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Clinical features and outcomes of immunocompromised adults hospitalized with laboratory-confirmed influenza in the United States, 2011 – 2015

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# Clinical features and outcomes of immunocompromised adults hospitalized with laboratory-confirmed influenza in the United States, 2011 – 2015

By

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M.D., Case Western Reserve University, 2011

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A thesis submitted to the Faculty of the
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ABSTRACT

Clinical features and outcomes of immunocompromised adults hospitalized with laboratory-confirmed influenza in the United States, 2011 – 2015

By Jennifer P. Collins, MD

Background: Limited data on immunocompromised (IC) adults with influenza suggest they may present differently and have worse outcomes. Methods: We analyzed data on adults (≥18 years of age) hospitalized with lab-confirmed influenza between 2011-2015 and reported to CDC's FluSurv-NET. IC patients had ≥1: HIV/AIDS, cancer, stem cell or organ transplant, non-steroid immunosuppressive therapy, immunoglobulin deficiency, asplenia, and other rare conditions. We compared IC and non-IC patients using descriptive statistics. Multivariable logistic regression was used to identify factors associated with mortality and Cox proportional hazards models determined whether length of hospital stay varied between the two groups. Results: Among 35,348 adults hospitalized over 4 seasons, 3633 (10%) were IC. The most common IC conditions were cancer (44%), non-steroid immunosuppressive therapy (44%), and HIV (17%). IC patients were younger than non-IC patients (median (IQR) 61.7 (55.0-74.0) vs. 70.2 (54.2-83.2) years; p<0.01). IC patients were more likely to have pre-existing renal disease (27% vs. 18%) and liver disease (7% vs. 3%) and less likely to have most other chronic pre-existing conditions including obesity (18% vs. 23%), cardiovascular disease (40% vs. 47%), and chronic lung disease (35% vs. 41%; p<0.01 for all). IC patients were more likely to have received influenza vaccination (53% vs. 46%; p<0.01) and antivirals (87% vs. 85%; p<0.01). Among cases with symptom data (2014-15), IC patients were more likely to present with fever (68% vs. 61%; p<0.01) but respiratory distress was similar (53% vs. 54%; p=0.3). IC patients were more likely to be diagnosed with pneumonia (34 vs. 31%; p<0.01). When controlling for confounders, IC patients 65-79 and >80 years of age were more likely to require intensive care than non-IC patients of those ages (aOR (95% CI): 1.20 (1.02-1.42) and 1.34 (1.05-1.71), respectively). In the multivariable analysis, IC adults had a longer length of stay (aHR of discharge (95% CI): 0.88 (0.85-0.90) and a higher odds of mortality than non-IC adults (aOR (95% CI): 1.48 (1.23-1.78)). Conclusions: Among adults hospitalized with influenza, IC patients had worse outcomes including a longer duration of hospitalization and increased all-cause mortality. Older IC adults had a higher odds of ICU admission.

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# INTRODUCTION

The immune system is comprised of a network of chemicals, proteins, cells, tissues, and organs that work to protect the body from infectious pathogens, including viruses, bacteria, and parasites. When these defense mechanisms are impaired, a host is said to be immunocompromised or immunosuppressed. Immunocompromised hosts are at risk of unique infections, called opportunistic infections, as well as more severe sequelae of typical infections.

Immunocompromising conditions can be inherited (i.e. primary immunodeficiencies) or acquired. They can impact specific aspects of the immune system, such as complement in the case of inherited complement deficiencies or CD4 T cells in the case of HIV, or affect it more broadly in the case of hematopoietic stem cell transplantation. Immunosuppression can also be iatrogenic, as in the case of chemotherapies used to treat cancer or immunosuppressive therapies used to treat autoimmune conditions and to prevent the rejection of solid organ transplants.

As our understanding of the immune system expands, so does our desire to understand how the presence of immunocompromising conditions influences the outcomes of infections such as influenza. Influenza is a common cause of morbidity in the United States with an estimated 32.6–100.3 hospitalizations per 100,000 persons and 3,000–49,000 deaths annually (1, 2). However, our understanding of how immunocompromising conditions influence the clinical outcomes of influenza is incomplete. Most of the existing data on immunocompromised patients with influenza comes from small, single-center studies, with limited generalizability.

Additionally, these studies are typically restricted to particular immunocompromising conditions such as cancer or solid organ transplantation.

The purpose of this study was to compare the clinical features and outcomes of immunocompromised and non-immunocompromised adults hospitalized with influenza. In this cross-sectional study, we analyzed data from four influenza seasons (2011-2012 through 2014-2015) using the CDC's Influenza Hospitalization Surveillance Network (FluSurv-NET). FluSurv-NET is a population-based surveillance system of hospitalized cases of laboratory-confirmed influenza in the United States, with a total catchment population of approximately 27 million people, or 9% of the total US population (3). FluSurv-NET has collected information on pre-existing immunocompromising conditions of patients hospitalized with influenza routinely since 2011. It is therefore a unique platform with which to explore the clinical features and outcomes of immunocompromised adults with influenza.

# BACKGROUND

General information on influenza:

Influenza or "flu" is a respiratory infection caused by influenza viruses. The two main types, influenza A and B, cause seasonal epidemics annually during the fall and winter months. Influenza A sub-types include H1N1 and H3N2, which are named for the surface hemagglutinin and neuraminidase proteins. Influenza B consists of two major lineages: Victoria and Yamagata. The circulating influenza types and sub-types vary from season to season, as well as over the course of a season. This is in part due to processes called antigenic drift and shift that allow the virus to change over time. The annual seasonal influenza vaccine covers the influenza types that are predicted to be most common during the upcoming season, including two influenza A sub-types (H1N1 and H3N2) and at least one B sub-type (4).

Classic symptoms of influenza include fever, cough, sore throat, nasal congestion, myalgias, headaches, and fatigue. Gastrointestinal symptoms (nausea, vomiting, and diarrhea) may also occur. Influenza illness severity can range from mild to severe. While most people with influenza will recover within two weeks, complications can occur. Influenza antiviral medications can help prevent serious complications and are most effective when given within two days of symptom onset (5).

Influenza causes an estimated 32.6–100.3 hospitalizations per 100,000 persons and 3,000–49,000 deaths annually in the United States (1, 2). The most commonly reported complication of influenza is pneumonia (6-9), and the greatest

burden of influenza hospitalization occurs in young children and the elderly (9-11). However, the epidemiology of influenza in immunocompromised patients has not been well characterized.

Influenza in immunocompromised hosts:

Severely immunosuppressed patients, such as those with AIDS or who have received hematopoetic stem cell transplantation, may have subclinical infections with certain organisms; their symptoms can then paradoxically worsen with immune system recovery, a phenomenon known as immune reconstitution inflammatory syndrome (12). While this phenomenon has not been described with influenza, recent data suggest that influenza infection may present more insidiously in the immunocompromised host. This could potentially be explained by a decreased inflammatory response in the setting of immunosuppression.

A small, prospective study of hematopoietic stem cell recipients with respiratory viruses infections found that a minority of those with influenza (two of seven) had fever (13). A recent prospective study explored the clinical features and ouctomes of influenza in 32 immunocompromised patients, primarily those with malignancies or receiving immunosuppressive therapy as well as hematopoietic stem cell transplant recipients, to 54 non-immunocompromised patients (14). The authors found that the immunocompromised patients were less likely to be symptomatic with chills, sweats, myalgias, dry cough, and shortness of breath, and were less likely to have pulmonary exam abnormalities (14). However, a 1995 study of patients with leukemia and influenza found that these patients had classic symptoms of influenza, including cough, nasal congestion, myalgias, and headache

(15). Gaining clarification about how influenza presents in immunocompromised hosts is important because, if it presents differently, this could potentially result in diagnostic delays or failures.

Influenza may also be associated with worse outcomes in immunocompromised patients. A higher rate of hospitalization, ICU admission, and a longer length of illness have been observed in immunocompromised patients with influenza compared to non-immunocompromised controls (14). Patients 13 years of age and older with AIDS have also been shown to have higher mortality than those without AIDS (16). Influenza-associated pneumonia has been reported to occur in 75-80% of patients with leukemia and 29- 70% of hematopoietic stem cell transplant recipients (15, 17-19). Case-fatality rates of influenza in patients with cancer have been reported to be 11% - 33%, and mortality rates of around 30% have been described in patients with leukemia or undergoing hematopoietic stem cell transplantation who develop influenza-associated pneumonia (15, 17, 18, 20, 21).

A recent study of adults with influenza hospitalized during the 2013-2014 influenza season found that seasonal influenza vaccination attenuated adverse outcomes (22). The US Centers for Disease Control and Prevention (CDC) recommends annual influenza vaccination for all persons aged 6 months and older who do not have a contraindication (23). Immunosuppressed hosts are included as a priority group when vaccine supply is limited. While immunocompromised patients seem to have a less robust serologic response to influenza vaccination, studies support that clinically it may still protect against adverse outcomes (24).

Clinical guidelines from both the US Centers for Disease Control and Prevention (CDC) and Infectious Disease Society of America (IDSA) recommend the empiric use of influenza antiviral agents among adults and children with laboratory confirmed or suspected influenza who are hospitalized with acute respiratory illness or community-acquired pneumonia (CAP) during influenza season (25-28). Included in these guidelines is the recommendation that hospitalized immunosuppressed patients with influenza be treated. However, data on influenza vaccination and antiviral treatment in immunocompromised adults is limited.

The purpose of this study was to compare the clinical features and outcomes of immunocompromised and non-immunocompromised adults hospitalized with laboratory-confirmed influenza using a national surveillance system.

# METHODS

## Study aims:

This study had the following aims:

1.) Compare the demographic and clinical features of hospitalized immunocompromised vs. non-immunocompromised adults with influenza
2.) Estimate the association between immunocompromising conditions and the following adverse outcomes among hospitalized adults with influenza:
    - Intensive care unit admission
    -All-cause mortality during hospitalization with influenza
3.) Determine whether immunocompromised status causes a longer duration of admission among adults hospitalized with influenza

## Study design & setting:

We conducted this cross-sectional study using the U.S. Centers for Disease Control and Prevention (CDC's) Influenza Hospitalization Surveillance Network (FluSurv-NET), a population based surveillance program in the United States. The FluSurv-NET network encompasses 267 acute care hospitals and laboratories in selected counties in California, Colorado, Connecticut, Georgia, Maryland, Michigan, Minnesota, Ohio, Oregon, New Mexico, New York, Tennessee, and Utah with a total catchment population of over 27 million people (or ~9% of the US population)(3). Cases of laboratory-confirmed influenza in children (<18 years old) and adults who both reside in and are hospitalized in one of the catchment areas during the influenza season (October 1 – April 30) are reported to FluSurv-NET. Laboratory-

confirmed influenza is defined as a positive influenza test by one of the following methods: rapid test, reverse-transcriptase polymerase chain reaction (RT-PCR), immunofluorescence antibody staining, serology, or viral culture. Influenza testing is performed at the discretion of the clinician caring for the patient. Cases are identified via hospital admission, discharge, and infection control databases and by contacting hospital laboratories. For each identified case, demographic and clinical information is collected via medical chart abstraction and recorded into a centralized database, as previously reported (9). To obtain the influenza vaccination history, state vaccination registries, medical providers, and patients/proxies are also queried. We analyzed data from four influenza seasons: 2011–2012 through 2014–2015.

Study population:

We included all adult cases (aged ≥18 years) with laboratory-confirmed community-acquired influenza. We defined community-acquired influenza as a positive influenza test between 14 days before and three days after the admission date. We excluded cases that were missing data on the outcomes of intensive care unit (ICU) admission, mechanical ventilation, and/or death.

Measurements:

Our primary exposure was the presence of at least one of the following pre-existing immunocompromising conditions based on the medical chart review: HIV/AIDS, cancer, stem cell or solid organ transplantation, receipt of non-steroid immunosuppressive therapy, immunoglobulin deficiency, complement deficiency, asplenia, and other rare conditions. Patients were categorized as non-

immunocompromised if they did not have any of the aforementioned conditions prior to the current illness. Because steroid use is common, and we did not have data on steroid dosing, cases with isolated receipt of steroids were classified as non-immunocompromised for the primary analysis.

Symptoms and signs at the time of hospital admission were first collected by FluSurv-NET in 2014–2015 and are therefore only reported for this season. Gastrointestinal symptoms were defined as nausea, vomiting, and/or diarrhea.

Our primary outcomes were all-cause mortality during the course of hospitalization with influenza, ICU admission, and duration of hospital admission. Secondary outcomes included pneumonia, mechanical ventilation, and length of ICU admission.

The following variables were considered as potential confounders *a priori* based on biologic plausibility: age (years), sex, race/ethnicity (non-Hispanic white/non-Hispanic black/Hispanic/other/unknown), current/prior smoking (yes/no), obesity or morbid obesity (yes/no), current alcohol abuse (yes/no), chronic lung disease (yes/no), cardiovascular disease (yes/no), chronic metabolic disease (yes/no), neurologic disorder (yes/no), neuromuscular disorder (yes/no), renal disease (yes/no), liver disease (yes/no), receipt of seasonal influenza vaccination (yes/no/ unknown), receipt of antiviral treatment (yes/no/unknown), influenza type (A, B, A and B, unknown), and influenza season (as a surrogate for influenza A sub-type). Antiviral treatment was defined as the receipt of an influenza antiviral medication for any period of time before or during the

hospitalization. Early antiviral treatment was defined as receipt of the first antiviral less than 2 days after the date of illness onset.

The following covariates had values that were missing or unknown: race/ethnicity (n=3151, 8.9%), receipt of influenza vaccine (n=3,473, 9.8%), receipt of antiviral treatment (n=93, 0.3%), and influenza type (n=91, 0.26%). An indicator variable was used for the missing/unknown category in the regression models. For the logistic regression model of the all-cause mortality outcome, additional analyses were performed using multiple imputation (with fully conditional specification and 20 imputed datasets) as well as including only those cases that had complete covariate data.

Sample size considerations:

This study was designed to optimize the generalizability of findings among adults hospitalized with influenza in the United States. We included data from all FluSurv-NET sites because the distribution of age, sex, race/ethnicity, and health indicators such as population density and percentage of persons at or below the poverty level, is similar to that for persons throughout the U.S.(3). Since influenza severity can vary across seasons, we chose to include four recent seasons of data. As such, our sample size is very large, and we are able to detect statistically significant differences that may not always be clinically meaningful.

Analytic Methods:

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA.) A p-value $<0.05$ was considered statistically significant. For the descriptive analysis, comparisons were made between the immunocompromised

and non-immunocompromised groups using the chi-square or Fisher's exact test for categorical variables and the two-sample t-test or Mann-Whitney U test for continuous variables.

Multivariable logistic regression was used to control for confounding of the association between immunocompromised status and the dichotomous primary outcomes (mortality, ICU admission). Model selection was performed by first including all of the potential confounders and interaction terms in the model. Variables were considered to be potential confounders based on both biologic plausibility (determined *a priori*) and demonstrated associations between the primary exposure (immunocompromised status) and outcomes in the univariable analysis. Likelihood ratio tests were used to assess for interaction. Confounding was then assessed by comparing models with and without each potential confounder to determine whether this meaningfully changed the parameter estimates for the association between immuncompromised status and the outcomes. Variables that are conventionally included in models (i.e. age, sex, race/ethnicity) were included regardless of whether they confounded this association. For variables that were judged to not confound the association between immunocompromised status and the outcomes, the effect on the precision of the parameter estimates was also assessed. The following models were developed (immunocompromised is abbreviated as IC, and race/ethnicity is abbreviated RE. Age refers to continuous age. For categorical age, the reference group 18-49 years, AgeCat1 is 50-64 years, AgeCat2 is 65-79 years, and AgeCat3 is $\geq$80 years.):

*1. Outcome: All-cause mortality during hospitalization with influenza*

$$\text{logit}\,(P(\text{mortality})) = B_0 + B_1(\text{IC}) + B_2(\text{Age}) + B_3(\text{Sex}) + B_4(\text{RE}) + B_5(\text{Vaccination})$$

*2. Outcome: Intensive care unit (ICU) admission:*

$$\text{logit}\,(P(\text{ICU})) = B_0 + B_1(\text{IC}) + B_2(\text{AgeCat1}) + B_3(\text{AgeCat2}) + B_4(\text{AgeCat3}) + B_5(\text{Sex}) + B_6(\text{RE}) + B_7(\text{Vaccination}) + B_8(\text{IC*AgeCat1}) + B_9(\text{IC*AgeCat2}) + B_{10}(\text{IC*AgeCat3})$$

Sub-group analyses were performed using cancer, non-steroid immunosuppressive therapy, and cancer and/or non-steroid immunosuppressive therapy as the primary exposure for the mortality outcome.

Cox proportional hazards models were used to model time to discharge from the hospital after controlling for confounders. In these models, a lower hazard ratio (i.e. HR<1) represents an increased length of stay. Confounding was assessed using the same method as described above for multivariable logistic regression. Log-log likelihood curves were examined to ensure the proportional hazards assumption was met for each covariate. The Fine & Gray method was used to handle death as a competing risk for hospital discharge. The following model was developed

*3. Outcome: Duration of hospitalization:*

$$h(t) = h_o(t)\exp(B_1(\text{IC}) + B_2(\text{Age}) + B_3(\text{Sex}) + B_4(\text{RE}) + B_5(\text{Vaccination}))$$

For each of the models above, a sensitivity analysis was performed including steroid therapy in the immunocompromised group.

# RESULTS

Immunocompromising Conditions:

A total of 36,716 adults were hospitalized with influenza in FluSurv-NET from 2011-2012 through 2014-2015. We excluded 1,036 patients who did not have an influenza test date within the specified range, and 332 patients who had incomplete outcome data. The remaining 35,348 adults were included in our analysis. Of these, 3,633 (10.3%) were immunocompromised (Figure 1). The most common immunocompromising conditions were cancer (n=1,613; 44.4%), non-steroid immunosuppressive therapy (n=1601; 44.1%), HIV/AIDS (n=660; 18.2%), and solid organ transplantation (n=532; 14.6%) (Figure 2).

Demographic characteristics:

The median age was 61.7 years (IQR: 55.0-74.0) among immunocompromised adults and 70.2 years (IQR: 54.2-83.2) among non-immunocompromised adults ($p<0.0001$) (Figure 3). The immunocompromised group had a higher proportion of males (52.5% vs. 43.7%; $p<0.0001$). The distribution of race/ethnicity differed between the groups with a lower proportion of non-Hispanic white adults in the immunocompromised group (56.6% vs. 62.0%; $p<0.0001$) (Table 1).

Pre-existing medical conditions*:*

Immunocompromised adults were more likely than non-immunocompromised adults to be current/prior smokers (51.5% vs. 47.5%; $p<0.0001$) and to have renal disease (26.8% vs. 18.2%; $p<0.0001$) and liver disease (6.7% vs. 2.8%; $p<0.0001$). Immunocompromised adults were less likely to have

obesity or morbid obesity (17.5% vs. 22.6%; p<0.0001), chronic lung disease (34.5% vs. 41.2%; p<0.0001), cardiovascular disease (40.4% vs. 46.7%; p<0.0001), chronic metabolic disease (37.0% vs. 41.9%; p<0.0001), and neurologic disorders (13.8% vs. 21.8%; p<0.0001). Among the 1,726 immunocompromised and 17,855 non-immunocompromised women, the immunocompromised group was less likely to be pregnant (0.7% vs. 5.4%; p<0.0001).

Influenza-related history:

Immunocompromised adults were less likely to have had a rapid influenza test (44.6% vs. 56.9%; p<0.0001) and more likely to have had a molecular test (75.1% vs. 70.2%; p<0.0001). Because cases could have up to four positive test results recorded, these results are not mutually exclusive. The majority of immunocompromised and non-immunocompromised patients had their first positive influenza test performed on the day of admission (median (IQR): 0 (0–0) for both groups). Influenza A was the most common type in both immunocompromised and non-immunocompromised adults (81.2% vs. 86.6%; p<0.0001). The distribution of people who were immunocompromised did not differ significantly across influenza season (Table 1).

Immunocompromised adults were more likely than non-immunocompromised adults to have received seasonal influenza vaccination (53.1% vs. 46.5%; p<0.0001). Treatment with antiviral medications was more common in immunocompromised patients (87.0% vs. 84.8%, p=0.003). Oseltamivir was the most common first antiviral received by both immunocompromised and non-immunocompromised adults (99.6% vs. 99.7%;

p=0.19). Immunocompromised patients were less likely to receive early antiviral treatment (19.3% vs. 22.4%; p=0.0001) (Table 1).

Presenting Symptoms/Signs:

Among the 1,542 immunocompromised adults and 13,824 non-immunocompromised adults hospitalized during the 2014-2015 influenza season, immunocompromised adults were more likely to present with fever (67.5% vs. 60.6%; p<0.0001), cough (82.1% vs. 79.9%; p=0.04), nasal congestion (27.3% vs. 24.7%; p=0.02), gastrointestinal symptoms (33.9% vs. 27.7%; p<0.0001), myalgias (25.9% vs. 22.8%; p=0.006), sore throat (15.3% vs. 12.4%; p=0.001), and headache (13.5% vs. 10.8%; p=0.002). Immunocompromised adults were less likely than non-immunocompromised adults to present with wheeze (16.3% vs. 19.5%; p=0.002) and altered mental status (12.8% vs. 16.4%; p=0.0003). About half of both immunocompromised and non-immunocompromised patients presented with respiratory distress (53.1% vs. 54.4%; p=0.32) (Table 1).

Univariable associations with outcomes:

*All-cause mortality*:

Immuncompromised adults were more likely than non-immunocompromised adults to die during their hospitalization (OR (95% CI): 1.26 (1.05-1.51)). Compared to adults 18-49 years of age, death was more likely in adults 50-64 years of age (OR (95% CI): 2.21 (1.75, 2.78)), 65-79 years of age (OR (95% CI): 2.02 (1.61-2.54)), and ≥80 years of age (OR (95%CI): 3.11 (2.51-3.86)). Women were less likely to die than men (OR (95% CI): 0.87 (0.77-0.99)). Compared to non-Hispanic white adults, non-Hispanic black and Hispanic adults

had a lower odds of mortality (OR (95% CI): 0.51 (0.42-0.62) and 0.51 (0.40-0.72), respectively)) (Table 2).

The following pre-existing medical conditions were associated with increased odds of mortality compared to the absence of said condition: cardiovascular disease (OR (95% CI): 1.75 (1.55-1.98)), neuromuscular disorders (OR (95% CI): 1.52 (1.22-1.91)), neurologic disorders ((OR (95% CI): 1.57 (1.37-1.79)), renal disease ((OR (95% CI): 1.63 (1.42-1.87)), and liver disease (OR (95% CI): 1.80 (1.38-2.36)) (Table 2).

Co-infection with influenza A and B was associated with increased odds or mortality compared to infection with only influenza A (OR (95% CI): 2.65 (1.43-4.92)). Mortality was more likely in the 2013-2014 season compared to the 2011-2012 season (OR (95% CI): 1.42 (1.04-1.95)). Adults with unknown influenza vaccination status had a higher odds of mortality than those who were vaccinated (OR (95% CI): 1.95 (1.64-2.33)). Non-receipt and unknown status of antiviral treatment were also associated with mortality (OR (95% CI): 1.47 (1.26-1.71) and 2.77 (1.28-6.00), respectively (Table 2).

*ICU admission:*

ICU admission was more likely in immunocompromised adults compared to non-immunocompromised adults (OR (95% CI): 1.12 (1.03-1.23)). Compared to adults 18-49 years of age, adults 50-64 years of age were more likely to require intensive care (OR (95% CI): 1.26 (1.16-1.37)) and adults $\geq$80 years of age were less likely to require intensive care (OR (95% CI): 0.67 (0.62-0.73)). Women were less likely to require intensive care than men (OR (95% CI): 0.80 (0.76-0.85)).

Compared to non-Hispanic white adults, non-Hispanic black and Hispanic adults had a lower odds of ICU admission (OR (95% CI): 0.89 (0.82-0.96) and 0.83 (0.74-0.94), respectively) (Table 3).

The following pre-existing medical conditions were associated with increased odds of intensive care compared to the absence of said condition: current/prior smoking (OR (95% CI): 1.44 (1.36-1.53)), current alcohol abuse (OR (95% CI): 2.17 (1.91-2.46)), obesity or morbid obesity (OR (95% CI): 1.19 (1.11-1.27), chronic lung disease (OR (95% CI): 1.39 (1.31-1.47)), cardiovascular disease (OR (95% CI): 1.26 (1.19-1.33)), chronic metabolic disease (OR (95% CI): 1.18 (1.11-1.25)), neuromuscular disorders (OR (95% CI): 1.19 (1.06-1.34)), neurologic disorders (OR (95% CI): 1.08 (1.01-1.15)), renal disease (OR (95% CI): 1.13 (1.06-1.22)), and liver disease (OR (95% CI): 1.37 (1.19-1.59)) (Table 2).

Co-infection with influenza A and B was associated with increased odds of ICU admission compared to infection with only influenza A (OR (95% CI): 1.64 (1.11-2.41)). Intensive care was more likely in the 2013-2014 season compared to the 2011-2012 season (OR (95% CI): 1.55 (1.36-1.78)). Compared to adults who were vaccinated against influenza, those who were unvaccinated and who had unknown vaccination status had a higher odds of ICU admission (OR (95% CI): 1.24 (1.17-1.32) and 1.33 (1.20-1.46), respectively). Non-receipt of antiviral treatment was associated with a lower odds of intensive care (OR (95% CI): 0.71 (0.65-0.78)).

Multivariable analysis:

*All-cause mortality:*

In the multivariable model controlling for age, sex, race/ethnicity, and influenza vaccination, mortality remained more likely among immunocompromised adults than non-immunocompromised adults (aOR (95% CI): 1.48 (1.23-1.78)). The results did not differ when multiple imputation was used or when including only those cases that had complete covariate data (data not shown). In the sensitivity analysis in which steroid therapy was included as an immunocompromising condition, the findings were unchanged (aOR (95% CI): 1.45 (1.24-1.70)) (Table 4A).

In the sub-group analysis, the adjusted odds of mortality were similar comparing patients with cancer to those without (aOR (95% CI): 1.64 (1.29-2.08)), comparing those receiving non-steroid immunosuppressive therapy to those not receiving this (aOR (95% CI): 1.57 (1.28-1.92)), and comparing patients with either of these two conditions to those without (aOR (95% CI): 1.67 (1.30-2.15)).

*ICU admission:*

The adjusted odds of ICU admission were age-stratified because the effect of immunocompromised status on ICU admission varied by age. When controlling for sex, race/ethnicity, and influenza vaccination, the odds of intensive care were higher in immunocompromised patients compared to non-immunocompromised patients among adults 65-79 years of age (aOR (95% CI): 1.20 (1.02-1.42)) and $\geq$80 years of age (aOR (95% CI): 1.34 (1.05-1.71)). In the sensitivity analysis in which steroids were included as an immunocompromising condition, the results were

similar with a higher odds of ICU admission in immunocompromised patients among adults 65-79 years of age (aOR (95% CI): 1.40 (1.23-1.60)) and ≥80 years of age (aOR (95% CI): 1.38 (1.14-1.66)) (Table 4B).

*Duration of Hospitalization:*

In the unadjusted analysis, the immunocompromised group had a longer duration of hospitalization (median (IQR): 4 (2-6) vs. 3 (2-6) days). In time-to-event models that considered time to discharge from hospital and controlled for age, sex, race/ethnicity, and influenza vaccination, immunocompromised adults had a longer duration of hospitalization (aHR of discharge (95% CI): 0.88 (0.85-0.90)). The findings were similar for the sensitivity analysis in which steroids were included as an immunocompromising condition (aHR of discharge (95% CI): 0.87 (0.85-0.89)).

*Secondary Outcomes:*

Immuncompromised adults were more likely than non-immunocompromised adults to be diagnosed with pneumonia (33.5% vs. 30.7%; p=0.0005) and to require mechanical ventilation (8.3% vs. 7.1%; p=0.0067). The duration of ICU admission did not differ between groups, among the 557 immunocompromised (median (IQR): 3 (2–7)) and 4,407 non-immunocompromised adults (median (IQR): 3 (1–7); p=0.13) with available data.

# DISCUSSION

In this large, population-based study of adults hospitalized with laboratory-confirmed influenza, we found that immunocompromised patients were younger and differed in the distribution of pre-existing medical conditions. Immunocompromised adults were more likely than non-immunocompromised adults to have received seasonal influenza vaccination and to be diagnosed with pneumonia. In the multivariable analysis, immunocompromised patients had increased odds of mortality and a longer duration of hospitalization, and elderly immunocompromised patients were more likely to require intensive care.

The majority of both groups of adults had a positive influenza test on the day of admission. Additionally, over 70% of both immunocompromised and non-immunocompromised adults had a positive RT-PCR test, although this was more common in the former group. This may be related to immunocompromised adults being seen at tertiary care centers where molecular testing is more readily available. Overall, molecular testing for influenza has increased substantially when compared with the 2003–2008 seasons, in which only 1-5% of children hospitalized with laboratory-confirmed influenza had a positive RT-PCR test, and 62-75% had a positive rapid test (11). While it is possible testing practices varied between children and adults in 2003-2008, we found a similar trend in our study of children, with 78.6% having positive RT-PCR test in FluSurv-NET between 2011-2015 (unpublished data).

We found that, like those who are non-immunocompromised, most immunocompromised patients with influenza present with classic symptoms

including fever, cough, and difficulty breathing. However, symptom data are limited to the 2014-2015 season and may not be generalizable across seasons. Our findings are consistent with a prior 1995 study of patients with leukemia and influenza, but contrary to more recent studies suggesting that immunocompromised patients with influenza present more insidiously (13-15). All of these prior studies are limited by quite small sample sizes and restriction to particular immunocompromisng conditions. It is certainly possible that the presentation of influenza differs only in adults with certain immnocompromising conditions such as leukemia or hematopoietic stem cell transplantation, and that aggregating the immunocompromising conditions attenuated this effect.

Our finding that immunocompromised adults hospitalized with influenza have worse outcomes is consistent with prior studies showing higher rates of ICU admission, longer duration of illness, and higher mortality (14, 16). Pneumonia and mortality were not as frequent in our immunocompromised population as in prior studies of patients with leukemia and hematopoietic stem cell transplantation. This may again relate to different outcomes based on the individual immunocompromising conditions. We did find slightly higher adjusted odds of mortality in our sub-group analyses of patients with cancer and those receiving immunosuppressive therapy.

Our results suggest there is room for improved utilization of influenza vaccination and antivirals in both groups of adults. Notably, only 53% of immunocompromised adults and 46% of non-immunocompromised adults received influenza vaccination during the influenza season in which they were

hospitalized. Our findings may underestimate vaccination rates in both of these populations since we analyzed adults who both acquired and were hospitalized with influenza. However, the CDC estimates that influenza vaccination coverage among adults >18 years of age in the United States ranged from 38.8%–43.6% between 2011 and 2015 (29). Our finding that unknown vaccination status was associated with mortality likely relates to the fact that vaccination history could not be validated via patient interview in those patients who died.

The higher vaccination utilization in immunocompromised patients may reflect an increased opportunity for vaccination in immunocompromised patients due to more frequent healthcare encounters or that vaccine is not as effective in immunocompromised hosts. However, studies of influenza vaccination in immunocompromised patients are limited and primarily rely on serologic correlates of protection rather than assessments of clinical vaccine effectiveness (24). Future studies should further examine the clinical vaccine effectiveness of influenza in immunocompromised hosts to determine whether current policies prioritizing vaccination in this population are warranted. Our data along with that from a large study of community-acquired pneumonia suggest the importance of vaccinating close contacts of immunocompromised patients since the vaccine may not be as effective in this population (30, 31).

The strengths of this study include its large size with data from multiple sites across the US over four recent influenza seasons. Adults in this study had laboratory-confirmed influenza, and the majority of them had a positive molecular test. We were able to have an inclusive definition of immunocompromised status,

whereas much of the published literature on influenza in immunocompromised patients is restricted to particular immunocompromising conditions such as cancer or solid organ transplantation.

This study has limitations including possible selection biases in admission and testing practices. Additionally, the sensitivity and the specificity of the different testing methods varies: rapid tests are estimated to have sensitivities between 50-70% and specificities between 90-95% when compared to viral culture or RT-PCR (32). This may result in the exclusion of false-negative or inclusion of false-positive influenza cases in FluSurv-NET, particularly among non-immunocompromised adults in whom use of rapid testing was more frequent. Misclassification of immunocompromised status could occur if relevant diagnoses were missed by chart review. Unmeasured confounders or factors unrelated to influenza infection could have contributed to the outcomes. Finally, our findings are not generalizable to all adults with influenza since we studied only hospitalized adults; our patient population is likely to be sicker overall and have worse outcomes given that they are hospitalized.

In conclusion, among adults hospitalized with influenza, immunocompromised were more likely than non-immunocompromised adults to be vaccinated, however our findings suggest room for improved utilization of influenza vaccination in all adults. We found that immunocompromised adults had worse outcomes including a longer duration of hospitalization and increased all-cause mortality, and elderly immunocompromised adults were more likely to require intensive care than elderly non-immunocompromised adults.

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# TABLES

TABLE 1: Demographic and clinical characteristics of immunocompromised (IC) and non-immunocompromised (non-IC) adults hospitalized with laboratory-confirmed influenza in the United States, 2011-2015

| Characteristic | Total N= 35,348 | Non-IC N=31,715 | IC N=3,633 | p-value[a] |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| Age (years): median (IQR) | | 70.2 (54.2-83.2) | 61.7 (50.0-74.0) | <0.0001 |
| Age groups, n (%) | | | | |
| 18-49 years | 7,220 | 6,311 (19.9) | 909 (25.0) | <0.0001 |
| 50-64 years | 7,981 | 6,824 (21.5) | 1,157 (31.8) | |
| 65-79 years | 9,429 | 8,407 (26.5) | 1,022 (28.1) | |
| ≥80 years | 10,718 | 10,173 (32.1) | 545 (15.0) | |
| Gender, n (%) | | | | |
| Male | 15,767 | 13,860 (43.7) | 1,907 (52.5) | <0.0001 |
| Female | 19,581 | 17,855 (56.3) | 1,726 (47.5) | |
| Race/ethnicity, n (%) | | | | |
| Non-Hispanic white | 21,737 | 19,679 (62.0) | 2,058 (56.6) | <0.0001 |
| Non-Hispanic black | 6,211 | 5,308 (16.7) | 903 (24.9) | |
| Hispanic | 2,515 | 2,294 (7.2) | 221 (6.1) | |
| Other | 1,734 | 1,576 (5.0) | 158 (4.3) | |
| Unknown/missing | 3,151 | 2,858 (9.0) | 293 (8.1) | |
| Pre-existing medical conditions, n (%) | | | | |
| Smoking - ever | 16,928 | 15,057 (47.5) | 1,871 (51.5) | <0.0001 |
| Smoking - current | 7,157 | 6,420 (20.2) | 737 (20.3) | 0.95 |
| Alcohol abuse - current | 1,235 | 1,117 (3.5) | 118 (3.2) | 0.39 |
| Obesity or morbid obesity | 7,800 | 7,163 (22.6) | 637 (17.5) | <0.0001 |
| Chronic lung disease | 14,331 | 13,076 (41.2) | 1,255 (34.5) | <0.0001 |
| Cardiovascular disease | 16,275 | 14,806 (46.7) | 1,469 (40.4) | <0.0001 |
| Chronic metabolic disease | 14,644 | 13,298 (41.9) | 1,346 (37.0) | <0.0001 |
| Neuromuscular disorder | 1,927 | 1,751 (5.5) | 176 (4.8) | 0.09 |
| Neurologic disorder | 7,424 | 6,921(21.8) | 503 (13.8) | <0.0001 |
| Renal disease | 6,732 | 5,759 (18.2) | 973 (26.8) | <0.0001 |
| Liver disease | 1,124 | 882 (2.8) | 242 (6.7) | <0.0001 |
| Pregnancy[b] | 976 | 964 (5.4) | 12 (0.7) | <0.0001 |
| Influenza-related history | | | | |
| Testing method[c], n (%) | | | | |
| Rapid | 19,673 | 18,052 (56.9) | 1,621 (44.6) | <0.0001 |
| Molecular | 24,995 | 22,265 (70.2) | 2,730 (75.1) | <0.0001 |
| Culture | 717 | 621 (2.0) | 96 (2.6) | 0.006 |
| Serology | 10 | 8 (0.03) | 2 (0.06) | 0.31 |
| IFA | 2,052 | 1,705 (5.4) | 347 (9.6) | <0.0001 |
| Unknown | 218 | 193 (0.6) | 25 (0.7) | 0.56 |

| | | | | |
|---|---|---|---|---|
| Day of first positive test relative to admission, median (IQR) | | 0 (0,0) | 0 (0,0) | <0.0001[d] |
| Influenza type, n (%) | | | | |
| A | 30,408 | 27,457 (86.6) | 2,951 (81.2) | <0.0001 |
| B | 4,707 | 4,046 (12.8) | 661 (18.2) | |
| A & B | 142 | 130 (0.4) | 12 (0.3) | |
| Unknown | 91 | 82 (0.3) | 9 (0.2) | |
| Season, n (%) | | | | |
| 2011-2012 | 1,857 | 1,656 (5.2) | 201 (5.5) | 0.12 |
| 2012-2013 | 10,104 | 9,090 (28.7) | 1,014 (27.9) | |
| 2013-2014 | 8,021 | 7,145 (22.5) | 876 (24.1) | |
| 2014-2015 | 15,366 | 13,824 (43.6) | 1,542 (42.4) | |
| Influenza vaccine, n (%) | | | | |
| Yes | 16,670 | 14,742 (46.5) | 1,928 (53.1) | <0.0001 |
| No | 15,205 | 13,881 (43.8) | 1,324 (36.4) | |
| Unknown/missing | 3,473 | 3,091 (9.7) | 381 (10.5) | |
| Antiviral treatment | | | | |
| Yes | 30,066 | 26,907 (84.8) | 3,159 (87.0) | 0.003 |
| No | 5,189 | 4,723 (14.9) | 466 (12.8) | |
| Unknown/missing | 93 | 85 (0.3) | 8 (0.2) | |
| First antiviral[e] | | | | |
| Oseltamivir | 29,715 | 26,589 (99.7) | 3,126 (99.6) | 0.19 |
| Other | 80 | 68 (0.3) | 12 (0.4) | |
| Early antivirals[f] | | | | |
| Yes | 6,198 | 19,454 (77.6) | 2,376 (80.7) | 0.0001 |
| No | 21,830 | 5,629 (22.4) | 569 (19.3) | |
| Presenting signs/symptoms[h], n(%) | | | | |
| Fever | 9,424 | 8,383 (60.6) | 1,041 (67.5) | <0.0001 |
| Cough | 12,318 | 11,052 (79.9) | 1,266 (82.1) | 0.04 |
| Dyspnea/ respiratory distress | 8,344 | 7,525 (54.4) | 819 (53.1) | 0.32 |
| Wheeze | 2,944 | 2,693 (19.5) | 251 (16.3) | 0.002 |
| Nasal congestion | 3,830 | 3,409 (24.7) | 421 (27.3) | 0.02 |
| Gastrointestinal symptoms | 4,346 | 3,824 (27.7) | 522 (33.9) | <0.0001 |
| Chest pain | 2,371 | 2,111 (15.3) | 260 (16.9) | 0.10 |
| Myalgias | 3,547 | 3,148 (22.8) | 399 (25.9) | 0.006 |
| Sore throat | 1,944 | 1,708 (12.4) | 236 (15.3) | 0.001 |
| Headache | 1,702 | 1,494 (10.8) | 208 (13.5) | 0.0015 |
| Altered mental status | 2,469 | 2,271 (16.4) | 198 (12.8) | 0.0003 |

[a] Median ages of immunocompromised and nonimmunocompromised cohorts were compared using Mann-Whitney U test. Proportions of immunocompromised and non-immunocompromised patients were compared for each variable using chi-square test except as noted.

[b] Among non-immunocompromised (n=17,855) and immunocompromised (n=1,726) women

[c] Tests are not mutually exclusive. Each case could have up to four positive results

[d]Mann-Whitney U test
[e] Among non-immunocompromised (n=26,657) and immunocompromised (n=3,138) adults with antiviral name data
[f] Receipt of the first antiviral less than 2 days after the date of illness onset; among non-immunocompromised (n=25,083) and immunocompromised (n=2,945) adults with antiviral timing data.
[h]Among non-immunocompromised (n=13,824) and immunocompromised (n=1,542) adults hospitalized in the 2014-2015 season
[i] Nausea/vomiting or diarrhea

TABLE 2: Association between demographic/clinical characteristics and all-cause mortality among adults hospitalized with laboratory-confirmed influenza in the United States, 2011-2015

| Characteristic | Death n=1,080 | No Death n=34,268 | OR of Death | 95% CI for OR |
|---|---|---|---|---|
| Immunocompromised, n(%) | | | | |
| No | 945 (3.0) | 30,770 (97.0) | REF | |
| Yes | 135 (3.7) | 3,498 (96.3) | 1.26 | 1.05 – 1.51 |
| Demographic characteristics, n (%) | | | | |
| Age groups | | | | |
| 18-49 years | 103 (1.4) | 7,117 (98.6) | REF | |
| 50-64 years | 247 (3.1) | 7,734 (96.9) | 2.21 | 1.75 – 2.78 |
| 65-79 years | 268 (2.8) | 9,161 (97.2) | 2.02 | 1.61 – 2.54 |
| ≥80 years | 462 (4.3) | 10,256 (95.7) | 3.11 | 2.51 – 3.86 |
| Gender | | | | |
| Male | 517 (3.3) | 15,250 (96.7) | REF | |
| Female | 563 (2.9) | 19,018 (97.1) | 0.87 | 0.77 – 0.99 |
| Race/ethnicity | | | | |
| Non-Hispanic white | 770 (3.5) | 20,967 (96.5) | REF | |
| Non-Hispanic black | 114 (1.8) | 6,097 (98.2) | 0.51 | 0.42 – 0.62 |
| Hispanic | 49 (1.9) | 2,466 (98.1) | 0.54 | 0.40 – 0.72 |
| Other | 56 (3.2) | 1,678 (96.8) | 0.91 | 0.69 – 1.20 |
| Unknown/missing | 91 (2.9) | 3,060 (97.1) | 0.81 | 0.65 – 1.01 |
| Pre-existing Medical Conditions, n (%) | | | | |
| Smoking - ever | 534 (3.2) | 16,394 (96.8) | 1.07 | 0.95 – 1.20 |
| Smoking - current | 184 (2.6) | 6,973 (97.4) | 0.80 | 0.69 – 0.94 |
| Alcohol abuse - current | 48 (3.9) | 1,187 (96.1) | 1.30 | 0.97 – 1.74 |
| Obesity or morbid obesity | 223 (2.9) | 7,577 (97.1) | 0.92 | 0.79 – 1.06 |
| Chronic lung disease | 410 (2.9) | 13,921 (97.1) | 0.89 | 0.79 – 1.01 |
| Cardiovascular disease | 642 (3.9) | 15,633 (96.1) | 1.75 | 1.55 – 1.98 |
| Chronic metabolic disease | 470 (3.2) | 14,174 (96.6) | 1.09 | 0.97 – 1.23 |
| Neuromuscular disorder | 86 (4.5) | 1,841 (95.5) | 1.52 | 1.22 – 1.91 |
| Neurologic disorder | 314 (4.2) | 7,110 (95.8) | 1.57 | 1.37 – 1.79 |
| Renal disease | 296 (4.4) | 6,436 (95.6) | 1.63 | 1.42 – 1.87 |
| Liver disease | 59 (5.2) | 1,065 (94.8) | 1.80 | 1.38 – 2.36 |
| Pregnancy[a] | 2 (0.2) | 2 (0.2) | 0.07 | 0.02 – 0.27 |
| Influenza-related history, n (%) | | | | |
| Influenza type | | | | |
| A | 934 (3.1) | 29,474 (96.9) | REF | |
| B | 132 (2.8) | 4,575 (97.2) | 0.91 | 0.76 – 1.10 |
| A & B | 11 (7.7) | 131 (92.3) | 2.65 | 1.43 – 4.92 |
| Unknown | 3 (3.3) | 88 (96.7) | 1.08 | 0.34 – 3.41 |
| Season | | | | |

| | | | | |
|---|---|---|---|---|
| 2011-2012 | 47 (2.5) | 1,810 (97.5) | REF | |
| 2012-2013 | 264 (2.6) | 9,840 (97.4) | 1.03 | 0.76 – 1.42 |
| 2013-2014 | 286 (3.6) | 7,735 (96.4) | 1.42 | 1.04 – 1.95 |
| 2014-2015 | 483 (3.1) | 14,883 (96.9) | 1.25 | 0.92 – 1.69 |
| Influenza Vaccine | | | | |
| Yes | 459 (2.8) | 16,211 (97.2) | REF | |
| No | 439 (2.9) | 14,766 (97.1) | 1.05 | 0.92 – 1.20 |
| Unknown/missing | 182 (5.2) | 3,291 (94.8) | 1.95 | 1.64 – 2.33 |
| Antiviral treatment | | | | |
| Yes | 858 (2.9) | 29,208 (97.1) | REF | |
| No | 215 (4.1) | 4,974 (95.9) | 1.47 | 1.26 – 1.71 |
| Unknown/missing | 7 (7.5) | 86 (92.5) | 2.77 | 1.28 – 6.00 |

[a] Among women (n=19,581)

TABLE 3: Association between demographic/clinical characteristics and intensive care unit (ICU) admission among adults hospitalized with laboratory-confirmed influenza in the United States, 2011-2015

| Characteristic | No ICU Admission n=29,641 | ICU Admission n=5,707 | OR of ICU Admission | 95% CI for OR |
|---|---|---|---|---|
| Immunocompromised, n (%) | | | | |
| No | 26,647 (84.0) | 5,068 (16.0) | REF | |
| Yes | 2,994 (82.4) | 639 (17.6) | 1.12 | 1.03 – 1.23 |
| Demographic characteristics, n (%) | | | | |
| Age groups | | | | |
| 18-49 years | 6,017 (83.3) | 1,203 (16.7) | REF | |
| 50-64 years | 6,373 (79.9) | 1,608 (20.1) | 1.26 | 1.16 – 1.37 |
| 65-79 years | 7,805 (82.8) | 1,624 (17.2) | 1.04 | 0.96 – 1.13 |
| ≥80 years | 9,446 (88.1) | 1,272 (11.9) | 0.67 | 0.62 – 0.73 |
| Gender | | | | |
| Male | 12,960 (82.2) | 2,807 (17.8) | REF | |
| Female | 16,681 (85.2) | 2,900 (14.8) | 0.80 | 0.76 – 0.85 |
| Race/ethnicity | | | | |
| Non-Hispanic white | 18,086 (83.2) | 3,651 (16.8) | REF | |
| Non-Hispanic black | 5,270 (84.8) | 941 (15.2) | 0.89 | 0.81 – 0.96 |
| Hispanic | 2,153 (85.6) | 362 (14.4) | 0.83 | 0.74 – 0.94 |
| Other | 1,450 (83.6) | 284 (16.4) | 0.97 | 0.85 – 1.11 |
| Unknown/missing | 2,682 (85.1) | 469 (14.9) | 0.87 | 0.78 – 0.96 |
| Pre-existing Medical Conditions, n (%) | | | | |
| Smoking - ever | 13,757 (81.3) | 3,171 (18.7) | 1.44 | 1.36 – 1.53 |
| Smoking - current | 5,575 (77.9) | 1,582 (22.1) | 1.66 | 1.55 – 1.77 |
| Alcohol abuse - current | 880 (71.3) | 355 (28.7) | 2.17 | 1.91 – 2.46 |
| Obesity or morbid obesity | 6,395 (82.0) | 1,405 (18.0) | 1.19 | 1.11 – 1.27 |
| Chronic lung disease | 11,636 (81.2) | 2,695 (18.8) | 1.39 | 1.31 – 1.47 |
| Cardiovascular disease | 13,376 (82.2) | 2,899 (17.8) | 1.26 | 1.19 – 1.33 |
| Chronic metabolic disease | 12,086 (82.5) | 2,558 (17.5) | 1.18 | 1.11 – 1.25 |
| Neuromuscular disorder | 1,570 (81.5) | 357 (18.5) | 1.19 | 1.06 – 1.34 |
| Neurologic disorder | 6,166 (83.1) | 1,258 (16.9) | 1.08 | 1.01 – 1.15 |
| Renal disease | 5,550 (82.4) | 1,182 (17.6) | 1.13 | 1.06 – 1.22 |
| Liver disease | 891 (79.3) | 233 (20.7) | 1.37 | 1.19 – 1.59 |
| Pregnancy[a] | 937 (96.0) | 39 (4.0) | 0.23 | 0.17 – 0.32 |
| Influenza-related history, n (%) | | | | |
| Influenza type | | | | |
| A | 25,495 (83.8) | 4,913 (16.2) | REF | |
| B | 3,960 (84.1) | 747 (15.9) | 0.98 | 0.90 – 1.07 |
| A & B | 108 (76.1) | 34 (23.9) | 1.64 | 1.11 – 2.41 |
| Unknown | 78 (85.7) | 13 (14.3) | 0.87 | 0.48 – 1.56 |
| Season | | | | |

| | | | | |
|---|---|---|---|---|
| 2011-2012 | 1,575 (84.8) | 282 (15.2) | REF | |
| 2012-2013 | 8,596 (85.1) | 1,508 (14.9) | 0.98 | 0.85 – 1.13 |
| 2013-2014 | 6,275 (78.2) | 1,746 (21.8) | 1.55 | 1.36 – 1.78 |
| 2014-2015 | 13,195 (85.9) | 2,171 (14.1) | 0.92 | 0.80 – 1.05 |
| Influenza Vaccine | | | | |
| Yes | 14,250 (85.5) | 2,420 (14.5) | REF | |
| No | 12,556 (82.6) | 2,649 (17.4) | 1.24 | 1.17 – 1.31 |
| Unknown/missing | 2,835 (81.6) | 638 (18.4) | 1.33 | 1.20 – 1.46 |
| Antiviral treatment | | | | |
| Yes | 25,027 (83.2) | 5,039 (16.8) | REF | |
| No | 4,539 (87.5) | 650 (12.5) | 0.71 | 0.65 – 0.78 |
| Unknown/missing | 75 (80.6) | 18 (19.4) | 1.19 | 0.71 – 2.00 |

[a] Among women (n=19,581)

TABLE 4A: All-cause mortality in immunocompromised vs. non-immunocompromised adults hospitalization with laboratory-confirmed influenza in the United States, 2011-2015

| | aOR of Mortality | 95% CI |
|---|---|---|
| Primary analysis[a] | 1.48 | 1.23 – 1.78 |
| Sensitivity analysis[a,b] | 1.45 | 1.24 – 1.70 |

TABLE 4B: ICU admission in immunocompromised vs. non-immunocompromised adults hospitalization with laboratory-confirmed influenza in the United States, 2011-2015

| | aOR of ICU Admission | 95% CI |
|---|---|---|
| Primary analysis[a] | | |
| 18-49 years | 0.79 | 0.65 – 0.96 |
| 50-64 years | 0.94 | 0.80 – 1.10 |
| 65-79 years | 1.20 | 1.02 – 1.42 |
| ≥80 years | 1.34 | 1.05 – 1.71 |
| Sensitivity analysis[a,b] | | |
| 18-49 years | 0.96 | 0.81 – 1.13 |
| 50-64 years | 1.06 | 0.93 – 1.21 |
| 65-79 years | 1.40 | 1.23 – 1.60 |
| ≥80 years | 1.38 | 1.14 – 1.66 |

TABLE 4C: Hazard ratio of discharge in immunocompromised vs. non-immunocompromised adults hospitalization with laboratory-confirmed influenza in the United States, 2011-2015

| | aHR of discharge | 95% CI |
|---|---|---|
| Primary analysis[a] | 0.88 | 0.85 – 0.90 |
| Sensitivity analysis[a,b] | 0.87 | 0.85 – 0.89 |

[a] Controlling for age, sex, race/ethnicity, and influenza vaccination
[b] Including receipt of steroid therapy in the immunocompromised group

FIGURES

FIGURE 1: Flow chart of included/excluded cases of adults hospitalized with laboratory-confirmed influenza in the United States, 2011-2015

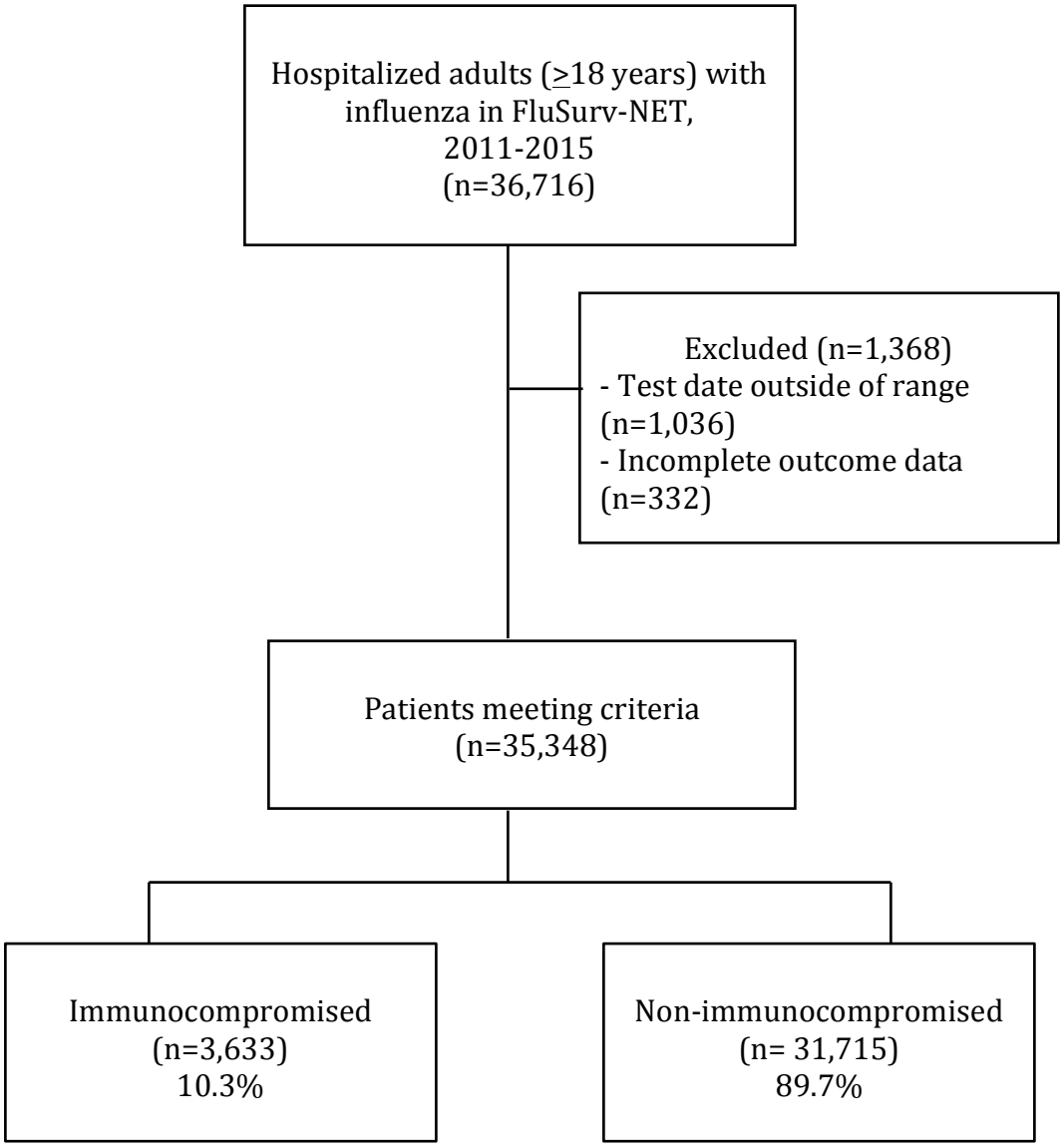
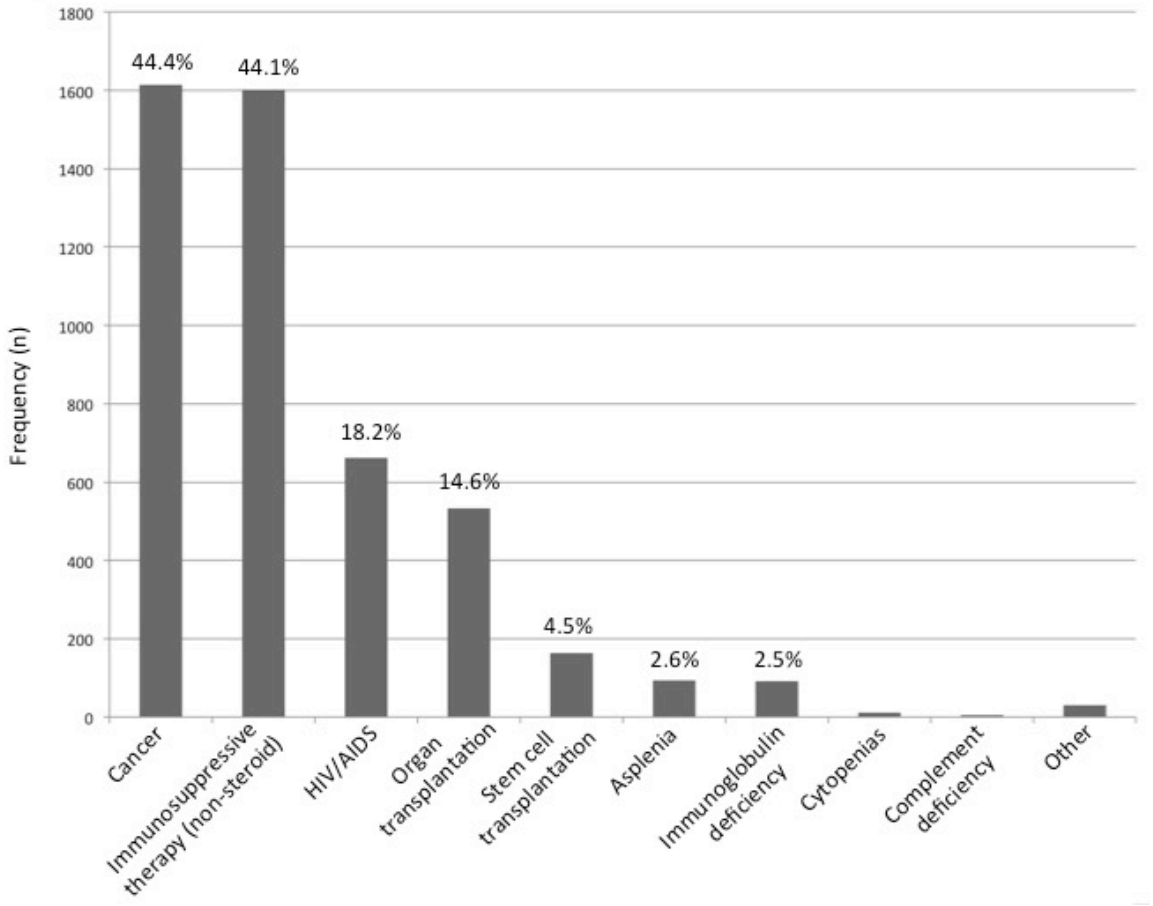
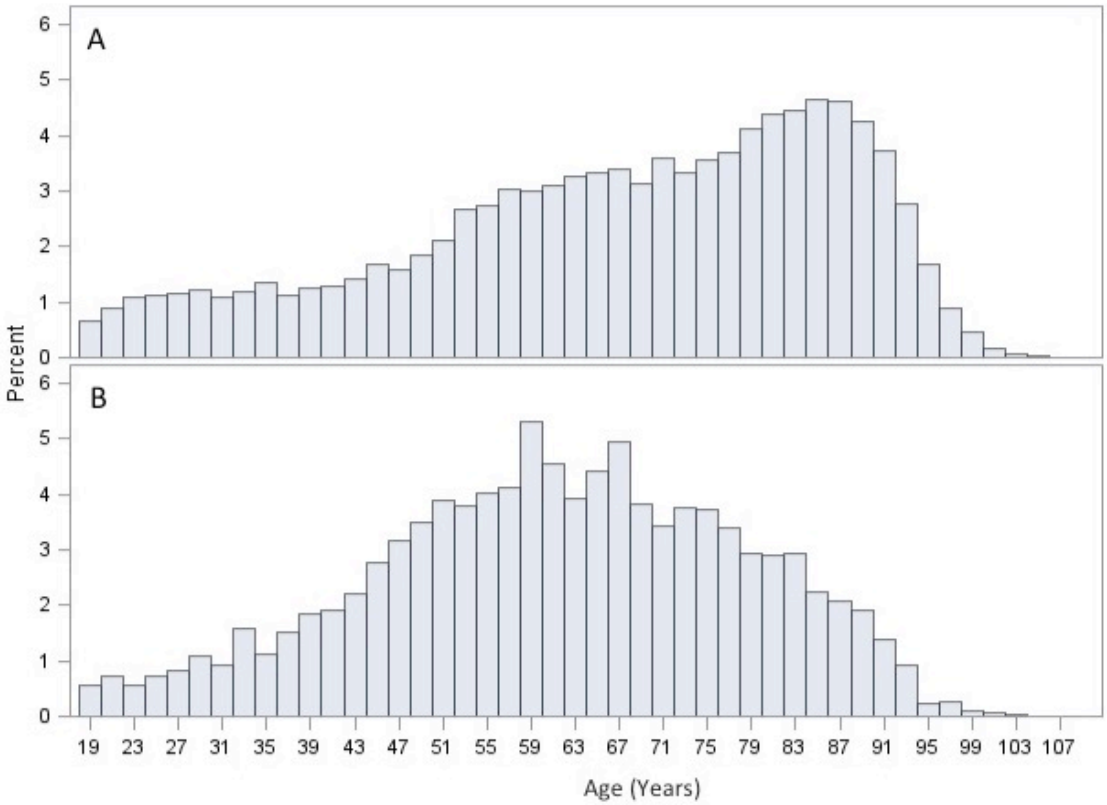


FIGURE 2: Frequency of immunocompromising conditions* among adults hospitalized with laboratory-confirmed influenza in the United States, 2011-2015




*Conditions are not mutually exclusive

FIGURE 3: Histogram of age (years) of non-immunocomrpomised (A) and immunocompromised (B) adults hospitalized with influenza in the United States, 2011-2015




The median age was 61.7 years (IQR: 55.0-74.0) among immunocompromised adults and 70.2 years (IQR: 54.2-83.2) among non-immunocompromised adults ($p<0.0001$)