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Influenza in hospitalised patients with malignancy: a propensity score matching analysis

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ABSTRACT

Background Patients with malignancy are vulnerable to influenza viruses and are at high risk of developing serious complications. However, few studies have investigated the impact of influenza infection among hospitalised patients with malignancy.

Methods Cancer-related hospitalisations were identified by using data from National Inpatient Sample in the USA between 2012 and 2014. We conducted a 1:1 propensity score matching analysis to compare the in-hospital outcomes between cancer patients with and without influenza. Multivariate logistic regression analyses were also performed to identify independent prognosis predictors of mortality.

Results We identified 13 186 849 weighted cancer-related hospitalisations during the study period, and 47 850 of them (0.36%) had a concomitant diagnosis of influenza. After propensity score matching, cancer patients with concomitant influenza had a higher mortality (5.4% vs 4.2%; OR, 1.30; 95% CI, 1.13 to 1.49; p<0.001), longer length of stay (6.3 days vs 5.6 days; p<0.001) but lower costs (US$14 605.9 vs US$14 625.5; p<0.001) in hospital than those without influenza. In addition, cancer patients with influenza had a higher incidence of complications, including pneumonia (18.4% vs 13.2%; OR, 1.49; 95% CI, 1.37 to 1.62; p<0.001), neutropenia (7.1% vs 3.4%; OR, 2.18; 95% CI, 1.91 to 2.50; p<0.001), sepsis (19.5% vs 9.3%; OR, 2.36; 95% CI, 2.16 to 2.58; p<0.001), dehydration (14.8% vs 8.8%; OR, 1.80; 95% CI, 1.65 to 1.97; p<0.001) and acute kidney injury (19.9% vs 17.6%; OR, 1.16; 95% CI, 1.08 to 1.25; p<0.001) than those without influenza. Older age, no insurance, more comorbidities, lung cancer and haematological malignancy were independently associated with higher mortality.

Conclusion Influenza is associated with worse in-hospital clinical outcomes among hospitalised patients with malignancy. Annual influenza vaccination and early initiation of antiviral therapy are recommended in this high-risk population.

Key questions

What is already known about this subject?

► Patients with malignancy are vulnerable to influenza viruses and are at high risk of developing serious complications that may lead to hospitalisations, disruptions in anticancer therapy schedule and even death.

What does this study add?

► We identified 47 850 cancer-related hospitalisations with a concomitant diagnosis of influenza by using data from the largest nationwide inpatient database in the USA. Hospitalised cancer patients with concomitant influenza had a higher morbidity and mortality than those without influenza.

How might this impact on clinical practice?

► Our study highlights the need for efforts to prevent influenza infection and manage related serious complications in hospitalised cancer patients.

INTRODUCTION

Influenza is a highly contagious respiratory disease and serious influenza can result in hospitalisation or death. In the USA, 9.2 million to 35.6 million people get influenza and the complications of influenza lead 140 000 to 710 000 people to be hospitalised and about 36 000 people to die each year.[1]

In particular, patients with malignancy have more concomitant diseases and may experience chemotherapy or radiotherapy, bone marrow transplant and other related medications (eg, systemic corticosteroids), which seriously impair their immune function.[2 3] These immunosuppressed population are more vulnerable to influenza viruses and are at high risk of developing serious complications that may lead to hospitalisations, disruptions in anticancer therapy schedule and even death.[4 5] Yearly, 441 per 100 000 cancer patients are hospitalised because of influenza infection in the USA, which is three to five times higher than in the general population.[6] Some studies also reported that during the influenza epidemic, 21% to 33% cancer patients admitted to hospital with respiratory symptoms might test positive for influenza.[7 8] Considering that at least 16.9 million people with a history of cancer are alive and about 650 000 cancer patients receive chemotherapy in an outpatient oncology clinic each year, influenza has become a substantial disease burden among cancer patients in the USA.[9] Despite

influenza infection poses prevailing concerns in patients with malignancy, the actual morbidity and mortality in this heterogeneous population is still not well defined. Therefore, we conducted this nationwide analysis to evaluate the impact of influenza infection among hospitalised patients with malignancy in the USA.

METHODS

Study design and sample population

Data for analysis were collected from the National Inpatient Sample (NIS) provided by the Healthcare Cost and Utilization Project (HCUP) between 2012 and 2014. The NIS is the largest inpatient database in the USA, which is a 20% stratified sample of nationwide inpatient hospitalisations and contains over 7 million hospital discharge data from about 1000 hospitals annually.

Hospitalisations among patients aged ≥18 years with a diagnosis of cancer were identified using the clinical classifications software (CCS) diagnostic codes. CCS is a diagnosis and procedure categorisation scheme that groups the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes into clinically meaningful categories. The detailed diagnostic codes are listed in online supplemental appendix A. Hospitalisations with missing value were excluded from any further analysis. All identified cancer-related hospitalisations were subsequently categorised into two groups: influenza and no influenza.

The ethics committee of Peking Union Medical College Hospital determined that this study was exempt from formal institutional review board review due to the retrospective design and de-identified data.

Characteristics and outcomes

Baseline characteristics included in this study are listed in table 1. The comorbidity burden was calculated by using Elixhauser comorbidity software developed by HCUP.[10 11] The primary outcome was in-hospital mortality. The secondary outcomes included length of stay, total cost and incidence of in-hospital complications, including pneumonia, neutropenia, sepsis, dehydration and acute kidney injury. The diagnostic codes of the complications are listed in online supplemental appendix A.

Statistical analysis

Data analysis was conducted following recommended methodological standards for NIS.[12] In an attempt to control for potential confounders, we performed 1:1 propensity score matching to balance the differences in baseline characteristics between cancer patients with influenza and without influenza. The propensity score analysis followed a recommended guideline modified from the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement.[13] Univariate and multivariate logistic regression analyses were performed to identify independent prognosis predictors of in-hospital mortality. Normally distributed continuous variables were compared using Student's t-test. Categorical variables were compared using χ^2 test or Mann-Whitney rank-sum test. A p value less than 0.05 (two-sided test) was considered to be statistically significant. All statistical analyses were performed with SAS (V.9.4, SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

Baseline characteristics

We identified 13 186 849 weighted cancer-related hospitalisations during the study period, and 47 850 of them (0.36%) had a concomitant diagnosis of influenza (figure 1). Baseline patient and hospital characteristics are shown in table 1. Cancer patients with concomitant influenza were more likely to be older (70.1 vs 68.2 years, p<0.001), have Medicare insurance (69.8% vs 64.0%, p<0.001), have more comorbidities (3.3 vs 2.8, p<0.001), have breast cancer (17.1% vs 15.7%, p<0.001) or haematological malignancy (24.1% vs 12.6%, p<0.001), admit to a hospital located in Midwest (26.3% vs 21.7%, p<0.001), admit to a rural hospital (10.6% vs 9.0%, p<0.001) and admit to a small hospital (16.2% vs 14.1%, p<0.001) than those without influenza infection. After propensity matching, a sample of 95 690 patients (47 845 in each group) with well-matched baseline characteristics was identified (table 1).

In-hospital outcomes

In the propensity score-matched population, patients with concomitant influenza had a higher in-hospital mortality (5.4% vs 4.2%; OR, 1.30; 95% CI, 1.13 to 1.49; p<0.001) (figure 2), longer length of stay (6.3 days vs 5.6 days; p<0.001) but lower costs (US$14 605.9 vs US$14 625.5; p<0.001) in hospital (table 2). In addition, patients with influenza had a higher incidence of complications, including pneumonia (18.4% vs 13.2%; OR, 1.49; 95% CI, 1.37 to 1.62; p<0.001), neutropenia (7.1% vs 3.4%; OR, 2.18; 95% CI, 1.91 to 2.50; p<0.001), sepsis (19.5% vs 9.3%; OR, 2.36; 95% CI, 2.16 to 2.58; p<0.001), dehydration (14.8% vs 8.8%; OR, 1.80; 95% CI, 1.65 to 1.97; p<0.001) and acute kidney injury (19.9% vs 17.6%; OR, 1.16; 95% CI, 1.08 to 1.25; p<0.001) (figure 2, table 2). Similar results were seen in multivariable regression analysis in the unmatched cohort (table 2).

Table 3 presents relevant factors associated with mortality in hospitalised cancer patients with influenza. In the multivariate logistic regression analysis adjusting for relevant variables, older age, no insurance (vs Medicare; OR, 1.90; 95% CI, 1.39 to 2.61; p<0.001), Elixhauser comorbidity ≥4 (vs <4; OR, 1.73; 95% CI, 1.56 to 1.92; p<0.001), lung cancer (vs colorectal cancer; OR, 1.56; 95% CI, 1.28 to 1.90; p<0.001) and haematological malignancy (vs colorectal cancer; OR, 1.30; 95% CI, 1.08 to 1.56; p<0.001) were independently associated with higher mortality. With regard to hospital level factors, admission to medium (vs small; OR, 1.25; 95% CI, 1.04 to 1.51; p<0.019) or large size hospital (vs small; OR, 1.50; 95% CI, 1.27 to 1.78; p<0.001), and admission to hospital located

Table 1 Baseline characteristics of hospitalised patients with malignancy before and after propensity score matching

	Pre-matching				Post-matching			
	Influenza (n=47 850)	No influenza (n=13 138 999)	P value	SMD	Influenza (n=47 845)	No influenza (n=47 845)	P value	SMD
Age (years), mean±SD	70.1±15.32	68.2±14.8	<0.001	0.128	70.1±15.3	70.2±14.4	0.836	0.003
Female, n (%)	24 449 (51.1%)	6 745 664 (51.3%)	0.628	0.005	24 449 (51.1%)	24 524 (51.3%)	0.831	0.003
Race, n (%)								
White	37 309 (78.0%)	10 138 468 (77.2%)	0.116	0.019	37 304 (78.0%)	37 370 (78.1%)	0.835	0.003
Black	4849 (10.1%)	1 486 179 (11.3%)	0.002	0.038	4849 (10.1%)	4834 (10.1%)	0.946	0.001
Hispanic	3509 (7.3%)	865 989 (6.6%)	0.015	0.029	3509 (7.3%)	3524 (7.4%)	0.940	0.001
Asian/Pacific Islander	909 (1.9%)	274 914 (2.1%)	0.215	0.014	909 (2.0%)	914 (1.9%)	0.958	0.001
Other	1269 (2.7%)	373 444 (2.8%)	0.326	0.012	1269 (2.7%)	1199 (2.5%)	0.532	0.009
Insurance status, n (%)								
Medicare	33 414 (69.8%)	8 414 813 (64.0%)	<0.001	0.123	33 409 (69.8%)	33 504 (70.0%)	0.772	0.004
Medicaid	3500 (7.3%)	1 040 045 (7.9%)	0.036	0.023	3500 (7.3%)	3405 (7.1%)	0.605	0.008
Private	9134 (19.1%)	3 078 754 (23.4%)	<0.001	0.106	9134 (19.1%)	9180 (19.2%)	0.873	0.002
Self	949 (2.0%)	280 814 (2.1%)	0.348	0.011	949 (2.0%)	939 (2.0%)	0.918	0.002
Uninsured	849 (1.8%)	324 570 (2.5%)	<0.001	0.048	849 (1.8%)	814 (1.7%)	0.701	0.006
Median household income, n (%)								
1^{st}–25^{th} percentile	12 154 (25.4%)	3 485 819 (26.5%)	0.025	0.026	12 149 (25.4%)	11 549 (24.14%)	0.059	0.029
26^{th}–50^{th} percentile	12 209 (25.5%)	3 374 363 (25.7%)	0.743	0.004	12 209 (25.5%)	12 819 (26.79%)	0.056	0.029
51^{st}–75^{th} percentile	11 704 (24.5%)	3 186 184 (24.3%)	0.654	0.005	11 704 (24.5%)	11 754 (24.57%)	0.874	0.002
75^{th}–100^{th} percentile	11 780 (24.6%)	3 092 630 (23.5%)	0.040	0.025	11 780 (24.6%)	11 720 (24.5%)	0.857	0.003
Elixhauser comorbidity, mean±SD	3.3±1.9	2.8±1.9	<0.001	0.277	3.3±1.9	3.3±1.9	0.192	0.019
Cancer type, n (%)								
Head and neck cancer	1084 (2.3%)	400 094 (3.1%)	<0.001	0.048	1084 (2.3%)	1144 (2.4%)	0.570	0.008
Gastrointestinal cancer	5579 (11.7%)	2 529 369 (19.3%)	<0.001	0.211	5579 (11.7%)	5369 (11.2%)	0.343	0.014
Lung cancer	5244 (11.0%)	1 556 910 (11.9%)	0.008	0.028	5244 (11.0%)	5405 (11.3%)	0.466	0.011
Sarcoma	204 (0.4%)	108 234 (0.8%)	<0.001	0.050	204 (0.4%)	205 (0.4%)	1.000	<0.001
Melanoma	1054 (2.2%)	320 449 (2.4%)	0.141	0.016	1054 (2.2%)	1234 (2.6%)	0.089	0.025
Breast cancer	8174 (17.1%)	2 055 629 (15.7%)	<0.001	0.039	8174 (17.1%)	8379 (17.5%)	0.434	0.011
Gynaecological cancer	2584 (5.4%)	1 012 714 (7.7%)	<0.001	0.093	2584 (5.4%)	2589 (5.4%)	0.974	<0.001
Genitourinary cancer	9559 (20.0%)	2 744 259 (20.9%)	0.036	0.023	9559 (20.0%)	9264 (19.4%)	0.298	0.016
Central nervous system tumours	379 (0.8%)	184 289 (1.4%)	<0.001	0.058	379 (0.8%)	250 (0.5%)	0.023	0.034

Continued

Table 1 Continued

	Pre-matching				Post-matching			
	Influenza (n=47 850)	No influenza (n=13 138 999)	P value	SMD	Influenza (n=47 845)	No influenza (n=47 845)	P value	SMD
Haematological malignancies	11 549 (24.1%)	1 650 219 (12.6%)	<0.001	0.303	11 544 (24.1%)	11 384 (23.8%)	0.608	0.008
Secondary malignancies	4334 (9.1%)	2 575 309 (19.6%)	<0.001	0.304	4334 (9.1%)	4130 (8.6%)	0.304	0.015
Other	8495 (17.8%)	2 279 709 (17.4%)	0.316	0.011	8495 (17.8%)	8820 (18.4%)	0.235	0.018
Region, n (%)								
Northeast	10 490 (21.9%)	2 894 889 (22.0%)	0.879	0.003	10 490 (21.9%)	10 260 (21.44%)	0.564	0.012
Midwest	12 599 (26.3%)	2 850 122 (21.7%)	<0.001	0.109	12 594 (26.3%)	12 409 (25.94%)	0.625	0.009
South	17 655 (36.9%)	5 090 587 (38.7%)	0.015	0.038	17 655 (36.9%)	18 060 (37.75%)	0.337	0.018
West	7104 (14.9%)	2 303 399 (17.5%)	<0.001	0.073	7104 (14.9%)	7115 (14.9%)	0.972	0.001
Hospital location and teaching status, n (%)								
Rural	5054 (10.6%)	1 187 798 (9.0%)	<0.001	0.051	5054 (10.6%)	4959 (10.4%)	0.691	0.006
Urban non-teaching	14 654 (30.6%)	4 320 174 (32.9%)	0.001	0.048	14 654 (30.6%)	14 774 (30.8%)	0.760	0.005
Urban teaching	28 139 (58.8%)	7 631 025 (58.1%)	0.333	0.015	28 134 (58.8%)	28 110 (58.8%)	0.953	0.001
Hospital size, n (%)								
Small	7750 (16.2%)	1 848 780 (14.1%)	<0.001	0.059	7745 (16.2%)	8025 (16.8%)	0.350	0.016
Medium	12 144 (25.4%)	3 320 623 (25.3%)	0.866	0.002	12 144 (25.4%)	12 179 (25.5%)	0.925	0.002
Large	27 954 (58.4%)	7 969 594 (60.7%)	0.003	0.046	27 954 (58.4%)	27 639 (57.8%)	0.459	0.013

SMD, standardised mean difference.

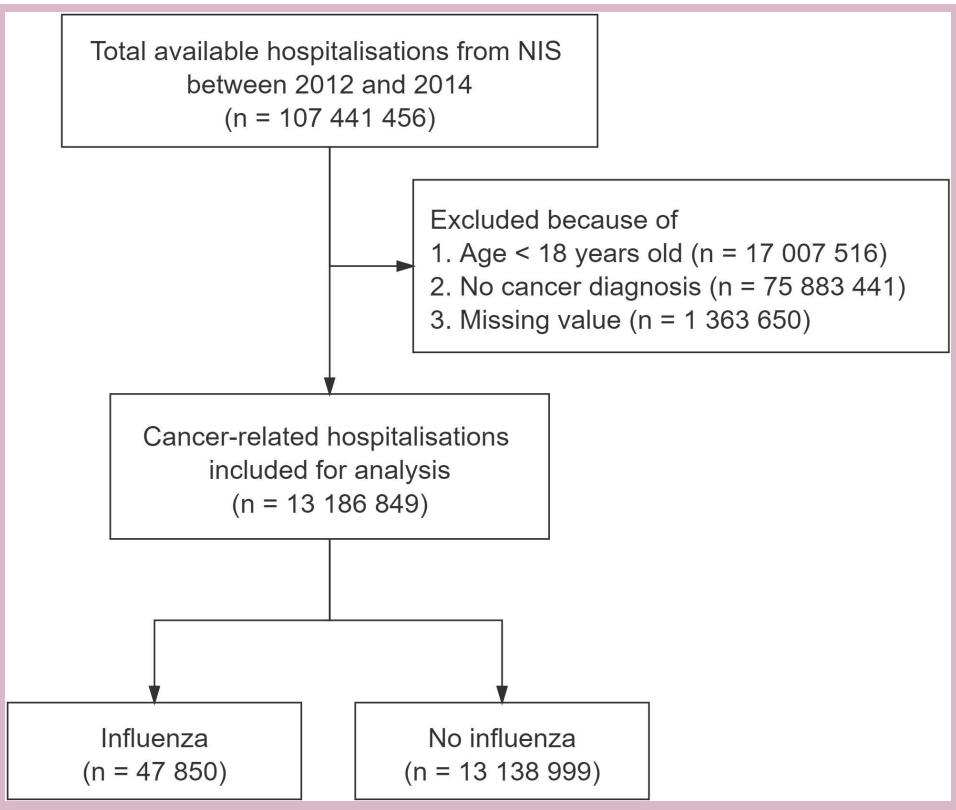

Figure 1 Flow diagram of study population selection. NIS, National Inpatient Sample.

in the South (vs Northeast; OR, 1.32; 95% CI, 1.14 to 1.53; p<0.001) or West (vs Northeast; OR, 1.25; 95% CI, 1.05 to 1.50; p=0.013) were independently associated with higher mortality.

DISCUSSION

During the past few decades, the rapid progress of cancer research has resulted in a prolonged survival in many patients with malignancy. However, since the malignant disease and its related treatment can seriously impair immune function, patients with cancer are especially susceptible to influenza and are at great risk of developing serious complications. In this propensity score-matched analysis of the largest nationwide database of hospitalisation in the USA, we found influenza infection was associated with worse in-hospital clinical outcomes among hospitalised patients with malignancy.

In this study, hospitalised cancer patients with influenza had a mortality rate of 5.4%, which was significantly higher than those without influenza. Consistently, previous studies also reported a mortality rate from 4% up to 10% in hospitalised cancer patients with influenza

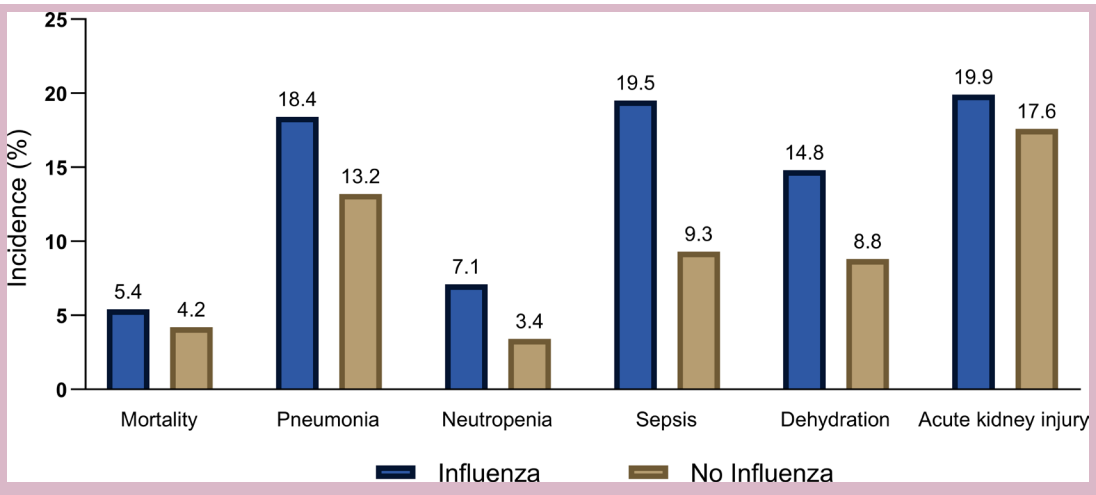

Figure 2 Comparison of in-hospital mortality and incidence of complications between hospitalised cancer patients with and without influenza after propensity score matching. All p values are less than 0.001.

Table 2 In-hospital outcomes among hospitalised patients with malignancy before and after propensity score matching

	Before propensity-score matching				After propensity-score matching			
	Influenza (n=47 845)	No influenza (n=13 138 999)	OR (95% CI)	Adjusted OR (95% CI)*	Influenza (n=47 845)	No influenza (n=47 845)	OR (95% CI)	Adjusted OR (95% CI)*
In-hospital mortality (%)	5.4	4.1	1.34 (1.22 to 1.47)	1.35 (1.23 to 1.49)	5.4	4.2	1.30 (1.13 to 1.49)	1.31 (1.14 to 1.51)
Length of stay (days), mean±SD	6.3±7.7	5.6±6.4	0.17 (0.01) †	0.12 (0.01)†	6.3±7.7	5.6±6.7	0.11 (0.02)†	0.10 (0.02)†
Total cost (US$), mean±SD	14 606.3±28 912.3	14 163.7±19 529.3	–0.16 (0.01)†	–0.17 (0.01)†	14 605.9±28 913.8	14 625.5±19 749.0	–0.17 (0.01)†	–0.17 (0.01)†
Complication incidence (%)								
Pneumonia	18.4	11.3	1.76 (1.66 to 1.86)	1.54 (1.45 to 1.64)	18.4	13.2	1.49 (1.37 to 1.62)	1.52 (1.40 to 1.65)
Neutropenia	7.1	2.8	2.62 (2.42 to 2.84)	2.08 (1.91 to 2.27)	7.1	3.4	2.18 (1.91 to 2.50)	2.18 (1.90 to 2.51)
Sepsis	19.5	8.5	2.59 (2.46 to 2.73)	2.33 (2.20 to 2.46)	19.5	9.3	2.36 (2.16 to 2.58)	2.41 (2.20 to 2.63)
Dehydration	14.8	8.4	1.90 (1.80 to 2.01)	1.80 (1.70 to 1.91)	14.8	8.8	1.80 (1.65 to 1.97)	1.81 (1.65 to 1.98)
Acute kidney injury	19.9	14.7	1.42 (1.35 to 1.50)	1.20 (1.13 to 1.27)	19.9	17.6	1.16 (1.08 to 1.25)	1.17 (1.08 to 1.27)

*Adjusted for age, sex, race, insurance status, household income, Elixhauser comorbidity, cancer type, region, hospital location and teaching status and hospital size (hospital cost was additionally adjusted for length of stay).
†Linear regression coefficient and its SE in linear regression model.

depending on different populations and approaches to disease management.[6 14] With regard to patient-related characteristics in this study, we found age, insurance status, comorbidity and cancer type as independent prognosis factors associated with mortality. Consistent with previous studies, higher mortality was observed in older patients and patients with more comorbidities.[6 15] According to the Centers for Disease Control and Prevention (CDC) in the USA, about 50% seasonal influenza-related hospitalisations and about 70% related deaths occurred in people 65 years and older.[16] In addition, our results identified significant differences in morbidity and mortality between patients with haematological malignancy and those with solid tumour. Patients with haematological malignancy tend to receive more aggressive interventions but less palliative care than those with solid tumour.[17–19] However, it is difficult to attribute this difference to the disease or treatment-associated immunosuppression. Hospital-level characteristics were also found to be associated with mortality in cancer patients with influenza. The mortality was significantly higher in patients admitted to large hospitals than those admitted to small hospitals. A possible explanation could be that complex patients are more likely to be referred to large specialised centres for more advanced care. According to geographical location, the mortality of patients was lower in hospitals in the Midwest and North-central and higher in hospitals in the South or West. This regional variation may suggest the difference of influenza infection prevention and control level across the hospitals in different regions.

The economic burden associated with influenza and its complications can be substantial. In the USA, influenza is estimated to result in 20.1 million days of lost productivity and 6.3 to 25.3 billion US$ economic burden to the healthcare system and society each year.[20] Compared with cancer patients without influenza, a longer length of stay but lower hospitalisation costs was observed among cancer patients with influenza in this study. Although influenza can cause a longer length of stay has already been reported in previous studies, the finding of lower hospitalisation costs is somewhat unexpected. This finding may in part be due to influenza and its complications compromise cytotoxic dose intensity and impede their planned cancer-associated treatment, which potentially reduces the hospitalisation cost.[5]

In the general population, influenza is an acutely debilitating but self-limited disease and most infected patients can recover without complications. However, this study identified that cancer patients with influenza were at a greater risk of serious complications than those without influenza. The major complication of influenza is pneumonia, which is also the leading causes of admission and mortality in patients with cancer.[21–23] Influenza virus can affect tracheobronchial epithelium of patients and contribute to secondary bacterial pneumonia and subsequent excess mortality.[24 25] Neutropenia is common among cancer patients undergoing active chemotherapy or radiotherapy with an impaired

Table 3 Univariable and multivariable logistic regression analysis of in-hospital mortality among hospitalised cancer patients with influenza

	Mortality (%)	OR	P value	Adjusted OR	P value
Age (years)					
18–49	4.4	Reference		Reference	
50–64	6.2	1.44 (1.23 to 1.69)	<0.001	1.54 (1.25 to 1.89)	<0.001
65–84	5.0	1.14 (0.98 to 1.33)	0.089	1.28 (1.02 to 1.60)	0.037
>=85	5.8	1.33 (1.13 to 1.57)	0.001	1.66 (1.28 to 2.15)	<0.001
Sex					
Male	5.9	Reference		Reference	
Female	4.8	0.81 (0.75 to 0.88)	<0.001	0.91 (0.80 to 1.02)	0.110
Race					
White	5.5	Reference		Reference	
Black	4.6	0.84 (0.73 to 0.97)	0.016	0.83 (0.70 to 0.99)	0.036
Hispanic	5.3	0.96 (0.82 to 1.12)	0.622	0.87 (0.71 to 1.07)	0.190
Asian/Pacific Islander	4.4	0.80 (0.58 to 1.10)	0.160	0.83 (0.56 to 1.21)	0.326
Median household income					
1^{st}–25^{th} percentile	5.7	Reference		Reference	
26^{th}–50^{th} percentile	4.6	0.79 (0.71 to 0.89)	<0.001	0.74 (0.63 to 0.86)	<0.001
51^{st}–75^{th} percentile	5.6	0.97 (0.87 to 1.08)	0.576	0.99 (0.85 to 1.15)	0.907
75^{th}–100^{th} percentile	5.6	0.98 (0.88 to 1.09)	0.694	1.03 (0.88 to 1.20)	0.747
Insurance status					
Medicare	5.3	Reference		Reference	
Medicaid	5.6	1.05 (0.90 to 1.22)	0.568	1.12 (0.89 to 1.41)	0.346
Private	5.1	0.95 (0.86 to 1.06)	0.340	1.12 (0.95 to 1.32)	0.174
Self	5.8	1.09 (0.83 to 1.44)	0.547	0.70 (0.44 to 1.12)	0.140
Uninsured	7.6	1.47 (1.13 to 1.90)	0.004	1.90 (1.39 to 2.61)	<0.001
Elixhauser comorbidity					
<4	4.0	Reference		Reference	
>=4	7.1	1.82 (1.68 to 1.97)	<0.001	1.73 (1.56 to 1.92)	<0.001
Cancer type					
Colorectal	5.8	Reference		Reference	
Lung	8.4	1.50 (1.24 to 1.82)	<0.001	1.56 (1.28 to 1.90)	<0.001
Breast	2.8	0.48 (0.38 to 0.59)	<0.001	0.51 (0.41 to 0.64)	<0.001
Prostate	3.5	0.58 (0.47 to 0.72)	<0.001	0.57 (0.46 to 0.72)	<0.001
Haematological malignancy	7.0	1.23 (1.04 to 1.47)	0.019	1.30 (1.08 to 1.56)	0.006
Region					
Northeast	5.1	Reference		Reference	
Midwest	4.3	0.85 (0.75 to 0.96)	0.009	0.91 (0.78 to 1.08)	0.279
South	5.7	1.14 (1.02 to 1.27)	0.017	1.32 (1.14 to 1.53)	<0.001
West	6.8	1.36 (1.20 to 1.55)	<0.001	1.25 (1.05 to 1.50)	0.013
Hospital location and teaching status					
Rural	4.3	Reference		Reference	
Urban non-teaching	5.0	1.18 (1.01 to 1.38)	0.037	0.94 (0.77 to 1.14)	0.514
Urban teaching	5.8	1.38 (1.19 to 1.59)	<0.001	1.04 (0.86 to 1.25)	0.687
Hospital size					
Small	4.6	Reference		Reference	
Medium	4.7	1.02 (0.89 to 1.17)	0.779	1.25 (1.04 to 1.51)	0.019
Large	5.8	1.27 (1.13 to 1.43)	<0.001	1.50 (1.27 to 1.78)	<0.001

immune system and patients with neutropenia are also proven to have higher rates of influenza-related bacterial complications compared with the general population. Although neutropenia can be attributed to viral infections in adult patients, there is a paucity of research regarding on the association between neutropenia and influenza viruses.[26 27] A number of mechanisms have been proposed, including development of antineutrophil antibodies, infection-induced bone marrow suppression or aplasia, enhanced neutrophil utilisation caused by hypersplenism and drug-related toxicity.[28] Sepsis is a life-threatening clinical syndrome caused by the dysregulated systemic response to infection. Among patients with cancer, one report estimated the in-hospital mortality rate associated with severe sepsis was 37.8%.[29] Although sepsis is associated with bacterial infection traditionally, influenza virus can also trigger deregulation of immune system with excessive cytokines release.[30] Dehydration can cause electrolyte abnormalities, compromising tissue perfusion and hypovolemic shock, and a higher incidence of dehydration was observed among cancer patients with influenza in our study. A possible explanation is that patients with influenza are commonly accompanied by fever and their fluids are seriously lost through sweating. However, cancer patients always reduce their oral intake because of anorexia, nausea, dysphagia and delirium, and therefore fail to adequately replace their lost fluids caused by fever.[31 32] Acute kidney injury can enhance toxicity of systemic chemotherapy and is associated with substantial morbidity among cancer patients.[33] Although the reasons for development of this complication in patients with influenza are multifold, insufficient resuscitation, inflammatory response, perfusion failure and cell injury of the influenza virus on the kidney provide tentative explanations.[34 35]

Based on our findings, it is reasonable to recommend annual influenza vaccination for patients with malignancy. Although immunosuppressed cancer patients may have poor serological response to vaccine, some studies demonstrated that influenza vaccination could reduce the risk of influenza infection effectively and safely.[36 37] A Cochrane meta-analysis also found vaccinated cancer patients had a significantly lower all-cause mortality than those who did not get vaccinated.[3] However, despite public health recommendations, the documented rates of vaccination are only 30% to 50% among patients with cancer, similar to the general population.[38 39] In contrast to their relatively low vaccination rates, proactive education approaches that raise awareness about the necessity of vaccination among cancer patients is warranted. Some studies showed that recommendations by physicians, especially oncologists could result in significant higher influenza vaccination coverage rates in patients with malignant disease.[40–42] In addition, rapid screening tests and early initiation of antiviral therapy within the first 48 hours of influenza symptoms are also crucial. When initiated promptly, antiviral therapy with a neuraminidase inhibitor can shorten the duration of influenza symptoms and decrease the mortality of patients.[14]

This study has several limitations. First, it is hard to determine whether influenza occurred before admission or during hospitalisation because of the cross-sectional study design. Second, this study cannot make a distinction between laboratory-confirmed influenza and clinical diagnosis influenza. Third, NIS lacks data regarding influenza virus type, tumour staging and medications; hence, we cannot account for related information that may influence in-hospital outcomes.

CONCLUSION

In conclusion, our study demonstrated that influenza was associated with worse clinical outcomes among hospitalised patients with malignancy. Annual influenza vaccination and early initiation of antiviral therapy are recommended in this high-risk population.

Contributors JL, DZ and LZ conceived and designed the study. JL collected the data and wrote the manuscript. JL and DZ performed the statistical analyses. LZ, ZS, and CB reviewed and revised the manuscript. All authors read and approved the final manuscript.

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