Explaining Hospital Length of Stay of Patients Admitted with Seasonal Influenza Infection

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Explaining Hospital Length of Stay of Patients Admitted with Seasonal Influenza Infection

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Background: The annual occurrence of seasonal influenza virus poses a significant health burden worldwide. There is evidence that certain populations are more at risk for influenza infection, such as cigarette smokers, the elderly, and patients with cardiopulmonary disorders. In some cases influenza virus presents itself as a nosocomially acquired infection. Thus, monitoring the length of time that patients are hospitalized with influenza is of clinical importance. The objectives of this study were to identify predisposing characteristics to hospitalization with influenza and to determine whether cigarette smoking correlates to extended LOS (length of stay in hospital). It was hypothesized that cigarette smoking and presence of COPD (Chronic Obstructive Pulmonary Disease) correlates most significantly to prolonged LOS.

Methods: After ethical approval was achieved from the University of Vermont Institutional Review Board, information was collected from a retrospective cohort of adult patients admitted to FAHC (Fletcher Allen Health Care) with influenza infection during the 2012-2013 flu season. Univariate analyses were performed to compare explanatory variables with LOS as an outcome. A generalized linear model was constructed to further explain correlations with LOS.

Results: Among 54 patients, the median age was 73.5 and the median BMI (Body Mass Index) was 26.1 kg/m². The cohort was split almost equally between males and females and exactly two-thirds were smokers, with just under one-third of the patients diagnosed with COPD. Univariate analyses determined that patients with COPD, diabetes, and more than one comorbid condition significantly increased LOS ($p = 0.0129^*, 0.0191^*, 0.0046^*$; respectively). A generalized linear model revealed that patients with COPD and more than one comorbid condition were estimated have a significantly prolonged LOS ($p = 0.0266^*$ and $0.0079^*$, respectively). Smoking status was not determined to be a significant explanatory variable in either set of analysis.

Conclusions: Significant indicators for longer LOS are explained by diagnosis of COPD and patients with more than one comorbidity. Promoting the use of vaccination for these at-risk individuals is imperative, as influenza infection is a serious issue.

One of the most common disease syndromes in humans are viral infections of the respiratory tract, and of these viruses, influenza viruses are one of the more significant causes of high morbidity and mortality. Epidemics of influenza occur annually in the temperate zones during the winter months. Influenza viruses are segmented, negative-sense, double-stranded RNA viruses.
Some viral particles contain envelope proteins, which increase virulence through three transmembrane proteins: HA (hemagglutinin), NA (neuraminidase), and M2, an ion channel facilitator. HA provides the receptor-binding site for viral-antibody neutralization, an essential function for virus infectivity. Removal of sialic acid, the cell surface receptor for influenza, a process that is aided by NA, allows for release of viral particles from the cell surface and viral spread. The ion channel is crucial during the uncoating process of the virus.

The arrangements of surface glycoproteins on HA and NA determine variable subtypes of influenza viruses. Because influenza virus is segmented, many arrangements are possible and explains the continual appearance of new antigenic strains of influenza, as well as accounting for the occurrence of historical pandemics and yearly epidemics. The evolution of new strains of viruses arises through antigenic drift and antigenic shift, which is characterized by point mutations in the surface glycoproteins of HA.

Influenza types A and B are the main human pathogens. Of the recently circulating influenza viruses, the H3N2 strain of influenza A is the most virulent. The aptitude of influenza virus to mutate explains its severe impact on humans in terms of morbidity and mortality, relative to respiratory viruses.

Influenza can cause a broad range of illness, ranging from symptomless infection to onset primary viral pneumonia and secondary bacterial pneumonia. In its full form, influenza is an acute respiratory disease characterized by high fever, cough, headache, and inflammation of the upper respiratory tree and trachea. Symptoms typically persist for seven to ten days.

The severity of viral illness is highly dependent on the particular virus and host factors. Much of the detrimental effects from influenza virus are concentrated in high-risk groups. These include cigarette smokers, the elderly, and those with comorbid cardiovascular and pulmonary disease.

Cigarette Smoking: A Risk Factor for Influenza Infection

According to researchers from the University of California San Francisco, infectious diseases could rival the usual suspects of sources of morbidity and mortality associated with smoking cigarettes, such as heart disease, cancer, and chronic lung disease. Indeed, there is increasing evidence that smokers are more susceptible to respiratory viral infections, although the mechanisms that mediate these effects are still being investigated.

Cigarette smoke is a heterogeneous, complex mixture, containing over 4,700 chemical compounds and oxidants. These chemical agents induce an oxidative burden on the body, causing disruptions in normal mechanisms of cellular signaling that can lead to cellular damage of the lungs, specifically the alveolar wall, which leads to airway enlargement.

Oxidative stress on the lungs can also result in loss of mucociliary function in the respiratory tract. It is likely that this loss of function contributes to an increased risk of microbial infection in smokers by reducing the ability of the respiratory tract to clear pathogens.

A research team from the University of North Carolina Chapel
created an in vitro model of differentiated nasal epithelial cells from smokers (which emulates many characteristics of airway epithelium in vivo) in order to determine how the immune response elicited by epithelial cells contributes to the enhanced susceptibility of smokers. Results indicated that the immune response to influenza for smokers is significantly downregulated in comparison with nonsmokers.7

These findings were confirmed in vivo, in a study in which human volunteers (smokers and non-smokers) were inoculated nasally with live-attenuated influenza virus vaccine.7

One group of researchers looked to establish links between influenza virus and cigarette smoke using a mouse model. The team demonstrated the effects of cigarette smoke on alterations to innate immunity, specifically with PAMP-(pathogen-associated molecular pattern) induced pulmonary inflammation and remodeling in mice.8 It was demonstrated that cigarette smoke selectively enhances responses already induced in the murine lung by influenza virus and viral PAMPs, such as airway and alveolar inflammation and remodeling.8

Importantly, it was shown that cigarette smoke and a synthetic analog of influenza virus interacted synergistically to enhance BAL (bronchoalveolar lavage) total cell recovery, airway, and alveolar inflammation. BAL is a technique often used in immunological research as a way to sample components of the epithelial lining fluid and to determine pathogen levels in the lung. It was also found that cigarette smoke selectively enhanced the ability of influenza analog to induce pulmonary emphysema and airway remodeling.8

Other experiments by these researchers demonstrated that this synergism relies on a specific molecular pathway involving a mitochondrial antiviral signaling protein, cytokines, and an RNA-dependent protein kinase. This pathway revealed that molecular facets of cigarette smoke could injure the lungs significantly enough to promote emphysema.8 The process of alveolar destruction is also thought to course with an imbalance between matrix protease and antiproteases, favoring the breakdown of extracellular matrix proteins.8, 9

**COPD Exacerbations and Viral Infection**

The leading cause of COPD (Chronic Obstructive Pulmonary Disease) is smoking cigarettes. It is estimated that COPD affects 43 million people and is the fourth leading cause of morbidity and mortality in the United States. By 2020, COPD is estimated to become the fifth leading cause of death worldwide.10

Acute exacerbations account for much of the morbidity and mortality associated with COPD, which result in patients having extreme difficulty in breathing.10 Infection of the tracheobronchial tree, the structure that forms the airways that supply air to the lungs, is the most common cause of COPD exacerbations.2

A study was conducted among patients hospitalized with acute respiratory disease during an influenza epidemic, and it was determined that COPD was the most common underlying disease, suggesting that pulmonary disease is a significant risk factor for adverse outcome with influenza infection.11
Direct studies of viral infections in COPD exacerbations suggest that there is an association of influenza with COPD. These studies have utilized modern diagnostic methods such as polymerase chain reaction (PCR) to detect virus-associated exacerbations.\textsuperscript{12, 13, 14}

The burden of COPD is proportionately greater in the elderly.\textsuperscript{2} A number of respiratory societies have published national or international guidelines for the optimal management of COPD, which generally recommend universal administration of annual influenza vaccination.\textsuperscript{10} It should be noted that there is evidence that vaccination is not necessarily effective at reducing hospitalization in patients with COPD, indicating that there could be a reduction in the efficacy of vaccination against influenza in patients diagnosed with COPD.\textsuperscript{15}

Prevalence of Smoking and COPD Among Vermonters

A 2012 report conducted by the Behavioral Risk Factor Surveillance System of the Vermont Department of Health investigated the prevalence risk factors and behaviors throughout the state. It was determined that 6\% of Vermont adults have been diagnosed with COPD.\textsuperscript{16}

Adults 65 and older have significantly higher rates of COPD than all other age groups, suggesting that the prevalence of COPD increases as Vermonters age.\textsuperscript{16}

Only 17\% of Vermonters reported being cigarette smokers in 2012, a value slightly lower than the national statistic of 18.1\% among U.S. adults being cigarette smokers.\textsuperscript{16, 17} Adults 65 and older smoke at significantly lower rates than those in other age groups. Less than 62\% of Vermont adult smokers made attempts to quit smoking in 2012, greater than the nationally reported value of 59\% seen among all adults in the United States. Quit attempts are highest among the 18-24 age group.\textsuperscript{16} This study did not report information about the specific smoking histories of adults over the age of 65.

2012-2013 Influenza Season

The 2012-2013 influenza season had an early start. Influenza activity in the United States peaked four weeks earlier in comparison to recent seasons. This jump-started a strenuous year characterized by more infection than usual.\textsuperscript{18}

A striking outcome from the 2012-2013 season was the ineffectiveness of a vaccine against strain A/H3N2 in the elderly population. A study of vaccine inefficacy suggested that an antigenic shift could not sufficiently explain this observation, as the vaccine in younger populations was shown to elicit a normal immune response.\textsuperscript{19}

A proposed interpretation of this outcome is that elderly populations generate a narrow antibody response to the vaccine strain of H3N2, incapable of protecting against H3N2 virus with shifted antigenicity.\textsuperscript{19} Other studies show evidence of an increase in influenza-attributable mortality rates among persons aged 65 years or older.\textsuperscript{20}

There is also an indication that older individuals who were vaccinated against influenza in 2012 were not necessarily fully protected. In an article
published in the Morbidity and Mortality Weekly Report by the Centers for Disease Control, vaccine effectiveness was reported to be 32.0% in the age group of > 65 years, with 17.1% of this age group prevented against hospitalization with influenza due to the vaccine.21

**Objectives of Study**

Nosocomial infections are hospital-acquired infections. As influenza virus is considerably contagious through airborne transmission and has a better chance of infectivity due to its ability to easily mutate, it can present itself as a nosocomial infection.1, 2

LOS (length of stay in hospital) measures the number of days that a patient will spend in the hospital. Shorter lengths of stay indicate more efficient and effective care, and usually, a better outcome for the patient.22 Moreover, shorter lengths of stay reduce the spread of unwanted nosocomial infections, like influenza.

This study is an epidemiological retrospective investigation seeking to determine which patient characteristics explained prolonged LOS, given admittance to hospital with influenza infection. It was hypothesized that increased LOS due to influenza infection would significantly correlate with a patient’s smoking status and COPD condition.

**METHODS**

**Study Area and Data Source**

PRISM, the hospital administrative database employed by FAHC (Fletcher Allen Health Care), was the source of data for this study. FAHC serves a population of greater than 1 million individuals in Vermont and northern New York.23 The hospital is based in Burlington, Vermont and provides a full range of tertiary-level inpatient and outpatient services.

**Data Preparation, Collection, and Management**

Inclusion criteria were established to incorporate any patient at least 18 years old that was admitted for at least one night between October 1, 2012 and June 1, 2013 with influenza infection as a primary reason for hospital admission, with confirmation from the Fletcher Allen Laboratory of presence of influenza viral infection. After ethical approval was granted from the University of Vermont Institutional Review Board, the data set was accessed. The following data was recorded into an Excel spreadsheet:

- Age
- Sex
- Height
- Weight
- Viral strain
- Current smoking status
- Presence of smoking history
- Presence of cardiac disease
- Presence of kidney disease
- Presence of cancer
- Presence of diabetes
- Presence of COPD

All data was copied from Microsoft Excel into a spreadsheet for statistical analysis by JMP Pro version 10.0.

Cardiac disease is a broad umbrella term with multiple definitions.24 For the purposes of this study, patients were defined as diagnosed with cardiac disease
if any of the following syndromes were included in their charts:

- Coronary artery disease
- Coronary atherosclerosis
- Congestive heart failure
- Primary hypertrophic cardiomyopathy
- Non-ST elevation myocardial infarction
- Acute coronary syndrome
- Diastolic heart failure

All the explanatory variables are characteristics possessed by the patient prior to admission and did not change over the course of the hospital stay. If patients died in hospital, they were excluded from analysis, as LOS no longer would adequately explain extent of morbidity from influenza infection.

Outlier Analysis: LOS is “bedeviled by the presence of outliers”\(^{26}\)

To calculate hospital LOS, the date the patient was initially admitted to FAHC was subtracted from the date the patient was discharged. Outliers, normally those of unusually lengthy stays that are extremely variable in length and occurrence, often characterize the distribution of LOS in hospital, resulting in a skewed, non-normal distribution of LOS.\(^{25, 26}\)

The issue with incorporating outliers into analysis is the disproportionate effects they have when developing models for explaining LOS. Efforts have been made to develop accurate and consistent statistical methods for analyzing outliers of LOS distribution. Current recommendations suggest that exclusion of outliers be accomplished by defining the maximum cut-off point as the sum of the third quartile and the IQR (interquartile range) multiplied by 1.5.\(^{26}\)

Log transformation of data is also recommended, as it is known to generate a near normal distribution.\(^{26}\) A Kolmogrov-Smirnov test was run after outlier analysis to assess the goodness of fit of LOS to a log-normal distribution.\(^{27}\)

**Descriptive statistics**

After outlier analysis, categorical and quantitative distributions were analyzed for

- Age
- Sex
- Comorbidities
- Viral strain
- Smoking status
- BMI (Body Mass Index categories shown in Table 1, page 12)
- Date admitted
- Hospital floor where the patient was initially admitted.

Median and IQR were noted for continuous data, as distributions followed non-normal curves, and different proportions were noted for categorical data.

**Non-Parametric Univariate Statistical Analyses**

Wilcoxon signed-rank tests were utilized as nonparametric significance tests to compare LOS to patient characteristics.\(^{27, 28}\) Because a leading cause of COPD is smoking, a Fisher’s exact probability test was performed to determine whether smoking status was independent of COPD status.\(^{28}\)

*Choosing a Generalized Linear Model to Explain LOS*
It is argued that when modeling LOS the purpose of the analysis must be seriously considered. Indeed, “the significance of the association between length of stay and patient characteristics, as reported in the clinical literature, is due in part to the statistical model chosen.”

Because this study has a descriptive purpose, with an emphasis placed on explaining LOS as a result of patient characteristics, a generalized linear model was thus constructed to relate factors associated with patient LOS as the response variable.

The number of days each patient stayed at the hospital is recorded as a count. As a consequence, the Poisson regression model is particularly appropriate when LOS is used as a response variable. A random variable will have Poisson distribution mean ($\mu$) set equal to the variance of the distribution, meaning that any factor that affects one will also affect the other.

A measure of discrepancy between observed and fitted values is the deviance. This deviance can be measured using Pearson’s chi-squared statistic in the same form as it would be used for binomial data.

For this study, the most representative model was picked by confirmation of good fit. The expected value of a chi-squared random variable is equal to its $dF$ (degrees of freedom); meaning, the closer to $1$ the ratio of the chi-squared expected value to $dF$ is, the better the fit of the model. An additional fit statistic that was utilized was the fitted Akaike Information Criterion ($AICc$). The model with the lowest $AICc$ value was chosen, as it is indicative of a good model.

RESULTS

After reviewing the distribution of LOS, outliers were cut out as recommended by the literature. This resulted in outliers being defined as any patient staying 14 days or longer. LOS data was log transformed after outlier analysis to assess the distribution’s normality, as shown in Figure 1 (page 13). The data did not follow a log normal distribution after outlier analysis, as the Kolmogrov-Smirnov test confirmed in Table 2 (page 14). Descriptions of the six outliers are presented in Table 3 (page 15).

Descriptive Statistical Analyses

As Table 4 depicts (page 16), the most common comorbidity associated with the group is cardiac disease ($n = 27; 50.0\%$), followed by kidney disease ($n = 18, 33.3\%$), and equal prevalence of COPD and diabetes ($n = 16, 29.6\%$). Cancer is only present in eight patients ($14.8\%$). Of the 54 patients included after outlier analysis, 48.1% of the patients have two or more of the observed comorbidities ($n = 26$).

The distribution of sex is split almost equally, with 28 females and 26 males. As expected for a group of hospitalized adult patients infected with influenza in the 2012-2013 season, the cohort is predominately representative of an elderly population. Thus, the age distribution is skewed to the right, with a median age of 73.5. The youngest patient is 36 years old and the oldest patient is 95 years old.
The group is predominantly diagnosed with Seasonal H-3 Influenza A virus, with 64.8% of patients with cultures positive \( (n = 35) \). 22.2% of the group has Influenza A virus \( (n = 12) \) and 13.0% of the group had Influenza B virus \( (n = 7) \).

Information about height and weight was missing in the charts for two patients, but for the rest of the group, 60.7% of the patients classify as either obese or overweight \( (n = 31) \), in accordance with BMI standards (Table 1, page 12). 38.4% of the group is classified with a normal BMI \( (n = 20) \), and only one patient is categorized as underweight. The median BMI is 26.1, overweight.

Information about smoking histories was missing in the charts for three patients. Exactly two-thirds of the rest of the group were designated as smokers \( (n = 34, 66.7\%) \). One-third of the patients were initially admitted to Baird 4, the Medicine unit of FAHC \( (n = 18, 33.3\%) \). The distribution of the months when patients first were admitted was also observed. Almost three-quarters of the patients were admitted in January \( (n = 28, 51.9\%) \) or December \( (n = 11, 20.3\%) \).

**Univariate Analyses**

Wilcoxon tests were performed for linear regression and one-way ANOVA univariate analyses, comparing one patient characteristic as an explanatory variable to LOS as the response variable. Table 5 (page 17) displays explanatory variables that significantly explained longer LOS. These included diabetes, COPD and having two or more comorbidities \( (p = 0.0191*, 0.0129*, \text{and} 0.0046*; \text{respectively}) \). Smoking did not significantly explain longer LOS.

Extent of comorbidities was coded as “A” (presence of 1 or 0 comorbid conditions) or “B” (presence of 2-5 comorbid conditions).

It was also determined that the probability of being a smoker was significantly greater for patients diagnosed with COPD \( (p = 0.0047*) \), according to a Fisher’s Exact test as displayed in Table 6 (page 18).

**Generalized Linear Model: COPD and Extent of Comorbidities Significantly Explain LOS**

50 patients were included in the construction of a generalized linear model fit, which was generated to determine what factors influencing LOS due to influenza infection could be deemed as independent explanations. Factors that were included in the model were standard demographic information (Age, Sex, BMI), smoking status, cardiac disease, diabetes, COPD, and extent of comorbidities (A or B).

Table 7 (page 19) displays multiple tests for goodness of fit, including Pearson and Deviance chi-square to dF ratios, and AICc values.

Finally, Table 8 (page 20) summarizes the parameter estimates from the generalized linear model. Patients without COPD and 1 or less comorbidities were estimated to significantly stay less \( (p = 0.0266* \text{and} 0.0079*, \text{respectively}) \). Smoking status, however, was not a significant explanatory value.

**DISCUSSION**

Significance of COPD and Extensiveness of Comorbidities: Why not Smoking Status?
The major findings of this study imply that COPD and patients with extensive comorbid conditions that are admitted to the hospital for influenza are estimated to stay longer in the hospital. These results are in accordance with clinical wisdom, considering that LOS is to an extent a measure of burden of disease.22

However, part of the initial hypothesis cannot be fully confirmed, which was the idea that smoking status would indirectly correlate with prolonged LOS. The underlying basis for the proposed hypothesis was the plethora of literature discussing the synergistic effects of cigarette smoking and viral infection, specifically influenza.4-9, 32 Yet univariate and multivariate analysis with smoking status as an explanatory variable did not significantly explain longer stays in hospital. There are two possible explanations why the hypothesis was not confirmed.

First, smoking status was defined in a broad sense. Smokers were designated as any patients with any form of smoking history (including new smokers, light smokers, heavy smokers, current non-smokers with history of smoking). Ideally, patients would have been categorized into different levels of smoking status, but unfortunately, there was not enough information about pack-years in the patient charts to determine extent of smoking history. It is suggested in the literature that repeated use of cigarettes could lead to worsened susceptibility to influenza infection, relative to lighter exposure to cigarette smoke.32 This finding implies that patients who have a heavier smoking history could be more susceptible to lengthier stays in hospital. Moreover, one study determined that after six weeks of smoking cessation, patients regained significant functionalities in adaptive immune response.32 The general way in which smoking status was assigned for this study was unlikely able to account for these variables.

Given the significant correlation of COPD to smoking status (Table 6, page 18), COPD could be considered a marker of the burden of heavy smoking. And as shown in Table 4 (page 16) a majority of the subjects designated as smokers in the study did not have COPD (55.9%), indicating that there might have been a wide range of levels of smoking usage in subjects designated as smokers. This implies that specifically heavy smoking, not just any general exposure to smoking, could be associated with prolonged LOS.

A second possible reason explaining why smoking status did not associate with extended LOS is that models were too underpowered to adequately address the issue of smoking. As depicted in Table 4 (page 16), a majority of the cohort were smokers (66.7%, n = 34). The sample size of non-smokers was consequently rather small, resulting in a plausible power issue in the model.

Cardiac Disease: An Anomaly in the Model

In the generalized linear model, absence of cardiac disease was almost significant as an explanatory factor of increased LOS due to flu infection (p = 0.0562). This finding is peculiar because cardiac diseases are associated among risk factors for influenza infection.2 A potential explanation for this outcome could be that preferential treatment is given to patients
with cardiac conditions by clinicians. However, there is no evidence to support this speculation in the literature, so this result is puzzling.

Modelling Bias and Other Limitations

Identifying the causes of a health outcome, such as LOS in an uncontrolled environment, is problematic because of the high prevalence of modeling bias. Model overfit, or more commonly, underfit, can lead to severely invalid conclusions due to confounding between relevant covariates or between covariates and casual variables. A plethora of potential significant explanatory values that were not included in this study may better explain extended LOS due to infection with influenza.

In retrospective studies such as this one, correlation does not imply causation. Ideally, it is recommended that future controlled experiments be conducted to confirm suspicions of COPD and extensive comorbidities by establishing causal relationships between explanatory variables and the health end point, LOS. In the context of this study, however, controlled experiments explaining LOS due to influenza infection may be difficult to construct.

Additionally, to reduce potential confounding between comorbidities, it is suggested in the literature to utilize comorbidity scores as a way to rank the severity of additional complications. Further studies could also try to account for the patients with cardiac disease, perhaps categorizing different cardiac disease syndromes and ranking them, as this was an unusual finding from the linear model.

A further limitation of this study is that COPD is commonly misdiagnosed. A final thought worth mentioning is that, given the high prevalence of elderly patients in the cohort’s age distribution, this investigation can be considered a geriatric study of sorts. There is a potential for a multitude of external biases, such as frailty, which is a significantly weakened state due to the cumulative decline over an individual’s lifetime of multiple physiological systems.

Conclusions

It is an important finding that LOS of patients hospitalized with influenza is estimated to be lengthier in patients with COPD and multiple comorbid conditions. Targeting these high-risk individuals for vaccination may reduce the burden of hospitalization and nosocomial risk. Indeed, these findings support current recommendations for emphasis of populations that should be vaccinated.

Insufficient evidence of vaccination in the charts excluded the possibility of accounting for vaccination histories of subjects. It could be that there is a limited adherence to vaccine standards in Vermont and northern New York, especially for at-risk populations. Further studies are necessary to validate this speculation.

With a burdensome infectious disease such as influenza, it is imperative to construct measures to reduce LOS to a minimum. The benefits include reduced costs, enhanced quality of life for patients, an improvement in the utilization of resources and a reduction in the risk of viral transmission to other patients in the hospital.
Dr. David Kaminsky, pulmonary disease physician at Vermont Lung Center and primary research mentor: contributed invaluably in study design conceptualization, attaining ethical approval, editing proposals and reports, analysis and interpretation of the data, literature searches, and preparing for the defense.

Dr. Douglas Johnson, advisor in the Microbiology and Molecular Genetics Department and the Honors College at the University of Vermont: contributed in the organization of this paper and preparation for the defense.

Alan Howard, Director of the Statistical Consulting Clinic: contributed in the choice of statistical analyses and interpretations of the data.

Fred Westenfeld, Medical Technologist and Infectious Disease Specialist at FAHC Microbiology Laboratory: contributed to the data preparation by securing a list of all the patients from FAHC that tested positive for influenza.

AICc Akaike Information Criteria Value
BMI Body Mass Index
BAL Broncholavear lavage
COPD Chronic Obstructive Pulmonary Disease
dF Degrees of freedom
FAHC Fletcher Allen Health Care
HA Hemagglutinin
IQR Interquartile Range
LOS Length of Stay
NA Neuraminidase
PAMP Pathogen-associated molecular pattern
<table>
<thead>
<tr>
<th>Category</th>
<th>BMI (kg/m^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
</tr>
<tr>
<td>Obesity, Class I</td>
<td>30.0-34.9</td>
</tr>
<tr>
<td>Obesity, Class II</td>
<td>35.0-39.9</td>
</tr>
<tr>
<td>Extreme Obesity, Class III</td>
<td>&gt; 40</td>
</tr>
</tbody>
</table>

Figure 1

Note. LOS Distribution, fitted log-normal.
Table 2

*Kolomogorov-Smirnov Goodness of Fit*

<table>
<thead>
<tr>
<th>Test Statistic (D)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1349</td>
<td>0.0211*</td>
</tr>
</tbody>
</table>

*Note.* Null hypothesis = the data is from Log Normal distribution. Small $p$-values reject null hypothesis. $\alpha = 0.05$. Significant at $P < 0.05$. 

### Table 3

**Profiles of the Outliers**

<table>
<thead>
<tr>
<th>Patient Identification</th>
<th>LOS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>V06</td>
<td>20 days</td>
<td>73-year-old female, non-smoker with cardiac disease, COPD, and diabetes</td>
</tr>
<tr>
<td>V07</td>
<td>65 days</td>
<td>67-year-old borderline overweight male, former smoker (105 pack years), cardiac disease and diabetes</td>
</tr>
<tr>
<td>V11</td>
<td>19 days</td>
<td>64-year-old overweight male, former smoker (168 pack years), cardiac disease and COPD</td>
</tr>
<tr>
<td>V12</td>
<td>14 days</td>
<td>59-year-old male, former smoker (60 pack years), COPD</td>
</tr>
<tr>
<td>V25</td>
<td>14 days</td>
<td>97-year-old female, non-smoker with cardiac disease</td>
</tr>
<tr>
<td>V64</td>
<td>21 days</td>
<td>57-year-old female, former smoker (3 pack years), kidney disease and diabetes</td>
</tr>
</tbody>
</table>

*Note.* Six outliers were excluded from the study.
### Table 4

**General Characteristics of Patient Cohort**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>n (%)</th>
<th>Demographic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td><strong>Smoking Status</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>28 (51.9)</td>
<td>Smoker</td>
<td>34 (66.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>COPD in Smokers</td>
<td>15 (44.1)</td>
</tr>
<tr>
<td><strong>BMI Category</strong></td>
<td></td>
<td><strong>Month Admitted</strong></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>1 (1.9)</td>
<td>December</td>
<td>11 (20.3)</td>
</tr>
<tr>
<td>Normal</td>
<td>20 (38.4)</td>
<td>January</td>
<td>28 (51.9)</td>
</tr>
<tr>
<td>Overweight</td>
<td>16 (30.8)</td>
<td>February</td>
<td>9 (16.7)</td>
</tr>
<tr>
<td>Obesity, Class I</td>
<td>4 (7.7)</td>
<td>March</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Obesity, Class II</td>
<td>4 (7.7)</td>
<td>April</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td>Obesity, Class III</td>
<td>7 (13.5)</td>
<td>May</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td><strong>Viral Strain</strong></td>
<td></td>
<td><strong>Floor Initially Admitted To</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>12 (22.2)</td>
<td>Medicine</td>
<td>18 (33.3)</td>
</tr>
<tr>
<td>B</td>
<td>7 (13.0)</td>
<td>Cardiology</td>
<td>11 (20.3)</td>
</tr>
<tr>
<td>Seasonal H3A</td>
<td>35 (64.8)</td>
<td>Orthopedics</td>
<td>7 (13.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiothoracic</td>
<td>7 (13.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical ICU</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td>Neurology</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>27 (50.0)</td>
<td>General Surgery</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>18 (33.3)</td>
<td>Surgical ICU</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>COPD</td>
<td>16 (29.6)</td>
<td>Emergency</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (29.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>8 (14.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2 of the above</td>
<td>26 (48.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td><strong>Median (IQR)</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>73.5 (20.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td>26.1 (8.3)</td>
<td></td>
</tr>
<tr>
<td><strong>LOS</strong></td>
<td></td>
<td>4 (4.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* * = Total n ≠ 54 for these patients; information missing from charts
<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>ChiSquare</th>
<th>dF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>5.4927</td>
<td>1</td>
<td>0.0191*</td>
</tr>
<tr>
<td>COPD</td>
<td>6.1888</td>
<td>1</td>
<td>0.0129*</td>
</tr>
<tr>
<td>&gt;2 Comorbidities</td>
<td>8.0387</td>
<td>1</td>
<td>0.0046*</td>
</tr>
</tbody>
</table>

*Note. Univariate analyses conducted at $\alpha = 0.05$. Significant at $P < 0.05$. Wilcoxon; Pearson’s ChiSquare Test.*
<table>
<thead>
<tr>
<th>Test</th>
<th>$P$</th>
<th>Alternative Hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>0.9997</td>
<td>$P$ (Smoking Status = Smoker) is greater for absence of COPD</td>
</tr>
<tr>
<td>Right</td>
<td>0.0047*</td>
<td>$P$ (Smoking Status = Smoker) is greater for presence of COPD</td>
</tr>
<tr>
<td>2-Tail</td>
<td>0.0089*</td>
<td>$P$ (Smoking Status = Smoker) is different across COPD</td>
</tr>
</tbody>
</table>

*Note. $n = 51$, $\alpha = 0.05$*
### Table 7

**Goodness of Fit**

<table>
<thead>
<tr>
<th>Fit Statistic</th>
<th>ChiSquare</th>
<th>dF</th>
<th>ChiSq:dF ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson</td>
<td>52.9536</td>
<td>41</td>
<td>1.2916</td>
<td>0.0999</td>
</tr>
<tr>
<td>Deviance</td>
<td>48.4508</td>
<td>41</td>
<td>1.1817</td>
<td>0.1976</td>
</tr>
</tbody>
</table>

**AICc**

236.15

*Note.* The closer the ChiSquare:dF ratio is to 1, the better the fit. Smaller AICc indicates a better fit.
<table>
<thead>
<tr>
<th>Term</th>
<th>Estimate</th>
<th>Std Error</th>
<th>dF</th>
<th>ChiSquare</th>
<th>P</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.5875</td>
<td>0.5054</td>
<td>1</td>
<td>9.4329</td>
<td>0.0021*</td>
<td>0.5831 to 2.5661</td>
</tr>
<tr>
<td>Age</td>
<td>-4.1e-6</td>
<td>0.0052</td>
<td>1</td>
<td>6.41e-7</td>
<td>0.9994</td>
<td>-0.010 to 0.0102</td>
</tr>
<tr>
<td>Female</td>
<td>0.0535</td>
<td>0.0729</td>
<td>1</td>
<td>0.5388</td>
<td>0.4629</td>
<td>-0.0894 to 0.1965</td>
</tr>
<tr>
<td>BMI</td>
<td>0.0005</td>
<td>0.0090</td>
<td>1</td>
<td>0.0029</td>
<td>0.9567</td>
<td>-0.0174 to 0.0179</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>-0.0188</td>
<td>0.0883</td>
<td>1</td>
<td>0.0456</td>
<td>0.8310</td>
<td>-0.1940 to 0.1528</td>
</tr>
<tr>
<td>Absence of Cardiac Disease</td>
<td>0.1538</td>
<td>0.0803</td>
<td>1</td>
<td>3.6458</td>
<td>0.0562</td>
<td>-0.0041 to 0.3109</td>
</tr>
<tr>
<td>Absence of Diabetes</td>
<td>-0.0742</td>
<td>0.0780</td>
<td>1</td>
<td>0.9053</td>
<td>0.3414</td>
<td>-0.2268 to 0.0789</td>
</tr>
<tr>
<td>Absence of COPD</td>
<td>-0.1693</td>
<td>0.0760</td>
<td>1</td>
<td>4.9163</td>
<td>0.0266*</td>
<td>-0.3181 to -0.0198</td>
</tr>
<tr>
<td>&lt;1 Comorbidity</td>
<td>-0.2416</td>
<td>0.0906</td>
<td>1</td>
<td>7.0593</td>
<td>0.0079*</td>
<td>-0.4193 to -0.0636</td>
</tr>
</tbody>
</table>

*Note.*  
\( n = 50, \ \alpha = 0.05, \ \text{Generalized linear model, log-link function with Poisson distribution.} \)


and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine, 164(9), 1618-1623.


