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Outcomes of Immunocompromised Adults Hospitalized With Laboratory-confirmed Influenza in the United States, 2011–2015

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Background. Hospitalized immunocompromised (IC) adults with influenza may have worse outcomes than hospitalized non-IC adults.

Methods. We identified adults hospitalized with laboratory-confirmed influenza during 2011–2015 seasons through CDC's Influenza Hospitalization Surveillance Network. IC patients had human immunodefiency virus (HIV)/AIDS, cancer, stem cell or organ transplantation, nonsteroid immunosuppressive therapy, immunoglobulin deficiency, asplenia, and/or other rare conditions. We compared demographic and clinical characteristics of IC and non-IC adults using descriptive statistics. Multivariable logistic regression and Cox proportional hazards models controlled for confounding by patient demographic characteristics, pre-existing medical conditions, influenza vaccination, and other factors.

Results. Among 35 348 adults, 3633 (10%) were IC; cancer (44%), nonsteroid immunosuppressive therapy (44%), and HIV (18%) were most common. IC patients were more likely than non-IC patients to have received influenza vaccination (53% vs 46%; $P < .001$), and ~85% of both groups received antivirals. In multivariable analysis, IC adults had higher mortality (adjusted odds ratio [aOR], 1.46; 95% confidence interval [CI], 1.20–1.76). Intensive care was more likely among IC patients 65–79 years (aOR, 1.25; 95% CI, 1.06–1.48) and those >80 years (aOR, 1.35; 95% CI, 1.06–1.73) compared with non-IC patients in those age groups. IC patients were hospitalized longer (adjusted hazard ratio of discharge, 0.86; 95% CI, .83–.88) and more likely to require mechanical ventilation (aOR, 1.19; 95% CI, 1.05–1.36).

Conclusions. Substantial morbidity and mortality occurred among IC adults hospitalized with influenza. Influenza vaccination and antiviral administration could be increased in both IC and non-IC adults.

Keywords. HIV; cancer; immunosuppressive; immunosuppression; influenza.

During recent seasons (from 2010–2011 through 2017–2018), there were an estimated 140 000–959 000 influenza-associated hospitalizations and 12 000–79 000 influenza-associated deaths annually in the United States [1, 2]. Older adults typically have the greatest burden of influenza hospitalizations and deaths [2, 3]. Most studies in immunocompromised adults with influenza are small, descriptive, and restricted to specific immunocompromising conditions. Data on the clinical features of influenza in immunocompromised patients are relatively sparse, in general, with some but not all studies suggesting that immunocompromised adults may not present with classic influenza-like signs and symptoms [4–7]. Adults with certain immunocompromising conditions have been shown to have severe influenza-associated outcomes, including higher rates of intensive care unit (ICU) admission, longer duration of illness, and increased mortality compared with patients without those conditions [4, 5].

The US Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America recommend annual influenza vaccination for all people 6 months and older and antiviral treatment for confirmed or suspected influenza infection in immunocompromised adults [6, 8]. However, data are limited on influenza vaccination coverage and antiviral treatment in the immunocompromised population. Whereas studies have shown that immunocompromised patients may

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have a less robust serologic response to influenza vaccination [7], vaccination may still protect against adverse outcomes [9, 10]. A recent study in transplant recipients demonstrated an association between receipt of influenza vaccine during the same season and a lower likelihood of pneumonia and ICU admission [11]. Using data from CDC's Influenza Hospitalization Surveillance Network (FluSurv-NET), we sought to compare clinical features and outcomes of immunocompromised and nonimmunocompromised adults hospitalized with laboratory-confirmed influenza.

METHODS

Study Design and Setting

We conducted this cross-sectional study using FluSurv-NET data from the 2011–2012 through 2014–2015 influenza seasons. FluSurv-NET conducts active, population-based surveillance for hospitalized cases of laboratory-confirmed influenza through a network of acute-care hospitals and laboratories in select counties in California, Colorado, Connecticut, Georgia, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Tennessee, and Utah, with a total catchment population of more than 27 million people (~9% of the US population) [12, 13]. Residents of the catchment area admitted to the hospital with laboratory-confirmed influenza during 1 October through 30 April of each influenza season were included. Laboratory-confirmed influenza was defined as 1 or more positive influenza test (rapid antigen test, reverse-transcription polymerase chain reaction, immunofluorescence antibody staining, or viral culture). Influenza testing was ordered at the clinician's discretion. Surveillance officers abstracted clinical information from patients' medical charts using a standardized case report form and detailed instructions manual, as previously described [3, 12, 14].

Study Population

We included adults (aged ≥18 years) with laboratory-confirmed community-acquired influenza, defined as a positive influenza test by any method between 14 days before and 3 days after the date of hospital admission. Patients missing data on the outcomes of ICU admission, mechanical ventilation, or death were excluded.

CDC's Human Research Protection Office determined this study was consistent with routine public health surveillance and exempt from human subjects regulations. FluSurv-NET sites obtained human subjects and ethics approvals from their respective academic partner and state health department institutional review boards as indicated.

Variables

The primary exposure was immunocompromised status, defined as the presence of 1 or more of the following pre-existing conditions identified during medical chart abstraction: human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), cancer, stem cell transplantation, solid organ transplantation, receipt of nonsteroid immunosuppressive therapy, immunoglobulin deficiency, complement deficiency, asplenia, and other rare conditions (Supplementary Table 1). Nonimmunocompromised patients did not have these conditions reported. We categorized patients with isolated receipt of steroids as nonimmunocompromised for the primary analysis because steroid use is common, and we did not have data on route or dosing of steroid therapy to determine whether steroids were immunosuppressive. Data on symptoms and signs at the time of hospital admission were only collected in the 2014–2015 season.

Our primary outcomes were all-cause mortality during the influenza-associated hospitalization, ICU admission, and duration of hospital admission. Pneumonia, mechanical ventilation, and duration of ICU admission (among patients with ICU dates) were secondary outcomes. We used discharge summary diagnoses to determine whether patients had pneumonia.

The following variables were considered potential confounders a priori: age, sex, race/ethnicity, smoking, obesity, chronic lung disease, cardiovascular disease, chronic metabolic disease, neurologic disorders, neuromuscular disorders, renal disease, liver disease, receipt of seasonal influenza vaccination, receipt of antiviral treatment, and influenza season. We employed a standard methodology to verify influenza vaccination status using medical charts, state vaccination registries, outpatient provider records, and patient/proxy interviews [9, 10]. We considered patients who received seasonal influenza vaccination 2 weeks or more prior to admission as vaccinated. We defined antiviral treatment as the receipt of any influenza antiviral medication before or during hospitalization. Antiviral treatment was not included as a covariate in the models for ICU admission or mechanical ventilation, which requires ICU admission, because the majority of patients admitted to the ICU received antivirals upon or after ICU admission (data not shown). Due to limited availability of influenza subtype data (ie, H1N1, H3N2, B lineages), we did not control for this directly. Instead, we used influenza season to serve as a proxy to control for seasonal variations in the predominant circulating influenza virus type and subtype and degree of match between influenza vaccine and circulating strain.

Statistical Methods

All statistical analyses were performed in SAS version 9.4 (SAS Institute), with an α level of 0.05. We compared the immunocompromised and nonimmunocompromised groups using descriptive statistics: chi-square or Fisher's exact test for categorical variables and the 2-sample *t* test or Mann-Whitney *U* test for continuous variables. We used multivariable logistic regression to control for confounding of the dichotomous outcomes (mortality, ICU admission, mechanical ventilation, and

pneumonia) and assessed effect modification by age group using the likelihood ratio test. We performed subgroup analyses using cancer, nonsteroid immunosuppressive therapy, solid organ transplantation, and HIV/AIDS as the primary exposure (versus no immunocompromising condition) for the mortality outcome; as in the primary analysis, patients in each subgroup could have other immunocompromising conditions.

We used Cox proportional hazards to model time to hospital discharge after controlling for potential confounders; in these models, a hazard ratio less than 1 represents an increased duration of admission. We examined log-log likelihood curves to ensure the proportional hazards assumption was met for each covariate and used the Fine and Gray method to account for death as a competing risk for hospital discharge [15]. Missing and unknown values were combined into a single stratum for the following covariates in all models: race/ethnicity, receipt of influenza vaccine, and receipt of antiviral therapy. For each primary outcome model, we performed a sensitivity analysis by including cases who received steroid therapy in the immunocompromised group.

RESULTS

Immunocompromising Conditions

During the 2011–2012 through 2014–2015 influenza seasons, 36 716 hospitalized adults with influenza were reported to FluSurv-NET. We excluded 1036 patients who did not meet our definition of community-acquired influenza based on testing dates and 332 patients with incomplete outcome data. The remaining 35 348 adults (96.3%) were included in our analysis. Of these, 3633 (10.3%) were immunocompromised (Figure 1). The most common immunocompromising conditions (nonexclusive) were cancer (n = 1613; 44.4%), nonsteroid immunosuppressive therapy (n = 1601; 44.1%), HIV/AIDS (n = 660; 18.2%), and solid organ transplantation (n = 532; 14.6%) (Figure 2, Supplementary Table 2). In total, 600 (37.5%) of the patients receiving nonsteroid immunosuppressive therapy had no other immunocompromising condition reported.

Demographic Characteristics and Comorbidities

Immunocompromised adults were younger than nonimmunocompromised adults (61.7 years vs 70.2 years; interquartile range [IQR], 50.0–74.0 vs 54.2–83.2 years, respectively; $P < .001$) and more likely to be male (52.5% vs 43.7%; $P < .001$) (Table 1). Immunocompromised adults were more likely than nonimmunocompromised adults to be former/current smokers and less likely to have cardiovascular disease and chronic lung disease (Table 1). They were also more likely than nonimmunocompromised adults to have received seasonal influenza vaccination (53.1% vs 46.5%; $P < .001$).

Presenting Symptoms/Signs During the 2014–2015 Season

Among the 1542 immunocompromised adults and 13 824 nonimmunocompromised adults hospitalized during the 2014–2015 influenza season (the only one in which symptom data were collected), the majority of both groups presented with fever, cough, and difficulty breathing (Table 1).

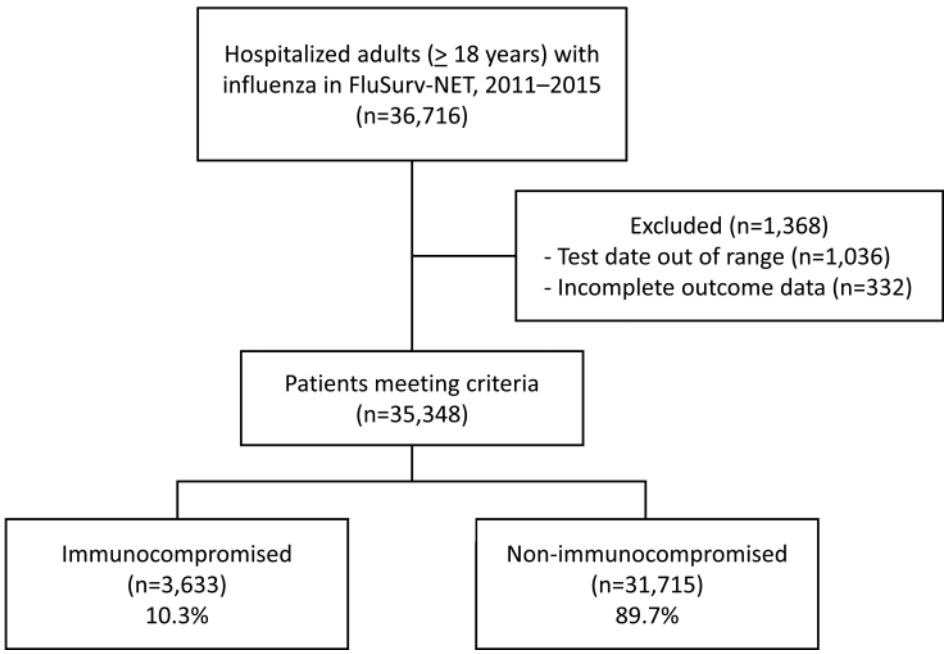

Figure 1. Flow chart of included/excluded cases of adults hospitalized with laboratory-confirmed influenza in FluSurv-NET, 2011–2015. Abbreviation: FluSurv-NET, Centers for Disease Control and Prevention Influenza Hospitalization Surveillance Network.

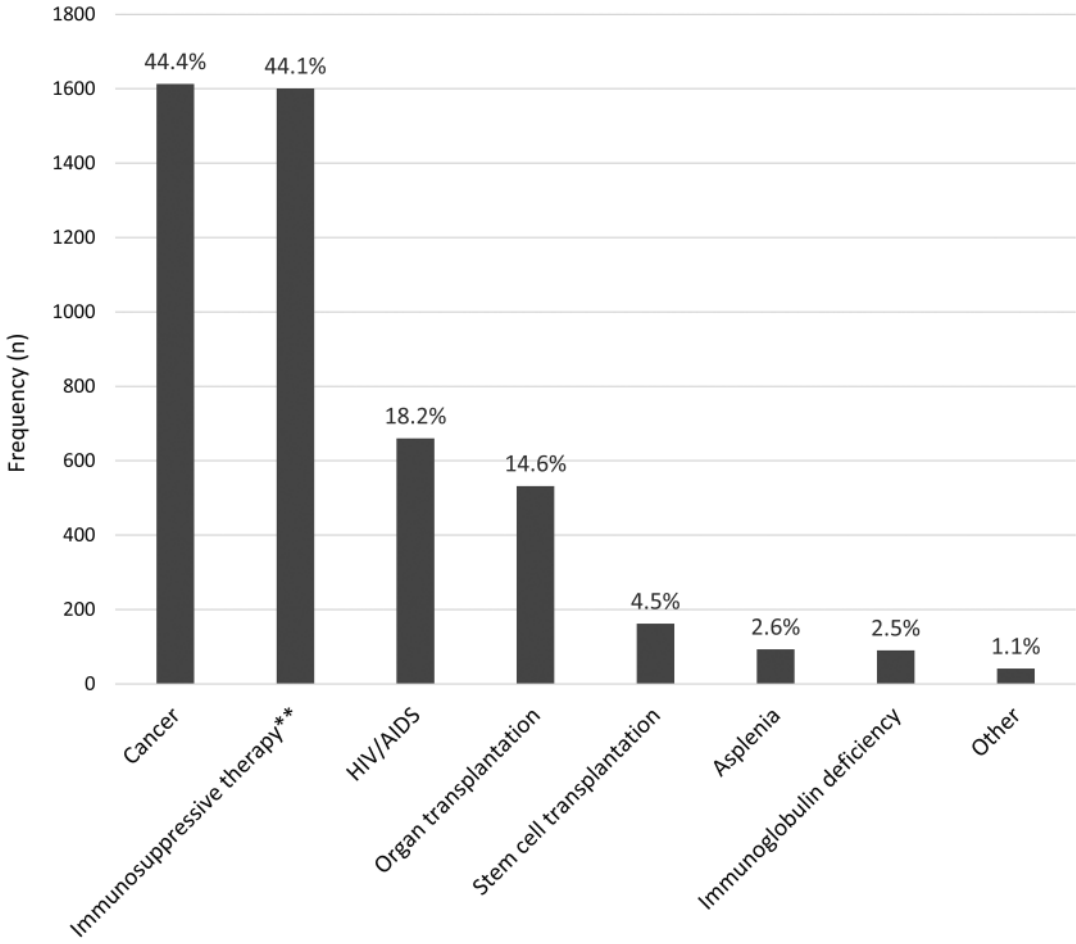

Figure 2. Frequency of various immunocompromising conditions* among immunocompromised adults hospitalized with laboratory-confirmed influenza in the US Influenza Hospitalization Surveillance Network, 2011–2015. *Conditions are not mutually exclusive. **Nonsteroidal immunosuppressive therapy included chemotherapy for cancer (within 2 weeks of admission), antibody-based agents (alemtuzumab, basiliximab, daclizumab, trastuzumab, rituximab, infliximab, and/or muromonab-CD3), immunosuppressants (cyclosporine, azathioprine, and/or leflunomide), and antirejection medications (tacrolimus, sirolimus, mycophenolate mofetil, and/or antithymocyte globulin).

Influenza Diagnostics and Treatment

Immunocompromised adults were more likely to have had influenza tested by a molecular assay (75.1% vs 70.2%; $P < .001$) and less likely to have influenza tested by only a rapid antigen test (22.2% vs 27.7%; $P < .001$). Immunocompromised and nonimmunocompromised adults had a similar duration between symptom onset and first influenza test (mean ± SD: 4.2 ± 8.4 vs 3.8 ± 22.9 days, respectively; $P = .36$) and between symptom onset and admission (mean ± SD: 4.1 ± 8.4 vs 3.7 ± 22.9 days, respectively; $P = .42$). The first influenza test was performed on the day of admission for the majority of both groups, although this was lower in immunocompromised patients (70.5% vs 74.2%; $P < .001$).

Influenza antiviral treatment was more common among immunocompromised patients (87.0% vs 84.8%; $P = .003$). Oseltamivir was the most common antiviral administered to both groups (>99%). Immunocompromised patients were slightly less likely to receive antiviral treatment less than 2 days after symptom onset (19.3% vs 22.4%; $P < .001$) (Table 1). Whereas a higher proportion of both groups received antiviral treatment less than 2 days after hospital admission, the percentage was again lower in immunocompromised adults (84.0% vs 89.3%; $P < .001$).

Outcomes

All-cause In-hospital Mortality

In the unadjusted analysis, immunocompromised adults were more likely than nonimmunocompromised adults to die during their hospitalization (odds ratio [OR], 1.26; 95% confidence interval [CI], 1.05–1.51) (Table 2). The associations between other covariates and all-cause mortality are shown in Table 2.

In the multivariable model, the odds of mortality remained higher among immunocompromised adults (adjusted OR [aOR], 1.46; 95% CI, 1.20–1.76) (Table 3). This association persisted in the sensitivity analysis that included receipt of steroid therapy as an immunocompromising condition (n = 1980) (aOR, 1.42; 95% CI, 1.21–1.66). In subgroup analyses comparing patients with the listed condition with nonimmunocompromised

Table 1. Demographic and Clinical Characteristics of Immunocompromised and Nonimmunocompromised Adults Hospitalized With Laboratory-confirmed Influenza in the US Influenza Hospitalization Surveillance Network, 2011–2015

Characteristic	Nonimmunocompromised (N = 31 715)	Immunocompromised (N = 3633)	*P*[a]
Influenza season, n (%)			
2011–2012	1656 (5.2)	201 (5.5)	.12
2012–2013	9090 (28.7)	1014 (27.9)	
2013–2014	7145 (22.5)	876 (24.1)	
2014–2015	13 824 (43.6)	1542 (42.4)	
Demographic characteristics			
Median (IQR) age, y	70.2 (54.2–83.2)	61.7 (50.0–74.0)	<.001
Age groups, n (%)			
18–49 years	6311 (19.9)	909 (25.0)	<.001
50–64 years	6824 (21.5)	1157 (31.8)	
65–79 years	8407 (26.5)	1022 (28.1)	
≥80 years	10 173 (32.1)	545 (15.0)	
Gender, n (%)			
Male	13 860 (43.7)	1907 (52.5)	<.001
Female	17 855 (56.3)	1726 (47.5)	
Race/ethnicity, n (%)			
Nonhispanic white	19 679 (62.0)	2058 (56.6)	<.001
Nonhispanic black	5308 (16.7)	903 (24.9)	
Hispanic	2294 (7.2)	221 (6.1)	
Other	1576 (5.0)	158 (4.3)	
Unknown/missing	2858 (9.0)	293 (8.1)	
Pre-existing medical conditions, n (%)			
Obesity or morbid obesity	7163 (22.6)	637 (17.5)	<.001
Chronic lung disease	13 076 (41.2)	1255 (34.5)	<.001
Cardiovascular disease	14 806 (46.7)	1469 (40.4)	<.001
Chronic metabolic disease	13 298 (41.9)	1346 (37.0)	<.001
Neuromuscular disorder	1751 (5.5)	176 (4.8)	.09
Neurologic disorder	6921(21.8)	503 (13.8)	<.001
Renal disease	5759 (18.2)	973 (26.8)	<.001
Liver disease	882 (2.8)	242 (6.7)	<.001
Pregnancy[b]	964 (5.4)	12 (0.7)	<.001
Other social factors			
Smoking—former/current	15 057 (47.5)	1871 (51.5)	<.001
Alcohol abuse—current	1117 (3.5)	118 (3.2)	.39
Influenza vaccine, n (%)			
Yes	14 742 (46.5)	1928 (53.1)	<.001
No	13 881 (43.8)	1324 (36.4)	
Unknown/missing	3092 (9.7)	381 (10.5)	
Presenting signs/symptoms,[c] n (%)			
Fever	8383 (60.6)	1041 (67.5)	<.001
Cough	11 052 (79.9)	1266 (82.1)	.04
Dyspnea/ respiratory distress	7525 (54.4)	819 (53.1)	.32
Wheeze	2693 (19.5)	251 (16.3)	.002
Nasal congestion	3409 (24.7)	421 (27.3)	.02
Gastrointestinal symptoms[d]	3824 (27.7)	522 (33.9)	<.001
Chest pain	2111 (15.3)	260 (16.9)	.10
Myalgias	3148 (22.8)	399 (25.9)	.006
Sore throat	1708 (12.4)	236 (15.3)	.001
Headache	1494 (10.8)	208 (13.5)	.0015
Altered mental status	2271 (16.4)	198 (12.8)	<.001
Influenza diagnostics and treatment			
Testing method,[e] n (%)			
Rapid only	8781 (27.7)	806 (22.2)	<.001
Molecular	22 265 (70.2)	2730 (75.1)	<.001
Culture	621 (2.0)	96 (2.6)	.006

Table 1. Continued

Characteristic	Nonimmunocompromised (N = 31 715)	Immunocompromised (N = 3633)	*P*[a]
Immunofluorescence antibody staining	1705 (5.4)	347 (9.6)	<.001
Unknown	193 (0.6)	25 (0.7)	.56
Duration between symptom onset and first influenza test,[f] mean ± SD, days	3.8 ± 22.9	4.2 ± 8.4	.36
Duration between symptom onset and admission,[f] mean ± SD, days	3.7 ± 22.9	4.1 ± 8.4	.42
First influenza test sent on the day of admission, n (%)	23 519 (74.2)	2562 (70.5)	<.001
Influenza type, n (%)			
A	27 457 (86.6)	2951 (81.2)	<.001
B	4046 (12.8)	661 (18.2)	
A and B	130 (0.4)	12 (0.3)	
Unknown	82 (0.3)	9 (0.2)	
Antiviral treatment, n (%)			
Yes	26 907 (84.8)	3159 (87.0)	.003
No	4723 (14.9)	466 (12.8)	
Unknown/missing	85 (0.3)	8 (0.2)	
First antiviral,[g] n (%)			
Oseltamivir	26 589 (99.7)	3126 (99.6)	.19
Other	68 (0.3)	12 (0.4)	
Antivirals <2 days after symptom onset,[h] n (%)			
Yes	5629 (22.4)	569 (19.3)	<.001
No	19 454 (77.6)	2376 (80.7)	
Antivirals <2 days after admission,[i] n (%)			
Yes	22 910 (89.3)	2542 (84.0)	<.001
No	2741 (10.7)	485 (16.0)	

Abbreviations: IQR, interquartile range; SD, standard deviation.

[a] Median ages of immunocompromised and nonimmunocompromised cohorts were compared using Mann-Whitney *U* test. Proportions of immunocompromised and nonimmunocompromised patients were compared for each variable using chi-square test except as noted. The mean duration between symptom onset/admission and first influenza test was compared with the 2-sample *t* test.

[b] Among nonimmunocompromised (n = 17 855) and immunocompromised (n = 1726) women.

[c] Among nonimmunocompromised (n = 13 824) and immunocompromised (n = 1542) adults hospitalized in the 2014–2015 season.

[d] Nausea/vomiting or diarrhea.

[e] Tests are not mutually exclusive. Each case could have up to 4 positive results.

[f] Among nonimmunocompormised (n = 26 840) and immunocompromised (n = 3087) adults with data.

[g] Among nonimmunocompromised (n = 26 657) and immunocompromised (n = 3138) adults with antiviral name data.

[h] Among nonimmunocompromised (n = 25 083) and immunocompromised (n = 2945) adults with data on antiviral timing relative to symptom onset.

[i] Among nonimmunocompromised (n = 25 651) and immunocompromised (n = 3027) adults with data on antiviral timing relative to admission.

patients, mortality was more likely in patients with cancer and patients receiving nonsteroid immunosuppressive therapy (aOR [95% CI], 1.71 [1.35–2.17] and 1.66 [1.29–2.15], respectively), less likely in solid organ transplant recipients (aOR, 0.36; 95% CI, .15–.88), and not statistically different in patients with HIV/AIDS (aOR, 1.31; 95% CI, .75–2.28).

ICU Admission

In the unadjusted analysis, ICU admission was more likely in immunocompromised adults compared with nonimmunocompromised adults (OR, 1.12; 95% CI, 1.03–1.23) (Table 2). The associations between other covariates and ICU admission are shown in Table 2.

The effect of immunocompromised status on ICU admission varied by age group (18–49 years, 50–64 years, 65–79 years, ≥80 years) in the multivariable model (likelihood ratio test, $P = .004$). The odds of ICU admission were higher in immunocompromised patients compared with nonimmunocompromised patients among those 65–79 years of age (aOR, 1.25; 95% CI, 1.06–1.48) and those 80 years of age or older (aOR, 1.35; 95% CI, 1.06–1.73) and no different among those 18–49 and 50–64 years of age. In the sensitivity analysis that included receipt of steroid therapy as an immunocompromising condition, the results were similar, with a higher odds of ICU admission among immunocompromised adults 65–79 years of age and 80 years of age or older (Table 4).

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; $P < .001$). In multivariable time-to-event models that considered time to hospital discharge in days, immunocompromised adults had a longer duration of hospitalization (adjusted hazard ratio of hospital discharge, 0.86; 95% CI, .83–.88). The findings were similar for the sensitivity analysis that included receipt of steroid therapy as an immunocompromising condition (Table 5).

Table 2. Association Between Demographic/Clinical Characteristics and All-Cause Mortality and ICU Admission Among Adults Hospitalized With Laboratory-confirmed Influenza in the US Influenza Hospitalization Surveillance Network, 2011–2015

			Death				ICU Admission	
Characteristic	Death (n = 1080)	No Death (n = 34 268)	OR[a]	95% CI	ICU Admission (n = 5707)	No ICU Admission (n = 29 641)	OR[a]	95% CI
Immunocompromised, n (%)								
No	945 (3.0)	30 770 (97.0)		Ref	5068 (16.0)	26 647 (84.0)	Ref	
Yes	135 (3.7)	3498 (96.3)	1.26	1.05–1.51	639 (17.6)	2994 (82.4)	1.12	1.03–1.23
Influenza season								
2011–2012	47 (2.5)	1810 (97.5)		Ref	282 (15.2)	1575 (84.8)	Ref	
2012–2013	264 (2.6)	9840 (97.4)	1.03	.76–1.42	1508 (14.9)	8596 (85.1)	0.98	.85–1.13
2013–2014	286 (3.6)	7735 (96.4)	1.42	1.04–1.95	1746 (21.8)	6275 (78.2)	1.55	1.36–1.78
2014–2015	483 (3.1)	14 883 (96.9)	1.25	.92–1.69	2171 (14.1)	13 195 (85.9)	0.92	.80–1.05
Demographic characteristics, n (%)								
Age groups								
18–49 years	103 (1.4)	7117 (98.6)		Ref	1203 (16.7)	6017 (83.3)	Ref	
50–64 years	247 (3.1)	7734 (96.9)	2.21	1.75–2.78	1608 (20.1)	6373 (79.9)	1.26	1.16–1.37
65–79 years	268 (2.8)	9161 (97.2)	2.02	1.61–2.54	1624 (17.2)	7805 (82.8)	1.04	.96–1.13
≥80 years	462 (4.3)	10 256 (95.7)	3.11	2.51–3.86	1272 (11.9)	9446 (88.1)	0.67	.62–.73
Gender								
Male	517 (3.3)	15 250 (96.7)		Ref	2807 (17.8)	12 960 (82.2)	Ref	
Female	563 (2.9)	19 018 (97.1)	0.87	.77–0.99	2900 (14.8)	16 681 (85.2)	0.80	.76–.85
Race/ethnicity								
Nonhispanic white	770 (3.5)	20 967 (96.5)		Ref	3651 (16.8)	18 086 (83.2)	Ref	
Nonhispanic black	114 (1.8)	6097 (98.2)	0.51	.42–.62	941 (15.2)	5270 (84.8)	0.89	.82–.96
Hispanic	49 (1.9)	2466 (98.1)	0.54	.40–.72	362 (14.4)	2153 (85.6)	0.83	.74–.94
Other	56 (3.2)	1678 (96.8)	0.91	.69–1.20	284 (16.4)	1450 (83.6)	0.97	.85–1.11
Unknown/missing	91 (2.9)	3060 (97.1)	0.81	.65–1.01	469 (14.9)	2682 (85.1)	0.87	.78–.96
Pre-existing medical conditions, n (%)								
Obesity or morbid obesity	223 (2.9)	7577 (97.1)	0.92	.79–1.06	1405 (18.0)	6395 (82.0)	1.19	1.11–1.27
Chronic lung disease	410 (2.9)	13 921 (97.1)	0.89	.79–1.01	2695 (18.8)	11 636 (81.2)	1.39	1.31–1.47
Cardiovascular disease	642 (3.9)	15 633 (96.1)	1.75	1.55–1.98	2899 (17.8)	13 376 (82.2)	1.26	1.19–1.33
Chronic metabolic disease	470 (3.2)	14 174 (96.6)	1.09	.97–1.23	2558 (17.5)	12 086 (82.5)	1.18	1.11–1.25
Neuromuscular disorder	86 (4.5)	1841 (95.5)	1.52	1.22–1.91	357 (18.5)	1570 (81.5)	1.19	1.06–1.34
Neurologic disorder	314 (4.2)	7110 (95.8)	1.57	1.37–1.79	1258 (16.9)	6166 (83.1)	1.08	1.01–1.15
Renal disease	296 (4.4)	6436 (95.6)	1.63	1.42–1.87	1182 (17.6)	5550 (82.4)	1.13	1.06–1.22
Liver disease	59 (5.2)	1065 (94.8)	1.80	1.38–2.36	233 (20.7)	891 (79.3)	1.37	1.19–1.59
Pregnancy[b]	2 (0.2)	2 (0.2)	0.07	.02–.27	39 (4.0)	937 (96.0)	0.23	.17–.32
Other social factors, n (%)								
Smoking–former/current	534 (3.2)	16 394 (96.8)	1.07	.95–1.20	3171 (18.7)	13 757 (81.3)	1.44	1.36–1.53
Alcohol abuse–current	48 (3.9)	1187 (96.1)	1.30	.97–1.74	355 (28.7)	880 (71.3)	2.17	1.91–2.46
Influenza vaccine, n (%)								
Yes	459 (2.8)	16 211 (97.2)		Ref	2420 (14.5)	14 250 (85.5)	Ref	
No	439 (2.9)	14 766 (97.1)	1.05	.92–1.20	2649 (17.4)	12 556 (82.6)	1.24	1.17–1.31
Unknown/missing	182 (5.2)	3291 (94.8)	1.95	1.64–2.33	638 (18.4)	2835 (81.6)	1.33	1.20–1.46
Influenza diagnostics and treatment, n (%)								
Influenza type								
A	934 (3.1)	29 474 (96.9)		Ref	4913 (16.2)	25 495 (83.8)	Ref	
B	132 (2.8)	4575 (97.2)	0.91	.76–1.10	747 (15.9)	3960 (84.1)	0.98	.90–1.07
A and B	11 (7.7)	131 (92.3)	2.65	1.43–4.92	34 (23.9)	108 (76.1)	1.64	1.11–2.41
Unknown	3 (3.3)	88 (96.7)	1.08	.34–3.41	13 (14.3)	78 (85.7)	0.87	.48–1.56
Antiviral treatment								
Yes	858 (2.9)	29 208 (97.1)		Ref	5039 (16.8)	25 027 (83.2)	Ref	
No	215 (4.1)	4974 (95.9)	1.47	1.26–1.71	650 (12.5)	4539 (87.5)	0.71	.65–.78
Unknown/missing	7 (7.5)	86 (92.5)	2.77	1.28–6.00	18 (19.4)	75 (80.6)	1.19	.71–2.00

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio; Ref, reference.

[a]All ORs are unadjusted.

[b]Among women (n = 19 581).

Secondary Outcomes

Pneumonia was more common among immunocompromised adults than among nonimmunocompromised adults in the bivariable analysis (33.5% vs 30.7%; $P < .001$), and multivariable analysis (aOR, 1.22; 95% CI, 1.13–1.32). Immunocompromised adults were more likely to require mechanical ventilation in the crude analysis (8.3% vs 7.1%; $P = .007$) and after controlling for confounding (aOR, 1.19; 95% CI, 1.05–1.36). The

Table 3. All-Cause In-Hospital Mortality in Immunocompromised vs Nonimmunocompromised Adults Hospitalized With Laboratory-confirmed Influenza In the US Influenza Hospitalization Surveillance Network, 2011–2015

	aOR of Mortality	95% CI
Primary analysis[a]	1.46	1.20–1.76
Sensitivity analysis[a,b]	1.42	1.21–1.66

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

[a]Controlling for age, sex, race/ethnicity, influenza vaccination, underlying medical conditions (smoking, obesity, chronic lung disease, cardiovascular disease, chronic metabolic disease, neuromuscular disorders, neurologic disorders, renal disease, liver disease), antiviral use, and influenza season.

[b]Including receipt of steroid therapy in the immunocompromised group.

duration of ICU admission did not differ between the 557 immunocompromised adults (median, 3 days; IQR, 2–7 days) and 4407 nonimmunocompromised adults (median, 3 days; IQR, 1–7 days) (P = .13) with available data.

DISCUSSION

Among adults hospitalized with laboratory-confirmed influenza during 4 recent influenza seasons, immunocompromised patients were more likely than nonimmunocompromised patients to have received seasonal influenza vaccination and antiviral treatment. Immunocompromised adults were more likely to experience severe influenza-associated outcomes, including death, pneumonia, and a longer duration of hospitalization. Older immunocompromised patients were also more likely to be admitted to the ICU.

Our findings are consistent with prior studies demonstrating a longer duration of illness and higher mortality in immunocompromised populations with influenza [4, 5]. Whereas 30% of both immunocompromised and nonimmunocompromised patients in this study developed influenza-associated pneumonia, this has been reported to occur among 29–80% of certain immunocompromised populations, including patients with leukemia and transplant recipients [16–20]. We observed lower influenza-associated mortality (3.7%) compared with prior studies, which observed mortality of 7–30% in patients with cancer and in those after hematopoietic stem cell or solid organ transplantation [16–21]. Because we used a broad, inclusive definition of immunocompromised status, our immunocompromised population is heterogenous and likely includes some patients who were less immunocompromised and might therefore have better outcomes. Our subgroup analyses suggest that influenza-associated mortality may depend on the underlying immunocompromising condition. Unfortunately, FluSurv-NET data do not include more detailed information regarding a patient's degree of immunosuppression, such as dates and types of chemotherapy received, time since transplantation, or CD4 counts. In addition, because we only analyzed data on in-hospital mortailty, we may have underestimated the contribution of deaths that occurred after discharge. Advances in supportive care may also have contributed to the less severe outcomes we observed.

In a related study in children hospitalized with influenza, we found that immunocompromised children were less likely to require intensive care than nonimmunocompromised children [14]. Such a phenomenon may account for rates of ICU admission differing based on age group in this study. These findings raise questions about whether there is a bias toward admitting younger immunocompromised patients with milder disease because of their immunocompromised status. If such an admission bias exists, this may have attenuated the severity of outcomes observed among the immunocompromised group in this study.

We found that the majority of immunocompromised patients with influenza presented with classic symptoms including fever, cough, and difficulty breathing during the 2014–2015 season. Although we identified statistically significant differences between groups, many of these differences were very small and may not be clinically relevant. Data on the clinical presentation of immunocompromised patients with influenza are mixed, with some studies noting classic symptoms and others suggesting that this population presents more subtly [5, 22]. Our

Table 4. ICU Admission in Immunocompromised vs Nonimmunocompromised Adults Hospitalized With Laboratory-confirmed Influenza In the US Influenza Hospitalization Surveillance Network, 2011–2015

	aOR of ICU Admission	95% CI
Primary analysis[a]		
18–49 years	0.83	.68–1.01
50–64 years	1.04	.88–1.22
65–79 years	1.25	1.06–1.48
≥80 years	1.35	1.06–1.73
Sensitivity analysis[a,b]		
18–49 years	0.95	.80–1.12
50–64 years	1.10	.96–1.26
65–79 years	1.38	1.21–1.58
≥80 years	1.31	1.09–1.58

Effect modification by age group was only observed for ICU admission. Likelihood ratio test P = .004. Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit.

[a]Controlling for age, sex, race/ethnicity, influenza vaccination, underlying medical conditions (smoking, obesity, chronic lung disease, cardiovascular disease, chronic metabolic disease, neuromuscular disorders, neurologic disorders, renal disease, liver disease), and influenza season. (Antiviral therapy was excluded because this was given upon or after ICU admission for most patients receiving intensive care.)

[b]Including receipt of steroid therapy in the immunocompromised group.

Table 5. Hazard ratio of Discharge in Immunocompromised vs Nonimmunocompromised Adults Hospitalized With Laboratory-confirmed Influenza In the US Influenza Hospitalization Surveillance Network, 2011–2015

	aHR of Discharge	95% CI
Primary analysis[a]	0.86	.83–.88
Sensitivity analysis[a,b]	0.87	.84–.89

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

[a]Controlling for age, sex, race/ethnicity, influenza vaccination, underlying medical conditions (smoking, obesity, chronic lung disease, cardiovascular disease, chronic metabolic disease, neuromuscular disorders, neurologic disorders, renal disease, liver disease), antiviral use, and influenza season.

[b]Including receipt of steroid therapy in the immunocompromised group.

findings do not support the latter assertion. However, by including only laboratory-confirmed cases of influenza, we may have selected for patients with classic influenza symptoms given that influenza testing was performed based on clinician discretion. Given that many influenza symptoms are nonspecific, a high index of suspicion is needed during the influenza season. Patient education about influenza symptoms and the need for prompt care seeking may be beneficial for immunocompromised hosts in particular.

Only 53% of immunocompromised adults and 46% of nonimmunocompromised adults in this study had received seasonal influenza vaccine. These frequencies correspond to patients who developed influenza despite vaccination. Immunocompromised hosts may have higher vaccination rates than the general population for multiple reasons. Frequent healthcare encounters may provide increased opportunities for vaccination, and providers may be more likely to recommend immunocompromised hosts be vaccinated. However, there is clearly an opportunity to increase seasonal influenza vaccination rates in immunocompromised patients. Data are needed to determine whether new vaccine options (eg, high-dose influenza vaccine, adjuvanted influenza vaccine) could provide better protection against influenza disease in immunocompromised adults. Findings of a recent study suggest that existing influenza vaccination is not as effective in preventing influenza-related community-acquired pneumonia in immunocompromised patients [23]. Some severely immunocompromised patients, such as those receiving intensive chemotherapy and recent bone marrow transplant recipients, should not receive influenza vaccination [24]. In light of possible decreased vaccine effectiveness in immunocompromised populations, vaccination of close contacts of immunocompromised patients is an important strategy for providing community protection [25]. Antiviral medications can also be considered for chemoprophylaxis following influenza exposure for severely immunocompromised people who either cannot receive or who might not respond to influenza vaccination [8].

CDC recommends early influenza antiviral treatment for all hospitalized patients with suspected or confirmed influenza [6]. Approximately 85% of both immunocompromised and nonimmunocompromised adults in this study received influenza antivirals, a proportion that could be improved. Early antiviral treatment (<2 days after symptom onset) was quite poor (<25% of both groups.) Delays in care seeking and limited clinical suspicion for influenza among providers are possible explanations for low early antiviral use; the mean duration between symptom onset and first influenza test and admission was approximately 4 days in both groups. Antiviral use within 2 days of admission was much higher in both groups. Public health messaging should emphasize early care seeking and antiviral treatment for immunocompromised patients. Influenza-associated hospitalizations and adverse outcomes of patients in this study might have been prevented through outpatient and early hospital initiation of antiviral therapy.

The data used in this study were collected for surveillance purposes, which limits their interpretation. First, there may be a selection bias because the decision whether to test for influenza and to admit a patient to the hospital is made by individual clinicians and may be associated with a patient's immunocompromised status (eg, immunocompromised patients may be more likely to be admitted with milder disease or for an indication other than influenza). Influenza cases may be misclassified due to imperfect sensitivity and specificity of testing methods. Misclassification of influenza may be more likely in immunocompromised patients, who may shed influenza virus longer than nonimmunocompromised patients [5]. Additionally, the determination of immunocompromised status was based on retrospective chart review, which could result in misclassification. Finally, observed differences in outcomes could have resulted from unmeasured confounders.

In conclusion, among adults hospitalized with influenza, we found that immunocompromised adults had worse outcomes including increased all-cause mortality and a longer duration of hospitalization. Our findings support the need for strategies to improve early medical treatment with an antiviral for immunocompromised adults hospitalized with suspected or confirmed influenza. Last, increasing influenza vaccination coverage is critical to provide the best protection against influenza for immunocompromised patients who are at high risk of severe outcomes.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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