K-medoids clustering of hospital admission characteristics to classify severity of influenza virus infection

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December 9, 2022

Abstract

Background: Patients are admitted to the hospital for respiratory illness at different stages of their disease course. It is important to appropriately analyse this heterogeneity in surveillance data to accurately measure disease severity among those hospitalized. The purpose of this study was to determine if unique baseline clusters of influenza patients exist, and to examine the association between cluster membership and in-hospital outcomes. Methods: Patients hospitalized with influenza at two hospitals in Southeast Michigan during the 2017/2018 (n=242) and 2018/2019 (n=115) influenza seasons were included. Physiologic and laboratory variables were collected for the first 24 hours of the hospital stay. K-medoids clustering was used to determine groups of individuals based on these values. Multivariable linear regression or Firth's logistic regression were used to examine the association between cluster membership and clinical outcomes. Results: Three clusters were selected for 2017/2018, mainly differentiated by blood glucose level. After adjustment, those in C171 had 5.6 times the odds of mechanical ventilator use than those in C172 (95%CI: 1.49,21.1) and a significantly longer mean hospital length of stay than those in both C172 (mean 1.5 days longer, 95%CI: 0.2,2.7) and C173 (mean 1.4 days longer, 95%CI: 0.3,2.5). Similar results were seen between the two clusters selected for 2018/2019. Conclusion: In this study of hospitalized influenza patients, we show that distinct clusters with higher disease acuity can be identified and could be targeted for evaluations of vaccine and influenza antiviral effectiveness against disease attenuation. The association of higher disease acuity with glucose level merits evaluation.

INTRODUCTION

Infectious respiratory diseases caused by influenza virus, respiratory syncytial virus, and SARS-CoV-2 can cause significant illness and are responsible for hundreds of thousands of hospitalizations in the United States annually[1]. Data on in-hospital progression of disease and treatment course are broadly available and used to evaluate severity of illness[2,3], or the impact of vaccination[4,5] and treatment[6-8]. However, the primary cause of admission, particularly in those with baseline multimorbidity, might not be due to acute illness but other causes either exacerbated by milder respiratory tract infection (e.g., asthma) or possibly unrelated to infection (e.g., dehydration). This might bias results of vaccine or antiviral effectiveness against prevention or attenuation of severe disease. Differences in general health and health care seeking behaviour are difficult to directly measure[9,10], and individuals may present and be admitted to the hospital at different stages in their disease course with varying disease severity. These patterns vary by population, health system, and

specific etiology[11-14]. While patients hospitalized with respiratory diseases such as influenza have historically been older with significant comorbidity[11,15], the pattern has differed in various phases of the COVID-19 pandemic[16].

The heterogeneity of the hospitalized population at admission creates challenges when examining events occurring during hospitalization. Differential baseline comorbidity and presenting symptomology can significantly confound the use of hospital data as a surveillance metric for respiratory disease severity, and can bias estimates of the effectiveness of interventions to reduce influenza morbidity or progression of disease.

Unsupervised machine learning algorithms provide a way to derive and characterize different groups of patients independent of an outcomes or treatment framework[17,18]. When applied to clinical data, this methodology can help identify distinct phenotypes of individuals driven by underlying relationships between health metrics. The aims of the current study were to develop clinically distinct clusters of patients based on laboratory and physiologic measurements within the first 24 hours of hospitalization, to determine if cluster membership was associated with worse in-hospital outcomes, and to evaluate the association of influenza vaccination on in-hospital outcomes within a given cluster.

METHODS

Institutional review board approval for the US Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) study was obtained from the University of Michigan. Cases were identified from 2017-2018 and 2018-2019 enrollees from a single site of the HAIVEN study, encompassing two major hospital systems in southeast Michigan (Michigan Medicine Hospital, Ann Arbor and Henry Ford Hospital, Detroit). Inclusion criteria for the HAIVEN cohort have been described elsewhere[15,19]. Briefly, adult patients [?]18 years of age were eligible for participation if they presented to the hospital within 10 days of symptom onset or worsening and had a diagnosis or chief complaint broadly consistent with an acute respiratory illness such as influenza or pneumonia. Patients were prospectively recruited and completed a brief interview and research-assistant performed specimen collection to determine laboratory-confirmed influenza illness. Only individuals who tested positive for influenza were included in our analysis.

All participants were interviewed in-person at the time of study enrollment by research personnel. Data obtained from the electronic health record (EHR) via trained research staff chart review or database queries included demographics and comorbid conditions, acute illness characteristics such as symptom duration/type, laboratory and physiologic measures, and outcomes including ICU admission and hospital length of stay[15,19].

Physiologic characteristics of interest

Minimum and maximum values for physiologic and laboratory variables of interest were collected from the EHR for the first 24 hours of the hospital stay. Physiologic data collected included heart rate, respiratory rate, systolic blood pressure (SBP), temperature, and oxygen saturation[20]. Laboratory data collected included blood glucose, haematocrit, haemoglobin, blood urea nitrogen (BUN), sodium, pH, white blood cell (WBC) count, creatinine, platelets, bilirubin, and lactic acid[20]. Estimated glomerular filtration rate (eGFR) was computed using the maximum creatinine value within the 24-hour window[21].

Clustering of data

Variables were selected for clustering algorithm inclusion based on clinical relevance to indicating illness severity. Specific variables selected for inclusion were as follows. Both minimum and maximum values were included unless otherwise specified: temperature, heart rate (maximum), SBP, blood glucose, creatinine (maximum), haematocrit (minimum), sodium, WBC, platelets (minimum), respiratory rate (maximum), oxygen saturation (minimum), eGFR, and time from symptom onset to admission. Missing data for all selected physiologic measures were imputed using the study population mean stratified by age group (18-49, 50-64, 65+) and hospital. A table of selected metrics can be found in Supplemental Table 1.

Prior to the creation of clusters, Hopkin's statistic was used to assess the randomness of the distribution of the data in relation to a uniform distribution. Values of 0.5 for this statistic indicate data are similar

to the univariate distribution, while values closer to 1 indicate the data may contain clusters. The use of this statistic helps reduce the risk of a machine learning algorithm detecting clusters when the data do not actually have clusters within[22].

Data were classified separately for each influenza season using the k-medoids Partitioning Around the Medoids (PAM) algorithm with Manhattan distance. Briefly, k-medoids clustering assigns groups to a set of data based on the distance to an assigned central data point of a cluster[23]. At the start, these medoids are randomly assigned, and the algorithm iterates through different selections of data centroids and cluster groupings until the distance from the centroid is minimized to all other data points in the cluster. K-medoids clustering is more robust in the presence of outliers than other centroid-based clustering algorithms such as k-means since the chosen centroid is an observed data point. Additionally, this algorithm assigns all data observations to a cluster; this is preferred in a cohort of hospitalized individuals where biologically plausible data outliers are of interest. The appropriate number of clusters to be assigned for a given season was chosen using the largest average silhouette width, a measure of the distance from points in one cluster to another, with one to a maximum of ten clusters tested.

The k-medoids clustering was performed using the "pam" function in R. Following group assignment, the silhouette width of each cluster was computed using the "silhouette" function. An average silhouette width close to 1 indicates perfect clusters, and an average silhouette width around 0 indicates clusters lie close together. A negative silhouette width for a given observation indicates that the data point may have been misclassified.

Additional Covariates

Additional covariates of interest for adjusted analyses included age group (18-49 years, 50-64 years, 65+ years), sex, BMI, Charlson Comorbidity Index (CCI), admitting hospital, influenza strain and subtype, and influenza vaccination status.

Hospitalization Severity Metrics

Outcomes considered for severity of illness during the hospitalization included intensive care unit (ICU) admission, mechanical ventilator use, and total hospital length of stay (continuous, and prolonged defined as [?]8 days[24]).

Statistical Analysis

General descriptive statistics of all data were computed separately for each influenza season (2017/2018 and 2018/2019) and were reported as means with standard deviations, medians with interquartile range, or frequency and percentage, as appropriate. The normality of data and presence of outliers were assessed using histograms and box-and-whisker plots. Data clustering was performed as above with each year using the PAM algorithm, and model results reported. Patient and clinical characteristics between clusters were compared using Chi-squared or Fisher's exact tests for categorical variables and independent t-tests, ANOVA, Mann-Whitney U, or Kruskal-Wallis tests for continuous variables, as appropriate.

To determine if different classes of early hospitalization characteristics were associated with severe hospital sequelae, a series of models were constructed separately for each influenza season. For binary outcomes (ICU admission, ventilator use, and prolonged hospital length of stay), Firth's logistic regression models were constructed. Generalized linear models were used for the continuous outcome of hospital length of stay. Variables chosen a priori for model inclusion were k-medoids cluster group, age, sex, CCI (as a continuous variable), hospital, and influenza vaccination status. An exploratory analysis was conducted as in the primary analysis with the removal of outliers prior to clustering, with an outlier conservatively defined as a value less than the 1st quartile-1.5*(interquartile range) or greater than the 3rd quartile+1.5*(interquartile range). Outliers were then imputed to the mean of remaining values stratified by age group and hospital. To maintain comparability with the primary analysis, the same number of clusters were implemented within a given influenza year.

Analysis was conducted using RStudio version 1.2.5042 and SAS v9.4 (SAS Institute, Cary, NC). A p-value of 0.05 was considered statistically significant.

RESULTS

There were 242 individuals who met inclusion criteria from the 2017/2018 influenza season and 115 individuals from the 2018/2019 season (Supplemental Table 2). Overall, patients were predominantly female, obese, and vaccinated against influenza. More individuals experienced ICU admission (13.0% vs. 6.2%; p=0.031) and mechanical ventilation (16.5% vs. 9.9%; p=0.074) in the 18/19 influenza season than the preceding season. Overall characteristics of values included in the clustering algorithm are shown in Table 1.

2017/2018 Cohort

The Hopkin's statistic for 2017/2018 was 0.810. The 3-cluster model was selected with the highest average silhouette width of 0.15 (Figure 1). The silhouette plots indicate the possibility of minor misclassification of some individuals. There were significant differences in race, age, CCI, and diabetes between clusters (Table 2). For the variables included in the PAM algorithm, those in Cluster 1 ($C_{17}1$) had significantly higher mean glucose (minimum mean 210.4mg/dL, SD 66.9) than those in Cluster 2 ($C_{17}2$) (minimum mean 90.5mg/dL, SD 16.4) and Cluster 3 ($C_{17}3$) (minimum mean 110.0mg/dL, SD 26.7). Those in $C_{17}2$ had significantly lower maximum heart rate, maximum systolic blood pressure, minimum white blood cell count, minimum platelets, and estimated glomerular filtration rate than the other two clusters. Those in $C_{17}2$ also had significantly higher maximum creatinine than the other clusters. The rate of being mechanically ventilated was higher in $C_{17}1$ than $C_{17}2$ (22.6% vs. 6.9%), and the overall hospital length of stay was longer for those in $C_{17}1$ than $C_{17}3$ (mean 4.5 days (SD 4.4) vs. mean 2.8 days (SD 2.4)).

After adjustment for age group, sex, hospital, continuous CCI, and influenza vaccination status, those in $C_{17}1$ had 5.6 times the odds of having a mechanical ventilator than those in $C_{17}2$ (95%CI:1.49,21.1; Figure 2). Additionally, those in $C_{17}1$ had a significantly longer model-adjusted mean hospital length of stay than those in both $C_{17}2$ (mean 1.5 days longer, 95%CI:0.2,2.7) and $C_{17}3$ (mean 1.4 days longer, 95%CI:0.3,2.5). There were no significant differences between clusters for the outcomes of ICU stay or prolonged hospital stay. Vaccination status was not associated with adverse outcomes in the fully adjusted models.

2018/2019 Cohort

The Hopkin's statistic for 2018/2019 was 0.837. The 2-cluster model was selected with the highest average silhouette width of 0.27 (Figure 3). The silhouette plots indicate the possibility of moderate misclassification of some individuals in Cluster 1 ($C_{18}1$). There were significant differences in underlying comorbidity between clusters, though there were no major differences in demographics (Table 2). For the variables included in the PAM algorithm, those in $C_{18}1$ had significantly higher mean glucose (minimum mean 157.2mg/dL, SD 82.2) than those in Cluster 2 ($C_{18}2$) (minimum mean 99.7mg/dL, SD 21.4). Additionally, those in C181 had significantly lower minimum oxygen saturation than those in $C_{18}2$ (mean 88.5 (SD 6.7) vs. mean 91.6 (SD 3.7)). The $C_{18}1$ group had higher rates of mechanical ventilation (32.4% vs. 9.0%) and prolonged hospital stay [?] 8 days (16.2% vs. 3.9%) than those in $C_{18}2$, as well as a longer hospital stay (mean 5.3 days (SD 5.7) vs. mean 2.8 days (SD 2.0)).

After adjustment for age group, sex, hospital, continuous CCI, and influenza vaccination status, those in $C_{18}1$ had 4.9 times the odds of being mechanically ventilated than those in $C_{18}2$ (95%CI:1.7,14.3; Figure 2), and 4.3 times the odds of having a prolonged hospital stay (95% CI:1.2,16.4). After adjustment, those in $C_{18}1$ had a significantly longer model-adjusted mean hospital length of stay than those in $C_{18}2$ (mean 2.5 days longer, 95%CI:1.1,3.9). Vaccination status was not associated with adverse outcomes in the fully adjusted models.

Sensitivity Analysis

Imputation of outliers in both influenza cohorts and their effect on the sample are shown in Supplemental Table 3. After model adjustment with the new clusters, there were no statistically significant differences in

the odds or model-adjusted means of outcomes for the 2017/2018 influenza season (Supplemental Figure 1). For the 2018/2019 influenza season, after adjustment those in new cluster 1 had significantly higher odds of an intensive care unit stay compared with those in new cluster 2 (OR 4.62, 95%CI:1.34,15.97; Supplemental Figure 1).

DISCUSSION

In this cohort of individuals in the 2017/2018 and 2018/2019 influenza seasons, we created clinically meaningful groups using k-medoids clustering to improve the analysis of severity in a population of patients hospitalized with influenza. Our results suggest that those who were in clusters with hyperglycemia and lower oxygen saturation at admission had higher risk of adverse in-hospital sequelae, and are thus potential cohorts of interest for further study of vaccine or antiviral effects.

We found glucose to be significantly different between clusters, with one cluster having significantly higher glucose in both years. The distribution of diabetes was also consistent across years, with approximately 70% prevalence in the high-glucose clusters and 30% prevalence in the non-hyperglycemic clusters. Together, these results highlight that the use of simple dichotomous classifications for complex conditions such as diabetes may not accurately indicate a patient's risk for adverse outcomes. Indeed, controlling for such complex confounding has long been problematic within infectious disease severity research, most recently when examining treatments and hospital outcomes related to infection with SARS-CoV-2, leading to inconsistent results[25-27]. This challenge is due in part to differential measurement and management of confounding, including analyses at the point of hospitalization admission, given model limitations in the number of confounders which can be included and their often-complex interrelationships. The use of techniques such as k-medoids clustering to simultaneously account for multiple measures of comorbidity and group like patients together independent of outcomes-based analysis provides a tool to increase homogeneity within groups and heterogeneity across groups for a more robust confounding adjustment.

More traditional dimensional reduction methods such as the use of propensity score matching have often been used to account for differential patterns of comorbidities between groups of interest. While propensity score matching is useful in reducing heterogeneity in the presence of a single exposure of interest, it becomes complex in instances where multiple treatments or exposures are being compared simultaneously. Additionally, there is inherent reduction in sample size when matching, limited by the number of individuals with and without the exposure having similar propensity scores; individuals in either group with uncommon comorbidity profiles may be overlooked and excluded from the matching if their propensity score does not align. For example, a 2020 study by Groeneveld et al examining the effective of oseltamivir lost 36% of oseltamivir patients and 65% of controls when matching, reducing the sample size to 88 pairs[6]. While use of propensity score matching has been shown to reduce bias[28], such significant loss of data, especially in a rare-outcomes setting, may lead to an increase in Type II error, and thus incorrect conclusions, due to inadequate power[29,30]. K-medoids clustering can be used to identify subgroups that are biologically different without such restrictions, maintaining sample size for more robust analysis of effect modification by multiple treatment types. It should be noted that outliers within the range of biologically normal values are of great clinical significance, as these individuals may be at higher risk for adverse outcomes. K-medoids clustering is robust to such outliers through use of data-derived centroids for the clusters, rather than an arbitrary mean.

This study has several strengths, most notably that the cohort was nested within a large prospective two-center study of influenza vaccine effectiveness across multiple seasons, allowing for a robust and diverse analytic cohort. Both case definition and EHR data capture were standardized across sites, reducing heterogeneity of data quality. Additionally, the use of two hospitals within our region allowed for a more generalizable analysis. The biggest limitation of the study is small sample size and small number of outcomes; however, we believe our analysis has minimized some of the bias from this limitation.

The use of k-medoids clustering to characterize heterogeneity in severity analysis has many direct and current applications. One of the most immediate applications can be for evaluating the effectiveness of new and existing antivirals for severe respiratory disease. Previous studies of such treatments have utilized

traditional methods of covariate adjustment, which may contribute to heterogeneity of study findings[31]. The use of this clustering method to phenotype baseline presentation can reduce this confounding, and can be quickly implemented for these analyses. Such a technique will be needed as we continue understand how new antiviral treatments affect severity, and how vaccination impacts severity in instances of low vaccine effectiveness.

CONCLUSIONS

In conclusion, we found it was possible to cluster adult patients hospitalized with influenza into clinically distinct groups by baseline characteristics independent of a clinical outcome. Those with hyperglycaemia and lower oxygen saturation at admission were more likely to experience adverse events in our cohort, including prolonged hospitalization. The k-medoids algorithm is a promising approach to disentangling the heterogeneity surrounding hospital admissions.

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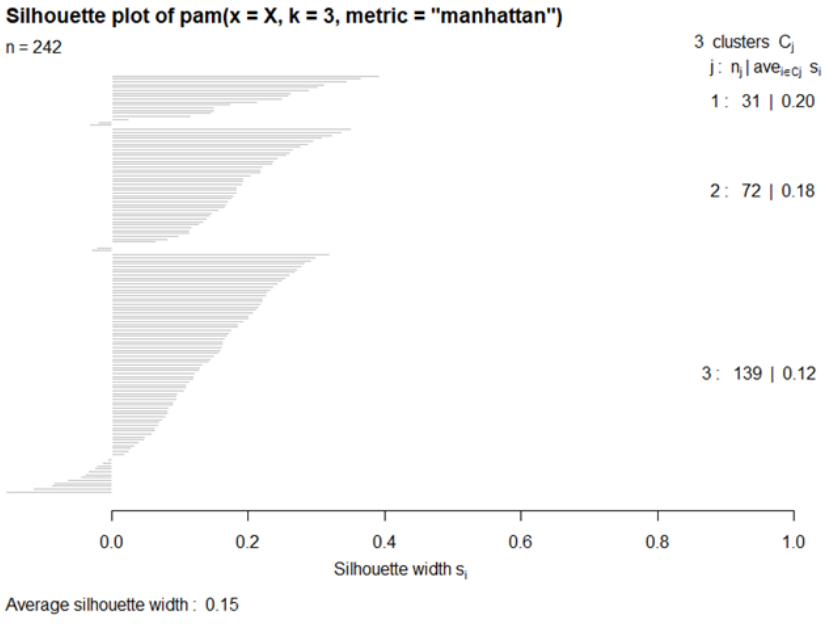
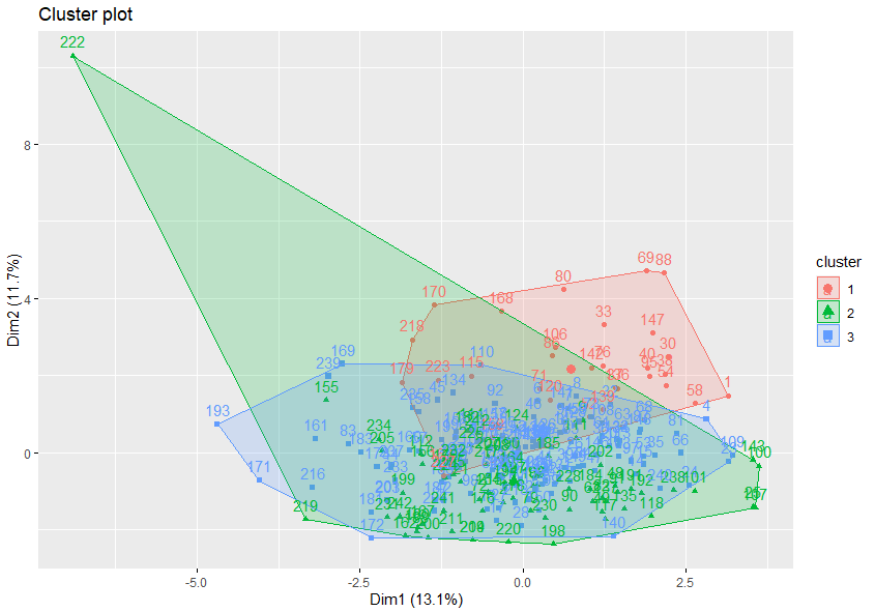
Table 1. Patient characteristics included in k-medoids algorithm overall by influenza season.

	2017/2018 Season (N=242)
Clustering Metrics Measured Within 24 Hours of Admission	**Clustering Metrics Measured Within 24 Hou**
Time from symptom onset to admission (days)	2.4 (2.1)
Temperature	
Min	97.9 (0.6)
Max	100.0 (1.5)
Heart Rate (Max)	107.0 (18.3)
Systolic Blood Pressure	
Min	111.5 (16.7)
Max	137.0 (30.3)
Glucose	
Min	117.0 (49.1)
Max	159.5 (83.5)
Creatinine (Max)	1.3 (1.6)
Hematocrit (Min)	35.6 (5.4)
Sodium	
Min	135.7 (3.1)
Max	138.1 (3.3)
White Blood Cells	
Min	6.5 (3.7)
Max	8.6 (7.6)
Platelets (Min)	178.6 (67.2)
Respiratory Rate (Max)	24.2 (5.5)
Oxygen Saturation (Min)	91.6 (4.4)
Estimated glomerular filtration rate	75.0 (39.8)

Data are presented as mean (standard deviation).





A.B.

Figure 1. Clustering metrics for the 2017/2018 influenza season, including the silhouette plot of k-medoids clusters(A) and the top two principal components of data in the k-medoids clustering algorithm(B), with cluster membership highlighted.

Table 2. Patient characteristics by k-medoids cluster by influenza season

	2017/2018 Influenza Season	2017/2018 Influenza Season	2017/2018 Influenza Season	2017/2018 Influenza Season	2018/2019 Influenza Season	2018/2019 Influenza Season	2018/2019 Influenza Season
	Cluster 1 (N=31)	Cluster 2 (N=72)	Cluster 3 (N=139)	P-Value	Cluster 1 (N=37)	Cluster 2 (N=78)	P-Value
Demographics	Demographics	Demographics	Demographics	Demographics	Demographics	Demographics	Demographic
Age				0.029[c]			0.704
18-49	6 (19.4)	15 (20.8)	44 (31.7)		14 (37.8)	24 (30.8)	
50-64	14 (45.2)	18 (25.0)	48 (34.5)		10 (27.0)	26 (33.3)	
[?]65	11 (35.5)	39 (54.2)	47 (33.8)		13 (35.1)	28 (35.9)	
Male Sex	10 (32.3)	35 (48.6)	54 (38.9)	0.226	14 (37.8)	40 (51.3)	0.177
Race							
White	10 (32.3)	51 (70.8)	48 (34.5)	<0.001[ac]	19 (51.4)	33 (42.3)	0.363
Black	18 (58.1)	20 (27.8)	79 (56.8)	<0.001[ac]	18 (48.7)	42 (53.9)	0.602
Asian	2 (6.5)	0 (0.0)	1 (0.7)	0.018	0 (0.0)	1 (1.3)	0.489
Hispanic	1 (3.2)	0 (0.0)	7 (5.0)	0.152	0 (0.0)	5 (6.4)	0.105
Hospital				<0.001[ac]			0.995
1	8 (25.8)	46 (63.9)	35 (25.2)		19 (51.4)	40 (51.3)	
2	23 (74.2)	26 (36.1)	104 (74.8)		18 (48.7)	38 (48.7)	
Flu Strain and Subtype/Lineage				0.852			0.744
Type A–H1	1 (3.2)	4 (5.6)	10 (7.2)		15 (40.5)	29 (37.2)	

	2017/2018 Influenza Season	**2017/2018 Influenza Season**	**2017/2018 Influenza Season**	**2017/2018 Influenza Season**	**2018/2019 Influenza Season**	**2018/2019 Influenza Season**	**2018/2019 Influenza Season**
Type A–H3	22 (71.0)	41 (56.9)	86 (61.9)		14 (37.8)	33 (42.3)	
Type B–Victoria	0 (0.0)	0 (0.0)	2 (1.4)		0 (0.0)	2 (2.6)	
Type B–Yamagata	7 (22.6)	23 (31.9)	32 (23.0)		0 (0.0)	1 (1.3)	
Unknown Subtype/Lineage	1 (3.2)	4 (5.6)	8 (5.8)		8 (21.6)	13 (16.7)	
Unknown Type	0 (0.0)	0 (0.0)	1 (0.7)		0 (0.0)	0 (0.0)	
Received Influenza Vaccine	17 (54.8)	48 (66.7)	82 (59.0)	0.429	24 (64.9)	49 (62.8)	0.832
Comorbidities	**Comorbidities**	**Comorbidities**	**Comorbidities**	**Comorbidities**	**Comorbidities**	**Comorbidities**	**Comorbiditie**
Charlson Comorbidity Index, mean (SD)	3.9 (2.8)	4.3 (3.1)	2.4 (2.3)	<0.001[bc]	4.4 (2.7)	3.5 (3.0)	0.139
Charlson Comorbidity Index Group				<0.001[bc]			0.031
0	1 (3.2)	8 (11.1)	25 (18.0)		0 (0.0)	13 (16.7)	
1-2	11 (35.5)	16 (22.2)	64 (46.0)		13 (35.1)	22 (28.2)	
[?]3	19 (61.3)	48 (66.7)	50 (36.0)		24 (64.9)	43 (55.1)	
BMI Category				0.353			0.177
Underweight (<18.5)	0 (0.0)	2 (2.8)	5 (3.6)		1 (2.7)	4 (5.1)	
Normal/Healthy weight (18.5-24.9)	3 (9.7)	14 (19.4)	34 (24.5)		7 (18.9)	17 (21.8)	
Overweight (25-29.9)	7 (22.6)	23 (31.9)	29 (20.9)		4 (10.8)	22 (28.2)	
Obese (30-39.9)	17 (54.8)	26 (36.1)	53 (38.1)		17 (46.0)	23 (29.5)	
Morbidly obese ([?]40)	4 (12.9)	7 (9.7)	18 (13.0)		8 (21.6)	12 (15.4)	
High-Risk Comorbidities							
Heart Disease	14 (45.2)	45 (62.5)	50 (36.0)	0.001[c]	23 (62.2)	38 (48.7)	0.177
Heart Failure	6 (19.4)	25 (34.7)	27 (19.4)	0.039[c]	17 (46.0)	17 (21.8)	0.008
Asthma	9 (29.0)	17 (23.6)	46 (33.1)	0.359	10 (27.0)	17 (21.8)	0.536
COPD	11 (35.5)	23 (31.9)	49 (35.3)	0.881	16 (43.2)	28 (35.9)	0.449

	2017/2018 Influenza Season	**2017/2018 Influenza Season**	**2017/2018 Influenza Season**	**2017/2018 Influenza Season**	**2018/2019 Influenza Season**	**2018/2019 Influenza Season**	**2018/2019 Influenza Season**
Other Lung Conditions	14 (45.2)	24 (33.3)	44 (31.7)	0.354	21 (56.8)	35 (44.9)	0.234
Diabetes	24 (77.4)	24 (33.3)	38 (27.3)	<0.001[ab]	29 (78.4)	25 (32.1)	<0.001
Renal	13 (41.9)	42 (58.3)	36 (25.9)	<0.001[c]	21 (56.8)	30 (38.5)	0.065
Blood Disorders	2 (6.5)	16 (22.2)	4 (2.9)	<0.001[c]	6 (16.2)	9 (11.5)	0.557
Immunosuppression	5 (16.1)	24 (33.3)	31 (22.3)	0.104	10 (27.0)	25 (32.1)	0.584
Malignancy	8 (25.8)	25 (34.7)	13 (9.4)	<0.001[bc]	7 (18.9)	22 (28.2)	0.284
Metabolic Disorders	20 (64.5)	39 (54.2)	49 (35.3)	0.002[bc]	20 (54.1)	43 (55.1)	0.914
Liver Disorders	3 (9.7)	11 (15.3)	14 (10.1)	0.501	5 (13.5)	5 (6.4)	0.288
Neurological/Musculoskeletal	11 (35.5)	20 (27.8)	30 (21.6)	0.228	11 (29.7)	26 (33.3)	0.699
Cerebrovascular Disorders	3 (9.7)	2 (2.8)	5 (3.6)	0.242	1 (2.7)	3 (3.9)	0.999
Endocrine	3 (9.7)	16 (22.2)	22 (15.8)	0.258	8 (21.6)	13 (16.7)	0.521
Long-term Medication	4 (12.9)	13 (18.1)	18 (13.0)	0.586	8 (21.6)	17 (21.8)	0.983
Morbid Obesity	5 (16.1)	11 (15.3)	18 (13.0)	0.844	12 (32.4)	12 (15.4)	0.036
Clustering Metrics Measured Within 24 Hours of Admission	**Clustering Metrics Measured Within 24 Hours of Admission**	**Clustering Metrics Measured Within 24 Hours of Admission**	**Clustering Metrics Measured Within 24 Hours of Admission**	**Clustering Metrics Measured Within 24 Hours of Admission**	**Clustering Metrics Measured Within 24 Hours of Admission**	**Clustering Metrics Measured Within 24 Hours of Admission**	**Clustering Metrics Measured Within 24 Hours of Admission**
Time from symptom onset to admission (days), mean (SD)	2.6 (2.1)	2.2 (2.0)	2.5 (2.0)	0.597	2.6 (1.7)	2.6 (2.1)	0.886
Temperature							
Min	97.8 (0.6)	97.9 (0.5)	97.9 (0.6)	0.691	97.9 (0.5)	98.1 (0.6)	0.036
Max	99.7 (1.5)	100.2 (1.5)	100.0 (1.5)	0.190	99.9 (1.4)	100.2 (1.5)	0.301
Heart Rate (Max), mean (SD)	109.1 (16.1)	101.3 (18.7)	109.5 (18.0)	0.006[ac]	110.5 (20.6)	110.7 (18.7)	0.966

	2017/2018 Influenza Season	**2017/2018 Influenza Season**	**2017/2018 Influenza Season**	**2017/2018 Influenza Season**	**2018/2019 Influenza Season**	**2018/2019 Influenza Season**	**2018/2019 Influenza Season**
Systolic Blood Pressure, mean (SD)							
Min	117.0 (15.2)	111.2 (17.0)	110.3 (16.7)	0.134	104.4 (18.2)	105.4 (14.3)	0.732
Max	149.5 (30.3)	126.5 (29.2)	139.7 (29.4)	0.001[ac]	127.3 (38.9)	125.9 (28.9)	0.828
Glucose, mean (SD)							
Min	210.4 (66.9)	90.5 (16.4)	110.0 (26.7)	<0.001[abc]	157.2(82.2)	99.7 (21.4)	<0.001
Max	311.6 (106.0)	139.4 (68.5)	136.0 (37.0)	<0.001[ab]	292.0 (133.4)	119.5 (26.3)	<0.001
Creatinine (Max), mean (SD)	1.2 (0.8)	1.8 (2.5)	1.2 (0.9)	0.018[ac]	1.9 (2.4)	1.6 (2.0)	0.502
Hematocrit (Min), mean (SD)	36.7 (4.7)	34.6 (5.6)	36.0 (5.4)	0.096	35.4 (6.2)	35.6 (6.2)	0.885
Sodium, mean (SD)							
Min	134.4 (3.9)	136.0 (2.9)	135.9 (3.0)	0.034[ab]	134.0 (5.4)	135.9 (3.0)	0.015
Max	137.1 (4.1)	139.3 (3.4)	137.7 (3.0)	0.001[ac]	138.3 (4.7)	138.0 (3.5)	0.754
White Blood Cells, mean (SD)							
Min	7.7 (3.4)	5.4 (5.0)	6.8 (2.7)	0.005[ac]	8.3 (4.2)	7.2 (9.8)	0.511
Max	9.4 (4.7)	8.9 (12.6)	8.3 (3.7)	0.710	12.0 (7.1)	9.4 (14.9)	0.317
Platelets (Min), mean (SD)	171.5 (44.7)	121.3 (39.8)	209.9 (62.5)	<0.001[abc]	190.9 (76.3)	195.2 (135.5)	0.856
Respiratory Rate (Max), mean (SD)	25.9 (5.7)	23.8 (5.3)	24.0 (5.6)	0.176	27.5 (9.3)	25.6 (7.7)	0.243

	2017/2018 Influenza Season	**2017/2018 Influenza Season**	**2017/2018 Influenza Season**	**2017/2018 Influenza Season**	**2018/2019 Influenza Season**	**2018/2019 Influenza Season**	**2018/2019 Influenza Season**
Oxygen Saturation (Min), mean (SD)	90.7 (4.9)	91.1 (5.3)	92.0 (3.7)	0.182	88.5 (6.7)	91.6 (3.7)	0.002
Estimated glomerular filtration rate, mean (SD)	71.6 (26.2)	59.4 (28.2)	83.8 (44.7)	<0.001[ac]	65.7 (40.8)	77.3 (40.6)	0.154
Outcomes	**Outcomes**	**Outcomes**	**Outcomes**	**Outcomes**	**Outcomes**	**Outcomes**	**Outcomes**
ICU Admission	3 (9.7)	4 (5.6)	8 (5.8)	0.690	8 (21.6)	7 (9.0)	0.060
Mechanical Ventilator use	7 (22.6)	5 (6.9)	12 (8.6)	0.038[a]	12 (32.4)	7 (9.0)	0.002
Hospital LOS, mean (SD)	4.5 (4.4)	3.5 (2.9)	2.8 (2.4)	0.009[b]	5.3 (5.7)	2.8 (2.0)	0.001
Prolonged LOS ([?]8 days)	4 (12.9)	4 (5.6)	7 (5.0)	0.250	6 (16.2)	3 (3.9)	0.021

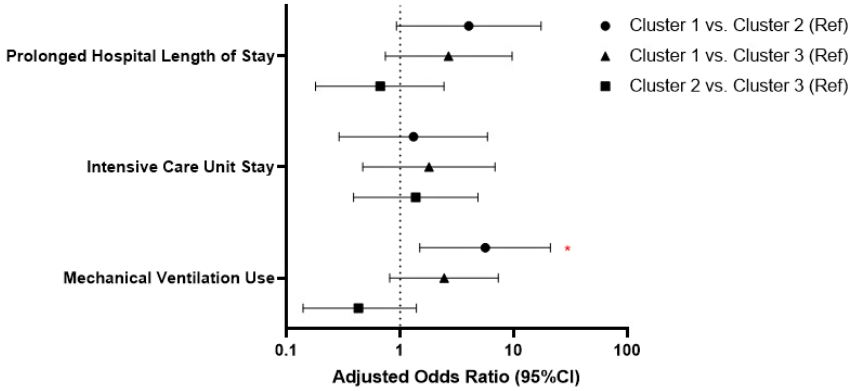
Data are presented as either column frequency (percentage) or mean (standard deviation(SD)), as appropriate. Overall p-values were computed using chi-square for categorical variables and ANOVA or Kruskal-Wallis for continuous variables.

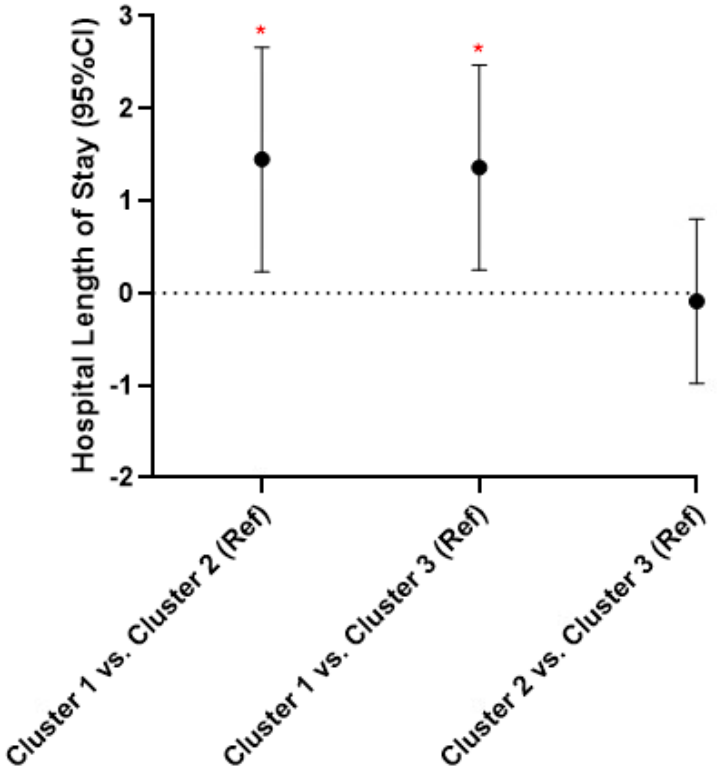
* Missing data were imputed based on age- and hospital-specific mean values.

[a] 2017/2018 Cluster 1 vs 2017/2018 Cluster 2, $p<0.05$

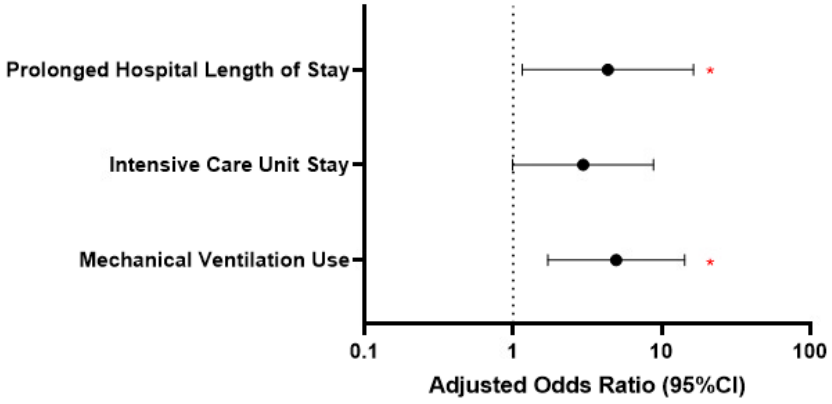
[b] 2017/2018 Cluster 1 vs 2017/2018 Cluster 3, $p<0.05$

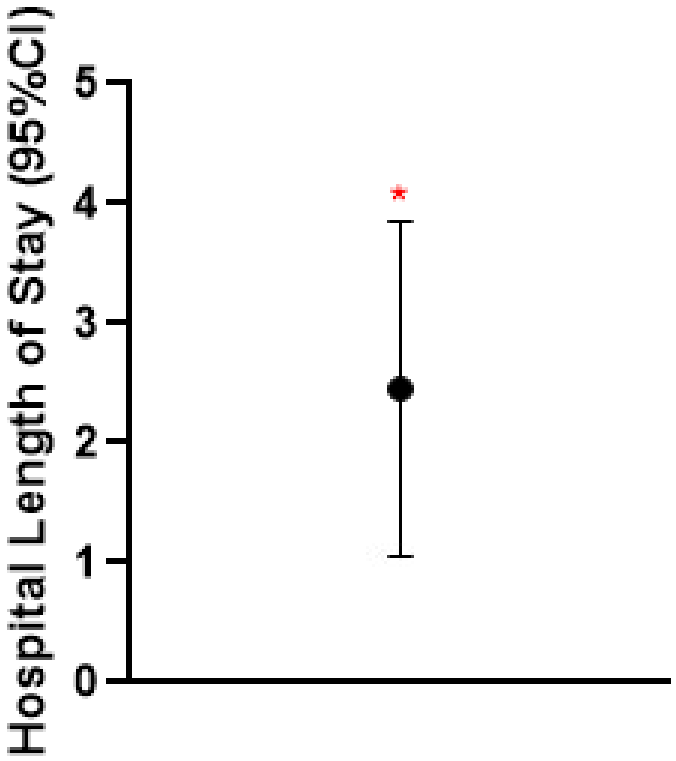
[c] 2017/2018 Cluster 2 vs 2017/2018 Cluster 3, $p<0.05$





A. B.

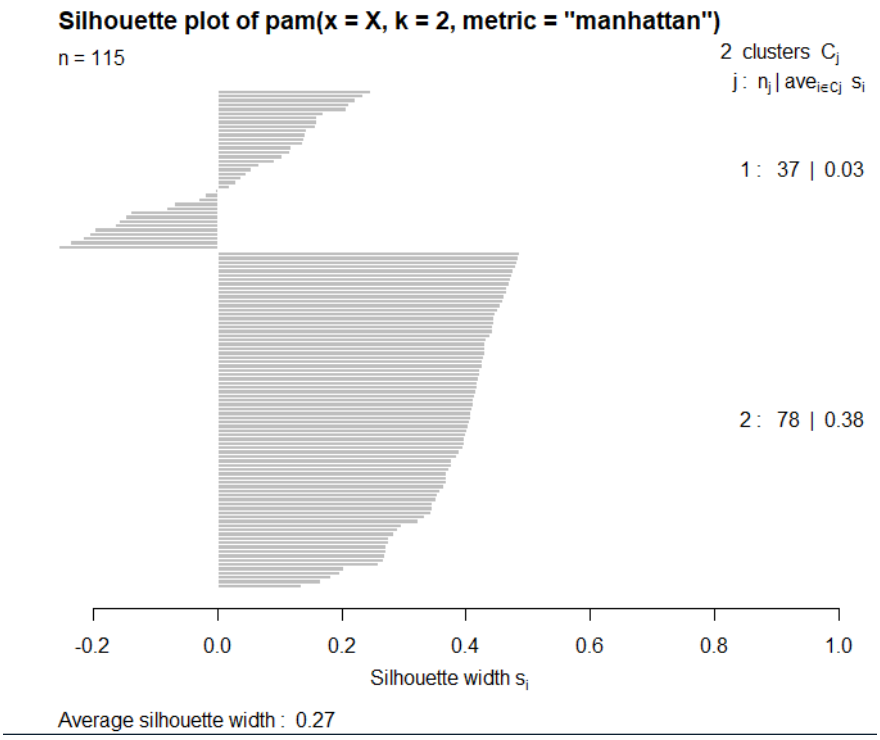




C.

D.

Figure 2. Adjusted odds ratios(A,C) and difference in model-adjusted means(B,D) with 95% confidence intervals for outcomes. * indicates statistically significant differences between comparison groups. Models were adjusted for age, sex, hospital, continuous CCI, and influenza vaccination status.



A.

B.

Figure 3. Clustering metrics for the 2018/2019 influenza season, including the silhouette plot of k-medoids clusters(A) and the top two principal components of data in the k-medoids clustering algorithm(B), with cluster membership highlighted.