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# Hospital trajectories and early predictors of clinical outcomes differ between SARS-CoV-2 and influenza pneumonia

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## Summary

**Background** A comparison of pneumonias due to SARS-CoV-2 and influenza, in terms of clinical course and predictors of outcomes, might inform prognosis and resource management. We aimed to compare clinical course and outcome predictors in SARS-CoV-2 and influenza pneumonia using multi-state modelling and supervised machine learning on clinical data among hospitalised patients.

**Methods** This multicenter retrospective cohort study of patients hospitalised with SARS-CoV-2 (March–December 2020) or influenza (Jan 2015–March 2020) pneumonia had the composite of hospital mortality and hospice discharge as the primary outcome. Multi-state models compared differences in oxygenation/ventilatory utilisation between pneumonias longitudinally throughout hospitalisation. Differences in predictors of outcome were modelled using supervised machine learning classifiers.

**Findings** Among 2,529 hospitalisations with SARS-CoV-2 and 2,256 with influenza pneumonia, the primary outcome occurred in 21% and 9%, respectively. Multi-state models differentiated oxygen requirement progression between viruses, with SARS-CoV-2 manifesting rapidly-escalating early hypoxemia. Highly contributory classifier variables for the primary outcome differed substantially between viruses.

**Interpretation** SARS-CoV-2 and influenza pneumonia differ in presentation, hospital course, and outcome predictors. These pathogen-specific differential responses in viral pneumonias suggest distinct management approaches should be investigated.

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**Keywords:** Viral pneumonia; SARS-CoV-2; Influenza; Hospital outcomes; Statistical modelling

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### Research in context

#### *Evidence before this study*

Pneumonia due to SARS-CoV-2 (Coronavirus Disease-2019, COVID-19) has been compared to other viral pneumonias, including influenza. Similarities between COVID-19 and influenza pneumonia include heterogeneous presentation and severe complications, such as acute respiratory distress syndrome (ARDS) and death. Despite these similarities, outcomes in COVID-19 are, overall, worse than for influenza.

Biological responses to SARS-CoV-2 and influenza infection differ and are notable for heterogeneous but overall decreased systemic inflammatory responses among COVID-19 patients. Recent findings suggest much of the underlying end-organ pathology in COVID-19 is due to viral infection in the setting of comorbid conditions, rather than specific immunological phenomena. These findings raise the possibility that differences in clinical outcomes in viral pneumonias represent observable pathogen-specific differential host responses, rather than differential risks for similar pathophysiologies.

#### *Added value of this study*

SARS-CoV-2 pneumonia and influenza pneumonia patients present differently upon hospital admission, progress differently through longitudinal oxygen requirements, and have different predictors of mortality among early clinical data.

#### *Implications of all the available evidence*

The findings emphasize the increased severity and higher mortality with SARS-CoV-2 pneumonia versus influenza pneumonia. Additionally, they suggest that pathogen-specific factors are implicated in the development of negative patient outcomes, conditional on hospitalisation with viral pneumonia. Future research should investigate these possibilities and their implications for pneumonia management strategies.

## Introduction

SARS-CoV-2 pneumonia has been compared to influenza pneumonia,<sup>1–5</sup> with similarities including heterogeneous presentation and severe complications such as acute respiratory distress syndrome (ARDS) and death.<sup>1</sup> Despite these similarities, SARS-CoV-2 pneumonia outcomes are, overall, worse than for influenza.<sup>1</sup> However, granular evaluations of dynamic resource utilisation during hospitalisation for these entities have not been performed. Empirically comparing organizational demands between these two pneumonias may inform resource management in future scenarios where the two viruses coexist,<sup>6</sup> particularly given ongoing resource availability variation, including intensive care unit (ICU) beds and appropriately trained staff.<sup>7–9</sup> Further, by

studying important outcome predictors in addition to trajectories of viral pneumonias, new insights into clinical course heterogeneity can be made that may inform future clinical trials.

Biological responses to SARS-CoV-2 and influenza infection differ and are notable for heterogeneous but overall decreased systemic inflammatory responses among Coronavirus Disease 2019 (COVID-19) patients.<sup>4,5,10–12</sup> Recent findings also suggest much of the underlying end-organ pathology in COVID-19 is due to viral infection in the setting of comorbid conditions, rather than specific immunological phenomena.<sup>13</sup> These findings raise the possibility that different clinical outcomes in viral pneumonias represent observable pathogen-specific differential host responses, rather than differential risks for similar pathophysiology,<sup>14,15</sup> and therefore may have different predictors of outcomes despite broadly similar clinical manifestations at the bedside.

Thus, we aimed to compare the clinical courses and predictors of clinical outcomes due to SARS-CoV-2 to those of the most ubiquitous viral pneumonia, influenza. Specifically, by comparing SARS-CoV-2 to influenza pneumonia, we sought to identify unique differentiating features specific to each pathogen. To these ends, we applied state-of-the-art modelling approaches to routinely available clinical data to evaluate the hospital course and clinical outcome predictors based on host response to infection. We hypothesized that early hospital courses and outcome predictors would differ between SARS-CoV-2 and influenza pneumonia.

## Methods

### Population, setting

At Barnes-Jewish Hospital (BJH) and 10 BJC HealthCare community hospitals, we performed a retrospective cohort study of all adults hospitalised with SARS-CoV-2 pneumonia between 03/16/2020 (BJC's first SARS-CoV-2 hospitalisation) and 12/31/2020 and influenza between 01/01/2015 and 03/17/2020 (both by polymerase chain reaction testing). We included hospitalisations with length of stay (LOS)  $\geq 24$  hours and requiring supplemental oxygen (as a pneumonia surrogate).

### Ethics

Washington University's Institutional Review Board approved this project (#202008041) with a waiver of informed consent. Additional methodology details can be found in the Supplement.

### Data, measurements

**Processing.** We extracted electronic health record (EHR) data from Washington University's research data warehouse.<sup>16,17</sup> For dynamic variables, we a priori

selected the most extreme (highest/lowest) observation during the first 24-hours of hospitalisation (Table-E1). In discrete 12-hour windows from presentation, we recorded each patient's maximal oxygen support in six ordinal groups: room air; 1-6 liters-per-minute (LPM); 7-15 LPM; humidified high-flow nasal cannula (HHFNC); non-invasive ventilation (NIV); invasive mechanical ventilation (IMV). Using diagnosis codes, we identified Elixhauser comorbidities and estimated comorbidity burdens as per van Walraven.<sup>18</sup>

**Chest radiographs.** To ascertain differences in pneumonia severity, we randomly selected 100 hospitalisations each with SARS-CoV-2 pneumonia and influenza from BJH hospitalisations. Two investigators reviewed the latest chest radiographs from Day-0 of hospitalisation to calculate the Radiographic Assessment of Lung Edema (RALE) score, a validated index of pulmonary edema severity in ARDS based on radiographic opacity extent and density (range: 0 [none] - 48 [dense consolidations >75% of each quadrant]).<sup>19</sup> Based on our planned use of medians as a measure of central tendency, we estimated that 97 images per cohort would yield 90% power to detect a RALE difference of 2 with a 2-sided alpha of 0.05.

**Outcomes.** The primary outcome was the composite of hospital mortality or hospice discharge. Secondary outcomes were these endpoints plus hospital/ICU LOS, ICU admission, HHFNC, NIV, and IMV, and 28-day ventilator-free-days (VFD).<sup>20,21</sup>

### Statistical analysis

**Modelling.** We evaluated all outcomes via hierarchical multivariable logistic regression, Fine-Gray (LOS accounting for the competing risk of hospital death)<sup>22</sup> and zero-inflated negative binomial (VFD) models.<sup>21</sup> In each model, the primary exposure was pathogen, and covariates were age, gender, BMI, race, and individual Elixhauser comorbidities, with hospital treated as a random effect. Because care delivery practices and outcomes, including intubation, evolved rapidly at the COVID-19 pandemic's beginning,<sup>16</sup> we used the SARS-CoV-2 cohort to fit a multivariable logistic regression model with linear time trends (by month) in which the outcome was invasive mechanical ventilation and the aforementioned covariates remained the same. To explore the relationship between intubation rates and SARS-CoV-2 pneumonia outcomes over time, we modeled the primary outcome as a function of monthly intubation rates, ranked ordinally, using an analogous multivariable logistic regression approach.

**Multi-state modelling.** To investigate differential oxygen requirement trajectories between pathogens, we performed multi-state modelling on the ordinal level of oxygen support for each patient over time. Within 12-hour discrete-time windows, we categorised patients into one of 8 mutually exclusive and exhaustive clinical states consisting of their maximal oxygen support or discharge/death (Figure-E1).

Using Alan-Johansen non-parametric analyses, we evaluated clinical state-switching per patient.<sup>23</sup> We estimated the longitudinal probability of a patient having a particular clinical status after entering one of four different states: admission, supplemental oxygen, NIV, and IMV. For each analysis, time-zero was entry into said state. At each time-point, we also estimated instantaneous hazard rates for NIV, intubation, death, and discharge. Finally, we estimated the duration of hospitalisation, IMV, NIV, and oxygen requirements and assessed the cumulative incidence of NIV, IMV, and death by Day-21 since hospitalisation.

**Imaging.** We used logistic regression to estimate the independent relationship between RALE score and the primary outcome, *a priori* adjusting for age and pathogen, which we expected to be important confounders. Based on unadjusted analyses, we tested for pathogen-RALE score interaction within this model.

**Outcome prediction.** To compare early predictors of mortality, we trained supervised machine learning classifier models using “extreme gradient boosting” (XGBoost) in each cohort to predict the primary outcome.<sup>24</sup> We chose XGBoost due to its high discrimination and the algorithm's ability to incorporate missing data without requiring imputation or excluding missing observations, both of which are encountered with more traditional approaches such as logistic regression.

We selected candidate predictors from the initial 24 hours in-hospital *a priori* (Table-E2) based on literature review and our clinical experience.<sup>25-28</sup> We tuned model hyperparameters (Supplement) to optimize area under the receiver operator characteristic curve (AUROC) through grid search in 1,000 bootstraps of each cohort.<sup>26</sup> We compared each model's in-sample AUROC to its discrimination in the alternate cohort (i. e., compared the SARS-CoV-2 model's bootstrap-replicated internal AUROC to the SARS-CoV-2 model's AUROC in the influenza cohort, and vice-versa).

We used information gain (estimated variable contributions for each tree in the model) to quantify variable importance to predicting primary outcome risk. Under the hypothesis that differential variable importance would represent pathogen-specific differences in risk for mortality, we used logistic regression – with the primary outcome as the dependent variable – to test for

interaction between pathogen and each of the top-five important variables in each classifier model.

To ensure that classifier models were not biased by inclusion of patients presenting with mild respiratory illness, we performed a sensitivity analysis in which we excluded patients receiving < 4 LPM supplemental oxygen within the first 24 hours of hospitalisation. In this analysis, we refit classifiers and evaluated them in identical fashion to the primary analysis.

**Statistical considerations.** We reviewed univariate data distributions via tabulations and density plots, visually noting kurtosis (e.g., age, blood pressures) and skewing (e.g., van Walraven comorbidity index, serum lactate concentration, peripheral O<sub>2</sub> saturation, LOS, and VFDs) among a number of variables and outcomes. For consistency, we chose to perform nonparametric statistical tests for all analyses, even though this risked lower statistical power for some comparisons. Thus, we summarized data using frequencies (proportions) or medians (interquartile ranges [IQRs]) and compared findings between viral cohorts using Kruskal-Wallis and

Chi-squared tests. We compared classifier model AUROCs via the Hanley/McNeil method with 2000-replication bootstrapped confidence intervals.<sup>29</sup> We used the Wald test for logistic regression interaction term significance. We evaluated variance inflation factors (VIFs) for exposure variables to avoid multicollinearity, with plans to exclude variables with VIF > 5. For all statistical tests, we considered p-values ≤ 0.05 significant.

**Role of funders**

The study funders had no role in study design, data collection, data analyses, interpretation, or writing this report.

**Results**

**Patient characteristics**

We identified 2,529 hospitalisations with SARS-CoV-2 pneumonia and 2,256 with influenza pneumonia (Figure-E2). SARS-CoV-2 patients were of similar age to influenza (Table 1; 68 vs 67 years; p = 0.30), but more

Variable	SARS-CoV-2 (n = 2529)	Influenza (n = 2256)	p-value
Age, years, median (IQR)	68 (56-77)	67 (57-77)	0.297
Female, n (%)	1224 (48.4)	1201 (53.2)	<0.001
Race, n (%)			<0.001
White	1387 (54.8)	1527 (67.7)	
Black	1055 (41.7)	681 (30.2)	
Other	56 (2.2)	48 (2.1)	
BMI, kg/m <sup>2</sup> , median (IQR)	30.4 (25.6-36.4)	28.8 (23.8-35.1)	<0.001
Van Walraven Comorbidity Index, median (IQR)	9.0 (2.5-17.0)	17.0 (8.0-27.0)	<0.001
Congestive Heart Failure, n (%)	706 (27.9)	1129 (50.0)	<0.001
Arrhythmias, n (%)	750 (29.7)	1159 (51.4)	<0.001
Peripheral Vascular Disease, n (%)	344 (13.6)	537 (23.8)	<0.001
Chronic Lung Disease, n (%)	821 (32.5)	1461 (64.8)	<0.001
Diabetes, n (%)	1120 (44.3)	1070 (47.4)	0.024
Chronic Kidney Disease, n (%)	683 (27.0)	889 (39.4)	<0.001
Cancer, n (%)	453 (17.9)	390 (17.3)	0.872
Coagulopathy, n (%)	255 (10.1)	544 (24.1)	<0.001
<b>Outcome</b>			
Composite of Death and Hospice Discharge, n (%)	535 (21.2)	204 (9.04)	<0.001
Hospital Death, n (%)	442 (17.5)	154 (6.83)	<0.001
Hospice Discharge, n (%)	93 (3.7)	50 (2.22)	0.030
ICU Admission, n (%)	1050 (41.5)	909 (40.3)	0.406
Hospital LOS, days, median (IQR)	7.1 (4.5-13.0)	5.2 (3.1-9.0)	<0.001
ICU LOS, days, median (IQR)	7.2 (2.9-14.1)	0.0 (0.0-1.2)	<0.001
HHFNC, n (%)	393 (15.5)	311 (13.8)	0.095
Noninvasive Ventilation, n (%)	791 (31.3)	330 (14.6)	<0.001
Mechanical Ventilation, n (%)	541 (21.4)	361 (16.0)	<0.001
Ventilator-Free Days at Day 28, median (IQR)	28 (17-28)	28 (28-28)	<0.001

**Table 1: Baseline Characteristics and Outcomes for Patients with SARS-CoV-2 Pneumonia and Influenza Pneumonia.**

IQR, interquartile range; BMI, body-mass index; ICU, intensive care unit; LOS, length of stay; HHFNC, humidified high flow nasal cannula.

likely to be Black (42% vs 30%,  $p < 0.001$ ). Patients with SARS-CoV-2 pneumonia had significantly fewer comorbidities than their influenza counterparts (van Walraven Index 9 vs 17), including heart failure (28% vs 50%), chronic lung disease (33% vs 65%), and chronic kidney disease (27% vs 39%;  $p < 0.001$  for all).

### Outcomes

Admissions with SARS-CoV-2 pneumonia more frequently ended with death or hospice (21% vs 9%,  $p < 0.001$ ) and were longer (LOS 7.1 vs 5.2 days,  $p < 0.001$ ) than those with influenza pneumonia. ICU admission rates were similar in the cohorts ( $p = 0.41$ ); however, SARS-CoV-2 patients had longer ICU stays and more received NIV and IMV than influenza patients ( $p < 0.001$  for both).

These differences remained significant after adjusting for age, gender, BMI, race, Elixhauser comorbidities, and potential hospital-level effects (primary outcome: SARS-CoV-2 aOR 3.38 [95%CI 2.71–4.21,  $p < 0.001$ ]; IMV aOR 6.64 [5.05–8.74,  $p < 0.001$ ]; hospital LOS subdistribution hazard ratio 0.46 [0.42–0.50,  $p < 0.001$ ]; VFD aOR for zero-inflation model 3.59 [2.89–4.48,  $p < 0.001$ ], VFD incident risk ratio for count model 0.97 [0.96–0.99,  $p < 0.001$ ]).

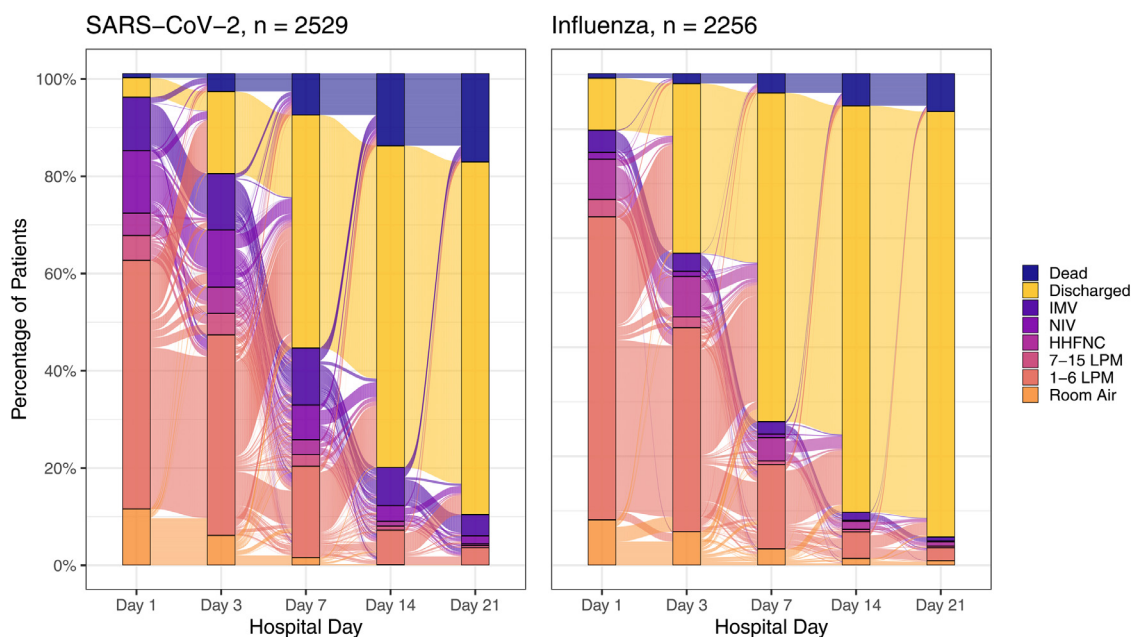
Among patients with SARS-CoV-2 pneumonia, the adjusted odds for invasive mechanical ventilation decreased monthly (with March 2020 as reference,

monthly aOR 0.34 [95% CI 0.21–0.53],  $p < 0.001$ , Figure-E3). Months in which mechanical ventilation rates were lower demonstrated lower adjusted mortality (with March 2020 as reference, monthly aOR 0.47 [95% CI 0.31–0.71],  $p < 0.001$ ).

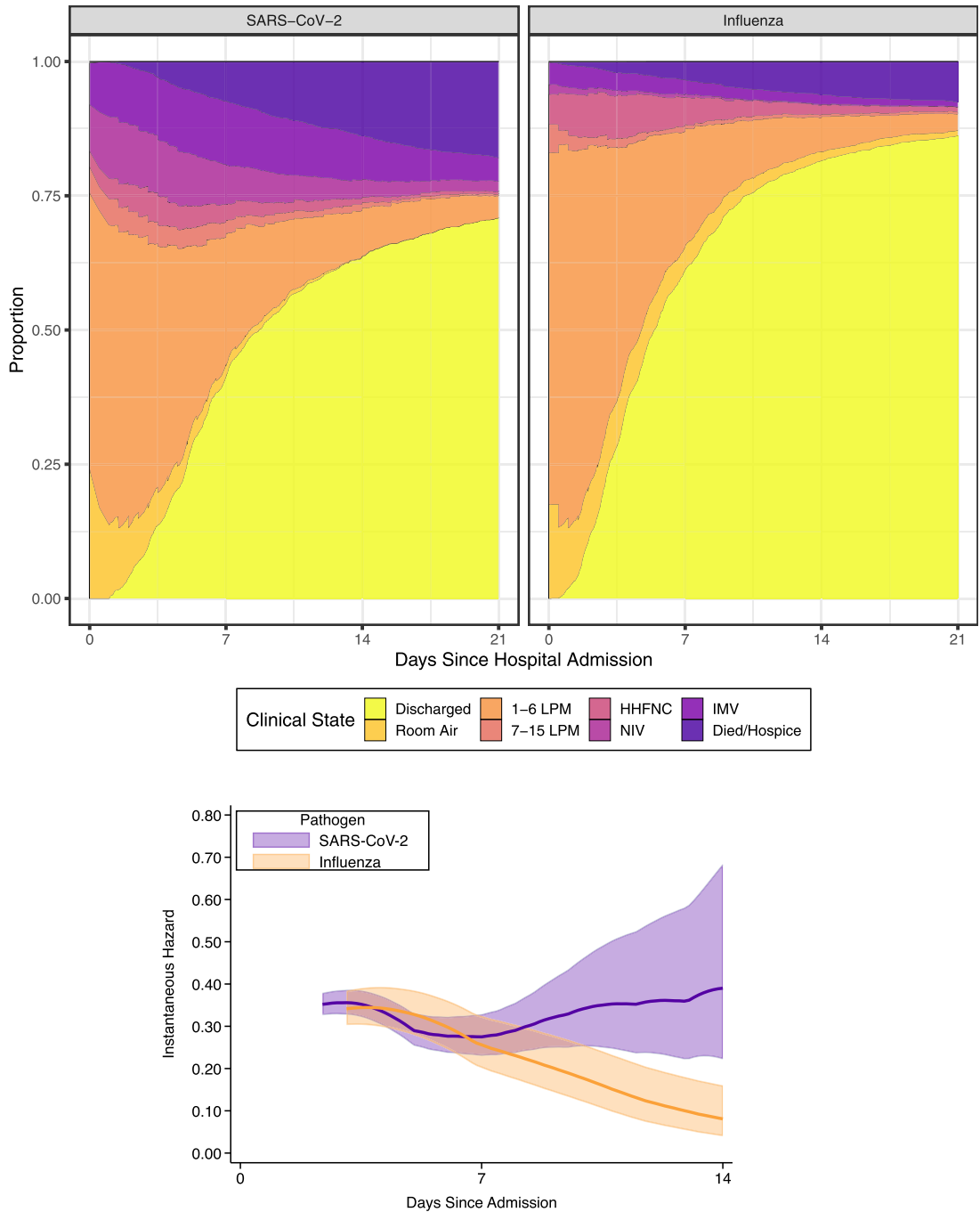
### Multi-state models

Using multi-state models, we observed pathogen-specific differences in oxygen requirement trajectories with differential rates of early levels of respiratory support between viruses (Figures 1/2a, Tables-E3/4). For instance, more SARS-CoV-2 pneumonia patients received NIV or IMV in the first week after admission compared to influenza pneumonia (Day-1: SARS-CoV-2 21.7% [CI: 19.8%–23.7%] vs influenza 16.7% [15.2%–18.3%]; Day-3: SARS-CoV-2 22.3% [20.1%–24.7%] vs influenza 12.2% [10.5%–13.9%]; Day-7, SARS-CoV-2 19.2% [17.0%–21.5%] vs influenza 7.1% [5.7%–8.6%];  $p < 0.001$  for all). Overall, in SARS-CoV-2, 44.1% received NIV or IMV, versus 27.3% in influenza ( $p < 0.001$ ).

Among IMV patients, the primary outcome was more common in SARS-CoV-2 (51.8%) than in influenza pneumonia (28.0%;  $p < 0.001$ ). By day 7 post-IMV, 14.6% (12.0%–17.3%) of SARS-CoV-2 patients were discharged alive versus 28.9% (25.4%–32.5%) of influenza patients. IMV-conditional trajectories diverged by 7 days after intubation, at which point 52.7%



**Figure 1.** Oxygenation Trajectories of Hospitalised Patients with SARS-CoV-2 ( $n = 2,529$ ) and influenza pneumonia ( $n = 2,256$ ). The alluvial plot depicts the oxygen requirement trajectories of patients over their hospital course after admission. Alluviums are color-coded by patient status and their width represents the number of patients. All patients had 28 days of observation time (inclusive of time after discharge or death). Abbreviations: IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; HHFNC, humidified high-flow nasal cannula; LPM, liters per minute.



**Figure 2.** Evolution of respiratory support among hospitalised patients with SARS-CoV-2 (n = 2,529) and influenza pneumonia (n = 2,256) based on multi-state analyses. (a) depicts the proportion of patients estimated to be in each care state at any given time point accounting for the transitions patients made between different clinical states over time ( $p < 0.001$  between cohorts at days 1, 3, 7, and 14). (b) depicts instantaneous hazards for increasing levels of respiratory support for SARS-CoV-2 pneumonia and influenza pneumonia, limited to Days 0 through 14 due to low n after this time point ( $p < 0.001$  at day 14). Abbreviations: IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; HHFNC, humidified high-flow nasal cannula; LPM, liters per minute.



(47.9%–57.5%) of SARS-CoV-2 patients remained mechanically ventilated, versus 30.2% (25.7%–34.8%) of influenza patients.

Instantaneous hazards for initiating supplemental oxygen were similar between cohorts from hospitalisation through day 7, but diverged thereafter (Figure 2b). Regardless of oxygenation status, however, SARS-CoV-2 pneumonia patients were approximately twice as likely to require next-day escalation on Days 1, 3, and 7 than influenza pneumonia ( $p < 0.01$  for all).

### Imaging

Of 100 randomly selected hospitalisations per cohort, 92 SARS-CoV-2 pneumonia admissions and 100 influenza admissions had chest radiographs within the first 24 hours. SARS-CoV-2 pneumonia radiographs had significantly higher RALE scores than influenza (median 8 [4–15] vs 0 [0–5],  $p < 0.001$ ; Table-E5; Figure 3). This subset was generally similar to the primary analysis cohort, although more patients were Black (Table-E6). In this subset, the primary outcome (29% vs 14%,  $p = 0.009$ ) and IMV (27% vs 6%,  $p < 0.001$ ) were more frequent in SARS-CoV-2 than influenza pneumonia. SARS-CoV-2 pneumonia RALE scores were similar regardless of whether the primary outcome occurred (9 vs 8,  $p = 0.99$ ) but differed across IMV (14 vs 7,  $p = 0.003$ ). In contrast, influenza pneumonia RALE was significantly higher for primary outcome patients (5 vs 0,  $p = 0.01$ ; Figure-E4) but not IMV patients (3 vs 0,  $p = 0.102$ ). In an adjusted model with the primary outcome as the dependent variable, we observed a significant interaction between viral pathogen and RALE ( $p = 0.002$ ), indicating that the relationship between RALE and the outcome differed based on pathogen.

### Outcome prediction

Classifier models within each viral cohort had similar discrimination for primary outcome (SARS-CoV-2 AUROC 0.81 [0.79–0.84]; influenza AUROC 0.84 [0.80–0.87];  $p = 0.90$ ). When each model was evaluated on the alternative cohort (e.g., SARS-CoV-2 model + influenza patients), the influenza-derived model's discrimination was statistically worse ( $p < 0.001$ , Figure-4a), suggesting that clinical outcome predictors differ meaningfully between the two pathogens.

Predictor variable importance differed between the models. In the SARS-CoV-2 model, the most contributory variables – in decreasing importance – were age, systolic blood pressure (SBP), oxygen saturation, creatinine, and absolute neutrophil count (ANC) (Figure 4b). Of these, age and SBP were among the top five contributory variables to the influenza model (Figure 4c); BMI, albumin, and hematocrit comprised the remainder. Significant outcome prediction interactions were present between pathogen and oxygen saturation ( $p < 0.001$ ), hematocrit ( $p < 0.001$ ), ANC ( $p = 0.001$ ), BMI ( $p = 0.018$ ), and albumin ( $p = 0.022$ ), but not creatinine

( $p = 0.473$ ). Although age was shared between the models' top five predictors, it also demonstrated significant interaction with pathogen ( $p < 0.001$ ), whereas SBP did not ( $p = 0.998$ ).

In a sensitivity analysis excluding patients receiving  $< 4$  LPM oxygen, classifier models performed similarly to the primary analysis (Table-E7). The influenza-derived model again had worse discrimination in the SARS-CoV-2 cohort than in the influenza cohort ( $p = 0.002$ ).

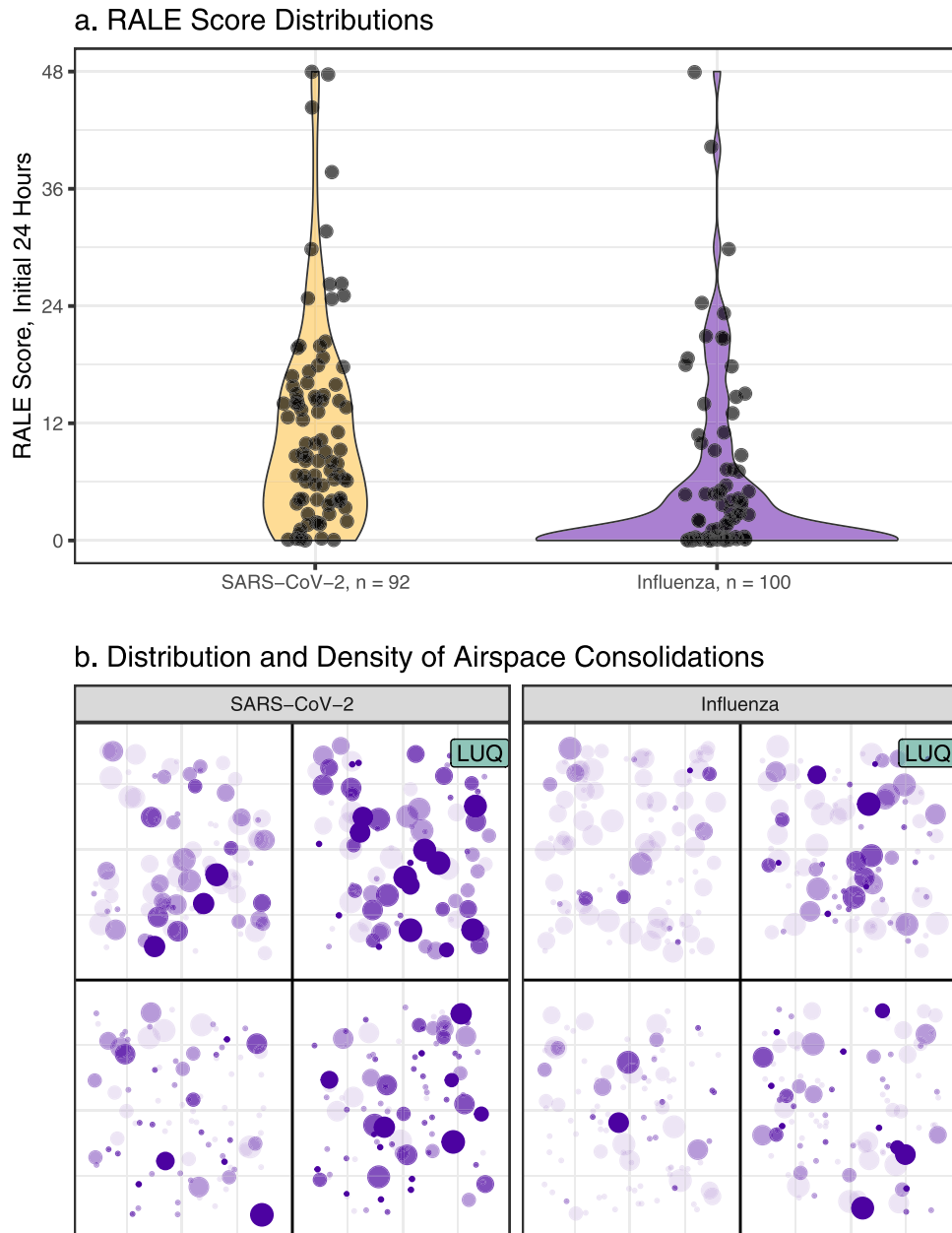
### Discussion

Across eleven hospitals, carefully applying several modern modelling approaches to EHR data demonstrated significant differences between SARS-CoV-2 and influenza pneumonia in terms of radiology, clinical courses, and outcome predictors. Our results suggest these pneumonias have less in common than might be expected of two viral infections which cause acute hypoxemic respiratory failure.

Uniquely, our study presents a detailed comparative mapping of differences in transitions of oxygenation support between SARS-CoV-2 and influenza pneumonia. SARS-CoV-2 pneumonia patients required higher levels and rapid escalation of support on, and shortly after, presentation, and they sustained increased risk for deterioration throughout hospitalisation. ICU requirements were similar between viruses; however, in SARS-CoV-2 pneumonia, rates of IMV were substantially higher and length of stay longer. Instantaneous hazard for escalation of care showed a linear decline during hospitalisation in influenza, whereas in SARS-CoV-2, we observed an initial decline followed by a gradual increase after Day 7. These findings suggest an important subset of patients that decline later during hospitalisation that is specific to SARS-CoV-2 pneumonia.

The evidence of greater radiological abnormalities at baseline in SARS-CoV-2 pneumonia suggests greater infection in the lower respiratory tract or alveoli and implicates viral pathogenicity as an important differentiator between the pneumonias.<sup>30</sup> Importantly, our findings validate recent work demonstrating that baseline radiography does not correlate with clinical outcomes in COVID-19 ARDS.<sup>31</sup> That influenza pneumonia patients differ in this regard – paired with the clinical trajectory patterns we observed – would indicate highly differential severity, rapidity, and resolution of respiratory impairment between viral pneumonias.

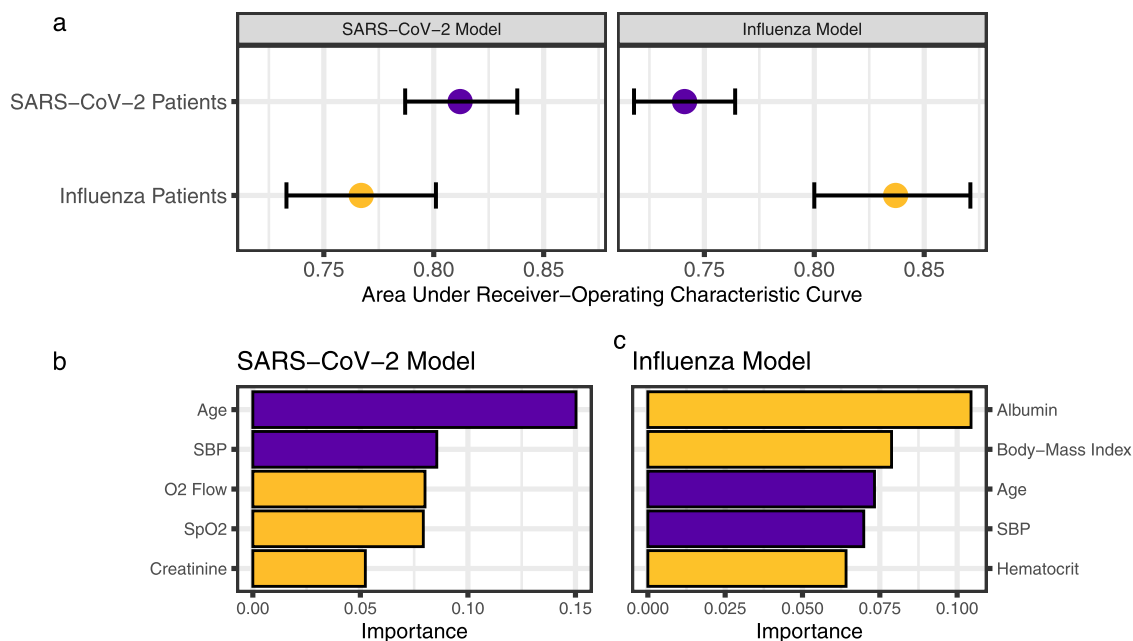
These implications underscore the importance of leveraging longitudinal and multidimensional clinical data for informing both individual prognosis and, more broadly, institution-level resource needs at a given time. Understanding granular epidemiological data at an interventional-level may be important in settings where SARS-CoV-2 and influenza are prevalent in the community concomitantly<sup>6</sup> and resources may be constrained (e.g., ICU



**Figure 3.** Viral differences in Radiographic Assessment of Lung Edema Scores. In (a), SARS-CoV-2 pneumonia patients (n = 92) had higher RALE Scores than influenza pneumonia patients (n = 100;  $p < 0.001$ ). (b) depicts the two-dimensional radiographic projection of RALE consolidation by quadrant, oriented as per traditional chest radiography convention. Scattered points within each quadrant reflect the relative breadth (size) and density (opacification) of airspace consolidations. While scattered points correspond to specific quadrants of airspace opacities, the points do not correspond to locations *within* individual quadrants. Abbreviations: RALE, radiographic assessment of lung edema; LUQ, left upper quadrant.

beds,<sup>32</sup> respiratory support devices<sup>33</sup> or appropriately trained staff<sup>6</sup>). For example, in such settings, the shorter lengths of stay coupled with lower levels of critical care support in influenza pneumonia may warrant expansion of high-dependency or step-down units, thereby freeing higher-level critical resources for SARS-CoV-2.

Our work demonstrates distinct pathogen-specific predictors of clinical outcomes between viral pneumonias. SARS-CoV-2 pneumonia outcome prediction relied most strongly on age and cardiorespiratory variables, in keeping with COVID-19’s well-described natural history of severe disease involving respiratory failure



**Figure 4.** Discrimination and relative variable importance from XGBoost classifier models indicate differential predictors of mortality between pathogens. In (a), discrete XGBoost classifier models to predict the composite of hospital mortality or hospice discharge showed similar discrimination on in-sample evaluation (SARS-CoV-2 AUROC 0.81 [purple, left; n = 2,529]; influenza AUROC 0.84 [yellow, right; n = 2,256]), but whereas the SARS-CoV-2 model did not have significantly different performance when evaluated in the influenza cohort (AUROC 0.77 [yellow, left]; p = 0.9), the influenza model had significantly worse discrimination when evaluated in the SARS-CoV-2 cohort (AUROC 0.74 [purple, right]; p < 0.001). Panels (b and c) show the relative variable importance, measured in information gain, for the SARS-CoV-2 (b) and influenza model (c) classifier models. Purple shading indicates variables shared among each model's top-five, while yellow shading indicates variables not shared. Abbreviations: AUROC, area under receiver operator characteristic curve.

and often shock.<sup>1</sup> Notably, ANC featured prominently among these outcome predictors in SARS-CoV-2 pneumonia but not influenza, underscoring the increasingly recognized role of neutrophil biology in COVID-19 pathophysiology.<sup>34–36</sup> By contrast, key predictors in influenza pneumonia were closely related to patients' baseline condition (e.g., BMI, serum albumin, anemia).

Diminishing performance when each pathogen's classifier model was evaluated on the alternative cohort further substantiates these differences in outcome predictors. The SARS-CoV-2 pneumonia model had modestly decreased performance in influenza, whereas the influenza model – with hematologic and hepatic markers providing substantial contributions – had a larger drop in discrimination in SARS-CoV-2 pneumonia. These findings suggest influenza outcomes may relate to accrual of multiple organ failures, whereas SARS-CoV-2 pneumonia may depend more on the severity and refractory nature of a few specific organ failures. Moreover, these results underscore our evolving understanding that SARS-CoV-2 pneumonia and COVID-19 do not necessarily induce a systemic “cytokine storm” of higher intensity than influenza pneumonia. Indicators of pathophysiological cytokine storm, such as temperature (inflammation),

hypotension (endothelial dysfunction), and serum bicarbonate (end-organ perfusion) were similarly represented as features of importance in both influenza and SARS-CoV-2 classifier models. Notably, serum bicarbonate – which has been identified as a critical biomarker in the identification of the hypoinflammatory ARDS phenotype<sup>37</sup> – was not a variable of importance in either pneumonia's outcome classifiers, suggesting that this particular phenotype may not be an important determinant of mortality in this population. These findings are further substantiated by lower levels of protein biomarkers in COVID-19 compared other critical illness syndromes.<sup>38,39</sup>

An important question raised by our study is “what are the distinct pathophysiological phenomena of SARS-CoV-2 infection which underpin these observed differences between viral pneumonias?” While our study's retrospective design limits interpretation of our findings to hypothesis generation, several interesting patterns have nevertheless emerged. Age being the most important predictor of SARS-CoV-2 pneumonia outcome – in the presence of fewer comorbidities than influenza – suggests that age-dependent, rather than acquired, immunosenescence may be more important in SARS-CoV-2-driven disease,<sup>40–43</sup> a finding with

particular relevance given analogous responses to SARS-CoV-2 spike protein vaccines.<sup>44</sup> The degree to which these hypothesized pathogen-specific differences are due to variable virus-host cell receptor binding affinity, immune evasion, host response variance, or some combination thereof requires further investigation.

Our study's strengths include modern modelling approaches to generate data-driven insights about viral pneumonias, with each technique lending important benefits to our work. Second, we used readily available EHR data to enhance generalizability and allow easier identification of subphenotypes in future studies. Adding to this generalizability is our inclusion of all hospitalised pneumonia patients rather than just those with critical illness, since ICU triage practices vary. Finally, our diverse mix of urban, suburban, and rural hospitals reinforces our findings' generalizability, given previously described sociodemographic determinants of COVID-19 outcomes.<sup>16</sup>

Limitations include potential temporal confounding, including data-acquisition changes (our cohort includes periods when two different EHRs were used), viral strain variation, and practice changes. While we address these limitations for influenza by including several years to diversify influenza strain mix, our data were collected prior to the emergence of the SARS-CoV-2 Delta and Omicron variants and before widespread availability of SARS-CoV-2 vaccines, monoclonal antibody therapy, and inflammatory pathway inhibitors such as baricitinib.<sup>45,46</sup> Further, influenza vaccine status was not available in our data. Due to unavailability of microbiology data in the influenza cohort, we could not evaluate differences in bacterial co-infection between cohorts; co-infection may be an important determinant of the clinical course and outcomes in these patients.<sup>47,48</sup>

Our automated pneumonia definition - hospitalisation with supplemental oxygen - may lack the specificity of a clinical diagnosis and could include some patients receiving oxygen for non-pneumonia reasons including chronic oxygen therapy. However, this operational definition benefitted our study by allowing standardized identification of patients across several years of data. Moreover, the observed rates of high-level oxygen support are more consistent with acute respiratory insufficiency rather than home oxygen continuation. Finally, while a large proportion of radiographs among the influenza population had no lung opacities, it is worth noting that our review was limited to the first 24-hours of admission and the accuracy of chest radiographs in early viral pneumonia remains uncertain.<sup>49,50</sup>

### Conclusions

SARS-CoV-2 pneumonia and influenza pneumonia differ markedly in hospital trajectories, radiography, and outcome predictors, with SARS-CoV-2 disease more severe in all evaluated parameters. These findings

emphasize observable pathogen-specific differential host responses in viral pneumonias, which may have implications beyond SARS-CoV-2 and influenza.

### Contributors

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PL, AB, and PS have directly accessed and verified the underlying data reported in the manuscript.

All authors provided final approval of the version to be published.

### Data sharing statement

Due to patient privacy concerns, identified supporting data cannot be made openly available; however, a de-identified data set is available at <https://doi.org/10.48765/c7ar-6g49>. This data set contain all data necessary to replicate the complete set of unadjusted and adjusted analyses from this report, including generation of comparison tables, adjusted outcomes models, multi-state models, and machine learning classifier models. A data dictionary also resides within the repository. These data will be made available beginning on the date of publication and may be shared without investigator support. Additional data, such as limited identifiers (e.g., dates) or other relevant electronic health record data,

may be available within collaboration with the study team. Investigators seeking to collaborate with the investigators on research using these data should contact the corresponding author to discuss a proposal and a data access/use agreement.

Analysis code will be available on GitHub (github.com/p-lyons) at the time of publication.

### Declaration of interests

PGL- Present work: efforts were supported by, BJC HealthCare Healthcare Innovation Lab “Big Ideas” award, Doris Duke Charitable Foundation, and Fund to Retain Clinical Scientists, # 2015215. Outside scope of present work- CDC

MMC- Outside scope of present work, grants to institution: DOD PRMRP W81XWH-21-1-0009, NIH/NIDDK Ro1-DK126933A -01, NIH/ NIGMS R35-13362546, NIH/NIGMS, Ro1-GM123193.

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APM- Outside scope of present work: Pfizer personal stock ownership.

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CCS- Outside scope of present work: Grants: NIH, Department of Defense, Roche-Genentech, Quantum Leap Healthcare Collaborative; Consultant: Vasomune, Genie Life Sciences, Cellenkos, Janssen.

SLW, AD, KD, TMP, SVB, AB, PS, EHG, BNR, MK, and AM have no conflicts of interest to report.

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### Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.104295.

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