Journal of Clinical Virology 117 (2019) 73–79

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Seasonal influenza-associated intensive care unit admission and death in tropical Singapore, 2011-2015

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ARTICLE INFO

Keywords:
Seasonal influenza
Mortality
Epidemiology

ABSTRACT

Background: Seasonal influenza can cause severe illness leading to intensive care unit (ICU) admission and death.

Objective: To define the clinical and epidemiological features of severe seasonal influenza infection and factors associated with mortality.

Study design: A retrospective review was conducted on all patients with laboratory-confirmed influenza infection who were either admitted into the ICU or died in the two largest tertiary hospitals in Singapore from 2011-2015.

Results: Of 520 patients included in our study, 423 (81.3%) had influenza A infection and the rest with influenza B. Of patients with influenza A infection, 70.0% (296/423) were subtyped, of whom 24.0% (71/296) had A/H1N1pdm2009 and 76.0% (225/296) had A/H3N2. The median age of patients was 72 years (IQR 61–82). Males constituted 53.1% (276/520). Median Charlson comorbidity index score was 1 (IQR 0–3). About 70% had physical or radiological evidence of pneumonia upon admission. In-hospital mortality was 58.1% (302/520). On multiple logistic regression analysis, factors positively associated with mortality were age ≥65 years (adjusted odds ratio, aOR = 3.64, 95%CI 2.21–5.99, $p < 0.001$), malignancy (aOR = 2.53, 95%CI 1.12–5.73; $p = 0.026$), and hypoalbuminemia (aOR = 2.16, 95%CI 1.26–3.73; $p = 0.005$), while antiviral therapy (aOR = 0.33, 95%CI 0.17-0.63; $p < 0.001$) and ventilation (aOR = 0.23, 95% CI 0.13-0.39; $p < 0.001$) were negatively associated.

Conclusions: Patients with severe seasonal influenza infection were characterized by advanced age, hypoalbuminemia and presence of pneumonia on admission. Age ≥65 years, malignancy, and hypoalbuminemia were associated with increased mortality, and antiviral therapy and ventilation with decreased mortality.

1. Background

Seasonal influenza is one of the most common acute respiratory infections worldwide, with an estimated annual attack rate of 5–10% in adults [1]. While infection usually only affects the upper respiratory tract, and symptoms typically resolve within one to two weeks without requiring medical treatment, some individuals may develop severe illness leading to intensive care unit (ICU) admission or even death. Annually, seasonal influenza results in 3–5 million cases of severe illness and 290,000–650,000 deaths globally [2].

Seasonal influenza occurs all year round in Singapore and has posed significant social and economic burden. Using acute respiratory infections (ARI) as a proxy indicator for influenza activity, approximately 820,000 (15%) of the Singapore resident population visited public primary care clinics and hospital emergency departments for ARI annually [3]. Influenza accounted for 12% of hospitalizations associated with pneumonia and influenza [4], slightly higher than the figure reported in temperate United States (US) (8.6%) [5,6]. Influenza-

Abbreviations: ICU, intensive care unit; HD, high dependency unit; RT-PCR, real-time reverse transcription-polymerase chain reaction; CCI, Charlson's comorbidity index; IQR, interquartile range; LOS, length of hospital stay; WHO, World Health Organization; CDC, Centers for Disease Control and Prevention

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https://doi.org/10.1016/j.jcv.2019.06.005
Received 9 February 2019; Received in revised form 6 June 2019; Accepted 15 June 2019

associated mortality constituted approximately 3.8% of total annual deaths in Singapore, which was comparable to the influenza-associated mortality rates reported in Hong Kong and the US [7,8]. From 1950–2000, influenza epidemics were the most likely cause of excess mortality in Singapore [9].

Determining the factors associated with severe influenza infection facilitates timely severity assessments, to aid in the identification of high-risk groups for primary and secondary prevention. Virus type, host factors and clinical management are the three key focus areas. Influenza A has a high attack rate and long incubation period [10]. Extremes of age, pregnancy, obesity, and comorbidity are associated with high rates of hospital admission, ICU admission and all-cause mortality [6,8,11–15]. Antiviral treatment [16] and ventilation [17] greatly affects the clinical outcome of the patients with influenza. A systemic review and meta-analysis of over 230 studies on risk factors for severe and complicated influenza reported that about 80% of the studies were conducted during pandemic influenza seasons. The evidence supporting risk factors for severe seasonal influenza is limited [18].

2. Objective

In this study, we aim to delineate the clinical and epidemiological features of severe seasonal influenza infection, and isolate prognostic factors associated with mortality. We believe that the findings would provide guidance on targeted influenza vaccination, early detection, and enhanced surveillance and management of high-risk individuals.

3. Study design

A retrospective review was conducted on all patients with laboratory-confirmed influenza infection who were either admitted into the ICU or died in the Singapore General Hospital (SGH) and Tan Tock Seng Hospital (TTSH) during the period from 01 Jan 2011 to 31 Dec 2015. SGH and TTSH were two largest adult tertiary care hospitals in Singapore with 1800 beds and 1600 beds respectively, where routine influenza surveillance was conducted year-round.

4. Participants

All the patients with laboratory confirmation of influenza viral infection were followed up for 4 weeks or until discharge, whichever was earlier. Cases with severe influenza infection were defined as those either having been admitted to the high dependency unit (HDU) or ICU, or had died during the follow-up period. Pneumonia was defined as an acute infection of the lung parenchyma characterized by symptoms of acute respiratory infection and the presence of an acute pulmonary infiltrate on chest X-ray or abnormal auscultatory findings [19].

5. Laboratory testing

For the patients in SGH, Influenza viral infection was diagnosed using reverse transcriptase (RT) polymerase chain reaction (respiratory viruses multiplex PCR) (SeeGene Technologies, South Korea). Nasal/throat/nasopharyngeal swabs or combined nasal and throat swabs were collected using Dacron-tipped or Copan flocked swabs. Specimens were kept at 2–8 °C and transferred to laboratory on ice-pack within 24 h of collection. Influenza subtyping of influenza A virus was only conducted at the discretion of the physician.

For the patients in TTSH, laboratory testing for influenza virus, including subtyping, was performed with a real-time assay, the AITbiotech abTESTM (AITbiotech, Singapore), using nasal swabs. This is a one-step multiplex rRT–PCR kit designed to detect influenza A, influenza B, and subtypes of A/H3N2 and A/H1N1-2009.

6. Data collection

Demographic information, medical history, clinical symptoms, physical examination findings, chest X-ray, and laboratory test results at the point of admission were collected. Antiviral treatment, ICU admission, mechanical ventilation, length of hospital stay (LOS) and in-hospital mortality were also recorded. Charlson's comorbidity index (CCI) score was calculated.

7. Statistical analysis

Categorical variables were expressed as counts (percentage), and the differences in frequencies were compared using X [2] test or Fisher's exact test. Continuous variables were expressed as medians with 25-75th interquartile range (IQR), and differences assessed using Mann-Whitney U test. Univariate analysis was performed to assess for potential factors associated with mortality, with statistically significant variables subsequently included in a multivariable logistic regression model. Odds ratios and 95% confidence intervals were calculated. All analyses were performed using Stata version 13 (StataCorp, College Station, TX). A two-tailed P value of < 0.05 was considered statistically significant.

Ethics approval was obtained from the Centralized Institutional Review Board, SingHealth Authority (2016/2477) and Domain Specific Review Board, National Healthcare Group (E/09/344), in Singapore.

8. Results

From Jan 2011 to Dec 2015, a total of 520 patients fulfilled the definition of severely ill influenza, comprising 423 (81.3%) infected with influenza A and 97 (18.7%) with influenza B. Subtyping was conducted for 70.0% (296/423) of patients with influenza A, of whom 71 (24.0%) had influenza A/H1N1pdm2009 and 225 (76.0%) had A/H3N2 (Fig. 1). The median duration from hospital admission to

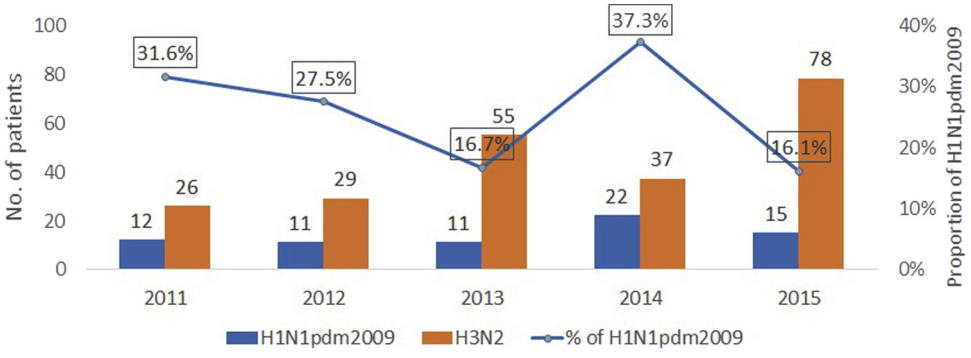

Fig. 1.

Table 1
Univariate analysis of prognostic factors of mortality among 520 patients with severely ill influenza, including 302 deaths and 218 survivals.

Variable	No. of patients with the data available	Total (n = 520)	Death (n = 302)	Survival (n = 218)	Odds Ratio (95%CI)	P value
Demographic						
Age (years), median (IQR)	520	72 (61-82)	77 (65-86)	64 (56-74)	1.06 (1.04-1.07)	< 0.001*
Age ≥ 65 years	520	338 (65.0)	233 (77.2)	105 (48.2)	3.6 (2.5-5.3)	< 0.001*
Male gender	520	276 (53.1)	154 (51.0)	122 (56.0)	0.82(0.58 - 1.16)	0.26
Chinese ethnicity	520	376 (72.3)	227 (75.2)	149 (68.3)	1.40 (0.95 - 2.06)	0.09
Comorbidities						
Cerebrovascular disease	520	41 (7.9)	29 (9.6)	12 (5.5)	1.82 (0.91 - 3.66)	0.09
Chronic pulmonary diseases*	520	105 (20.2)	56 (18.5)	49 (22.5)	0.79 (0.51 - 1.21)	0.27
Congestive heart failure/myocardial infarction	520	150 (28.9)	87 (28.8)	63 (28.9)	1.0 (0.69 - 1.46)	0.98
Diabetes mellitus	520	131 (25.2)	75 (24.8)	56 (25.7)	0.96 (0.64 - 1.43)	0.83
Renal disease	520	77 (14.8)	51 (16.9)	26 (11.9)	1.50 (0.90 - 2.49)	0.12
Malignancy	520	61(11.7)	44 (14.6)	17 (7.8)	2.02 (1.12 - 3.63)	0.02*
Charlson's comorbidity index, median (IQR)	520	1 (0-3)	2 (0-3)	1 (0-2)	1.10 (1.00-1.21)	0.039*
Prior hospitalization in past six months	520	181 (34.8)	124 (41.1)	57 (26.2)	1.97 (1.35 - 2.86)	< 0.001*
Presenting Symptoms						
Fever	520	336 (64.6)	194 (64.2)	142 (65.1)	0.96 (0.67 - 1.38)	0.83
Cough	520	361 (69.4)	206 (68.2)	155 (71.1)	0.87 (0.60-1.23)	0.48
Breathlessness	520	284 (54.6)	149 (49.3)	133 (61.0)	0.62 (0.44 - 0.89)	0.009*
Chest Pain	406	40 (9.9)	18 (7.9)	22 (12.5)	0.60 (0.31-1.16)	0.131
Physical exam findings						
Altered mental status	520	61 (11.7)	33 (10.9)	28 (12.8)	0.83 (0.47 - 1.48)	0.50
Temp > 40 °C or < 35 °C	520	16 (3.1)	9 (3.0)	7 (3.2)	0.93 (0.30-2.98)	0.88
Pulse rate (PR) ≥ 125 per min	485	187 (38.6)	91 (32.0)	96 (47.8)	0.52 (0.36 - 0.75)	< 0.001*
Systolic Blood Pressure < 90 mmHg	520	86 (16.5)	51 (16.9)	35 (16.1)	0.94 (0.59-1.51)	0.80
SaO2 < 90 mmHg	501	97 (19.4)	51 (17.4)	46 (22.0)	0.85(0.55 - 1.30)	0.44
Crackling breathing sound	519	297 (57.3)	172 (57.0)	125 (57.3)	0.98 (0.68 - 1.42)	0.93
Laboratory Results and Chest X-ray						
Leucocytes < 4 or > 10 × 10^9/L	520	264 (50.8)	149 (49.3)	115 (52.8)	0.87(0.62-1.22)	0.44
Lymphocytes (x 10^9/L), median (IQR)	520	10.3 (5.9 - 17)	10.2 (5.7 - 16.5)	10.4 (6.1 – 17.5)	0.99 (0.98 - 1.01)	0.31
Haemoglobin < 13 g/dl (men) or < 12 g/dl (women)	519	294 (56.7)	191 (63.5)	103 (47.3)	1.9 (1.4-2.8)	< 0.001*
Sodium < 130 (mmol/L)	516	108 (20.9)	69 (23.0)	39 (18.1)	1.3 (0.85 – 2.0)	0.17
Potassium > 5.5 or < 3.5 (mmol/L)	516	130 (25.2)	74 (25.6)	56 (25.9)	0.93 (0.62 - 1.39)	0.73
Urea ≥ 9 mmol/L	520	216 (41.5)	138 (45.7)	78 (35.8)	1.63 (1.14 - 2.33)	0.024*
Serum albumin < 34 g/L	441	311 (70.5)	200 (77.2)	111 (60.1)	2.2 (1.4-3.3)	< 0.001*
C-reactive protein (mg/L) median (IQR)	428	47.4 (15.1 - 120.2)	50.9 (16.3 – 119.8)	44.1 (12.7 – 121.2)	1.00 (1-1)	0.94
Chest x-Ray - Consolidation	520	201 (38.7)	125 (41.4)	76 (34.9)	1.32 (0.92 - 1.89)	0.13
Influenza A	520	423 (81.3)	241 (79.8)	182 (83.5)	0.78 (0.50 - 1.23)	0.29
Positive Blood culture	520	41 (7.9)	26 (8.6)	15 (6.9)	1.27 (0.66-2.47)	0.471
Treatment given						
Antiviral therapy	517	402 (77.8)	214 (71.1)	188 (87.0)	0.37 (0.23-0.59)	< 0.001*
Empiric antiviral therapy (started before laboratory detection of influenza virus)	336	224 (66.7)	119 (64.0)	105 (70.0)	0.75 (0.48-1.12)	0.23
Prompt antiviral therapy (started within a week of symptom onset)	336	246 (73.2)	126 (67.7)	120 (80.0)	0.53 (0.32-0.87)	0.012*
Mechanical ventilation	520	312 (60.0)	133 (44.0)	179 (82.1)	0.17 (0.11-0.26)	< 0.001*

Note: the data was presented as number (%) otherwise specified. Univariate analysis was performed to assess the difference in observed variables between survivors and non-survivors. Categorical variables were tested by Chi-square test or Fisher's exact test if frequencies in any cells were < 5. Continuous variables were analysed using non-parametric Mann-Whitney U test.

* Chronic pulmonary diseases include COPD, bronchiectasis, and asthma.

laboratory diagnosis of influenza viral infection was 1 day (IQR 0–2).

8.1. Demographics and baseline clinical characteristics

The median age of all the study subjects was 72 years (IQR 61–82 years). Patients infected with A/H1N1pdm2009 (median: 62 years; IQR: 53–74) were significantly younger compared to those infected with A/H3N2 (median: 77 years; IQR: 67–85) (P < 0.001). Males comprised 53.1% of the study subjects (276/520) (Table 1). No pregnant women were involved in the study. The median CCI was 1 (IQR 0–3), with 31.1% (162/520) of patients having no identifiable chronic medical conditions. Cardiovascular diseases (congestive heart failure or myocardial infarction) (150, 28.9%), diabetes mellitus (DM) (131, 25.2%), and chronic pulmonary disease (105, 20.2%) were the top three comorbidities. Cough (361, 69.4%), fever (336, 65%), and breathlessness (284, 54.6%) were the major presenting symptoms. Pulse rate ≥125 beats per min (191, 36.7%) and lung crackles (297, 57.3%) were the main abnormal findings on physical examination. Anaemia [haemoglobin < 13 g/dl (men) or < 12 g/dl (women)] [20] and hypoalbuminemia (serum albumin level < 34 g/L) [21] were respectively present in 56.7% and 70.5% of patients respectively. Chest X-ray revealed that airspace opacity or consolidation was present among 201 (38.8%) patients. Jointly taken respiratory symptoms, auscultatory findings and the changes of airspace opacity or consolidation in chest X-ray into account, 78% (406/520) of the patients in the study cohort had clinical or radiological signs of pneumonia at the time of their ED visits.

For clinical management, majority of the patients received oseltamivir therapy (402/520, 77.3%) and had an ICU/HDU admission (409/520, 78.7%) with the median length of ICU/HDU stay being 3 days (IQR 1–7). Over three-quarters (312/409, 76.3%) of ICU/HD patients had mechanical ventilation. The median LOS was 12 days (IQR 6–25). In-hospital all-cause mortality rate was 58.1% (302/520).

Table 2
Multivariable logistic regression analysis on factors associated with mortality among patients with severe influenza.

Factors	Multivariable logistic regression analysis	
	Adjusted Odds Ratio	P value
Age ≥65 years	3.64 (2.21-5.99)	< 0.001*
Malignant lymphoma or solid tumour	2.53 (1.12-5.73)	0.026*
Charlson's Comorbidity Index score	0.70 (0.39-1.25)	0.23
Prior hospitalization in the past six months	1.55 (0.89-2.72)	0.12
Breathlessness	0.73 (0.45-1.19)	0.21
Pulse rate ≥125/min	0.58 (0.35-0.95)	0.031*
Haemoglobin < 13 g/dl (men) or < 12 g/dl (women)	1.521 (0.92-2.52)	0.10
Serum urea level ≥ 9 mmol/L	1.09 (0.65-1.85)	0.74
Serum albumin < 34 g/L	2.17 (1.26-3.73)	0.005*
Antiviral therapy	0.33 (0.17-0.63)	0.001*
Ventilation	0.23 (0.13-0.39)	< 0.001*

Note: Variables with P value < 0.05 on univariate analysis were included into the multivariable logistic regression model.

8.2. Factors associated with mortality, ICU admission and mechanical ventilation

Univariate analysis revealed 11 variables significantly associated with mortality, including age, malignancy, CCI, prior hospitalization in the past 6 months, breathlessness, tachycardia (pulse rate ≥125 per min), anaemia, hypoalbuminemia, urea ≥9 mmol/L, antiviral therapy, and mechanical ventilation. After adjustments in a multivariable logistic regression model, patients aged ≥65 years and those with malignancy and hypoalbuminemia were at increased risk of mortality (Table 2). In contrast, severely ill patients who received antiviral therapy and mechanical ventilation were about 3 and 4 more times to survive. Logistic regression by backward stepwise selection generated similar results (Supplementary Table S1).

In addition, 336 patients treated with oseltamivir had symptom onset date recorded. Oseltamivir therapy initiated within one week of symptom onset (prompt treatment) led to better survival compared to delayed treatment (started beyond one week of symptom onset) on univariate analysis (OR = 0.53, P = 0.012). As only a subset of patients had the symptom onset date recorded, this variable was not included in the multivariable analysis so as to avoid losing sample size and statistical power.

We also evaluated risk factors for ICU admission and mechanical ventilation. Age, diabetes and hypoalbuminemia were independently associated with ICU admission (Table 3). Age, SaO2 < 90 mm Hg, serum sodium < 130 (mmol/L), and hypoalbuminemia were significantly associated with mechanical ventilation (Table 4).

9. Discussion

The presentation of influenza ranges from asymptomatic infection to fulminant disease. In this study, advanced age, significant comorbidities, and poor nutritional status were common characteristics associated with severely ill influenza patients. In addition, a large proportion of patients (78%) had clinical or radiographic evidence of pneumonia at the time of presentation to the hospitals.

Elderly people are generally vulnerable to influenza viral infection and prone to severe complications [11,22]. Reed et al estimated that adults aged ≥65 years accounted for 54–70% of influenza-associated hospitalizations and 71–85% of influenza-associated deaths in the US during 2010–2013 [23]. In Canada, over 65% of influenza hospitalization burden was in those aged ≥65 years [24]. In Singapore, influenza-associated hospitalization and mortality rates in the elderly population were 15 and 11.3 times respectively higher than the general population [4]. In this study, the median age of patients with severe seasonal influenza was 72 years, much older than the severe cases reported during the 2009 influenza A/H1N1 pandemic [25]. Age ≥65 years was an independently associated factor for mortality, with seniors being at three times the odds of dying during the admission compared to younger adults aged < 65 years. Our study also revealed that age was a significant factor taken into account when deciding whether to give intensive care (ICU) and critical life support (mechanical ventilation) to a severe patient.

Presence of comorbidities, which is also very common among the elderly, is significantly associated with severity and mortality in influenza infections [11,26]. In this study, approximately 70% of the patients had at least one chronic disease. Chronic heart disease (congestive heart failure/ myocardial infarction) was the most common condition, followed by diabetes, chronic pulmonary disease, renal disease, and malignant disease. A meta-analysis comprising data from 239 studies has revealed that all of the abovementioned chronic diseases significantly increased the odds of hospitalization and mortality with odds ratios ranging from 1.71 to 5.11 [11]. On the other hand, it is worth noting that one third of the study subjects had no identifiable chronic medical conditions (CCI = 0), although their mortality rate was similar to that reported in chronically ill patients (56.8% vs 58.7%, P = 0.69). This phenomenon was also noted during the 2009 influenza pandemic [27,28]. This group of "healthy elderly", who give the general impression of being in good health, should be considered a special high risk group as they are more likely to be overlooked by family members or physicians when they fall ill.

Hypoalbuminemia, a common condition among older people, increases the risk of infections, complications and mortality [29,30]. A meta-analysis revealed that each 10 g/l decline in serum albumin level significantly raises the odds of mortality by 137% [29]. In this study, hypoalbuminemia was present in over 70% of the patients with severely ill influenza. Together with age, hypoalbuminemia significantly decreased the likelihood of ICU admission and mechanical ventilation,

Table 3
Factors associated with ICU admission among patients with severe influenza infection.

Variable	ICU admission (N = 410)	No ICU admission (N = 110)	Univariate analysis P value	Multivariable analysis P value	Adjusted Odds Ratio (95% CI)
Age (years), median (IQR)	69 (59-78)	83 (74-89)	< 0.001	Not included	–
Age≥ 65 years	244 (59.5)	94 (85.5)	< 0.001*	< 0.001*	0.27 (0.14-0.51)
Diabetes Mellitus	114 (27.8)	17 (15.5)	0.008*	0.014*	2.36 (1.19-4.70)
Prior hospitalization in past six months	133 (32.4)	48 (43.6)	0.029*	0.055	0.59 (0.35-1.01)
Pulse rate (PR) ≥ 125 per min	155 (41.3)	32 (29.1)	0.020*	0.143	1.51 (0.87-2.62)
Haemoglobin < 13 g/dl (men) or < 12 g/dl (women)	222 (54.2)	72 (66.1)	0.026*	0.700	0.90 (0.52-1.55)
Serum albumin < 34 g/L	243 (67.7)	68 (82.9)	0.006*	0.020*	0.46 (0.24-0.89)

Note: the data was presented as number (%) otherwise specified. Univariate analysis was performed to assess the difference in observed variables between ICU admission and no ICU admission. Categorical variables were tested by Chi-square test or Fisher's exact test if frequencies in any cells were < 5. Continuous variables were analysed using non-parametric Mann-Whitney U test.

Table 4
Factors associated with mechanical ventilation among patients with severe influenza infection.

Variable	Ventilated (n = 313)	Non-ventilated (n = 207)	Univariate analysis P value	Multivariable analysis P value	Adjusted Odds Ratio (95% CI)
Age (years), median (IQR)	67.5 (58-76)	79(65-87)	< 0.001*	Not included	–
Age ≥ 65 years	178 (57.1)	159 (76.8)	< 0.001*	< 0.001*	0.42 (0.27-0.68)
Cerebrovascular disease	17 (5.5)	23 (11.1)	0.018*	0.210	0.59 (0.25-1.36)
Prior hospitalization in past six months	97 (31.1)	84 (40.6)	0.026*	0.250	0.76 (0.48-1.21)
Pulse rate (PR) ≥ 125 per min	93 (30.8)	98 (45.0)	0.001*	0.580	1.14 (0.72-1.79)
SaO2 < 90 mmHg	69 (23.1)	28 (13.9)	0.010*	0.008*	2.22 (1.23-3.99)
Sodium < 130 (mmol/L)	76 (24.5)	32 (15.5)	0.014*	0.006*	2.20 (1.25-3.86)
Serum albumin < 34 g/L	182 (66.7)	129 (77.3)	0.018*	0.021*	0.56 (0.34-0.92)

Note: the data was presented as number (%) otherwise specified. Univariate analysis was performed to assess the difference in observed variables between those who had mechanical ventilation and those who had not. Categorical variables were tested by Chi-square test or Fisher's exact test if frequencies in any cells were < 5. Continuous variables were analysed using non-parametric Mann-Whitney U test.

and it was independently associated with mortality with an adjusted odds ratio of 2.11. Inadequate food intake, poor nutrient absorption, or chronic illnesses are the usual causes [31,32]. The traditional Asian diet in Singapore, which is relatively high in carbohydrates and low in meat and dairy foods, may also contribute to the occurrence of hypoalbuminemia among the elderly. Regular nutritional screening and assessment would help to understand special nutritional needs and optimize nutritional support for elderly people. Improved nutritional status would consequently strengthen their immune systems and reduce their risk of severe influenza infection and mortality. On the other hand, recent studies also revealed that obesity (Body Mass Index, BMI ≥ 30.0) increases the risk of severe seasonal influenza infection [33,34]. However, this data was not available for evaluation in our study.

Elderly patients do not always develop "typical" influenza symptoms, which might have resulted in their influenza infection being easily overlooked. A recent study reported that individuals ≥65 years were less likely to be tested for influenza than younger adults even when hospitalized for respiratory symptoms [35]. Delayed or completely missed diagnosis would make timely antiviral influenza therapy impossible. Consequently, these elderly patients may develop various severe complications, especially among those with comorbidities. Pneumonia is the most common respiratory complication of influenza [36–38]. Influenza viral pneumonia itself can be fatal. Worst still, combined viral-bacterial pneumonia and secondary bacterial pneumonia are the most common complications, which drastically increase influenza-associated hospitalization and mortality [39,40].

The association of viral type and subtype with the severity of seasonal influenza infection is controversial. A/H3N2 infection is often believed to result in more severe illness and high mortality [41,42]. However, recent studies have indicated that A/H1N1pdm2009 is more associated with lower respiratory tract infection and ICU admissions [26,43,44]. According to the Singapore national influenza sentinel surveillance program, A/H3N2 was the predominant subtype during the study period, except in 2011 when A/H1N1pdm2009 was the major circulating influenza subtype [3]. Consistent with national surveillance data, A/H3N2 was the most often detected viral subtype among our study subjects. However, we did not observe significant difference in mortality between A/H1N1pdm2009 infection and A/H3N2 infection in our patient cohort. As A/H1N1pdm infection affected a younger population than A/H3N2, this might have offset the more severe impact of A/H1N1pdm2009 on disease severity and mortality as young people were less likely to have severe comorbidities [45]. However, a higher rate of ICU admission and death has been reported among the elderly (≥ 65 years) infected with A/H1N1pdm2009 compared to A/H3N2 and influenza B [43,44].

The World Health Organization (WHO) and United States Centers for Disease Control and Prevention (CDC) have recommended that antiviral agents be prescribed for hospitalized patients with confirmed or suspected influenza as early as possible [2,46]. In this study, about 80% of the study subjects received oseltamivir treatment, and they were more likely to survive compared to those not treated with any antiviral agent. We also noted that patients who received oseltamivir therapy prior to influenza test (empirical therapy) had lower mortality rate than those treated after influenza test (definite therapy) although it was not statistically significant, possibly due to limited sample size. In addition, oseltamivir therapy started within one week of symptom onset led to better survival compared to the delayed group.

Vaccination is the most effective way to prevent influenza and severe influenza-related outcomes [47–49]. Singapore's Ministry of Health (MOH) recommends annual influenza vaccination for people aged 65 years or older, immunocompromised individuals, and those with comorbidities. The cost of vaccination can be claimed from Medisave (a compulsory national medical savings scheme in Singapore) [50,51]. However, the overall vaccine uptake rate was only about 17.0% among seniors aged ≥65 years [5]. Low perceived risk of influenza infections, fear of side effects of vaccination, and cost issues significantly influence the acceptance of influenza vaccination [52]. In this study, 88% of the study subjects were eligible for influenza vaccination as they were either ≥ 65 years or had a chronic medical condition(s). As the vaccination data was not routinely recorded in the patient's health records, we could not assess the effect of influenza vaccination on mortality. However, we believed that the influenza vaccination rates in our patients were likely low and similar to that of general Singapore population, as there were no concerted hospital-wide influenza vaccination programs for patients over the study period.

To our knowledge, this is the largest epidemiological study to address the factors associated with severe seasonal influenza and subsequent mortality in recent years. We believe that the findings would increase awareness among patients and their relatives about influenza, its severe consequences, and help enhance their understanding of the importance of influenza vaccination. The insights gained would also guide physicians through the process of identifying high risk patients, predicting the severity of illness, and customizing clinical management plans. This study has several limitations. Firstly, this is a retrospective study and available data was limited to that collected as part of routine care. Nonetheless, we managed to identify several clinical factors associated with severe influenza infection and mortality, with data collected at the point of hospitalization. Secondly, the study was conducted in two, but not all adult tertiary care hospitals in Singapore. Nonetheless, as these two are the largest institutions, and patients from all over Singapore are free to seek care from any tertiary care hospital, any selection bias was likely to be minimal.

In conclusion, patients with severe seasonal influenza infection were characterized by advanced age, hypoalbuminemia and presence of pneumonia on admission. Age ≥65 years, malignancy, and hypoalbuminemia were associated with increased mortality, and antiviral therapy and mechanical ventilation with decreased mortality. Improving nutritional status and influenza vaccination uptake rate among elderly patients, as well as early antiviral treatment, would be areas of interest to target for interventions that could improve survival

from seasonal influenza infection.

Declaration of Competing Interest

There was no competing interest associated with this project.

Credit author statement

ZZ, WMK and AC designed the project and set up the patient cohort. ZZ, WMK and HJH performed data extraction and cleaning. ZZ, WMK, and AAH did statistical analysis and data interpretation. ZZ and MZT drafted the original manuscript. HJH and AC performed critical review and revision. AC supervised the progression of the project. All the authors read and approved the final manuscript.

Funding

None.

Ethical approval

Stated in the methodology session.

Acknowledgement

The authors are grateful for Dr Yang Yong's support for his participation in designing the study. We also express appreciation to Mr Joshua Wong for his suggestions for data analysis. Zoe Zhang was a former staff in Singapore General Hospital.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcv.2019.06.005.

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