Prognostic accuracy of qSOFA score for in-hospital mortality among influenza patients in the emergency department

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Abstract

Background

The annual seasonal influenza pandemic is an important public health issue around the world. Early prediction of patients with potentially worse outcome is important in the emergency department (ED). However, a simple and accurate predictor is yet to be developed. In this study, we aimed to investigate the effectiveness of the quick Sequential Organ Failure Assessment (qSOFA) score as a prognostic predictor of patients with influenza in the ED.

Methods

This is a single-center, retrospective cohort study. All the data were retrieved from a hospital-based research database. Adult patients (age ≥ 18 at admission) with a positive influenza rapid screening test or a positive influenza virus polymerase chain reaction (PCR) from 2010 to 2016 were enrolled for data analysis. qSOFA score and Systemic Inflammatory Response Syndrome (SIRS) in the ED were both collected. The primary outcome was the utility of each score in predicting in-hospital mortality.

Results

In the study period, 3,561 patients met the inclusion criteria. The overall in-hospital mortality was 2.7% (95 patients). When the qSOFA score was 0, 1, 2, and 3, the percentage of in-hospital mortality was 0.6%, 7.2%, 15.9%, and 25%, respectively. Accordingly, the odds ratios were 7.72, 11.92, and 22.46, respectively. The sensitivity and specificity when qSOFA score ≥ 2 was 24% and 96.2%, respectively. The area under depicted receiver operating characteristic curve (AUC) was 0.864, which is significantly higher than with SIRS criteria, where the AUC was 0.786 ($p < 0.01$).

Conclusions

The qSOFA score is a useful prognostic tool for influenza and can be applied in the ED. However, it might not be a good screening triage tool because of poor sensitivity to detect high-risk patients. The SIRS score had poor performance in influenza to predict outcomes. Further studies should be performed to define its role in influenza.

Background

Influenza has long been a threat to public health throughout the world.[1] Patients' outcomes range from simple upper respiratory infection (URI) to acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome. Influenza progress rapidly and lead to morbidity and mortality within days.[2] Further, it increases the mortality of vulnerable patient groups.[3] A modeling study estimated global influenza-associated respiratory mortality in 33 countries between 1999 and 2015 and showed the estimated mean annual influenza-associated respiratory excess mortality rate ranged from 0.1 to 6.4 per 100,000 individuals in those <65 years of age, 2.9 to 44.0 per 100,000 in those between 65 and 74 years, and 17.9 to 223.5 per 100,000 in those ≥75 years of age.[4] There was a pandemic outbreak of influenza in Taiwan from late 2015 to early 2016. The outbreak resulted in more than 2000 severe influenza cases (85.5 per million population) and over 160 deaths (6.9 per million) nationwide during this period.[5]

Early recognition of patients with potentially worse outcomes is important in the emergency department (ED).[6] The first clinical prediction rule of influenza infection including 9 parameters was published in 2004.[7] In 2011, Oh, et al. reported four risk factors associated with disease severity: altered mental status, hypoxia, bilateral lung infiltration, and old age.[8] The geriatric influenza death (GID) score and shock index were recently reported to be the prediction rule for influenza patients.[9] However, not all the prediction rules described provided satisfactory diagnostic strength. Also, some laboratory tests in these studies were not routinely checked in the ED, so they may not be feasible in all EDs. A simple and accurate prediction rule is yet to be developed.

Influenza can result in severe inflammation and end organ damage. The deterioration of pulmonary function can be extremely rapid and detrimental.[10] In 1992, the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) Consensus Conference committee introduced the Systemic Inflammatory Response Syndrome (SIRS) criteria to define sepsis and predict in-hospital mortality. It is a scoring tool combined with vital signs and white blood cell (WBC) data.[6] In 2016, sepsis was redefined as “life-threatening organ dysfunction caused by a dysregulated host response to infection” by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis–3).[11] Instead of SIRS criteria, Sepsis–3 developed the quick Sequential (Sepsis-related) Organ Failure Assessment (qSOFA) score, a simplified version of the SOFA score, as a new sepsis screening tool outside the intensive care unit (ICU).[12] The items included in the qSOFA are readily available in the ED after triage. The performance of the qSOFA score in predicting adverse outcomes has been validated among patients in various clinical settings.[13–19] Most of the results suggested that the qSOFA score is specific but lacks sensitivity in predicting either mortality or ICU admission.[20] However, in these studies, no article had described the relationship between qSOFA score and influenza specifically.

The aim of this study is to evaluate the diagnostic accuracy of SIRS criteria and qSOFA score in predicting in-hospital mortality in patients with influenza infection. An accurate prediction tool will aid in early risk stratification and rapid treatment of influenza patients in the ED.

Methods

Study design and setting

This is a single-center, retrospective cohort study of patients who visited the ED of Linkou Chang Gung Memorial Hospital from 2010 to 2016. Linkou Chang Gung Memorial Hospital is a tertiary medical center in Taiwan with 3406 beds and approximately 17,000 monthly ED visits in 2017. All the patients’ data were retrieved from the Chang Gung Research Database (CGRD). CGRD is one of the largest multi-institutional electronic medical record systems for real-world epidemiological studies in Taiwan.[21] This large database contains all necessary records from every visiting patient, including vital signs, blood tests, image reports, diagnosis, treatments, and daily medical records of doctors and nursing staff. All data are de-identified and encrypted to protect participants’ privacy.

Patients with flu-like syndrome in ED were evaluated by at least an emergency physician and managed according to the guidelines approved by our ED committee. Some patients with only minor symptoms were discharged without laboratory tests. The study was approved by the Institute Review Board, Chung Gang Memorial Hospital.

Selection of Participants

Patients aged 18 years or older visiting the ED were enrolled in the analysis if they had a diagnosis of influenza, confirmed by either positive rapid influenza diagnostic test (RIDT) or influenza reverse transcription-polymerase chain reaction (RT-PCR) test. If patients visited the ED more than once in 30 days with the same diagnosis, they were defined as having the same influenza episode. Data from their last visit data would be enrolled.

Measurements

Vital signs and Glasgow coma scale (GCS) at triage were recorded. The qSOFA score ranges from 0 to 3, comprising one point for each of the following: respiratory rate ≥ 22 breaths per minute, altered mentation, and systolic blood pressure ≤ 100 mmHg. We defined altered mentation as GCS at triage < 15 or decreased coma scale compared to baseline level. A positive qSOFA score was defined as 2 or above. Additionally, we collected SIRS criteria including body temperature > 38 °C or < 36.0 °C, heart rate > 90 beats per min, respiratory rate ≥ 20 breaths per min, WBC count > 12,000 cells/mm^3 or <4000 cells/mm^3 or > 10% immature (band) form. The SIRS score ranges from 0 to 4, and a positive SIRS score was defined as 2 or more points.

All vital signs and GCS presenting at triage and the initial laboratory tests in the ED were extracted from the electronic medical records and used to calculate qSOFA and SIRS scores by trained hospital personnel who was blinded to the objective of the study. For patients without blood tests, we defined their WBC score of SIRS as 0, because these patients were relatively few and were discharged after physicians' assessment. Associated data were obtained, including sex, age, and comorbidities. We used the Charlson Comorbidity Index (CCI) [22] to define all patients' comorbid condition. The patients' outcomes including ICU admission and in-hospital mortality were collected.

Outcomes

The primary outcome of this study was in-hospital mortality, and the secondary outcome was the percentage of ICU admission.

Analysis

Statistical analysis was performed on data from CGRD. Means and standard deviations were expressed for continuous variables, whereas numbers and percentages were expressed for categorical variables. We also calculated the percentages of outcomes by each level of SIRS and qSOFA. Logistic regression models were built to evaluate the predictive ability of these two scoring tools for ICU admission and in-hospital mortality. Akaike's Information Criteria (AIC) and Receiver Operating Characteristic (ROC) curves with c-statistics were used to compare their predictive performance. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and Stata 14 (StataCorp, College Station, TX, USA). Significance level α was set at 0.05.

Results

There were 1,183,226 ED visits to Chung Gang Memorial Hospital, Linkou, from January 2010 to December 2016. The flow diagram of this study is shown as Figure 1. A total of 27,550 patients underwent either RIDT or influenza PCR. Among all ED visits, 9,693 patients were positive for influenza A or B, of whom 3,561 were adults and included in our analysis. There were four major influenza pandemics between 2010 to 2016 in Taiwan (Figure 2). Patient numbers increased accordingly in our database. The greatest pandemic occurred between late 2015 and early 2016, with more than 350 adult influenza patient visits per month.

Baseline patient characteristics are shown in Table 1. The mean age was 48 years old, and 1,716 cases (48.9%) were male. The mean CCI was 3.94 ± 4.19. Of the cases, 1,527 (42.9%) were admitted to the hospital (Table 2) and 286 (8.0%) were admitted to the ICU. Overall in-hospital mortality was 2.7%. Only 31 patients (0.9%) were re-admitted within 72 hours after direct discharge from the ED. The primary outcome, in-hospital mortality rate, was 0.6%, 7.2%, 15.9%, and 25% when the qSOFA score was 0, 1, 2, and 3, respectively. Patients with qSOFA score 0, 1, 2, and 3 had ICU admission rate of 2.8%, 21%, 34.8%, and 58.3%, respectively (Figure 3A). We also compared the performance of SIRS criteria in predicting in-hospital mortality, which was not associated with SIRS criteria according to our results (Figure 3B).

In-hospital mortality increased significantly with male sex, age, higher CCI, and qSOFA score (Table 3). Crude odds ratio was 12.1 (95% CI 6.9–21.0), 29.6 (15.3–57.3), and 52.1 (13–209.3) when qSOFA score was 1, 2, and 3, respectively, showing significant difference. The adjusted odds ratio by c-statistics was 7.7 (95% CI 4.4–13.7), 11.9 (5.7–24.8), and 22.5 (4.3–116.3) when qSOFA score was 1, 2, and 3, respectively.

The area under the receiver operating characteristic curve (AUC) of the qSOFA model for predicting in-hospital mortality was 0.861, which was significantly higher than that of the SIRS model, 0.79 (Figure 4). When qSOFA score ≥ 2, the cutpoint defined by Sepsis–3, the accurate prediction of ICU admission and in-hospital mortality was high: 94.5% and 94.7%, respectively. However, sensitivity was low: 26.3% and 24%, respectively. If the cutpoint was qSOFA ≥1, we could get the best Youden's Index (0.587 for ICU admission, 0.590 for in-hospital mortality) as well as better sensitivity (82.1% and 82.7%, respectively), which could help emergency physicians to rule out severe complicated influenza.

For the SIRS model, when SIRS score ≥ 2, the cutpoint defined by Sepsis–2, accuracy was just 25.9% for ICU admission and 25.6% for in-hospital mortality (Table 4). If we hope to get the best Youden's Index (0.195 for ICU admission, 0.207 for in-hospital mortality), the cutpoint should be SIRS ≥ 3. However, the sensitivity, specificity, and likelihood ratio of SIRS ≥ 3 were still poorer than those of qSOFA ≥1. In short, qSOFA score is a better tool to predict influenza outcomes.

Discussion

An influenza pandemic develops almost every year worldwide. Patient visits to the ED increase dramatically during the pandemic seasons. Most of influenza infections are self-limited with symptomatic treatment, so antiviral therapy might not be necessary in most patients. However, during the outbreak in 2016, we observed that the disease progression in some patients was extremely fast. Patients might progress to acute hypoxic respiratory failure within 24 hours even if the initial chest X-ray was normal, and 8% of patients with positive influenza diagnostic tests were admitted to the ICU. A simple early prognostic indicator might be clinically

important to an emergency physician. We found that the qSOFA score was a better prognostic indicator compared with SIRS criteria.

Previous studies have reported using different prognostic scales of pneumonia to evaluate influenza.[23–26] Myles, et al.[23] compared the performance of Community Assessment Tools (CATs), CURB–65 score, and the Pandemic Medical Early Warning Score (PMEWS) in influenza. They found CATs were a useful triage tool to predict severe outcomes. However, this study was a case-control study and was limited to H1N1, which might cause some bias. There was a small sample sized retrospective study performed by Estella.[24] She used CURB–65 and Pneumonia Severity Index (PSI) to evaluate H1N1 patients in the ED, and concluded that both tools might underestimate the risk and were therefore useless in the ED.

Others have tried to use serum biomarkers to predict outcome in patients with influenza. Zimmerman, et al. reported that C-reactive protein serum levels were an early predictor of outcome in the ED.[27] Another article concluded that lactate dehydrogenase (LDH) serum level > 600 IU/L was associated with mortality in influenza pneumonia.[28] However, both studies were limited to H1N1 influenza. Also, serum biomarkers were not good enough to be early prognostic predictors because we would not perform blood tests for every influenza patient in a busy emergency department, especially during pandemic period.

Patel, et al. developed a predictive classification tree model to estimate human highly pathogenic avian influenza (HPAI) A/H5N1 mortality based on the significant predictors of influenza mortality including age, delay from symptom onset to hospitalization, country, and per capita government expenditure on health. However, the quality of data was inconsistent. [29] In total, those authors enrolled 617 H5N1 cases, taken from articles published in any language. There were wide variabilities in their database such as surveillance and clinical care, vaccination policy, lack of data on antiviral treatment, and time from illness onset to start of antiviral treatment. Also, that study was limited to HPAI A/H5N1, rather than all influenza.

SIRS criteria have been used to predict mortality among geriatric patients with influenza in the ED. Tai, et al. conducted a retrospective study and enrolled 409 geriatric ED patients (age ≥ 65 years) who had a positive rapid influenza pharyngeal or throat swab test.[30] They found SIRS criteria ≥ 3 to be an acceptable mortality predictor in this group of patients, with odds ratio 3.37 (95% CI 1.05–10.73), sensitivity 60% (95% CI 46–80%), and specificity 70% (95% CI 66–75%). In our study, we included all adult influenza patients, not limited to elderly patients, and also included patients with positive PCR, to reduce bias. Our data showed the qSOFA score to have much better performance than SIRS criteria as a prognostic predictor of influenzas in the ED.

Since qSOFA was developed, many people have evaluated its clinical value for sepsis. Some articles supported qSOFA as a good prognostic predictor.[14, 31] But other studies found that qSOFA may not be a good enough screening tool in the ED, because of its poor sensitivity.[32–34] Recently, some studies found that qSOFA could be a useful prognosis predictor of pneumonia in the ED.[35–37] However, a Spanish study reached the opposite conclusion, and reported that qSOFA had a lower prognostic performance than CURB–65 and PSI.[18] For influenza, qSOFA had not been well validated in the ED. In our study, we tried to use qSOFA to predict the prognosis of influenza patients and found that qSOFA achieved a good prognostic accuracy.

In our data, the CCI, admission rate, and mortality rate were relatively higher than in previous studies. This means that our cohort had more serious illness, and was therefore much closely representative of the real ED. We believe our results are reliable and can be well applied to clinical practices, especially in the ED.

There were limitations in this study. This is a single-center study, which has inherent limitations. In addition, we might not order an influenza test for everyone presenting to the ED with fever or URI symptoms, especially in the non-flu season. Also, all tests for influenza have false negatives. These factors might cause some bias. Further studies to confirm our findings and prospectively validate the use of qSOFA in this patient population are required.

The definition of “altered mentation” of qSOFA score had two versions in the literature. One was GCS score ≤ 13, which was in the original study of Sepsis–3 [12]. The other was GCS <15, in the definitions of sepsis and septic shock set by the Third International Consensus [11]. In our study, we used GCS < 15. This might cause patients with unclear baseline mental status due to underlying disease to have an overestimated qSOFA score.

Conclusions

The qSOFA score is a useful prognostic predictor for influenza. It is readily available in the ED after triage. Patients with a qSOFA score ≥ 1 might be admitted to the hospital; patients with and initial qSOFA score of 3 need intensive monitoring and aggressive treatment. ICU admission might be indicated. We recommend using qSOFA score in early risk stratification of influenza patients and advance planning for hospital/ICU admission to improve patient outcomes.

Abbreviations

ALI: acute lung injury

ARDS: acute respiratory distress syndrome

ACCP: American College of Chest Physicians

AIC: Akaike’s Information Criteria

AUC: area under the receiver operating characteristic curve

CGRD: Chang Gung Research Database

CCI: Charlson Comorbidity Index

CI: Confidence interval

CATs: Community Assessment Tools

ED: Emergency department

GID: Geriatric influenza death

GCS: Glasgow coma scale

HPAI: highly pathogenic avian influenza

ICU: intensive care unit

LDH: lactate dehydrogenase

PMEWS: Pandemic Medical Early Warning Score

PSI: Pneumonia Severity Index

qSOFA: quick Sequential (Sepsis-related) Organ Failure Assessment

RIDT: rapid influenza diagnostic test

PT-CPR: reverse transcription-polymerase chain reaction

ROC: Receiver Operating Characteristic

SCCM: Society of Critical Care Medicine

SIRS: Systemic Inflammatory Response Syndrome

URI: upper respiratory infection

WBC: White blood cell

Declarations

Ethics approval and consent to participate:

The study was approved by the Institute Review Board, Chung Gang Memorial Hospital.

Consent for publication:

Not applicable. All the patients' data were retrieved from the Chang Gung Research Database (CGRD). CGRD is one of the largest multi-institutional electronic medical record systems for real-world epidemiological studies in Taiwan. All data are de-identified and encrypted to protect participants' privacy.

Availability of data and materials:

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: No authors have any potential conflicts of interest

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Author contributions:

Study concept and design: S.E.C., C.H.L. ; Acquisition of the data: S.E.C., C.H.L. ; Analysis and interpretation of the data: S.E.C., C.H.L. ; Drafting of the manuscript: S.E.C. ; Critical revision of the manuscript for important intellectual content: C.H.L., C.J.S., T.H.S., C.H.C. ; Statistical expertise: H.J.T. All authors read and approved the final version of this manuscript.

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Tables

Table 1. Baseline characteristics of influenza patients

	Mean ± SD / N (%)
Age	48.08 ± 19.51
Sex=male	1716 (48.19)
Vital signs	
Body temperature, °C	38.11 ± 1.17
Heart rate, beats/min	107.64 ± 18.83
Respiratory rate, breaths/min	19.80 ± 3.35
Systolic blood pressure, mmHg	142.03 ± 28.47
Diastolic blood pressure, mmHg	84.06 ± 22.84
Glasgow Coma Scale score	14.65 ± 1.55
White blood cell count (1,000/mm^3)	8.14 ± 4.31
Charlson Comorbidity Index (CCI)	3.94 ± 4.19
Comorbidities	
Myocardial infarction	169 (4.75)
Congestive heart failure	438 (12.3)
Peripheral vascular disease	140 (3.93)
Cerebrovascular disease	491 (13.79)
Dementia	137 (3.85)
Chronic pulmonary disease	960 (26.96)
Connective tissue disease-rheumatic disease	157 (4.41)
Peptic ulcer disease	850 (23.87)
Mild liver disease	706 (19.83)
Diabetes mellitus, without complications	767 (21.54)
Diabetes, with complications	300 (8.42)
Paraplegia and hemiplegia	77 (2.16)
Renal disease	644 (18.08)
Cancer	469 (13.17)
Moderate or severe liver disease	83 (2.33)
Metastatic carcinoma	124 (3.48)
AIDS/HIV	14 (0.39)

SD: standard deviation

Table 2. The outcome distributions

	ED re-admission within 72 hours	Hospitalization	ICU admission	In-hospital mortality
All	31 (0.87)	1527 (42.88)	286 (8.03)	95 (2.67)
By SIRS				
0	0 (0.00)	115 (64.61)	17 (9.55)	4 (2.25)
1	5 (0.73)	331 (48.04)	53 (7.69)	16 (2.32)
2	13 (0.91)	562 (39.52)	87 (6.12)	23 (1.62)
3	8 (0.73)	413 (37.51)	91 (8.27)	37 (3.36)
4	5 (2.92)	106 (61.99)	38 (22.22)	15 (8.77)
By qSOFA				
0	19 (0.71)	915 (34.23)	76 (2.84)	17 (0.64)
1	12 (1.63)	492 (66.67)	155 (21.00)	53 (7.18)
2	0 (0.00)	111 (80.43)	48 (34.78)	22 (15.94)
3	0 (0.00)	9 (75.00)	7 (58.33)	3 (25.00)

ED: Emergency department; ICU: intensive care unit

Table 3. Logistic regression models for predicting in-hospital mortality

	Univariate Analysis			Model (SIRS)			Model (qSOFA)		
	OR	p	95% CI	OR	p	95% CI	OR	p	95% CI
Sex (M vs F)	2.93	<0.001	(1.86–4.62)	2.47	<0.001	(1.53–3.98)	2.29	0.001	(1.41–3.72)
Age	1.04	<0.001	(1.03–1.05)	1.03	<0.001	(1.02–1.05)	1.02	0.01	(1.01–1.04)
CCI	1.13	<0.001	(1.09–1.18)	0.96	0.262	(0.90–1.03)	0.95	0.167	(0.89–1.02)
SIRS	1.52	<0.001	(1.21–1.91)						
SIRS 0	1.00			1.00					
1	1.03	0.953	(0.34–3.13)	1.26	0.689	(0.40–3.97)			
2	0.72	0.54	(0.24–2.09)	0.94	0.92	(0.31–2.87)			
3	1.51	0.437	(0.53–4.30)	2.52	0.095	(0.85–7.43)			
4	4.18	0.013	(1.36–12.87)	4.81	0.009	(1.49–15.49)			
qSOFA	4.72	<0.001	(3.67–6.07)						
qSOFA 0	1.00						1		
1	12.09	<0.001	(6.96–21.01)				7.72	<0.001	(4.35–13.70)
2	29.63	<0.001	(15.32–57.31)				11.92	<0.001	(5.74–24.77)
3	52.08	<0.001	(12.96–209.28)				22.46	<0.001	(4.33–116.61)
Hospital stay	1.04	<0.001	(1.03–1.05)	1.06	<0.001	(1.05–1.07)	1.05	<0.001	(1.04–1.06)
				AIC = 717.991			AIC = 664.974		

OR, odds ratio; CI, confidence interval; AIC: Akaike information criterion

Table 4. The predictive performance of SIRS and qSOFA model in each cut-off point

	Cut-off	ICU admission					In-hospital mortality				
		Sen(%)	Sp(%)	Acc(%)	LR+	LR-	Sen(%)	Sp(%)	Acc(%)	LR+	LR-
SIRS	(≥1)	95.8	5	7.4	1.01	0.84	96	5	6.9	0.99	1.21
	(≥2)	79	24.4	25.9	1.04	0.86	78.7	24.4	25.6	1.00	1.01
	(≥3)	54.7	64.8	64.5	1.56	0.7	56	64.7	64.5	1.29	0.84
	(≥4)	15.8	95.5	93.4	3.51	0.88	16	95.4	93.8	3.27	0.90
qSOFA	(≥1)	82.1	76.6	76.8	3.51	0.23	82.7	76.3	76.4	3.55	0.34
	(≥2)	26.3	96.4	94.5	7.3	0.76	24	96.2	94.7	6.63	0.83
	(≥3)	3.2	99.7	97.2	12.16	0.97	1.3	99.7	97.6	16.03	0.98

Sen, sensitivity; Sp, specificity; Acc, accuracy; LR+, positive likelihood ratio; LR-, negative likelihood ratio

Figures

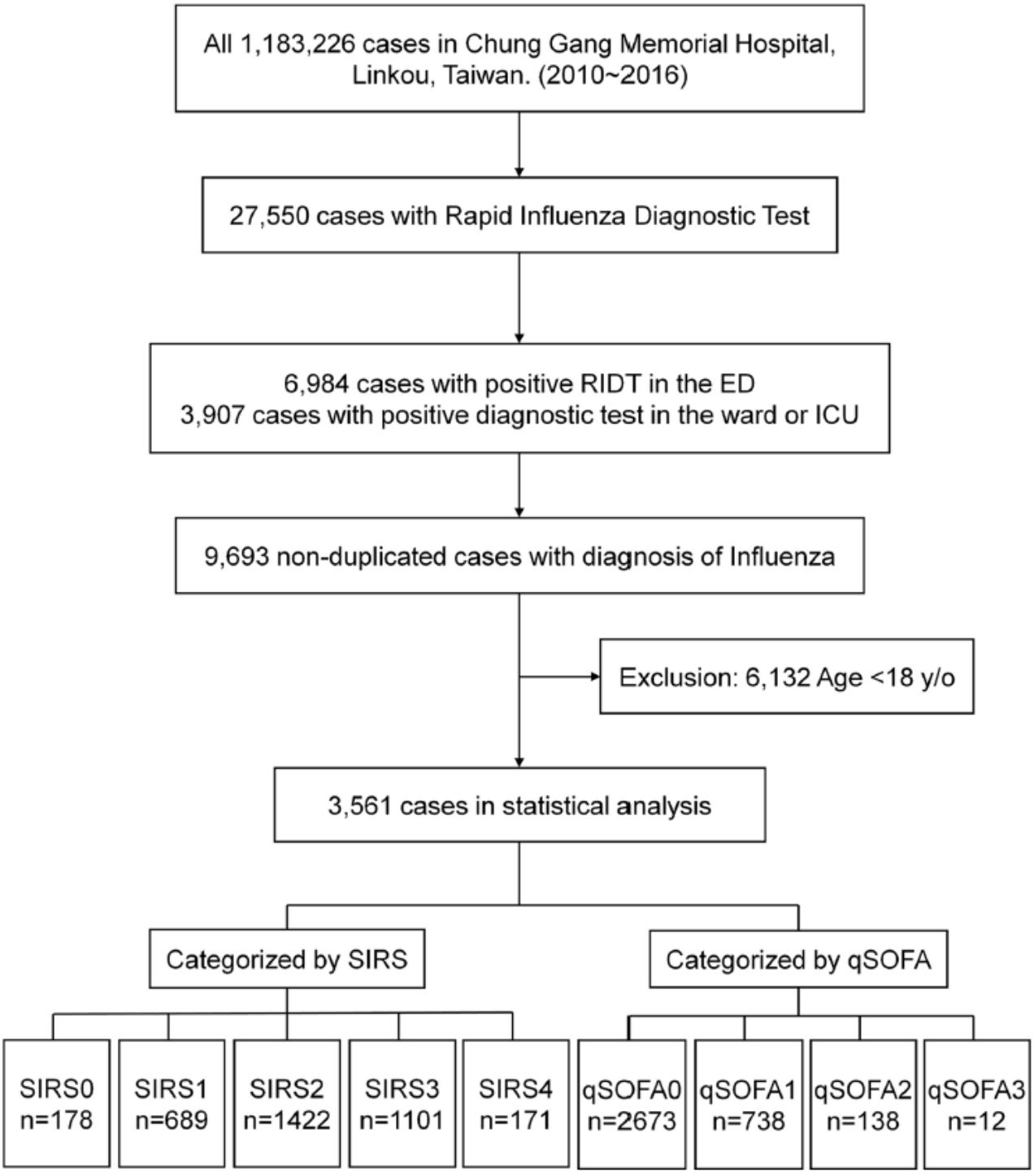


Figure 1

The flow chart of selecting samples for analysis

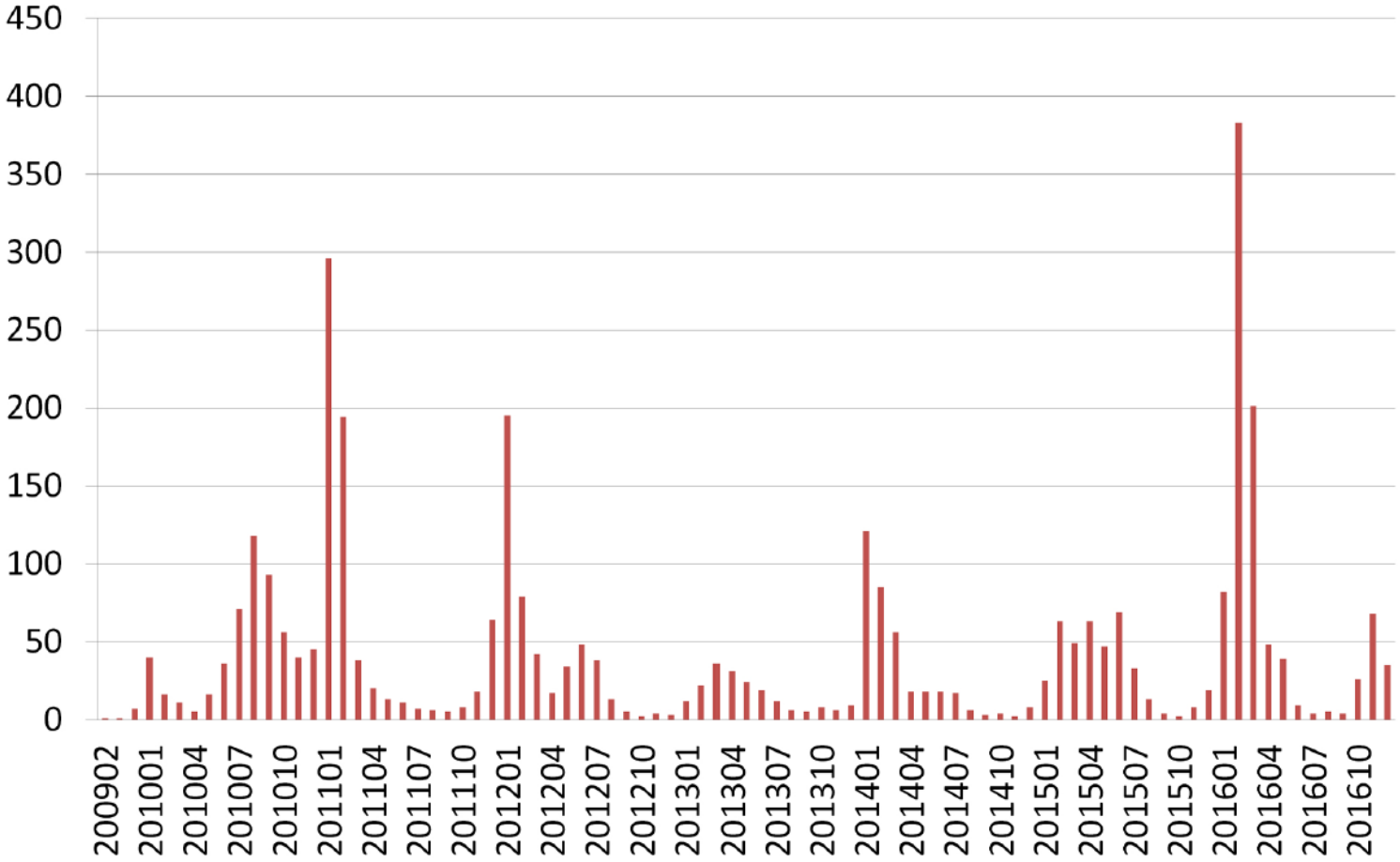
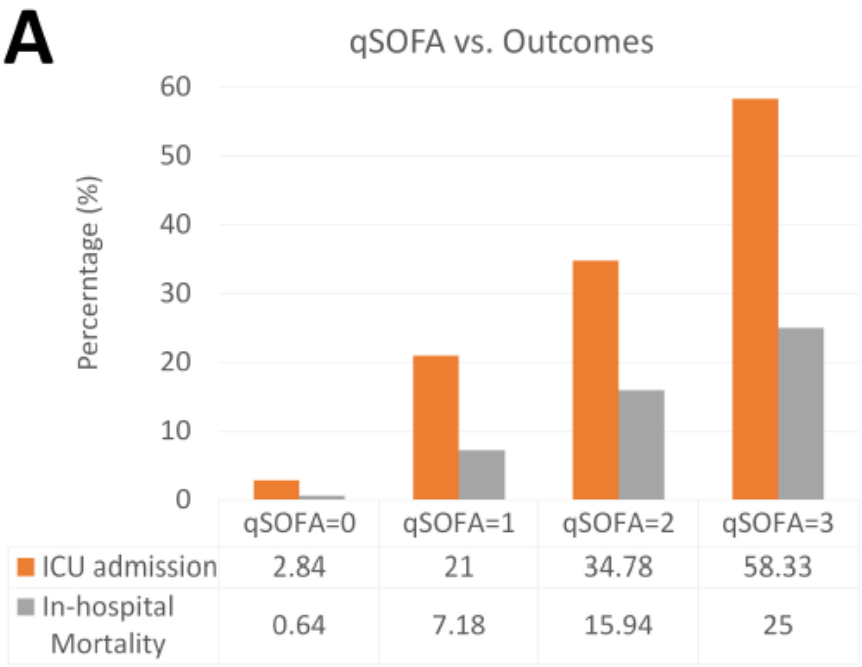


Figure 2

Number of patient visits with positive influenza diagnostic test by months



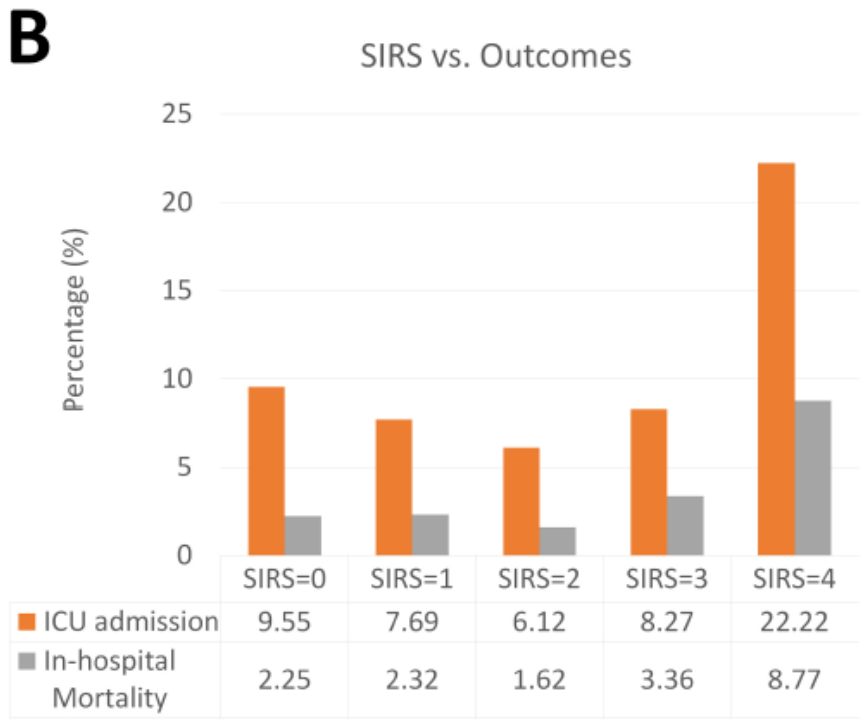


Figure 3

qSOFA and SIRS models by outcomes

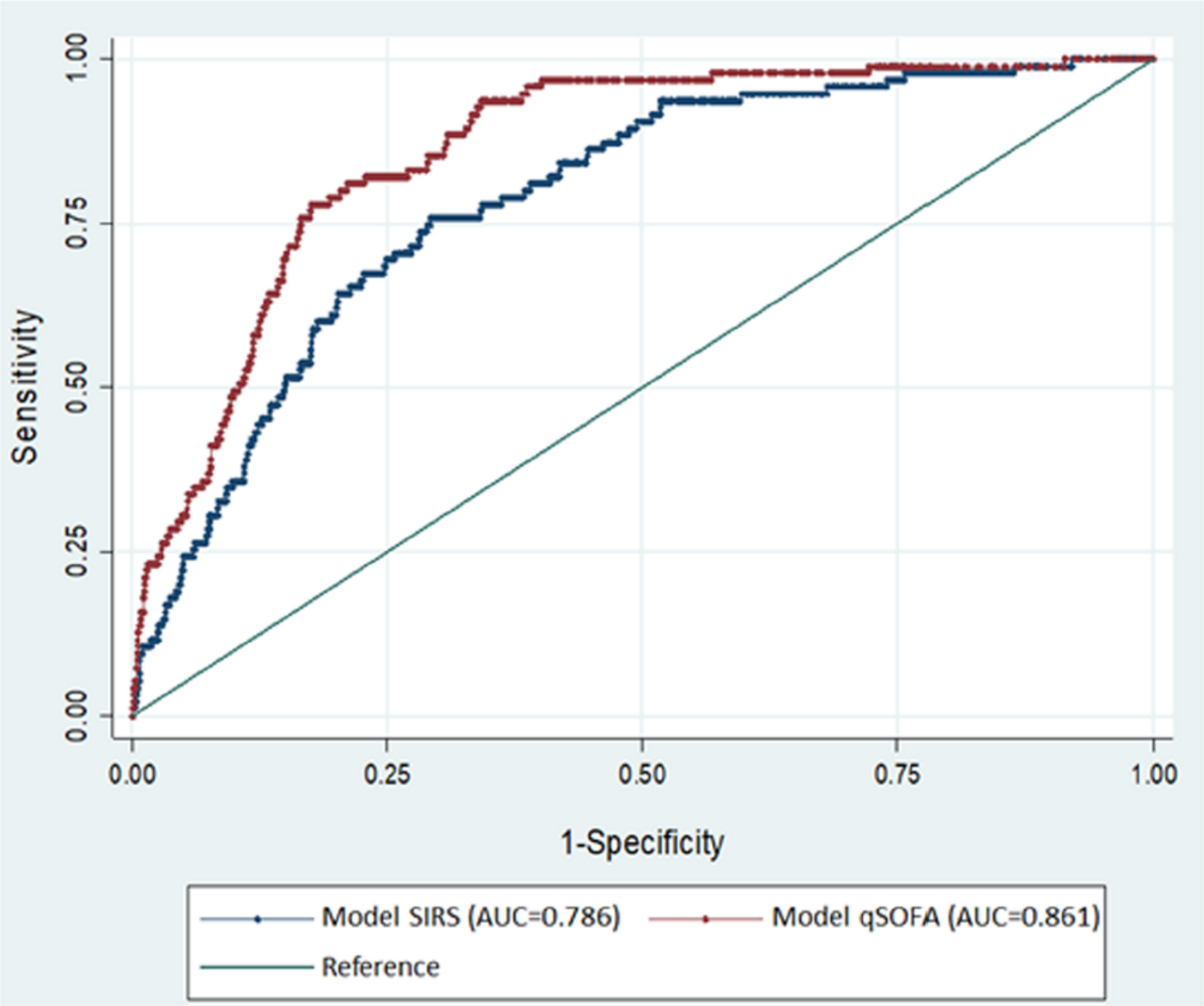


Figure 4

Receiver operating characteristic (ROC) curves of SIRS model and qSOFA model for predicting in-hospital mortality