

Factors associated with early hospital discharge of adult influenza patients

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Background: Understanding factors affecting length of hospital stay (LOS) in patients with severe influenza may improve their management.

Methods: A retrospective cohort study on laboratory-confirmed, adult influenza patients hospitalized in 2004 and 2005 was conducted. For all influenza cases during that period, immunofluorescence assay on nasopharyngeal aspirate was used for rapid diagnosis, and oseltamivir (75 mg twice daily for 5 days) prescribed if the patient presented within 2 days of symptom onset. Independent factors associated with time to discharge were identified using Cox proportional hazards models. An adjusted hazard ratio (aHR) >1 signifies a higher chance of early discharge. Viral shedding and influenza vaccination history were studied during one 'flu' season.

Results: A total of 356 patients (influenza A 93.5%) were studied. The majority of patients were old (70.2

±8.4 years), had ≥1 comorbid illness (69.1%) and developed respiratory or cardiovascular complications (69.4%). Oseltamivir initiated within 2 days of illness was associated with shorter total LOS (Kaplan–Meier estimated median 4 versus 6 days [–33%]; aHR for discharge 1.54, 95% confidence intervals [95% CI] 1.23–1.92, $P<0.0001$). Older age (≥70 years), comorbidities and complications were associated with prolonged LOS. Prolonged viral RNA detection >day 4 of illness (23 out of 99 consecutive patients) was also independently associated with longer LOS (aHR 0.36 [95% CI 0.19–0.71], $P=0.003$), whereas influenza vaccination within 6 months was associated with shorter LOS (aHR 2.14 [95% CI 1.18–3.85], $P=0.012$).

Conclusion: Our analyses suggest that timely oseltamivir treatment is independently associated with shorter LOS in patients hospitalized for severe influenza. Efforts to ensure early diagnosis and therapeutic intervention are warranted.

Introduction

Influenza is estimated to be responsible for more than 226,000 excess hospital admissions annually in the USA. Of these hospital admissions, 63% occur among individuals aged over 65 years, and the rate of these hospitalizations has increased over the past decade [1,2]. The risk of complications and/or death from influenza are highest among individuals at the extremes of age and those with comorbidities [1,3,4]. These patients often require prolonged hospitalization; the median and mean hospital lengths of stay (LOS) are estimated to be around 6–7 days and 8–9 days, respectively, in the older age group [2]. In Hong Kong, the disease burden of influenza is substantial and the associated mortality comparable with Western countries [4–7]. It has been estimated that 13–58 per 10,000 elderly individuals are hospitalized annually for influenza-associated complications such as pneumonia, exacerbation of chronic obstructive pulmonary disease (COPD) or asthma, and acute cardiovascular events.

With an aging population, this creates a heavy burden on the healthcare system [5,6].

However, few studies have described these influenza patients and their in-hospital management [1,8–12]. Host and virus factors that may determine disease severity and affect the duration of stay in hospital are not well characterized [2]. The impact of antiviral treatment on serious, complicated influenza infections and the hospital LOS is also unclear [1,13,14]. Neuraminidase inhibitors, for example, oseltamivir, have been shown to reduce the duration of illness and complications in influenza patients (including elderly patients) [1,13–16], and these newer drugs are increasingly being prescribed to treat severe influenza infections in the hospital setting. In this context, we aim to examine factors that are associated with earlier hospital discharge of adult influenza patients. Understanding such factors may help to improve management of influenza patients and

shorten their duration of hospitalization. This is important as the threat of another influenza pandemic becomes imminent [17–20].

Methods

Study population

To investigate factors affecting hospital LOS, a retrospective cohort study was performed on all laboratory-confirmed, adult (age ≥ 18 years) influenza patients admitted to the medical department of the Prince of Wales hospital, Hong Kong, between 1 January 2004 and 31 December 2005. During that 2-year period, influenza patients were diagnosed according to a standard protocol (described below). A complete list of patients in alphabetical order was generated via the hospital's computerized Clinical Management System (searching The International Classification of Diseases, Ninth Revision [ICD-9] code for 'influenza') and the Laboratory Information System of the virology laboratory. Laboratory confirmed influenza was defined as a positive result from an influenza-specific immunofluorescence assay on a nasopharyngeal aspirate sample, and/or with influenza virus isolated from the sample. The Prince of Wales Hospital is a 1,400 bed teaching hospital operated by the Hospital Authority of Hong Kong. It serves an urban population of 1.5 million in the eastern New Territories of the Hong Kong Special Administrative Region [6]. The Hospital Authority is the key provider of acute medical services in Hong Kong.

A total of 561 laboratory-confirmed, adult influenza cases were identified during the 2-year study period. As indicated by sample size estimation, 365 (65%) cases were randomly selected from the patient list for chart review. Demographic, clinical, treatment and virological data were analysed. Only nine patients were subsequently excluded, this was due to (i) their LOS was prolonged due to reasons other than influenza infection (incidental finding of malignancy in five, haematuria/renal stone in one), or (ii) their influenza infections were considered hospital-acquired (in three patients). Thus a total of 356 sets of patient data were analysed. We also examined the available basic demographic data and LOS of the remaining 196 patients; they were similar to the studied cohort, suggesting lack of bias.

Diagnosis and management of influenza patients

Following the severe acute respiratory syndrome (SARS) outbreak in our hospital in 2003 [21], all adult patients presenting during 2004–2005 to the emergency department with fever, respiratory (cough, sore throat, sputum production or shortness of breath), and systemic (chills, myalgia, malaise or headache) symptoms, with or without pneumonia, and requiring hospitalization were admitted directly to designated medical

wards and put on droplet precautions. Patients were admitted if they developed potentially serious medical conditions and if the exacerbation of their chronic illnesses or their severe symptoms were considered impossible to be taken care of at home. According to a standard protocol, nasopharyngeal aspiration (NPA) was performed for all such patients to test for influenza A and B infections using immunofluorescence assay (IFA) (see below) on admission. The results were available to clinicians within a few hours. Sputum bacterial culture was also routinely performed.

All adult patients hospitalized with severe influenza, once diagnosis was confirmed by IFA, were prescribed oseltamivir if they presented within 2 days (<48 h) of symptom onset based on our current guidelines [20]. Patients presenting/diagnosed on day 3 or beyond only received oseltamivir at the individual attending physician's discretion. A standard course of oseltamivir (75 mg twice daily for 5 days) was prescribed, except in the few renal failure cases that required dosage adjustment. Zanamivir, rimantadine or amantadine were seldom prescribed in our unit, mainly because of the difficult administration of zanamivir and the side effect profiles of these drugs in our mostly elderly patients, many of whom had underlying airway disease. Patients' medical conditions were managed according to usual procedures. Patients who recovered from the acute illness (for example, becoming afebrile and oxygen independent) were discharged home. Patients requiring convalescence care (for example, COPD exacerbation) were transferred to a convalescent hospital. They were managed and discharged according to usual procedures.

Data collection and definitions

Patients' admission records, clinical records and in-hospital medication prescription forms were reviewed. Total hospital LOS was defined as the time interval between the date of hospital admission and the date of discharge from either the acute-care or the convalescent hospital. Acute-care LOS was similarly defined, but included only patients that were discharged directly from the Prince of Wales hospital. The time interval between the fever onset date (as reported by the patient) and the oseltamivir prescription date was calculated for each patient. Medical complications related to acute influenza infection were defined as new or exacerbated medical problems documented by appropriate history, physical examination, laboratory, radiographic and/or other clinical studies that required additional management by the attending physician.

Previous studies have suggested that few 'non-hospitalized' influenza patients shed viruses beyond day 4 of their illness [22]; however, few data exist for hospitalized patients with severe influenza. An addi-

tional observational study aimed at detection of persistent viral shedding in hospitalized patients with severe influenza was therefore performed. Combined nasal and throat swabs were taken from each consecutive patient admitted with influenza (confirmed by NPA/IFA) during March–June 2005 (period of peak community influenza activity) [5], who remained hospitalized for longer than 4 days of illness because of persistent symptoms, with or without oseltamivir treatment. Both virus isolation and RT-PCR assay (see below) were performed. Patients were also asked if they had received any influenza vaccinations during the 6 months prior to admission; vaccination data are therefore only available for this patient subgroup. Informed consent was obtained from all patients. Ethics approval for this study was obtained from the institutional review board (IRB) of The Chinese University of Hong Kong.

Virological investigations

Nasopharyngeal aspirates were collected using a standard technique under appropriate infection control measures [18,20,23]. The nasopharyngeal aspirate was mixed with 2 ml of viral transport medium (VTM) and subjected to immunofluorescent staining, virus isolation and subsequent typing of influenza. A commercial IFA for influenza A and B (Chemicon International, Inc., Temecula, CA, USA) was used for the initial diagnosis of influenza infection. Influenza virus isolation was conducted using MDCK cells, and cell monolayers were examined daily for cytopathic effect. After 14 days of incubation, the growth of influenza was examined using haemadsorption, and confirmed by immunofluorescent staining using influenza group-specific antibodies (Chemicon International, Inc.), which identified the isolate as influenza A and B. Influenza A isolates were further differentiated into H1 and H3 subtypes by the National Influenza Reference Laboratory at the Centre for Health Protection in Hong Kong [5].

Nasal and throat swabs were collected using a standard technique [20] and put into 2 ml VTM bottles together. All specimens were aliquoted to two equal parts for virus isolation (as described above), and real-time PCR assay. RNA extraction was performed using the QIAamp viral RNA Mini Kit (Qiagen, Hilden, Germany). Influenza RNA was detected by the SuperScript III Platinum One-Step Quantitative RT-PCR System with ROX (Invitrogen, Carlsbad, CA, USA). Influenza A was detected by using primers 5'-AAG ACC AAT CCT GTC ACC TCT GA-3' and 5'-CAA AGC GTC TAC GCT GCA GTC C-3', and probe 5'-TTT GTG TTC ACG CTC ACC GT-3' targeting a Matrix gene region consensus for H3 and H1 subtypes; whereas primers 5'- CCG GAG TGA GAC GAG AAA T-3' and 5'-CGT CTT CTC CTT TTC CCA TTC CAT

T-3', and probe 5'-CAT AGC TGA GAC CAT CTG C-3' were used to target the matrix gene of influenza B.

Statistical analysis

The Kaplan–Meier method was used to estimate time to discharge (hospital LOS) (unadjusted median and interquartile range [IQR]); and univariate associations between clinical characteristics (age, sex, comorbidity, complications, oseltamivir treatment within 2 days: 'yes' versus 'no') and LOS were examined using the log rank test. The χ^2 test (with continuity correction) or Fisher's exact test was used to evaluate other dichotomous and categorical associations, whenever appropriate. For the variable 'age', an receiver operator characteristic (ROC) curve was constructed to identify a cutoff value that was associated with the best sensitivity and specificity combination to discriminate patients with or without convalescence care (a categorical outcome), which was found to be at 70 years.

Multivariate Cox proportional hazards models were constructed to identify factors independently associated with time to discharge (hospital LOS), the outcome variable of interest [24]. All patients who died during hospitalization were censored at the time of death. Variables with a *P*-value <0.1 in the univariate analyses were entered into the multivariate models as covariates. Backward stepwise analysis was performed; only variables with a *P*-value <0.05 were retained in the models. Adjusted hazard ratios (aHR) for discharge and 95% confidence intervals (CI) were calculated for each explanatory variable. An aHR >1 signifies a higher chance of being discharged from hospital (that is, shorter LOS); whereas an aHR <1 signifies a lower chance of being discharged from hospital (that is, longer LOS). A Kaplan–Meier curve was also developed to show the effect of explanatory variables on time to discharge in the final model. Data collected in the viral shedding study were similarly analysed in a separate Cox proportional hazards model. A *P*-value of <0.05 was considered to indicate statistical significance. All probabilities were two-tailed. Statistical analysis was performed with the SPSS software version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics and clinical outcomes

A total of 356 laboratory-confirmed, hospitalized influenza cases were analysed. Peak timing of patient admission coincided with the peak seasonal influenza activities in the community [5] (see 'Additional file 1: seasonal influenza activities in Hong Kong' online). A total of 304 patients were both IFA positive and had influenza virus isolated from NPA; 21 were IFA negative but culture positive, and 31 were IFA positive only.

Overall, there were 333 cases of influenza A and 23 of influenza B. Sub-typing results for influenza A were only available in 292 cases; all except one were of the H3N2 subtype, which was the predominant circulating virus during the study period (the remaining one being H1N1) [5].

Baseline characteristics and clinical outcomes of our study cohort are summarized in Table 1. Patients were of advanced age (mean 70.2 ±18.4 years), with one or more comorbidities (69%) and the majority presented with complications (69%). A total of 24% of patients were subsequently transferred to a convalescent hospital and 3% died during the hospital stay. Overall, the median (IQR) time interval between fever onset and presentation to hospital was 1 (0–2)

day. The mean total LOS (acute care plus convalescence care) was 10.2 ±12.8 days, and the mean acute-care LOS was 4.9 ±3.3 days. The median (IQR) total LOS was 5 (3–11) days and acute-care LOS was 4 (3–6) days.

Use of oseltamivir treatment

A total of 257 (72.2%) patients received oseltamivir: 161 (45.2%) were treated within 2 days of fever upon presentation whereas 195 (54.8%) patients who presented late received either no treatment ($n=99$) or late treatment (mostly on days 3–4, $n=96$) at the physician's discretion. No serious side effect was noted with oseltamivir treatment, and it was generally well tolerated. Transient vomiting was recorded in six patients

Table 1. Baseline characteristics and clinical outcomes of hospitalized influenza patients 2004–2005 ($n=356$)

Descriptive	<i>n</i> (%)
Baseline characteristics	
Influenza A	333 (93.5)
Influenza B	23 (6.5)
Age, ≥70 years	241 (67.7)
Age, <70 years	115 (32.3)
Gender	
Male	183 (51.4)
Female	173 (48.6)
Sources	
Living in community	322 (90.4)
Nursing home residents	34 (9.6)
Without comorbidity	110 (30.9)
With comorbidity	246 (69.1)
Congestive heart failure, cerebrovascular, neoplastic, chronic liver and renal diseases*	108
Others: diabetes, ischaemic heart disease, autoimmune, endocrine, neurological diseases and immunosuppression	139
Chronic respiratory diseases: asthma, COPD, bronchiectasis	96
No documented fever (≥37.5°C)	17 (4.8)
Contact or travel history [†]	18 (5.1)
Clinical outcomes	
Death [‡]	12 (3.4)
Supplemental oxygen prescribed	215 (60.4)
Intensive care unit admission	11 (3.1)
Ventilatory support [§]	17 (4.8)
Direct discharge from acute-care hospital	258 (72.5)
Transferred to convalescence care facilities	86 (24.2)
Without complication	109 (30.6)
With complication(s) [¶]	247 (69.4)
Pneumonia [#]	89
Bronchitis or exacerbation of chronic pulmonary diseases (without pneumonia)	92
Acute cardio-/cerebrovascular events (atrial fibrillation, acute coronary syndromes, congestive heart failure, TIA/stroke)	27
Others (mental dullness, dehydration/azotemia, syncope, delirium)	39

*Classification based on the Pneumonia PORT Severity Index scoring system; patients with these conditions may also have other comorbid illnesses. [†]History of contact with other influenza patients in households or nursing homes; travel history outside Hong Kong (for example, to mainland China). [‡]All cause' mortality occurred within the same period of hospitalization. [§]Including invasive and non-invasive ventilatory support (for example, bi-level positive airway pressure). [¶]Patients may have more than one complication developed throughout the whole clinical course; listed categories are based on the predominant complication noted on presentation. [#]Radiographically-confirmed pneumonia, with/without other complications; sputum culture confirmed secondary bacterial infection on presentation ($n=30$: *Haemophilus influenzae* $n=10$, *Streptococcus pneumoniae* $n=6$, *Pseudomonas aeruginosa* $n=7$, *Staphylococcus aureus* $n=4$ and gram-negative bacilli $n=3$). COPD, chronic obstructive pulmonary disease; IQR, interquartile range; TIA, transient ischemic attack.

(3.7%) while on oseltamivir and one patient developed a mild skin rash suspected to be oseltamivir-related, which subsided after its termination.

Data on viral shedding

A total of 99 consecutive influenza patients were studied for viral shedding during one 'flu' season. Of these, 87% of patients were prescribed oseltamivir, and 23% had received an influenza vaccination within the 6 months prior to hospital admission. RT-PCR for influenza virus RNA detection was positive in 23 (23.2%) patients (A=21, B=2). The sampling interval was 5.4 ± 1.5 days for those with positive RT-PCR results and 5.5 ± 1.6 days for those with negative RT-PCR results ($P=0.69$). Oseltamivir treatment was associated with a negative RT-PCR result (viral RNA detected in 18.6% with treatment versus 53.8% without treatment; Fisher's exact $P=0.01$). Influenza viruses were isolated from the nasal/throat swabs in nine (9.1%) patients. Based on the admission NPA virus isolation results to diagnose influenza A/B, the rate of persistent isolation of influenza A and influenza B from repeated swabs was 7/94 and 2/5 respectively (Fisher's exact, $P=0.06$). Oseltamivir treatment was associated with a trend towards negative viral isolation ($P=0.09$).

Univariate analysis on LOS

Univariate analyses showed that age ≥ 70 years ($P=0.001$), comorbidity ($P=0.001$) and complications ($P<0.0001$) were associated with longer total LOS, whereas oseltamivir treatment within 2 days of fever onset was associated with shorter LOS (4 versus 6 days or 33% reduction, $P<0.0001$). We assumed day 2 to be the cutoff for optimal treatment efficacy [25]. Gender was not shown to be significant ($P=0.52$). Groups under comparison and the estimated median total LOS associated with each factor are listed in Table 2. There was no difference in baseline characteristics (age, comorbidity) between patients treated with oseltamivir within 2 days and those who failed to receive 'timely' treatment (all $P>0.05$). It was also noted that patients who received late oseltamivir treatment on day 3 or beyond had similar total LOS when compared with the untreated patients (estimated median LOS = 6 days in both groups, $P=0.431$).

The same factors of age, comorbidity and complications were found to be associated with convalescent care (χ^2 , all $P<0.05$). Fewer patients who received oseltamivir within 2 days required convalescent care (18.5%) when compared with those who received no or late treatment (30.3%) (χ^2 , $P=0.01$). It was also observed that timely oseltamivir treatment was associated with shorter total duration of fever (3.4 ± 1.5 days versus 5.3 ± 2.1 days; t -test, <0.0001).

Table 2. Factors associated with total LOS in hospital

Characteristics	Unadjusted median LOS (IQR), days*	aHR (95% CI) for hospital discharge [†]	P-value
Age			
≥ 70 years	6.0 (5.2–6.8)	0.63 (0.50–0.80)	<0.0001
<70 years	4.0 (3.5–4.5)	1.00	
Comorbidity			
Yes	6.0 (5.2–6.8)	0.73 (0.58–0.92)	<0.01
No	4.0 (3.5–4.5)	1.00	
Complication			
Yes	7.0 (5.9–8.1)	0.39 (0.31–0.51)	<0.0001
No	4.0 (3.7–4.3)	1.00	
Oseltamivir within 2 days [‡]			
Yes	4.0 (3.5–4.5)	1.54 (1.23–1.92)	<0.0001
No	6.0 (4.9–7.1)	1.00	

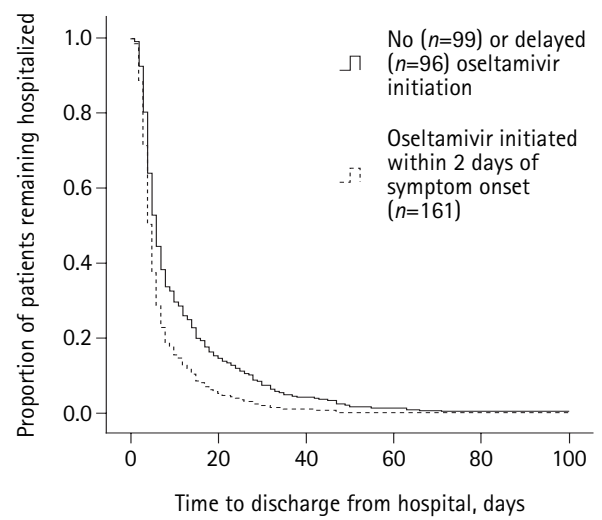
Total length of stay in hospital (LOS; acute care plus convalescent care) as outcome of interest. *Unadjusted Kaplan–Meier estimates of hospital LOS are shown for all explanatory variables (median and interquartile range [IQR], days). [†]Multivariate Cox proportional hazards models: an adjusted hazard ratio (aHR) >1 signifies a higher chance of being discharged from hospital (that is, shorter LOS); an aHR <1 signifies a lower chance of being discharged from hospital (that is, longer LOS). [‡]'Yes' = oseltamivir initiated within 2 days of fever onset ($n=161$); 'No' = no oseltamivir ($n=99$) or treatment initiated after 2 days of fever (mostly on days 3 and 4, $n=85$), or at uncertain time interval ($n=11$). Subgroup univariate analyses show that patients treated within 2 days had shorter total LOS when compared with those untreated (estimated median 4 [3.5–4.5] versus 6 [4.6–7.4] days; $P<0.0001$), and those who received late treatment [estimated median 4 (3.5–4.5) versus 6 (4.8–7.2) days; $P=0.003$], respectively. For comorbidity and complication descriptions refer to Table 1. CI, confidence interval.

Independent factors associated with early hospital discharge

Significant variables identified in the univariate analyses ($P<0.1$) were entered into Cox proportional hazards models as covariates to determine independent factors associated with time to discharge. In these models, an aHR >1 signifies a higher chance of being discharged from hospital (that is, shorter LOS); whereas an aHR <1 signifies a lower chance of being discharged from hospital (that is, longer LOS). The results are shown in Table 2. In a final model, oseltamivir initiated within 2 days of symptoms was independently associated with earlier hospital discharge (aHR for discharge 1.54 [95% CI 1.23–1.92]; Figure 1); whereas older age ≥ 70 years, comorbidity and complications were associated with prolonged total LOS (aHR for discharge <1). Similar observations were made when acute-care LOS was analysed as the outcome of interest (see 'Additional file 2: factors associated with 'acute care' length of stay (LOS)', online).

To identify additional factors that might affect hospital LOS, a separate Cox proportional hazards model for data obtained in the viral shedding study was constructed. It showed that persistent viral detection by

Figure 1. Kaplan–Meier curve showing the effect of early oseltamivir treatment on time to discharge from hospital



RT-PCR (aHR for discharge 0.36 [95% CI 0.19–0.71]) and development of complications were associated with prolonged LOS, whereas influenza vaccination received within 6 months (aHR for discharge 2.14 [95% CI 1.18–3.85]) and oseltamivir initiated within 2 days of symptoms were associated with early discharge, adjusted for age and comorbidity (Table 3).

Discussion

Previous studies have shown that oseltamivir given within 48 h can ameliorate symptoms, shorten duration of illness, reduce complications and lower the rate of hospitalization of influenza patients (including ‘high-risk’ individuals) [1,13,14,22,26–28]. The clinical benefits appear to be greatest if treatment is initiated shortly after symptom onset [13,14,29,30]. However, most studies did not include hospitalized patients.

This analysis adds to existing knowledge and suggests that timely oseltamivir treatment may be associated with earlier discharge of hospitalized influenza patients. Overall, a 33% reduction of LOS is observed (or 1.5 times more likelihood of being discharged at any time point), which appears to be independent of age, comorbidity and complications, the other major determinants of LOS. There are several implications. Firstly, the findings suggest that the clinical benefits of oseltamivir therapy may extend to patients with severe influenza infections requiring hospitalization. As shown in our cohort, these patients are usually old, have multiple comorbid illnesses and frequently develop complications such as pneumonia and exacerbation of chronic obstructive airway diseases and often require prolonged in-patient care. Secondly, given the annual disease burden of influenza [1–3,5,6,19], the

Table 3. Factors associated with total length of stay (LOS) in 99 consecutive influenza patients recruited in the viral shedding study

Characteristics	Unadjusted median LOS (IQR), days*	Adjusted HR (95% CI) for hospital discharge†	P-value
Prolonged viral RNA detection‡			
Yes	18.0 (12.4–23.6)	0.36 (0.19–0.71)	0.003
No	6.0 (4.9–7.1)	1.00	
Complication			
Yes	8.0 (4.2–11.8)	0.31 (0.17–0.57)	<0.0001
No	5.0 (3.8–6.2)	1.00	
Oseltamivir within 2 days			
Yes	6.0 (4.6–7.4)	2.12 (1.30–3.47)	0.003
No	13.0 (7.3–18.7)	1.00	
Influenza vaccination§			
Yes	5.0 (3.6–6.4)	2.14 (1.18–3.85)	0.012
No	7.0 (6.0–8.0)	1.00	

*Unadjusted Kaplan–Meier estimates of hospital LOS are shown for all explanatory variables (median and IQR, days). †Multivariate Cox proportional hazards models: an adjusted hazard ratio (HR) >1 signifies a larger chance of being discharged from hospital (that is, shorter LOS); an adjusted HR <1 signifies a smaller chance of being discharged from hospital (that is, longer LOS). ‡‘Yes’ = positive RT-PCR result for influenza virus RNA detection in combined nasal and throat swabs collected >day 4 of illness (n=23; mean 5.4 ±1.5 days); ‘No’ = negative result for specimens collected in the same time interval (n=76; mean 5.5 ±1.6 days). §Influenza vaccination within 6 months prior to hospital admission (‘Yes’=23%). ¶For patient characteristics in the viral shedding study, see ‘Additional file 3: other patient characteristics in the viral shedding study’ online.

reduction in LOS with appropriate antiviral treatment may significantly benefit the healthcare system. To achieve this goal, prompt case recognition, efficient laboratory diagnosis and early therapeutic intervention should constitute integral parts of the management of severe/complicated influenza infections. Since the presentations of influenza could be diverse (thus easily underdiagnosed), implementation of specific diagnostic and management algorithm/guidelines in individual hospital may be helpful, especially during seasonal peaks [1,9,13,14,29,31,32]. Application of ‘rapid tests’ is useful, since it may curtail the misuse of both antibiotics and antiviral agents [1,18,23,32–34]. Encouraging ‘high risk’ individuals to present early, and improving the accessibility to antivirals, especially in less developed and poorly resourced areas, are also important [13].

Two additional factors affecting LOS are identified in the substudy. It was observed that prolonged viral shedding, as detected by RT-PCR (23% of hospitalized influenza patients; probably reflecting higher viral loads) is associated with prolonged LOS, whereas annual influenza vaccination appears to be associated with shortened LOS. These findings are consistent with the results from previous studies, which showed that

high influenza virus titres in nasal secretions correlated with severe symptoms [35] and reported clinical benefits of annual influenza vaccination among high-risk individuals (including reduced LOS) [1,7,36–39]. The effect of oseltamivir on viral shedding as shown may also have infection-control implications in the hospital setting, which warrants further study [27,31]. Collectively, this study shows that host factors, virus factors, antiviral treatment and immunization may all affect the clinical course of acute influenza infection.

This study is the first to examine factors affecting LOS in a large hospital cohort. The effect of age, comorbidity, complication on presentation and oseltamivir treatment on LOS are analysed in multivariate models. It appears that ‘timely’ oseltamivir treatment is independently associated with shorter LOS after adjusting for potential confounders. As suggested by existing data, we assumed in our analyses that oseltamivir initiated within 2 days produced optimal treatment efficacy [13,14,22]; thus these patients were compared with those who failed to receive ‘timely’ treatment as a whole [25]. We are not able to determine the effect of ‘late’ treatment from this retrospective study, as attending physicians might have prescribed oseltamivir late to patients whom they regarded as severely ill. Randomized controlled trials are needed to address this question. As the clinical benefit of influenza vaccination was only studied in a small patient subgroup with more prolonged hospitalization, further investigation is needed to confirm its overall impact on LOS [39]. Finally, as the great majority of our viral isolates were found to be influenza A (and of the H3 subtype) the effect of influenza subtypes on LOS cannot be examined. The H3N2 subtype has been responsible for the majority of influenza-related hospitalizations [1,4].

Further studies on hospitalized influenza patients are warranted. Prospective, controlled trials are needed to confirm the benefits of antivirals in treating serious/complicated influenza infections [13,14,40]. The efficacy of higher dose, extended duration or even delayed oseltamivir treatment in very ill patients [13,41], the impact of antiviral treatment on reducing nosocomial transmission of influenza [42,43], the effect of viral load, viral subtypes and immunization on disease severity [1,4,22,26,36–39,44] and ways to improve the efficiency of diagnosis and therapeutic intervention [1,9,13,14,29,31,45] are other important areas to study.

In conclusion, our analyses suggest that timely oseltamivir treatment is independently associated with shorter LOS in patients hospitalized for severe influenza. Efforts to ensure early diagnosis and therapeutic intervention are warranted. The benefit of annual vaccination in shortening illness duration deserves further evaluation.

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Disclosures

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Authors' contributions

NL had the idea for the study and has overseen the planning, execution, analysis and preparation of the manuscript. He has full access to all data in the study and had final responsibility for the integrity and the accuracy of the data in the manuscript, and the decision to submit for publication. PKSC, JWT and RL were responsible for the virological and microbiological investigations. KWC, GL and BW participated in the planning, execution and analysis. CSC, DSCH and JJYS supervised the clinical assessment of patients after admission and contributed to the preparation of the manuscript. NL wrote the first draft of the paper and all authors have contributed to the final version.

Additional files

The following additional files: ‘Additional file 1: seasonal influenza activities in Hong Kong’, ‘Additional file 2: factors associated with ‘acute care’ length of stay (LOS)’ and ‘Additional file 3: other patient characteristics in the viral shedding study’, can be accessed via the Volume 12 Issue 4 contents page for Antiviral Therapy, which can be found at www.intmedpress.com (by clicking on ‘Antiviral Therapy’ then ‘Journal PDFs’).

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