyses

We performed four sensitivity analyses to assess the robustness of the primary analysis estimates. First, we examined the comparative outcomes of mechanically ventilated hospitalizations with COVID-19 and influenza using in-hospital mortality as an outcome. Second, we repeated the primary analysis on the subset of mechanically ventilated hospitalizations with COVID-19 and influenza, restricted to the periods from October 1, 2021 to March 31, 2022 and October 1, 2022 to March 31, 2023, approximating the approach of the Centers of Disease Control and Prevention for the definition of the influenza season in the USA [55, 56], as influenza-related mortality would be expected to be higher during this period. Third, because COVID-19 mortality was reported to decrease over time, we examined the comparative short-term mortality of the subsets of mechanically ventilated hospitalizations with COVID-19 and influenza during the third and fourth quarters of 2022 (from July 1 to September 30 and October 1 to December 31, respectively), as well as last study quarter (from January 1 to March 31, 2023), with the latter representing the latest time period in our cohort prior to the end of the public health emergency phase of the pandemic in the USA [2], and thus potentially reflecting the smallest mortality gap between the examined groups.

Finally, to account for unmeasured confounding, we computed E-values [57] to assess the magnitude of a potential unmeasured confounder required to nullify the estimates of the primary model of the comparative short-term mortality of mechanically ventilated hospitalizations with COVID-19 and influenza. The E-value represents the minimum strength of association, on a risk ratio scale, that an unmeasured confounder would need with both the exposure and outcome, conditioned on the measured covariates, to fully explain a specific association [57]. A large E-value implies that a considerable unmeasured confounding would be needed to explain away the effect estimate. We report the E-values for the point estimate and the lower bound of the 95% CI for our primary model.

Data management was performed using Microsoft Excel (Microsoft, Redmond, Washington) and statistical analyses were performed with R 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value < 0.05 was considered statistically significant.

Results

Cohort characteristics

There were 22,195 mechanically ventilated hospitalizations during the study period, of which 19,659 (88.6%) had COVID-19 and 2,536 (11.4%) had a diagnosis of influenza.

The characteristics of the mechanically ventilated hospitalizations with COVID-19 and influenza are detailed in Table 1. Compared to those with influenza, mechanically ventilated hospitalizations with COVID-19 had similar frequency of those with older age (aged $\geq$ 65 years in 54.9% vs. 54.8%), had higher frequency of racial and ethnic minorities (49.3% vs. 48.4%), but with lower mean (SD) burden of comorbidities (Deyo comorbidity index 2.04 (2.03) vs. 2.53 (1.91)). Among individual comorbid conditions, mechanically ventilated hospitalizations with COVID-19 had higher frequency of diabetes (42.4% vs. 39.0%) and obesity (33.6% vs. 30.8%), but lower frequency of congestive heart failure (33.8% vs. 48.5%) and lung disease (28.5% vs. 57.7%) compared to those with influenza. The mean (SD) number of organ dysfunctions was higher among mechanically ventilated hospitalizations with COVID-19 than among those with influenza (2.60 (1.37) vs. 2.13 (1.27)). The frequency of do-not-resuscitate state and use of palliative care was markedly higher among mechanically ventilated hospitalizations with COVID-19 than among those with influenza (33.1% vs. 19.0% and 22.1% vs. 12.5%, respectively).

Discharge to home occurred in 29.7% of mechanically ventilated hospitalizations with COVID-19 and in 57.5% of those with influenza, while rates of discharge to a post-acute care facility were similar (19.8% vs. 19.2%, respectively).

Mortality among mechanically ventilated hospitalizations with COVID-19 and influenza

Crude short-term mortality among mechanically ventilated hospitalizations with COVID-19 and influenza was 49.1% vs. 20.7%, respectively. The corresponding hospital mortality was 40.5% among those with COVID-19 and 13.5% among those with influenza.

Estimates of the risk of short-term mortality among mechanically ventilated hospitalizations with COVID-19 compared to those with influenza are detailed in Table 2. Details of the weighted cohorts following overlap weighting and entropy balancing are provided here (Supplementary Materials 1, 2, jocmr.elmerjournals.com), respectively, and the standardized differences between mechanically ventilated hospitalizations with COVID-19 and influenza in the unweighted vs. overlap weighted and entropy balanced cohorts are presented here (Supplementary Materials 3, 4, jocmr.elmerjournals.com), respectively. After applying overlap propensity score weighting, the comparative risk of short-term mortality among mechanically ventilated hospitalizations with COVID-19 vs. those with influenza was attenuated but remained higher among the former (aRR 1.24 (95% CI: 1.18 - 1.30); aRD 8.8% (95% CI: 6.7 - 10.4)). The estimates of the risk of short-term mortality among mechanically ventilated hospitalizations with COVID-19 vs. those with influenza in the alternative models were consistent with those in the primary model. Similarly, the findings in subgroup analyses (Fig. 1) were consistent with those in the primary model, but the higher risk of short-term mortality on point estimates among those aged 18 - 44 years and in the other group of race and ethnicity categories with COVID-19 did not reach statistical significance.

The findings on sensitivity analyses are detailed here (Supplementary Material 5, jocmr.elmerjournals.com), with crude mortality being markedly higher among mechanically ventilated hospitalizations with COVID-19 compared to those with in-

Table 1. The Characteristics and Outcomes of Mechanically Ventilated Hospitalizations With COVID-19 and Influenza

Variables	COVID-19[a] N = 19,659	Influenza[a] N = 2,536	P value
Age, years			0.9212
18 - 44	2,252 (11.5)	285 (11.2)	
45 - 64	6,612 (33.6)	861 (34.0)	
≥ 65	10,795 (54.9)	1,390 (54.8)	
Gender			
Female	8,189 (41.7)	1,220 (48.1)	< 0.0001
Male	10,036 (51.1)	1,026 (40.6)	
Suppressed[b]	1,434 (7.3)	290 (11.4)	
Race/ethnicity			< 0.0001
White	9,974 (50.7)	1,308 (51.6)	
Hispanic	5,413 (27.5)	557 (22.0)	
Black	2,755 (14.0)	504 (19.9)	
Other	1,517 (7.7)	167 (6.6)	
Health insurance			< 0.0001
Private	8,597 (43.7)	1,085 (42.8)	
Medicare	6,909 (35.1)	846 (33.4)	
Medicaid	1,383 (7.0)	238 (9.4)	
Uninsured	1,688 (8.6)	297 (11.7)	
Other	869 (4.4)	57 (2.2)	
Missing	213 (1.1)	13 (0.5)	
Deyo comorbidity index[c]	2.04 (2.03)	2.53 (1.91)	< 0.0001
Comorbid conditions			
Diabetes	8,341 (42.4)	990 (39.0)	0.0011
Liver disease	1,125 (5.7)	136 (5.4)	0.5386
Malignancy	1,272 (6.5)	145 (5.7)	0.1216
Congestive heart failure	6,639 (33.8)	1,231 (48.5)	< 0.0001
Chronic lung disease	5,597 (28.5)	1,463 (57.7)	< 0.0001
Myocardial infarction	2,998 (15.3)	475 (18.7)	< 0.0001
Peripheral vascular disease	715 (3.6)	107 (4.2)	0.1304
Dementia	1,509 (7.7)	163 (6.4)	0.0197
Peptic ulcer disease	303 (1.5)	33 (1.3)	0.4320
Hemiplegia/paraplegia	535 92.7)	46 (1.8)	0.0073
HIV	99 (0.5)	18 (0.7)	0.1882
Cerebrovascular disease	1,684 (8.6)	161 (6.3)	0.0001
Chronic renal disease	4,994 (25.4)	588 (23.2)	0.0163
Rheumatological disease	614 (3.1)	101 (4.0)	0.0154
Obesity	6,605 (33.6)	781 (30.8)	0.0049
Tobacco use	1,938 (9.9)	564 (22.2)	< 0.0001
Alcohol use	745 (3.8)	121 (4.8)	0.0145
Substance use	767 (3.9)	176 (6.9)	< 0.0001
Number of organ dysfunctions[c]	2.60 (1.37)	2.13 (1.27)	< 0.0001
Hemodialysis	1,493 (7.6)	114 (4.5)	< 0.0001

Table 2. Adjusted Analyses of the Comparative Short-Term Mortality[a] Among Mechanically Ventilated Hospitalizations With COVID-19 Versus Influenza - *(continued)*

Variables	COVID-19[a] N = 19,659	Influenza[a] N = 2,536	P value
ECMO	63 (0.3)	2 (0.07)	0.0369
Do-not-resuscitate	6,513 (33.1)	483 (19.0)	< 0.0001
Palliative care	4,348 (22.1)	318 (12.5)	< 0.0001
Teaching hospital	5,093 (25.9)	684 (27.0)	0.2348
Hospital admission period			
Fourth quarter 2021	5,646 (28.7)	137 (5.4)	< 0.0001
First quarter 2022	7,792 (39.6)	305 (12.0)	< 0.0001
Second quarter 2022	716 (3.6)	261 (10.3)	< 0.0001
Third quarter 2022	2,267 (11.5)	101 (4.0)	< 0.0001
Fourth quarter 2022	1,281 (6.5)	1,230 (48.5)	< 0.0001
First quarter 2023	1,957 (10.0)	502 (19.8)	< 0.0001
Hospital disposition			
In- hospital mortality	7,968 (40.5)	342 (13.5)	< 0.0001
Hospice	1,675 (8.5)	182 (7.2)	0.0259
Home	5,837 (29.7)	1,459 (57.5)	< 0.0001
Post-acute care facility[d]	3,892 (19.8)	488 (19.2)	0.4749
Leave against medical advice	287 (1.5)	65 (2.6)	< 0.0001

[a]The parenthesized figures represent percents, except for the Deyo comorbidity index and number of organ dysfunctions; percentage figures may not add to 100 due to rounding. [b]The State of Texas suppresses gender data of hospitalizations with HIV infection, alcohol use, and substance use. [c]Mean (standard deviation). [d]Post-acute care facilities include long-term acute care hospitals, inpatient rehabilitation, skilled nursing facilities, and nursing homes. COVID-19: coronavirus disease 2019; HIV: human immunodeficiency virus; ECMO: extracorporeal membrane oxygenation; Do-not-resuscitate: a do-not-resuscitate state.

fluenza for all analyzed strata. These analyses were consistent with the findings of the primary model, though the estimates for aRR and aRD for the third quarter of 2022, while higher for COVID-19 vs. influenza, did not reach statistical significance due to a very small number of mechanically ventilated influenza hospitalizations during the off-season period. The risk of short-term mortality remained higher among mechanically ventilated hospitalizations with COVID-19 compared to those with influenza during the last quarter of the study (aRR: 1.19 (95% CI: 1.07 - 1.34); aRD: 5.4% (95% CI: 2.3 - 9.0)). The E-values for the point estimate and the lower bound 95% CI of risk ratio of short-term mortality in the primary model were 1.79 and 1.64, respectively.

Discussion

Principal findings

In this population-based study, a diagnosis of COVID-19 was associated with higher risk of death among adult mechanically

Table 2. Adjusted Analyses of the Comparative Short-Term Mortality[a] Among Mechanically Ventilated Hospitalizations With COVID-19 Versus Influenza

Model[b]	aRR (95% CI)[c]	aRD[d] (95% CI)[c]
Overlap propensity score weighting	1.24 (1.18 - 1.30)	8.8 (6.7 - 10.4)
Alternative analyses		
Entropy balance	1.25 (1.19 - 1.33)	9.3 (7.4 - 11.7)
Hierarchical multivariable logistic regression	1.23 (1.22 - 1.34)	8.8 (8.3 - 12.0)

[a]Short-term mortality is the composite of in-hospital death or discharge to hospice. [b]All models were adjusted for patients' sociodemographic characteristics, coexisting conditions, measures of severity of illness, organ support, use of palliative care, do-not-resuscitate status, hospitals' teaching status, and year and calendar quarter of hospitalization. [c]Non-parametric bootstrap 95% CIs were determined using 10,000 bootstrap samples. [d]The risk difference represents the absolute difference in risk of short-term mortality between mechanically ventilated hospitalizations with COVID-19 vs. those with influenza, expressed as percentage. COVID-19: coronavirus disease 2019; aRR: adjusted risk ratio; CI: confidence interval; aRD: adjusted risk difference.

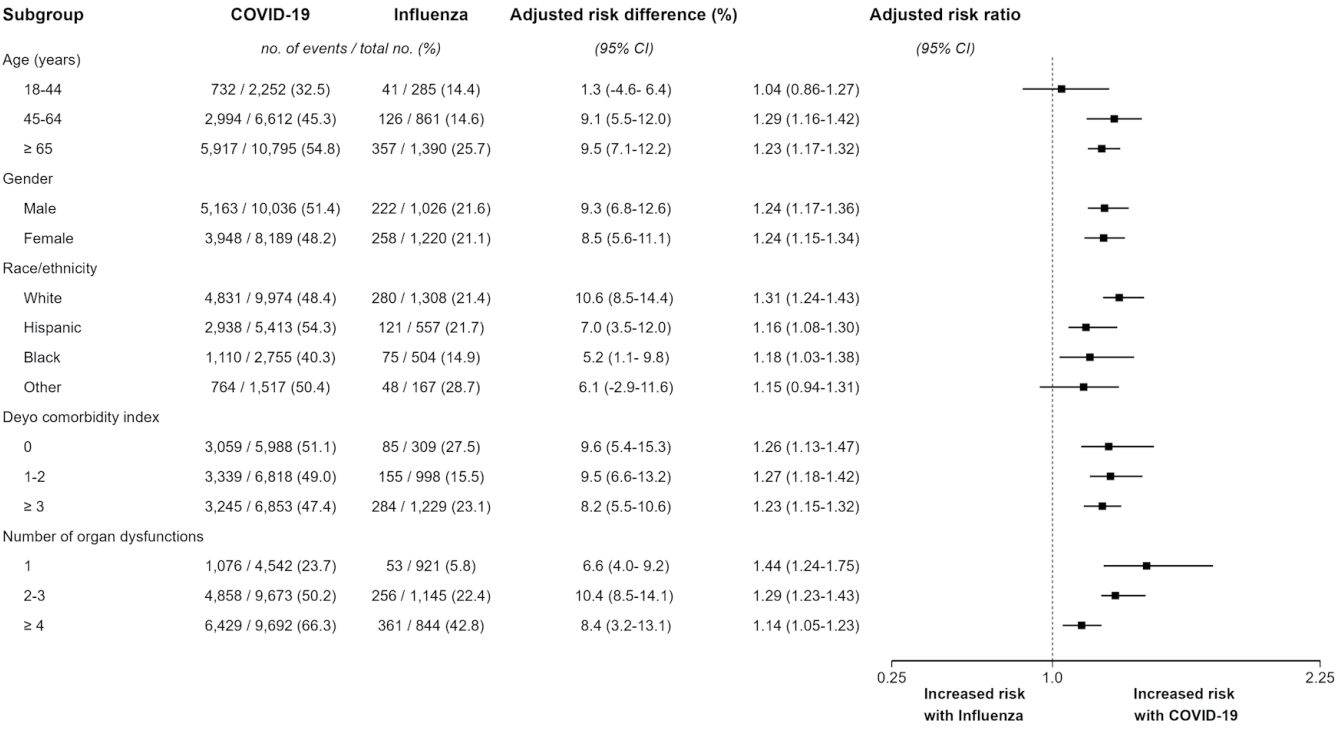

Figure 1. Subgroup analysis of comparative short-term mortality among mechanically ventilated hospitalizations with COVID-19 and influenza. Analyses were conducted using overlap propensity score weighting. Adjusted risk ratio represents the risk of short-term mortality among mechanically ventilated hospitalizations with COVID-19 compared to those with influenza. Adjusted risk difference represents the absolute difference in short-term mortality among mechanically ventilated hospitalizations with COVID-19 compared to those with influenza, expressed as percentage. Non-parametric bootstrap 95% confidence intervals (CIs) were determined using 10,000 bootstrap samples and the percentile method. The width of the CIs was not adjusted for multiplicity and should not be used to infer definite effects. COVID-19: coronavirus disease 2019.

ventilated hospitalizations compared to those with influenza. We found that the relative risk of short-term mortality was 24% higher among those with COVID-19, corresponding to nearly 9% higher absolute risk of death on adjusted analyses. The higher risk of short-term mortality among mechanically ventilated hospitalizations with COVID-19 was consistent on alternative modelling, subgroups analyses, and remained robust on sensitivity analyses. To our knowledge, this study represents the first population-level examination of comparative short-term mortality among mechanically ventilated hospitalizations with COVID-19 and those with contemporaneously managed influenza during the later years of the pandemic.

Comparison with other studies

Our findings of higher risk of death among mechanically ventilated hospitalizations with COVID-19 compared to those with influenza are concordant with those in several prior reports [17, 18, 27, 29, 58]. The largest among these works was a population-based study from France by Naouri et al, which compared mechanically ventilated patients with COVID-19 from March to June 2020 to those with influenza, hospitalized between 2014 and 2019 [18]. The other studies showing similar findings examined patients with COVID-19 in France [27, 29], Germany [17], and Mexico [58], mostly during the first few months of the pandemic in 2020 [17, 18, 29, 58] or through April 2021 [27], and all have used historical influenza comparators. Although influenza hospitalizations occur year-round, beyond the influenza season, the investigators likely chose historical influenza comparators in part due to lack of overlap between the study period of their COVID-19 patients and seasonal influenza and the substantial decrease in influenza activity during the 2020 - 2021 influenza season [9], which could have led to insufficient number of influenza patients for comparative estimates.

However, despite similar findings, our study cannot be directly compared to the above reports. The outcomes of patients with COVID-19 during the early phase of the pandemic when patients' mortality was at its highest do not reflect the substantial decrease in their risk of death in latter pandemic years [4, 5], thus resulting in higher gap in mortality when compared to those with influenza. Correspondingly, the use of historical, rather than contemporaneous, influenza comparators may have led to further overestimation of the mortality difference between them and those with COVID-19 in these studies. This likely impact of the use of historical instead of contemporaneous influenza comparators stems from not accounting for the reported increased mortality among non-COVID-19 hospitalizations, especially during the early period of the pandemic [59], which may have similarly affected mechanically

ventilated patients with influenza. These worsened outcomes among hospitalized non-COVID-19 patients may reflect in turn both pre-hospital and hospital-level pandemic-related changes. The COVID-19 pandemic has been associated with substantial increase in the severity of illness [60] and, specifically, illness requiring critical care [61], among non-COVID-19 patients presenting to the emergency department, compared to the prepandemic period, which could have increased patients' risk of death. These pandemic-associated changes in baseline illness severity may have been driven by reported prevalent delays in health care, related to avoidance of medical encounters due to patients' concerns of exposure to COVID-19 [62, 63], but also due to increased difficulties getting an appointment [62, 64], or access to care location [64]. Moreover, once acute health crises have developed, requiring emergent hospital care, pandemic-related strains on emergency medical services have resulted in delayed on-site care [65] and in arrival to the emergency department [66]. At the hospital level, pandemic-related strains, including those on critical care services [67], have been associated with delays in intensive care unit (ICU) admission [68] and have likely affected adversely time-sensitive and other processes of care. Together, these pandemic-related adverse prognostic changes in non-COVID hospitalizations would be expected to result in higher mortality among mechanically ventilated patients with influenza managed during the pandemic period compared to prepandemic years, and thus could have affected estimates of comparative outcomes with patients with COVID-19.

In contrast to our results, several studies of cohorts from Europe [19, 21, 69-72] and Asia [20, 22, 73] reported either similar mortality rates among mechanically ventilated patients with COVID-19 and influenza [21, 22, 69-73] or lower mortality rates among the former [19, 20]. The findings in these studies, which were generally conducted during an earlier phase of the pandemic, may reflect in part small cohorts with monocentric design [19, 20, 22, 70, 72, 73], and lack of adjustment for confounders [19, 20, 69, 71-73]. In addition, the observed similar or lower mortality among mechanically ventilated patients with COVID-19 compared to those with influenza may reflect the reported over seven-fold across-country variation in the risk of death among mechanically ventilated patients with COVID [14]. Thus, in several studies describing lower or similar risk of death among mechanically ventilated patients with COVID-19 vs. influenza, 28-day mortality among the former was as low as 8.9% [19] to 10.7% [70]. On the other hand, the influenza comparators in one study reflected an epidemic in the year prior to onset of the COVID-19 pandemic, which was considered by the authors to be as severe as that among the latter [72], while several studies included influenza hospitalizations that took place during the 2009 H1N1 influenza pandemic [19, 21, 70]. The latter influenza comparators may not be representative of the mortality outcomes of mechanically ventilated patients with influenza managed during other periods and would have increased overall mortality in the influenza group. There have not been, to our knowledge, studies restricting examination of comparative outcomes of mechanically ventilated patients with COVID-19 to those of contemporaneously managed comparators with influenza during the latter years of the pandemic and showing either similar or lower short-term mortality among the former.

Implications of study findings

Our study shows that despite the substantial decrease in mortality of patients infected with COVID-19 over the pandemic years, its lethality among mechanically ventilated patients remained substantially higher than among those with influenza hospitalized contemporaneously during the latter years of the pandemic. More soberingly, we show that even during the first quarter of 2023, shortly prior to the end of the public health emergency phase of the COVID-19 pandemic in the USA, short-term mortality remained higher among mechanically ventilated hospitalizations with COVID-19 compared to those with influenza. This persistent prognostic gap serves as a reminder that despite the aforementioned growth in population immunity against COVID-19 and major advances in the care of affected patients, COVID-19 cannot be considered another "bad flu" among these critically ill patients.

Presently, although the pandemic-related hospital strain has decreased compared to the early pandemic years, the pandemic's adverse effects on the healthcare system linger. Thus, a recent study showed that following the end of the public health emergency phase of the pandemic in May 2023 [2], the USA has achieved in 2024 a new hospital occupancy steady state, 11% higher than the prepandemic period (2009 - 2016), driven by a 16% decrease in staffed hospital beds, with hospital occupancy projected to reach a critical level by 2032 [6]. In addition, COVID-19 remains a major cause of respiratory viral hospitalizations in the USA in 2024 [23], while the uptake of the COVID-19 vaccine among adults has decreased in early 2025 to 21.6% (compared to 42.9% who received a 2024 - 2025 influenza vaccine) [74]. Thus, the earlier widespread population immunity against COVID-19 may decrease in the coming years, risking increase in COVID-19-related lethality. Together, the aforementioned evolving trends suggest that COVID-19 remains a clinically relevant health burden, whose lethality may continue to exceed that of influenza.

Further investigations are needed to elucidate the patient-, pathogen-, and health system-related factors underlying the persistent higher lethality of COVID-19 in severely ill patients to inform preventive measures against deterioration of infected patients, development of novel antiviral agents, and refine care of the critically ill.

Strengths and limitations of study

Our study has relevant strengths and limitations. In terms of strengths, our study leverages a population-based, high-quality administrative dataset for the most contemporary estimates of the comparative short-term mortality of consecutive mechanically ventilated hospitalizations with COVID-19 and contemporaneously managed, rather than historical, influenza comparators from a state with a diverse large population of over 30 million. This approach allowed the transcending of local variation in case mix and practice patterns. We adhered closely to reporting guidelines and used multiple statistical methods to limit confounding and enhance the trustworthiness of our estimates of comparative outcomes.

However, population-level analyses using administrative health databases have important limitations, in addition to those noted earlier. The use of ICD codes could have resulted in group misclassification. Although our ICD coding approach has been used by other investigators and was validated, misclassifications could have occurred between hospitalizations with COVID-19 and influenza. However, such potential misclassification would have blurred the difference in mortality between groups. In that case, our findings would represent an underestimate of the true difference in risk of death between mechanically ventilated hospitalizations with COVID-19 and those with influenza.

Our dataset did not include information of patients' vaccination status, pre-hospitalization and in-hospital pharmacological therapy, data for derivation of prognostic scales (such as Acute Physiology and Chronic Health Evaluation), and processes of care. In addition, our most granular time-based model adjustments were restricted to calendar quarters of hospitalization, rather than dates or weeks, precluding adequate approximation to corresponding evolvement of COVID-19 variants. These variants varied in timing across states, and the reported periods of dominance of a specific variant in the USA notably varied across reports [5, 75, 76]. Further, variation over time in pandemic-induced hospital strain, shown to increase mortality of both COVID-19 and non-COVID critically ill patients during COVID-19 surge conditions [77, 78], could have led to higher mortality among mechanically ventilated patients with both COVID-19 and influenza during high-strain periods and possibly lower mortality for both when hospital strain was lower. However, the resultant strain-related impact on their comparative mortality could not be estimated in our data. Thus, although our adjustment for time-based clustering may have addressed indirectly the variation over time in pandemic-induced hospital strain during the study period, our dataset did not include metrics of hospital strain, precluding credible inferences on its direct impact of our estimates. However, our sensitivity analysis for the last quarter of the study period, which preceded the end of public health emergency in the USA [2] and thus was likely associated with the lowest hospital strain, showed persistence of higher mortality among mechanically ventilated patients with COVID-19 compared to their contemporaneous influenza counterparts. Nevertheless, we cannot exclude residual confounding in our models. However, the E-value for our primary model indicates that the point estimate could be nullified only by an unmeasured confounder with a risk ratio of at least 1.79 for both COVID-19 vs. influenza and for short-term mortality.

Last, our findings may not be generalizable to other states in the USA or to other health systems and geographical regions with different resources and policies.

Conclusions

In this population-based cohort study, short-term mortality among mechanically ventilated hospitalizations with COVID-19 was higher than that among contemporaneously managed influenza comparators during the later years of the pandemic, including in the period preceding the end of the resultant public health emergency in the USA. Additional studies are needed to examine the mechanisms underlying the persistent higher lethality of COVID-19 in severely ill patients, to inform efforts to mitigate its burden in this population.

Supplementary Material

Suppl 1. The overlap propensity score weighted characteristics of mechanically ventilated hospitalizations with COVID-19 and influenza.

Suppl 2. The entropy balancing weighted characteristics of mechanically ventilated hospitalizations with COVID-19 and influenza.

Suppl 3. Standardized differences between mechanically ventilated hospitalizations with COVID-19 and influenza for the variables used in the overlap propensity score derivation in the unadjusted and propensity-score weighted cohorts.

Suppl 4. Standardized differences between mechanically ventilated hospitalizations with COVID-19 and influenza for the variables used in the entropy balancing weight derivation in the unadjusted and entropy balance-weighted cohorts.

Suppl 5. Sensitivity analyses of the comparative mortality among mechanically ventilated hospitalizations with COVID-19 vs. influenza.

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Conflict of Interest

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Informed Consent

Not applicable.

Author Contributions

LO: conceptualization, project administration, supervision, and writing - original draft. LO, JG: data curation, investigation, methodology, resources, software, formal analysis, vali-

dation, visualization, writing- review and editing. Both authors have read and approved the final manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are available in the TIPUDF repository, at: http://www.dshs.state.tx.us/thcic/hospitals/Inpatientpudf.shtm.

Abbreviations

aRD: adjusted risk difference; aRR: adjusted risk ratio; CCSR: Clinical Classifications Software Refined; COVID-19: coronavirus disease 2019; ICU: intensive care unit; ICD-10: International Classification of Diseases, 10th Revision; TIPUDF: Texas Inpatient Public Use Data File; USA: United States

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