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National retrospective cohort study to identify age-specific fatality risks of comorbidities among hospitalised patients with influenza-like illness in Taiwan

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ABSTRACT

Objectives This study aimed to examine comprehensively the prognostic impact of underlying comorbidities among hospitalised patients with influenza-like illness (ILI) in different age groups and provide recommendations targeting the vulnerable patients.

Setting and participants A retrospective cohort of 83 227 hospitalised cases with ILI were identified from Taiwan's National Health Insurance Research Database from January 2005 to December 2010. Cases were stratified into three different age groups: paediatric (0–17 years), adult (18–64 years) and elderly (≧65 years), and their age, sex, comorbidity and past healthcare utilisation were analysed for ILI-associated fatality.

Main outcome measures ORs for ILI-related fatality in different age groups were performed using multivariable analyses with generalised estimating equation models and adjusted by age, sex and underlying comorbidities.

Results Hospitalised ILI-related fatality significantly increased with comorbidities of cancer with metastasis (adjusted OR (aOR)=3.49, 95% CI: 3.16 to 3.86), haematological malignancy (aOR=3.02, 95% CI: 2.43 to 3.74), cancer without metastasis (aOR=1.72, 95% CI: 1.54 to 1.91), cerebrovascular (aOR=1.24, 95% CI: 1.15 to 1.33) and heart diseases (aOR=1.19, 95% CI: 1.11 to 1.27) for all age groups. Adult patients with AIDS; adult and elderly patients with chronic kidney disease, tuberculosis and diabetes were significantly associated with elevated risk of death. Severe liver diseases and hypothyroidism among elderly, and dementia/epilepsy among elderly and paediatrics were distinctively associated with likelihood of ILI-related fatality.

Conclusions Different age-specific comorbidities were associated with increasing risk of death among hospitalised ILI patients. These findings may help update guidelines for influenza vaccination and other prevention strategies in high-risk groups for minimising worldwide ILI-related deaths.

Strengths and limitations of this study

- The study used a large database, 83 227 hospital admissions with influenza-like illness (ILI) from January 2005 to December 2010, providing high statistical power.
- The nationwide cohort design provides high generalisability with comprehensive analysis of 25 clinically important comorbidities covering all the three age groups in paediatrics, adults and elderly.
- Multivariable analyses, performed with generalised estimating equation models and adjusted covariates including age, sex, comorbidities, influenza periods, hospital levels and prior healthcare utilisations, provide independent risk factors of ILI-related death.
- A more complete data on vaccination history, laboratory-confirmed influenza, antiviral treatment, body mass index measurements and smoking status may further improve our models.

INTRODUCTION

The global burden of influenza involves seasonal epidemics and occasional pandemics.[1 2] As poultry and swine farms have expanded and thus increased dynamic changes in influenza viruses via transmission among different host species, the future threat of novel influenza viruses leading to pandemics may be inevitable.[3] However, accurately diagnosing influenza virus in suspected patients is a common challenge faced by all clinicians.[2] Influenza virus infection may not be identified in many instances because influenza virus is only detectable for a short period of time and/or many people do not seek medical care until after the first few days of acute illness. Influenza-like illness (ILI) became a surrogate indicator for practical use in the timely surveillance and measurement of the disease burden of influenza.[2 4] The aim of this study is to assess the prognosis of hospitalised patients with ILI, which includes common presentations of influenza: fever,

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sore throat, headache, musculoskeletal and gastrointestinal symptoms.[5–7] The outcomes from ILI cases are mostly mild or self-limited, but a small percentage of them can develop into severe morbidity or mortality.[2] The severe cases of ILI typically occur in the very young, the elderly and patients with chronic illness.[8–14] It is essential to identify, at an early stage, the most vulnerable ILI patients with higher risk to death[15 16] and provide clinical recommendations and public health prevention strategies to minimise fatality.

Elderly and young children, as well as patients with chronic underlying medical conditions, are typically associated with complications of respiratory infections.[8 11 13 15 17] Clinicians and public health decision-makers are expecting better evidence that requires careful and thorough examining of the roles that comorbidities play in patients of different age groups. The better evidence aims to assist in the prognosis at the beginning of the first medical visit for patients presenting ILI.[18–20] To date, global guidelines on the prevention and management of ILI-related complications are mostly consensus-based; thus, evidence-based guidelines about the risks of comorbidities have been under investigation.[8 21 22]

Free influenza vaccination programme in Taiwan started in 1998, for population aged over 65 years. The target vaccination population expanded year after year with the consideration of age, comorbidity and occupational exposure. In 2018, all adults over 50 years and paediatric population from 6 months to 18 years were recommended for vaccination. In addition, high-risk occupations in healthcare, livestock workers, live-poultry market workers and residents in long-term care facilities or prisons and jails were all covered. Furthermore, patients with obesity and chronic underlying diseases and pregnant women are recommended to receive vaccination after physician evaluation.[23] In this study, using a nationwide cohort data, we aimed to conduct a comprehensive analysis on the age-specific comorbidities associated with fatality on hospitalised patients with ILI.

We believe that the identification of patients with high-risk comorbidities can lead to the support of clinical recommendations and guideline directions for public health policies, including the timely management of antibiotics/antiviral treatments[20] and other preventions, such as influenza and pneumococcal immunisation[3 21] and non-pharmaceutical preventive measures through health education.[24 25]

METHODS

We conducted a database analysis using the National Health Insurance Research Database (NHIRD) containing records of approximately 1 million patients randomly selected from the 24 million beneficiaries of the National Health Insurance in Taiwan. The database collects encrypted claim records of emergency department (ED) patient, outpatient and inpatient data for billing purposes. The nationwide cohort study was conducted using the diagnostic codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).[26] Hospitalised ILI patients from January 2005 to December 2010 were included for data analyses. The definition of ILI was based on Taiwan Emergency Department-Based Syndromic Surveillance System.[4] We added six codes (382.9, 461.9, 465.8, 466.0, 487.1, 780.6) after comparing the code-based syndromic surveillance for ILI from the USA.[27] The codes are presented in online supplementary table 1 . In the instances where the patient had been re-admitted to the hospital with ILI within 14 days from a previous discharge of ILI-related hospitalisation, the two admissions were combined as the same episode. The flow diagram of the selection process of the study subjects is shown in figure 1.

Comorbidities included in the study analyses were selected after a literature review and a group discussion among physicians specialising in infection and emergency medicine, paediatrics, occupational medicine, and public health professionals. The comorbidities related to malignant diseases were defined, based on the records from the Taiwan Catastrophic Illness Card (TCIC) codes for malignant diseases both 12 months before and 6 months after the first ILI admission date. We included pregnant women when the first date of hospitalisation with ILI occurred up to 3 months before delivery/abortion. We included postpartum women when delivery/abortion occurred up to 3 months before the first date of ILI hospitalisation. Data on other type of comorbidities were collected through diagnoses from reimbursement records 12 months before the first date of ILI admission. A comorbidity was confirmed with at least one diagnosis of hospitalisation claim or through two or more diagnoses from outpatient and/or ED visits. Grouping of comorbidity with ICD-9-CM codes was modified from the Charlson *et al*,[28] Deyo *et al*[29] and Elixhauser *et al*[30] measurements using the most frequently applied codes. For autoimmune disease, organ transplantation, congenital immunodeficiency and malignant, hepatic and mental diseases, we also confirmed the disease status through the TCIC information to improve specificity. Definition of each comorbidity is shown in online supplementary table 2. The ILI-associated fatalities were the main outcome of interest. Fatality case was defined by discharge information recorded in the NHIRD as 'hospital mortality' (discharge transfer code '4'). Additionally, we also included cases that discharged under critical conditions (discharge transfer code 'A'), who also withdrew from the National Health Insurance and had not received any healthcare services in the following 12 months after hospital discharge. All analyses were performed in the overall study population, as well as stratified by three age groups: paediatric patients (0–17 years), adult patients (18–64 years) and elderly patients (≧65 years).

In total, 25 clinically important comorbidities were selected after panel discussion and logistic regression analyses were used to evaluate the significance of individual comorbidity. Furthermore, the outcome measures

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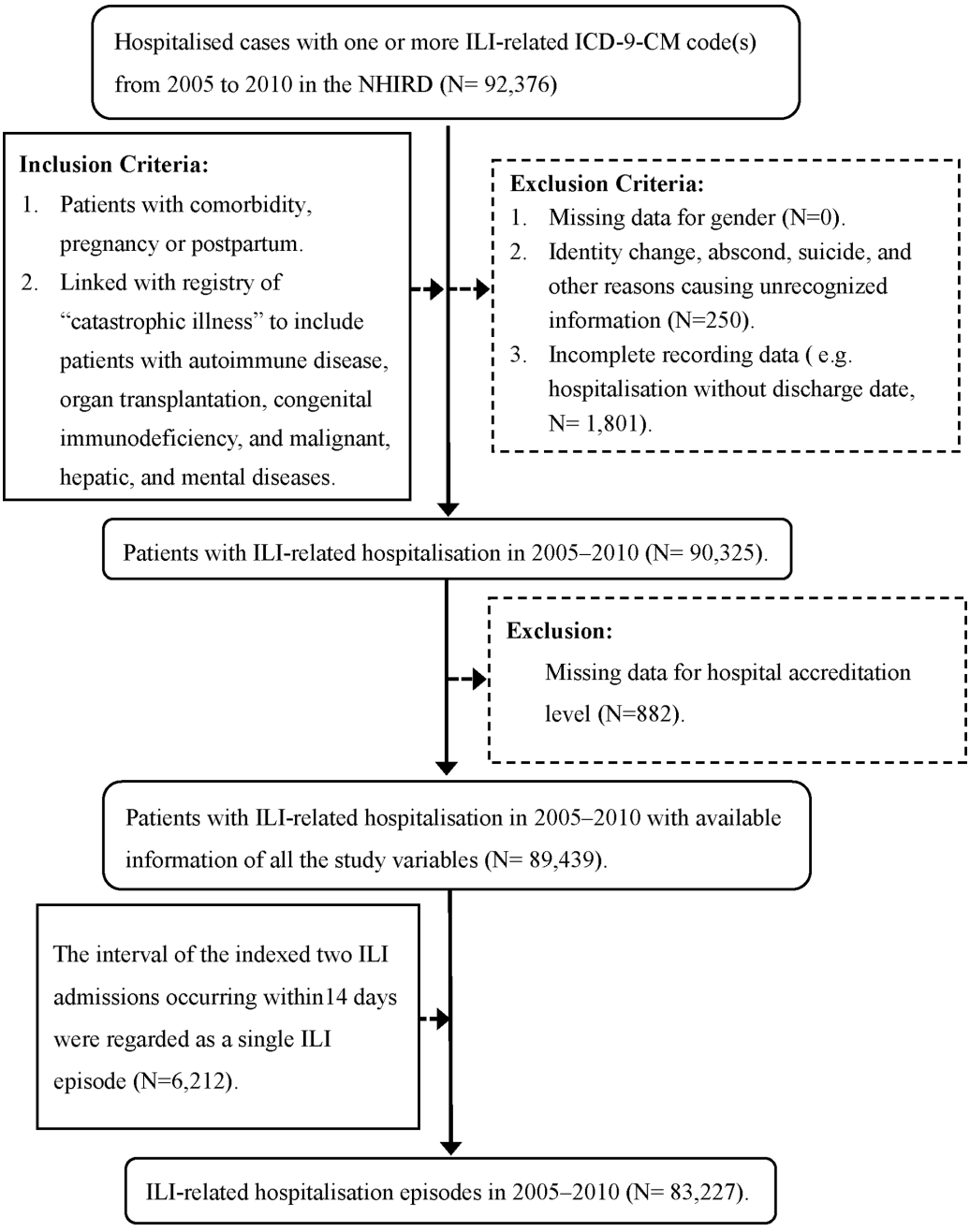


Figure 1 Flow diagram of the selection process of the study population. ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ILI, influenza-like illness; NHIRD, National Health Insurance Research Database in Taiwan.

were stratified by influenza season months (December to April) and non-influenza season months[31] to compare and evaluate the fatalities by different comorbidities in hospitalised ILI patients. Finally, we performed multivariable analyses to measure the independent predictability of death from these comorbidities among the three age groups. We used stepwise logistic regression analyses with forward selection method at the entry criteria of $p<0.15$ to achieve a good model fit.[32 33] Stepwise logistic regression analyses selected 16 comorbidities in the 'all patients group', 9 in the 'paediatric patient group', 13 in the 'adult patient group' and 17 in the 'elderly patient group'. We performed generalised estimating equation (GEE) models to adjust for the hospital clustering effect and repeated hospitalisations as patients had two or more ILI-related admissions within an ILI episode.[32] The variables adjusted in the GEE model included age, sex and different study periods (from previous year's July to next year's June), patient-admitted hospital levels (local hospital, regional hospital or medical centre), and prior frequencies of hospitalisation in the past 12 months (0, 1–2 or >3 admissions). The statistical analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). A two-tailed $p<0.05$ was considered statistically significant.

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Table 1 Demographic data and proportions of comorbidities in patients hospitalised with influenza-like illness among the three age groups and all patients in Taiwan, 1 January 2005 to 31 December 2010

Age groups (years)	All patients	Paediatric (0–17)	Adult (18–64)	Elderly (≥65)	
Population, N (% of all)	83 227 (100.00)	19 847 (23.85)	25 988 (31.23)	37 392 (44.93)	
N (%) of variable	N (%)	N (%)	N (%)	N (%)	P value*
Gender					
Female	33 488 (40.24)	8739 (44.03)	11 263 (43.34)	13 486 (36.07)	<0.001
Male	49 739 (59.76)	11 108 (55.97)	14 725 (56.66)	23 906 (63.93)	
Deaths	5282 (6.35)	37 (0.19)	984 (3.79)	4261 (11.40)	<0.001
Comorbidities					
Heart disease	21 776 (26.16)	101 (0.51)	3945 (15.18)	17 730 (47.42)	<0.001
PVD	1689 (2.03)	5 (0.03)	292 (1.12)	1392 (3.72)	<0.001
Hypertension	30 663 (36.84)	28 (0.14)	6726 (25.88)	23 909 (63.94)	<0.001
Hyperlipidaemia	7171 (8.62)	25 (0.13)	2924 (11.25)	4222 (11.29)	<0.001
CVA	16 935 (20.35)	33 (0.17)	2843 (10.94)	14 059 (37.60)	<0.001
Dementia/Epilepsy	8443 (10.14)	471 (2.37)	1214 (4.67)	6758 (18.07)	<0.001
COPD/Asthma	32 646 (39.23)	4564 (23.00)	5830 (22.43)	22 252 (59.51)	<0.001
Allergic rhinitis	10 713 (12.87)	4894 (24.66)	3307 (12.73)	2512 (6.72)	<0.001
Autoimmune disease	635 (0.76)	29 (0.15)	336 (1.29)	270 (0.72)	<0.001
Severe liver disease	289 (0.35)	0 (0.00)	206 (0.79)	83 (0.22)	<0.001
Peptic ulcer disease	14 514 (17.44)	119 (0.60)	4150 (15.97)	10 245 (27.40)	<0.001
Diabetes	16 416 (19.72)	35 (0.18)	4298 (16.54)	12 083 (32.31)	<0.001
Gout	4673 (5.61)	12 (0.06)	1385 (5.33)	3276 (8.76)	<0.001
Hyperthyroidism	542 (0.65)	5 (0.03)	297 (1.14)	240 (0.64)	<0.001
Hypothyroidism	558 (0.67)	31 (0.16)	174 (0.67)	353 (0.94)	<0.001
CKD	6617 (7.95)	70 (0.35)	1400 (5.39)	5147 (13.76)	<0.001
Cancer without metastasis	4113 (4.94)	60 (0.30)	1217 (4.68)	2836 (7.58)	<0.001
Metastatic cancer	4264 (5.12)	34 (0.17)	1863 (7.17)	2367 (6.33)	<0.001
Haematological malignancy	922 (1.11)	147 (0.74)	333 (1.28)	442 (1.18)	<0.001
Congenital immunodeficiency	30 (0.04)	23 (0.12)	7 (0.03)	0 (0.00)	<0.001
Organ transplantation	123 (0.15)	4 (0.02)	100 (0.38)	19 (0.05)	<0.001
AIDS	63 (0.08)	3 (0.02)	57 (0.22)	3 (0.01)	<0.001
Tuberculosis	3083 (3.70)	34 (0.17)	713 (2.74)	2336 (6.25)	<0.001
Mental illness	1821 (2.19)	39 (0.20)	1211 (4.66)	571 (1.53)	<0.001
Pregnancy/Post partum	334 (0.40)	3 (0.02)	331 (1.27)	0 (0.00)	<0.001

*X^2 test to evaluate whether there would be a significant difference among the three age groups.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; PVD, peripheral vascular disease.

Patient and public involvement statement

This study was conducted by using a National Health Insurance claims database. All records were de-identified and there were no patients' identifiable information.

RESULTS

In total, 83 227 events of ILI-related hospitalisation from 1 January 2005 to 31 December 2010 were included for analysis. The demographic data are shown in table 1. There were significantly more male than female ILI cases with a ratio of 1.49 (p<0.001). The majority of ILI-related admissions were elderly patients (44.93%), followed by adult patients (31.23%), then paediatric patients (23.85%). We identified 5282 deaths (6.35%) in our study population, where the case fatality rate of these hospitalised ILI cases was significantly higher among elderly patients (11.40%) than among adult (3.79%) and paediatric patients (0.19%) (p<0.001). Among the overall comorbidities, chronic obstructive pulmonary disease

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(COPD)/asthma (39.23%) was the top prevalent comorbidity, followed by hypertension (36.84%), heart disease (26.16%), cerebrovascular accident (CVA) (20.35%) and diabetes (19.72%).

Logistic regression analyses were used to evaluate the significance of the 25 comorbidities relating to ILI-associated fatality in patients of different age groups. The case fatality rate and univariate OR of each comorbidity are summarised in table 2. Ten comorbidities showed small difference in proportions between influenza and non-influenza seasons among hospitalised ILI cases with statistical differences in table 3. Among them, three comorbidities (cardiovascular diseases, dementia/epilepsy and tuberculosis) demonstrated slightly higher case fatality rates during influenza seasons than those in non-influenza seasons with statistical significance.

The results of the multivariable analysis by GEE models are shown in figure 2. In all patients, the highest adjusted OR (aOR) of ILI-associated fatality was in those patients with AIDS (aOR 6.53, 95% CI: 2.89 to 14.76), followed by those with metastatic cancer (aOR 3.49, 95% CI: 3.16 to 3.86), haematological malignancy (aOR 3.02, 95% CI: 2.43 to 3.74) and solid organ cancer without metastasis (aOR 1.72, 95% CI: 1.54 to 1.91). Other high-risk underlying medical conditions with statistical significance included chronic kidney disease (CKD) (aOR 1.57, 95% CI: 1.44 to 1.71), tuberculosis (aOR 1.37, 95% CI: 1.22 to 1.54), hypothyroidism (aOR 1.37, 95% CI: 1.04 to 1.79), CVA (aOR 1.24, 95% CI: 1.15 to 1.33), peripheral vascular disease (PVD) (aOR 1.22, 95% CI: 1.05 to 1.42), diabetes (aOR 1.22, 95% CI: 1.13 to 1.30), heart diseases (aOR 1.19, 95% CI: 1.11 to 1.27) and dementia/epilepsy (aOR 1.12, 95% CI: 1.03 to 1.22). However, hypertension (aOR 0.75, 95% CI: 0.70 to 0.81), hyperlipidaemia (aOR 0.69, 95% CI: 0.62 to 0.76) and allergic rhinitis (aOR 0.61, 95% CI: 0.54 to 0.70) showed decreased risk of ILI-related deaths.

For the risk of age-specific comorbidity, we further stratified our study population into three age groups. In paediatric patients, hypertension (aOR 23.82, 95% CI: 6.84 to 82.97) and dementia/epilepsy (aOR 4.87, 95% CI: 1.83 to 13.01) were distinctively associated with increased risk of ILI-associated deaths ($p<0.05$) (figure 2). In adult patients, AIDS (aOR 9.34, 95% CI: 4.18 to 20.91), CKD (aOR 1.85, 95% CI: 1.44 to 2.36), tuberculosis (aOR 1.89, 95% CI: 1.41 to 2.55) and diabetes (aOR 1.50, 95% CI: 1.26 to 1.80) displayed significantly increased risk of ILI-associated deaths ($p<0.001$), whereas hyperlipidaemia showed decreased risk (figure 2). In elderly patients, hypothyroidism (aOR 1.48, 95% CI: 1.11 to 1.98) and severe liver disease (aOR 1.94, 95% CI: 1.13 to 3.30) showed significantly increased risk of ILI-associated deaths ($p<0.05$) (figure 2).

DISCUSSION

This study, using a large national cohort dataset with simultaneously adjusted clinically important comorbidities and several epidemiological covariates, is the first to demonstrate the independent effect of certain age-specific comorbidities on fatality risk among hospitalised ILI patients. Identifying high-risk patients with ILI or influenza to support evidence-based preventive strategies has been advocated in many high-income countries.[8 13] Although meta-analyses have highlighted the important effect of comorbidities on influenza, most of these observational studies have either lacked power or inadequately adjusted for important covariates and thus provided limited evidence.[8 11 13] Moreover, most of the published guidelines regarding ILI preventive strategies have targeted elderly populations or those over 50 years of age, thus limiting the applicability of these guidelines to other age groups.[34–36] Furthermore, previous studies found that several comorbidities were associated with the increased fatality of ILI patients[8 13]; however, their analyses did not fully control for important covariates (e.g., age, sex and relevant comorbidities). Our results showed that the contribution of a comorbidity to fatality risk among hospitalised ILI patients was age-specific.

Host defence responses, targeting viral entry, transcription, translation, replication and extracellular release, can limit the disease severity and spread of influenza virus infection.[37] We found that malignant diseases were associated with increased fatality rate among hospitalised ILI patients across all three age groups. The trends of aORs were also consistent in all three groups, with the highest trend being cancer with metastasis, followed by haematological malignancy and cancer without metastasis. Because cancer patients tend to have more depressed immunity directly from malignancy or indirectly from anticancer therapy-related immunodeficiency, our study again highlights the important role of malignant diseases, particularly cancer with metastasis, in contributing to increased fatality risk among hospitalised patients with ILI. Furthermore, heart disease and CVA were another two risky comorbidities across the three age groups. Patients with cardiovascular diseases were associated with increased risk of mortality during influenza epidemics, possibly due to the exacerbation of limited cardiovascular reserve from silent or fulminant viral myocarditis or the induction of acute myocardial infarction in patients with pre-existing coronary artery disease.[38 39] The three comorbidities of cancer, heart disease and CVA with higher prevalence rates in all age groups provide evidence-based recommendations for clinical management as well as public health planning.

However, age-specific differences were present in several comorbidities associated with ILI-related fatality. AIDS was an independent predictor for death only in hospitalised adult ILI patients. Other chronic diseases, such as tuberculosis, diabetes and CKD, predicted hospital fatality in both adult and elderly patients and showed similar trends in increasing ILI-associated fatality. In fact, ILI patients with co-infection of HIV are associated with a higher risk of superimposed bacterial infections and increased severity of influenza.[40–42] Patients with tuberculosis have

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Table 2 The case fatality rate (CFR) of each comorbidity in patients hospitalised with influenza-like illness among the three age groups and all patients in Taiwan, 1 January 2005 to 31 December 2010

	All patients			Paediatric patients (0–17 years)			Adult patients (18–64 years)			Elderly patients (≥65 years)		
	CFR (%)	Diff (%)†	OR (95% CI)	CFR (%)	Diff (%)†	OR (95% CI)	CFR (%)	Diff (%)†	OR (95% CI)	CFR (%)	Diff (%)†	OR (95% CI)
Fatality rate in the group	6.3			0.2			3.8			11.4		
Comorbidities†												
Heart disease	11.0	+6.3	2.52 (2.38 to 2.66)*	6.9	+6.8	48.94 (20.97 to 114.19)*	5.6	+2.1	1.66 (1.42 to 1.93)*	12.3	+1.6	1.17 (1.10 to 1.25)*
PVD	13.3	+7.1	2.32 (2.01 to 2.68)*	0.0	−0.2	–	9.3	+5.5	2.63 (1.76 to 3.93)*	14.2	+2.9	1.30 (1.12 to 1.52)*
Hypertension	9.5	+5.0	2.24 (2.11 to 2.36)*	7.1	+7.0	43.48 (9.94 to 190.24)*	5.2	+1.9	1.61 (1.41 to 1.84)*	10.7	−1.8	0.84 (0.78 to 0.89)*
Hyperlipidaemia	6.2	−0.2	0.97 (0.88 to 1.07)	0.0	−0.2	–	3.4	−0.4	0.89 (0.72 to 1.10)	8.2	−3.7	0.66 (0.59 to 0.74)*
CVA	11.6	+6.7	2.51 (2.36 to 2.66)*	9.1	+8.9	58.18 (16.94 to 199.76)*	7.1	+3.7	2.19 (1.86 to 2.57)*	12.6	+1.9	1.20 (1.12 to 1.28)*
Dementia/Epilepsy	12.1	+6.4	2.28 (2.12 to 2.45)*	1.9	+1.8	13.46 (6.32 to 28.69)*	5.9	+2.2	1.62 (1.27 to 2.08)*	14.0	+3.1	1.34 (1.24 to 1.44)*
COPD/Asthma	7.7	+2.3	1.45 (1.37 to 1.53)*	0.1	−0.1	0.65 (0.27 to 1.55)	4.2	+0.6	1.17 (1.01 to 1.35)*	10.2	−3.0	0.75 (0.70 to 0.80)*
Allergic rhinitis	2.3	−4.7	0.31 (0.27 to 0.35)*	0.0	−0.2	0.08 (0.01 to 0.62)*	1.1	−3.1	0.25 (0.18 to 0.35)*	8.2	−3.4	0.68 (0.59 to 0.79)*
Autoimmune disease	7.7	+1.4	1.24 (0.92 to 1.66)	0.0	−0.2	–	4.8	+1.0	1.27 (0.77 to 2.12)	12.2	+0.8	1.08 (0.75 to 1.56)
Severe liver disease	9.3	+3.0	1.52 (1.02 to 2.27)*	–		–	6.3	+2.5	1.72 (0.98 to 3.03)	16.9	+5.5	1.58 (0.89 to 2.81)
Peptic ulcer disease	10.1	+4.6	1.91 (1.79 to 2.04)*	0.0	−0.2	–	5.2	+1.7	1.51 (1.29 to 1.76)*	12.2	+1.1	1.11 (1.04 to 1.20)*
Diabetes	10.6	+5.3	2.10 (1.98 to 2.23)*	0.0	−0.2	–	6.6	+3.4	2.13 (1.85 to 2.46)*	12.0	+0.9	1.09 (1.02 to 1.16)*
Gout	9.0	+2.8	1.49 (1.34 to 1.66)*	0.0	−0.2	–	4.5	+0.7	1.20 (0.93 to 1.57)	10.9	−0.5	0.95 (0.84 to 1.06)
Hyperthyroidism	7.6	+1.2	1.21 (0.88 to 1.66)	0.0	−0.2	–	4.4	+0.6	1.17 (0.67 to 2.04)	11.7	+0.3	1.03 (0.69 to 1.53)
Hypothyroidism	13.1	+6.8	2.24 (1.75 to 2.87)*	0.0	−0.2	–	5.8	+2.0	1.56 (0.82 to 2.95)	17.9	+6.5	1.70 (1.29 to 2.24)*
CKD	14.0	+8.3	2.70 (2.51 to 2.92)*	1.4	+1.3	7.95 (1.07 to 58.78)*	8.4	+4.8	2.50 (2.04 to 3.05)*	15.7	+5.0	1.56 (1.43 to 1.69)*
Cancer without metastasis	12.9	+7.8	2.75 (2.50 to 3.03)*	6.7	+6.5	53.79 (18.18 to 159.17)*	8.2	+6.0	3.91 (3.13 to 4.89)*	15.0	+4.8	1.55 (1.39 to 1.73)*
Metastatic cancer	19.9	+14.8	4.64 (4.27 to 5.03)*	5.9	+5.8	47.07 (10.72 to 206.65)*	17.8	+15.6	9.48 (8.17 to 10.99)*	21.8	+11.6	2.46 (2.21 to 2.73)*
Haematological malignancy	14.9	+9.8	3.25 (2.70 to 3.91)*	3.4	+3.3	26.52 (10.04 to 70.04)*	14.1	+11.9	7.18 (5.21 to 9.90)*	19.2	+9.0	2.10 (1.65 to 2.67)*
Congenital immunodeficiency	3.3	−3.0	0.51 (0.07 to 3.74)	0.0	−0.2	–	14.3	+10.5	4.24 (0.51 to 35.24)	–		–
Organ transplantation	4.1	−2.3	0.62 (0.26 to 1.53)	0.0	−0.2	–	3.0	−0.8	0.79 (0.25 to 2.48)	10.5	−0.9	0.91 (0.21 to 3.96)
AIDS	14.3	+8.0	2.46 (1.21 to 4.99)*	0.0	−0.2	–	15.8	+12.0	4.80 (2.35 to 9.81)*	0.0	−11.4	–
Tuberculosis	13.2	+7.2	2.36 (2.11 to 2.62)*	0.0	−0.2	–	9.0	+5.3	2.61 (2.00 to 3.40)*	14.7	+3.6	1.37 (1.22 to 1.55)*
Mental illness	6.9	+0.5	1.09 (0.91 to 1.31)	2.6	+2.4	14.45 (1.93 to 108.12)*	3.6	−0.2	0.96 (0.70 to 1.30)	14.0	+2.7	1.27 (1.00 to 1.61)*
Pregnancy/Post partum‡	0.0	−5.2	–	0.0	−0.1	–	0.0	−2.5	–	–		–

*P<0.05.
†The difference of CFR represented the value of CFR in patients with the index comorbidity minus the value of CFR in patients without the index comorbidity.
‡Comparison between the females in each group.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; PVD, peripheral vascular disease.

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Table 3 Proportions of comorbidity and case fatality rates (CFRs) of comorbidity in patients hospitalised due to influenza-like illness in Taiwan, 1 January 2005 to 31 December 2010

Population, N (% of all)	Proportion of comorbidity			CFR of comorbidity		
	Influenza season†	Non-influenza season		Influenza season†	Non-influenza season	
	36 197 (43.49)	47 030 (56.51)		36 197 (43.49)	47 030 (56.51)	
Comorbidity	N (%)	N (%)	P value‡	Fatality (N) CFR (%)	Fatality (N) CFR (%)	P value‡
Heart disease	9339 (25.80)	12 437 (26.44)	0.036*	1064 (11.39)	1336 (10.74)	0.129
PVD	716 (1.98)	973 (2.07)	0.357	95 (13.27)	130 (13.36)	0.956
Hypertension	12 897 (35.63)	17 766 (37.78)	<0.0001*	1246 (9.66)	1673 (9.42)	0.472
Hyperlipidaemia	2988 (8.25)	4183 (8.89)	0.001*	197 (6.59)	247 (5.90)	0.233
CVA	6996 (19.33)	9939 (21.13)	<0.0001*	869 (12.42)	1102 (11.09)	0.008*
Dementia/Epilepsy	3481 (9.62)	4962 (10.55)	<0.0001*	452 (12.98)	571 (11.51)	0.041*
COPD/Asthma	14 198 (39.22)	18 448 (39.23)	0.996	1124 (7.92)	1397 (7.57)	0.248
Allergic rhinitis	4686 (12.95)	6027 (12.82)	0.577	110 (2.35)	133 (2.21)	0.628
Autoimmune disease	275 (0.76)	360 (0.77)	0.925	18 (6.55)	31 (8.61)	0.334
Severe liver disease	123 (0.34)	166 (0.35)	0.749	14 (11.38)	13 (7.83)	0.305
Peptic ulcer disease	6153 (17.00)	8361 (17.78)	0.003*	645 (10.48)	821 (9.82)	0.190
Diabetes	6930 (19.15)	9486 (20.17)	<0.0001*	756 (10.91)	977 (10.30)	0.209
Gout	1980 (5.47)	2693 (5.73)	0.112	194 (9.80)	225 (8.35)	0.088
Hyperthyroidism	230 (0.64)	312 (0.66)	0.619	16 (6.96)	25 (8.01)	0.646
Hypothyroidism	225 (0.62)	333 (0.71)	0.130	32 (14.22)	41 (12.31)	0.512
CKD	2829 (7.82)	3788 (8.05)	0.207	419 (14.81)	508 (13.41)	0.105
Cancer without metastasis	1640 (4.53)	2473 (5.26)	<0.0001*	204 (12.44)	325 (13.14)	0.510
Metastatic cancer	1722 (4.76)	2542 (5.41)	<0.0001*	347 (20.15)	503 (19.79)	0.771
Haematological malignancy	372 (1.03)	550 (1.17)	0.053	58 (15.59)	79 (14.36)	0.607
Congenital immunodeficiency	13 (0.04)	17 (0.04)	0.986	1 (7.69)	0 (0.00)	0.245
Organ transplantation	58 (0.16)	65 (0.14)	0.412	3 (5.17)	2 (3.08)	0.557
AIDS	26 (0.07)	37 (0.08)	0.722	3 (11.54)	6 (16.22)	0.601
Tuberculosis	1264 (3.49)	1819 (3.87)	0.004*	188 (14.87)	220 (12.09)	0.025*
Mental illness	774 (2.14)	1047 (2.23)	0.390	57 (7.36)	68 (6.49)	0.468
Pregnancy/ Post partum	150 (0.41)	184 (0.39)	0.600	0 (0.00)	0 (0.00)	–

*P<0.05.
†Influenza season was defined as the patients hospitalised on index date from 1 December to 30 April of next year; non-influenza season was defined as the patients admitted on the date other than influenza season months.
‡X^2 test between influenza seasons and non-influenza seasons.

also proven to be associated with increased influenza deaths in both the 1918 pandemic[43] and seasonal influenza.[44] Lost immune homeostasis of patients with CKD during influenza infection may result in further renal cell damage,[45] eventually leading to kidney failure and subsequent fatality. In hospitalised ILI adult patients, metabolic diseases have more impact on deaths. A previous study found that diabetes tripled the risk of hospitalisation and quadrupled the risk of intensive care unit admission during the 2009 pandemic influenza.[46] All these data illustrate the importance of considering preventive measures for age-specific immunocompromised patients to prevent subsequent ILI fatality.

Infants and young children with pre-existing conditions, particularly neurological disorders, are over-represented among influenza-associated paediatric deaths.[47 48] However, previous studies were mostly conducted with univariable analysis without using multivariable analysis

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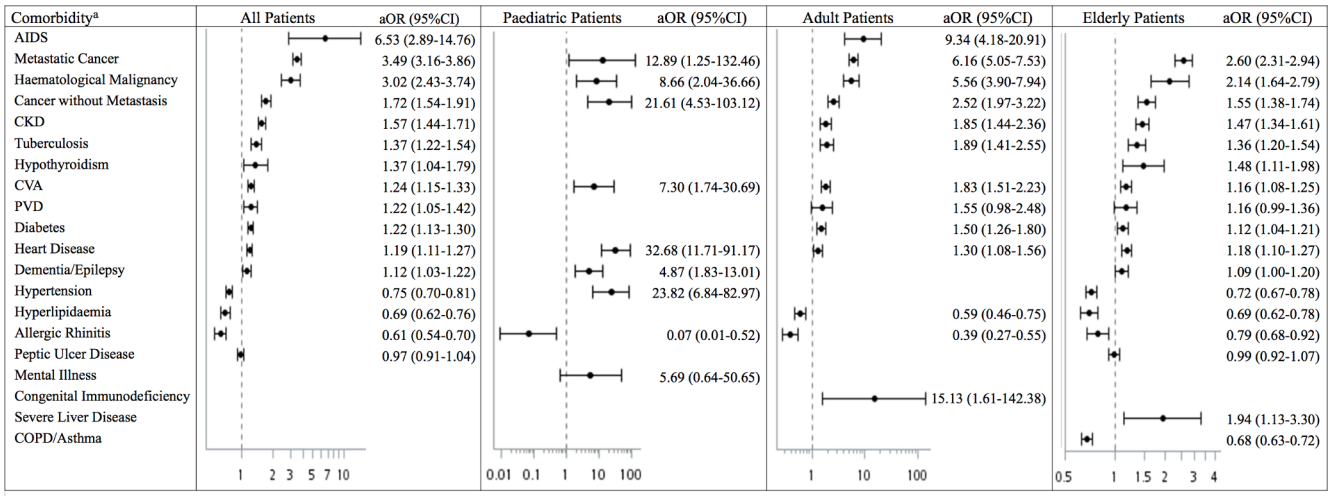


Figure 2 Adjusted OR (aOR) of death in admitted patients with influenza-like illness among the three age groups and all patients in Taiwan, 1 January 2005 to 31 December 2010. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; PVD, peripheral vascular disease.

to adjust for other comorbidities; hence the level of evidence was low.[8 11] Our study showed that epilepsy was a specific risk for paediatric patients. However, epilepsy was not documented as a risk in a previous meta-analysis.[8] In addition, hypertension was another significant comorbidity risk only in paediatric ILI cases. The identification of 2 deaths among the 28 paediatric hypertension cases led to a high fatality rate. However, these two fatal cases also showed other comorbidities—one had leukaemia, while the other had moyamoya disease. Certainly, there was not enough evidence to derive any conclusions on hypertension in the paediatric group. Conversely, epilepsy/dementia and hypothyroidism were the specific high-risk comorbidities for elders in this study. A previous meta-analysis showed increased risk of epilepsy/dementia in seasonal and pandemic influenza patients and also indicated that endocrinological disease documented increased risk of death in seasonal influenza patients.[8] However, this meta-analysis did not specify which endocrinological disease. By contrast, we addressed hypothyroidism to be the most probable disease predisposing fatality among the endocrinological diseases.

On the other hand, several comorbidities were associated with a reduced case fatality rate of ILI either for all age groups (allergic rhinitis) or in a specific age group (e.g., COPD/asthma in the elderly group). ILI patients with allergic rhinitis and COPD/asthma may be more likely to be hospitalised when they presented more prominent respiratory manifestations.[49 50] Conversely, the non-infectious airway symptoms caused by allergic rhinitis and asthma/COPD could also mimic ILI, resulting in increased ILI-related hospitalisation. Our study showed a lower mortality risk for COPD/asthma in the study population of hospitalised ILI patients in Taiwan. We should carefully interpret the results since that risk was different from outpatient setting. The hospitalised patients in our study was 39.23% with COPD/asthma (table 1). However, the prevalence of COPD was about 6%,[51] and the prevalence of asthma was about 11%[52] among general population in Taiwan. Certainly, it is important to consider probable mitigation efforts, including vaccination and antiviral medication to alleviate disease burden.[23 53] Adult and elderly ILI patients with hyperlipidaemia associated with lower case fatality rates could be explained by the use of statin to treat hyperlipidaemia. Pre-admission statin use has been shown to reduce 30-day mortality of less severe sepsis patients.[54] Therefore, the use of statin in hyperlipidaemia patients may benefit the outcome of ILI. As hypertension is a common comorbidity in adult and elderly populations, our results adjusted for covariates and other comorbidities, thereby demonstrating that hypertension had no influence on adult ILI case fatality and decreased elderly ILI-related fatality. These findings are different from those of a previous meta-analysis showing that hypertension increased all-cause mortality in pandemic influenza patients.[8] Certainly, adjusting for other comorbidities should be important in generating final conclusions for patients with multiple comorbidities.

This study had several limitations. First, our study population involved ILI cases (rather than laboratory-confirmed influenza cases) that have more variations in terms of virulence, vaccination and antibacterial/antifungal/antiviral treatment to influenza and other respiratory pathogens. The fatality risk assessment of ILI in our study was not equal to influenza. It is difficult to obtain laboratory confirmation for every case of influenza in clinical settings due to virological identifications for influenza are time-consuming, expensive and impractical to cover all suspected cases with mild outcomes. Therefore, studying patients with ILI provided more clinically relevant scenarios for physicians to identify vulnerable patients. Second, the severity of comorbidity, compliance of medical treatment and possible mitigation efforts of vaccination, early admission and antiviral treatment could not be evaluated in this study. The coding-associated diagnostic error[55] may also have limited the accuracy of our disease/comorbidity diagnosis. Third, the comorbidities that we selected here according to the literature review and

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subsequent group discussion may still have had limitations, such as being unstudied or lower prevalent comorbidities. Obesity is associated with increased risk of mortality following influenza infections.[56–58] However, obesity, immunisation and tobacco use were seldom coded in the National Health Insurance system. Fourth, the aetiology of ILI with/without co-infections of other microbial agents and environmental factors may also have influenced the ILI prognoses.[59–61] Lastly, infants aged under 1 year have distinctive physiology and immunology responses to infections. The prognosis in this age group may be different from other young children, but subgroup analysis could not be done for limited cases.

The prevalence of comorbidities and environmental factors varied across the globe, with variations on national guidelines.[22 34–36 62] The current vaccination guideline in Taiwan suggested patients with chronic underlying diseases, obesity and pregnant women to be evaluated for influenza vaccination, but the level of evidence for high-risk comorbidities was low.[8] Our study analysed a national dataset in Taiwan with good representativeness and well-adjusted covariates. The results could support a reference of vulnerable groups to target, which may reduce the burden and prevent the ILI fatalities caused by influenza and other respiratory infectious disease agents.[63 64] Since early antiviral treatment may be beneficial for patients with severe influenza,[65–67] our findings may assist policy makers in amending guidelines to promptly prescribe antiviral medications for high-risk individuals during the influenza season or pandemic outbreak. Therefore, we offer the following recommendations: first, higher priority should be given to patients with malignancy, heart disease, CVA and AIDS. Second, adult and elderly patients with tuberculosis, diabetes and CKD should also receive more attention. Third, paediatric patients with epilepsy and elderly patients with dementia and hypothyroidism should also be treated with more attention.

In conclusion, our study confirmed that age-specific chronic medical conditions were associated with increased fatalities in hospitalised ILI patients. In the era of personalised medicine and an increasingly ageing population involving various comorbidities, we suggest future studies to calculate the combined risks of comorbidities in an individual patient for better prediction and case management.

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Contributors Conceived and designed this study: C-CF, C-CK, F-YS, S-YC, H-YRC and T-CW. Analysed the data: H-YRC. Wrote this manuscript: T-CW, H-YRC, S-YC, F-YS, C-CK and C-CF. Initiated this study: C-CK and C-CF. Revised this manuscript: S-YC, F-YS, C-CK and C-CF. All authors critically revised the manuscript and agreed to the final version.

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