OPEN

Association Between Cardiac Injury and Mortality in Hospitalized Patients Infected With Avian Influenza A (H7N9) Virus*

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Objectives: To evaluate the prevalence of cardiac injury and its association with mortality in hospitalized patients infected with avian influenza A (H7N9) virus.

Design: Retrospective cohort study.

Setting: A total of 133 hospitals in 17 provinces, autonomous regions, and municipalities of mainland China that admitted influenza A (H7N9) virus–infected patients between January 22, 2015, and June 16, 2017.

Patients: A total of 321 patients with influenza A (H7N9) virus infection were included in the final analysis.

Interventions: None.

Measurements and Main Results: Demographics and clinical characteristics were collected from medical records. Cardiac injury was defined according to cardiac biomarkers, electrocardiography, or echocardiography. Among the 321 patients, 203 (63.2%) showed evidence of cardiac injury. Compared with the uninjured group, the cardiac injury group had lower Pao_2/Fio_2 (median, 102.0 vs 148.4 mm Hg; $p < 0.001$), higher Acute Physiology and Chronic Health Evaluation II score (median, 17.0 vs 11.0; $p < 0.001$), longer stay in the ICU (10.0 vs 9.0 d; $p = 0.029$), and higher proportion of in-hospital death (64.0% vs 20.3%; $p < 0.001$). The proportion of virus clearance until discharge or death was lower in the cardiac injury group than in the uninjured group (58.6% vs 86.4%; $p < 0.001$). Multivariable-adjusted Cox proportional hazards regression analysis showed that cardiac injury was associated with higher mortality (hazards ratio, 2.06; 95% CI, 1.31–3.24) during hospitalization.

Conclusions: Cardiac injury is a frequent condition among hospitalized patients infected with influenza A (H7N9) virus, and it is associated with higher risk of mortality. (*Crit Care Med* 2020; 48:451–458)

Key Words: avian influenza A (H7N9); cardiac injury; mortality

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Avian influenza A (H7N9) virus has caused five major waves of human infection in mainland China since March 2013, and the mortality was greater than 40% in three waves (1). A recent case report showed one death after H7N9 virus infection in late March 2019, and potential reemergence of the highly pathogenic zoonotic viral strain may cause public health concern (2). Even though we know that infection with H7N9 virus can cause acute respiratory distress syndrome (ARDS), pneumonia, acute kidney injury (AKI), shock, and rhabdomyolysis (3), we still know little about cardiac injury after H7N9 viral infection.

Many studies reported that influenza virus infection was associated with cardiac injury (4–11). A recent study found that at least 70.8% of critically ill patients with H7N9 viral infection

had cardiac injury (12). Cardiac injuries, such as an ejection fraction (EF) lower than 50% and elevated troponin I (TNI), were associated with higher mortality during the 2009 pandemic of influenza A (H1N1) (9). Mortality caused by cardiac injury increases significantly during influenza epidemics (13, 14), and cardiac injuries are more common in fatal cases of influenza (15). However, the relationship between cardiac injury and risk of mortality among people infected with influenza A (H7N9) virus has not been clearly elucidated.

These findings highlight the need to understand more about the link between H7N9 viral infection and cardiac injury and whether cardiac injury in such patients is associated with mortality. The present multicenter study collected data from several clinical centers in mainland China to examine the potential association between cardiac injury and mortality among patients with laboratory-confirmed avian influenza A (H7N9) viral infection.

METHODS

Study Participants

The Chinese Surveillance System for Pneumonia was used to retrospectively collect data of inpatients with laboratory-confirmed avian influenza from hospitals throughout China. Database for data collection of H7N9 virus–infected patients has been established and described previously (16). In brief, based on the database, copies of original medical records of 338 patients from 17 provinces, autonomous regions, and municipalities of mainland China between January 22, 2015, and June 16, 2017, were available. For each hospital, the collaborators contributed all the patients with H7N9 viral infection from their hospital. H7N9 viral infection was confirmed by real-time reverse transcriptase-polymerase chain reaction, viral isolation, or serologic testing (17). Cardiac testing was ordered by the treating physicians. If there was more than one test for a single patient, all the results were captured. Patients were followed up from admission to death during hospitalization or hospital discharge. Loss to follow-up was defined as the survival status that cannot be ascertained.

This study was approved by the National Health Commission of China and the institutional review boards at China-Japan Friendship Hospital (Beijing, China). As a national public health surveillance study, written informed consent was exempted.

Data Collection

Copies of original patient medical records were sent from the participating hospitals to the central data collection center in Beijing (16). Clinical data were reviewed by trained physicians of pulmonary and critical care medicine to determine the accuracy of diagnoses. Demographic characteristics (age and gender), clinical characteristics (comorbidities, laboratory findings, severity of illness scores, treatments, complications, and outcomes), and results of cardiac examinations (cardiac biomarkers, electrocardiography, and echocardiography) for participants during hospitalization were collected and independently entered into the computer database by two analysts. Results of cardiac biomarkers included values of TNI and creatinine kinase-myocardial band (CK-MB). Results of electrocardiography included heart rate, heart rhythm, and waveform change of P, QRS, and ST-T. Results of echocardiography included value of EF, ventricular wall motion assessment, pericardial effusion, and mean pulmonary artery pressure (PAPm).

The number of patients for each type of cardiac examinations was counted and the time of first test for each examination was recorded. As the different normal range of testing equipment in different hospitals, the ratio of the detected value to the upper limit of the normal range was used as a unified evaluation index. For any discrepancies between the two datasets, the original medical records were checked to make sure the data accuracy.

All the clinical data were collected till discharge or death. Data of cardiac test collected within 28 days after influenza illness onset were used to evaluate cardiac injury (11, 18), which was assessed on the basis of cardiac biomarkers (TNI and CK-MB), electrocardiography, and echocardiography.

Cardiac injury was defined as one or more of the following (1): blood levels of cardiac biomarkers (TNI or CK-MB) above the 99th percentile upper reference limit (2, 19), new abnormalities in electrocardiography, including supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, ventricular fibrillation, bundle branch block, ST-segment elevation/depression, T-wave flattening/inversion, and QT interval prolongation (3, 10, 12, 15, 20), new abnormalities in echocardiography, including decreased EF value (EF < 50%) or a worsening of the underlying state (patients with basal state of EF <50%), regional/global ventricular wall motion abnormalities, the presence of pericardial effusion, and pulmonary arterial hypertension (PAH) (9, 10, 12, 15, 20). PAPm was calculated by adding estimated right atrial pressure to mean tricuspid regurgitation pressure, echocardiographic estimation of PAPm with a cutoff value of greater than or equal to 25 mm Hg at rest with regard to the diagnosis of PAH (21–23). Clinical manifestations, cardiac evaluation, hemodynamic variables, documents of physician diagnoses, and related guidelines or standards were used to identify heart failure, myocarditis, sudden cardiac arrest, cardiogenic shock, and acute myocardial infarction.

Moderate-to-severe ARDS was diagnosed according to the Berlin definition (24): Pa_{O_2}/F_{IO_2} ratio of less than or equal to 200 mm Hg and a positive end-expiratory pressure of greater than or equal to 5 cm H_2O. AKI was defined according to Kidney Disease Improving Global Guidelines (KDIGO) clinical practice guidelines: an increase in serum creatinine values greater than or equal to 0.3 mg/dL (26.5 μmol/L) within 48 hours, serum creatinine values greater than or equal to 1.5 times the baseline within the previous 7 days, or urine volume less than or equal to 0.5 mL/kg/hr for 6 hours (25). Preexisting cardiac conditions were defined as congestive heart failure, known conduction system abnormality, or ischemic heart disease. Corticosteroid treatment was defined as at least a dose (≥ 0.5 mg/kg) of methylprednisolone during hospitalization (26, 27).

Statistical Analysis

Continuous data were presented as mean ± SD if they were normally distributed, or as median (interquartile range [IQR])

if they showed a skewed distribution. Frequency data were expressed as proportions. Comparisons of continuous variables were made with Student *t* test or the Mann-Whitney *U* test when appropriate, whereas differences in categorical variables were assessed using the Chi-square test or Fisher exact test, as appropriate.

Survival curves were plotted using the Kaplan-Meier method and compared between patients with or without cardiac injury using the log-rank test. Multivariate Cox regression models were used to determine the independent risk factors for death during hospitalization. Variables with *p* values less than 0.2 in univariate Cox proportional hazard regression (**Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/F283) were included in the multivariate model. Probabilities of entering and removing variables in a stepwise manner in the multivariate model were 0.05 and 0.10, respectively. To determine the association between cardiac injury and mortality, hazard ratios (HRs) and 95% CIs were estimated with adjustment of age (< 65 yr, ≥ 65 yr), Acute Physiology and Chronic Health Evaluation (APACHE) II score (< 21, ≥ 21), Pao_2/Fio_2 (≤ 200 mm Hg, > 200 mm Hg), AKI, and preexisting cardiac conditions (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/F283). Subgroup analysis according to ARDS, age, and APACHE II score was also performed with the multivariable-adjusted Cox proportional hazard regression model.

Data were analyzed using SPSS 25.0 (IBM, Chicago, IL). Statistical charts were performed using Excel 2016, GraphPad Prism 7 (GraphPad Software, San Diego, CA), and R x64 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/). A two-tailed *p* value of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Of the 338 patients, 14 lost to follow-up and three with missing laboratory examination results were excluded. A total of 321 patients from 133 hospitals in 17 provinces, autonomous regions, and municipalities in China were included in the final analysis (Fig. S1, Supplemental Digital Content 1, http://links.lww.com/CCM/F283). The mean age was 54.9 ± 15.8 years, 27.1% were women, and 48.0% of all patients died of infection or comorbidities.

Most patients (63.2%, 203/321) had cardiac injury. Information detailing cardiac injury diagnosis is shown in **Table 1**. Among the 203 patients with cardiac injury, 128 patients had at least two kinds of evidence of cardiac injury. The proportions of heart failure were 34.6% (111/321), followed by myocarditis 1.9%, sudden cardiac arrest 2.8%, and cardiogenic shock 1.2%.

All the 321 patients had at least one type of cardiac examinations (cardiac biomarkers, electrocardiography, and echocardiography), with 305 patients (95.0%) having at least one result of TNI or CK-MB and 293 patients (91.3%) having at least one electrocardiography examination. The first examination of TNI, CK-MB, and electrocardiography was performed at a same median of day 0 (IQR, day 0–1) after admission. Of 321 patients, 132 (41.1%) had at least once echocardiography examination, with the first test of echocardiography performed at a median of day 2 (IQR, day 1–6) after admission. The last test of TNI, CK-MB, electrocardiography, and echocardiography was performed at a median of day 10 (IQR, day 4–20), 10 (IQR, day 5–19), 6 (IQR, day 2–13), and 14 (IQR, day 9–20), respectively.

TABLE 1. Evidence of Cardiac Injury in 321 Hospitalized Patients Infected With H7N9 Virus

Evidence of Cardiac Injury	No. of Patients
Markers[a] only	31
Electrocardiogram[b] only	34
Echocardiography[c] only	10
Markers + electrocardiogram	62
Markers + echocardiography	21
Electrocardiogram + echocardiography	12
Markers + electrocardiogram + echocardiography	33

[a]Markers included the cardiac biomarkers troponin I (TNI) and creatinine kinase-myocardial band (CK-MB).

[b]Electrocardiogram changes included supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, ventricular fibrillation, bundle branch block, ST-segment elevation/depression, T-wave flattening/inversion, and QT interval prolongation.

[c]Echocardiography changes included decreased ejection fraction (EF) value (EF < 50%) or a worsening of the underlying state (patients with basal state of EF < 50%), regional/global ventricular wall motion abnormalities, the presence of pericardial effusion, and pulmonary arterial hypertension.

Altogether, 147 patients (45.8%) had elevated TNI or CK-MB values, 141 (43.9%) had abnormal electrocardiogram changes, and 76 (23.7%) had abnormal echocardiography changes.

The levels of TNI and CK-MB were shown as the ratio of the detected value to the upper limit of the normal range (**Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F283). The median levels of TNI and CK-MB on the first day of admission were 0.5 (IQR, 0.2–2.1) and 0.9 (IQR, 0.5–1.5), respectively. The maximum level of TNI and CK-MB during hospitalization was 1.1 (IQR, 0.3–5.1) and 1.3 (IQR, 0.8–2.4), respectively. Among patients with decreased EF, the median level of EF was 0.5 (IQR, 0.4–0.5).

Comparison of Demographic and Clinical Characteristics Between Patients With or Without Cardiac Injury

Patients with cardiac injury had a higher mean age than those without cardiac injury (57.4 ± 15.9 vs 50.5 ± 14.8 yr; $p < 0.001$), and a higher proportion of preexisting cardiac conditions (11.3% vs 2.5%; $p = 0.005$) than those without cardiac injury (**Table 2**). Clinical characteristics of study participants are presented in **Table 3**. Patients with cardiac injury presented with higher median values of WBC counts at the time of admission (4.7 vs 3.6×10^9/L; $p = 0.023$), but a lower median value of Pao_2/Fio_2 (102.0 vs 148.4 mm Hg; $p < 0.001$). Furthermore,

TABLE 2. Comparison of Demographic and Preexisting Medical Conditions of Influenza A (H7N9)–Infected Hospitalized Patients With or Without Cardiac Injury

Characteristics	All Patients ($n = 321$)	With Cardiac Injury ($n = 203$)	Without Cardiac Injury ($n = 118$)	p
Age (yr), mean ± SD	54.9 ± 15.8	57.4 ± 15.9	50.5 ± 14.8	< 0.001
Female, *n* (%)	87 (27.1)	56 (27.6)	31 (26.3)	0.798
Current smokers, *n* (%)	64 (19.9)	44 (21.7)	20 (16.9)	0.307
Preexisting condition, *n* (%)				
Diabetes	42 (13.1)	29 (14.3)	13 (11.0)	0.402
Cardiovascular disease[a]	26 (8.1)	23 (11.3)	3 (2.5)	0.005
Cerebrovascular disease[b]	18 (5.6)	15 (7.4)	3 (2.5)	0.069
Chronic renal disease	17 (5.3)	14 (6.9)	3 (2.5)	0.093
Chronic obstructive pulmonary disease	14 (4.4)	11 (5.4)	3 (2.5)	0.224
Pregnancy	3 (0.9)	1 (0.5)	2 (1.7)	0.557[c]

[a]Cardiovascular disease was defined as congestive heart failure, known conduction system abnormality, or ischemic heart disease.
[b]Cerebrovascular disease was defined as ischemic or hemorrhagic stroke.
[c]Fisher exact test was used.

a greater proportion of patients with cardiac injury required invasive mechanical ventilation (78.8% vs 30.5%; $p < 0.001$), continuous renal replacement therapy (24.6% vs 5.9%; $p < 0.001$), extracorporeal membrane oxygenation (20.2% vs 6.8%; $p = 0.001$), vasopressor therapy (75.4% vs 28.0%; $p < 0.001$), and admission to ICU (86.2% vs 72.0%; $p = 0.002$) than those without cardiac injury. The cardiac injury group had a lower proportion of virus clearance until discharge or death (58.6% vs 86.4%; $p < 0.001$). The severity of cardiac injury was underscored by higher median values of the APACHE II score (17.0 vs 11.0; $p < 0.001$), longer stay in the ICU (10.0 vs 9.0 d; $p = 0.029$), and a higher proportion of in-hospital death (64.0% vs 20.3%; $p < 0.001$).

Cardiac Injury and Mortality

Patients with cardiac injury had significantly higher in-hospital mortality than those without cardiac injury (log-rank $p < 0.001$) (**Fig. 1**). In the multivariable-adjusted Cox proportional hazard regression model, a significantly higher risk of death was shown in patients with cardiac injury than those without (HR, 2.06; 95% CI, 1.31–3.24) (**Fig. 2**).

Subgroup analysis showed that in patients with moderate-to-severe ARDS, cardiac injury was an independent risk factor for in-hospital mortality (adjusted HR, 2.00; 95% CI, 1.27–3.15) (Fig. 2). The analysis was not conducted among patients without ARDS, because only seven deaths were recorded. An association between cardiac injury and in-hospital mortality was observed in patients under 65 years old (HR, 1.90; 95% CI, 1.12–3.24) as well as in those greater than or equal to 65 years old (HR, 2.55; 95% CI, 1.04–6.24). Among patients with an APACHE II score less than 21, cardiac injury was significantly associated with in-hospital mortality (HR, 2.14; 95% CI, 1.20–3.80). No significant association between cardiac injury and mortality was observed among those with APACHE II scores greater than or equal to 21 (HR, 1.82; 95% CI, 0.86–3.86). No significant association was found between preexisting cardiac conditions and mortality in all patients (HR, 1.21; 95% CI, 0.71–2.05) (Table S3, Supplemental Digital Content 1, http://links.lww.com/CCM/F283) or subgroups (**Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/F283).

DISCUSSION

To the best of our knowledge, this is the largest study investigating cardiac injury in hospitalized patients with influenza A (H7N9) viral infection. In this retrospective multicenter study, a high proportion (63.2%) of cardiac injury was found in hospitalized patients with influenza A (H7N9) viral infection. We found that cardiac injury was independently associated with increased risk of mortality during hospitalization among patients infected with H7N9 virus.

Cardiac injury was also common in the infection caused by other subtypes of influenza virus (6–10, 14, 15, 20, 28). A retrospective studies found that about 54% individuals infected during the severe H1N1 pandemic in 2009 had cardiac injury (9). A study of 600 U.S. patients who underwent cardiac biomarker testing within 30 days after a laboratory-confirmed influenza infection specimen collection showed that 143 (24%) had elevated TNI and/or CK-MB (29). Severe infections, ARDS, and related mechanical ventilation settings were associated with cardiac injury (12, 30). These common conditions in patients with H7N9 viral infection may partly explain the high proportion of cardiac injury (3).

The mechanism of cardiac injury among patients with H7N9 viral infection is still uncertain. In one study, autopsy

TABLE 3. Comparison of Selected Laboratory Abnormalities, Treatment, and Clinical Outcomes of Influenza A (H7N9)–Infected Hospitalized Patients With or Without Cardiac Injury

Characteristics	All Patients ($n = 321$)	With Cardiac Injury ($n = 203$)	Without Cardiac Injury ($n = 118$)	p
Laboratory findings at admission, median (IQR)				
WBC count ($\times 10^9$/L)	4.3 (2.8–6.7)	4.7 (3.0–7.2)	3.6 (2.7–5.5)	0.023
Lymphocyte count ($\times 10^9$/L)	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.5 (0.3–0.8)	0.470
Pao_2/Fio_2 (mm Hg)	118.2 (68.2–183.2)	102.0 (60.1–169.7)	148.4 (97.0–222.3)	< 0.001
Acute Physiology and Chronic Health Evaluation II score, median (IQR)[a]	15.0 (10.0–20.0)	17.0 (13.0–22.0)	11.0 (7.0–15.0)	< 0.001
Treatments, *n* (%)				
Interval between symptom onset and start of antiviral treatment (d)				0.880[b]
0–2	9 (2.8)	5 (2.5)	4 (3.4)	
3–5	62 (19.3)	39 (19.2)	23 (19.5)	
> 5	250 (77.9)	159 (78.3)	91 (77.1)	
Use of invasive mechanical ventilation	196 (61.1)	160 (78.8)	36 (30.5)	< 0.001
Use of continuous renal replacement therapy	57 (17.8)	50 (24.6)	7 (5.9)	< 0.001
Use of extracorporeal membrane oxygenation	49 (15.3)	41 (20.2)	8 (6.8)	0.001
Vasopressor therapy	186 (57.9)	153 (75.4)	33 (28.0)	< 0.001
Admission to ICU	260 (81.0)	175 (86.2)	85 (72.0)	0.002
Rate of virus clearance, *n* (%)[c]	221 (68.8)	119 (58.6)	102 (86.4)	< 0.001
Outcomes				
Length of ICU stay in days, median (IQR)	10.0 (3.0–19.5)	10.0 (4.0–21.0)	9.0 (0.0–15.0)	0.029
In-hospital death, *n* (%)[d]	154 (48.0)	130 (64.0)	24 (20.3)	< 0.001

IQR = interquartile range.

[a]Acute Physiology and Chronic Health Evaluation II score was assessed within 24 hr of admission to hospital.

[b]Fisher exact test was used.

[c]Reconfirmed until death or discharge.

[d]Including 20 "do not resuscitate" cases.

of two patients who died after H7N9 viral infection failed to detect the virus in heart tissue (31). On the other hand, several studies have demonstrated the association between influenza infection and cardiac complications as well as higher risk of out-of-hospital cardiac arrest and myocardial necrosis (4, 5, 32, 33). Influenza viral antigen was demonstrated in the cardiocytes of mice by immunofluorescence (34). Case reports indicated the presence of influenza A (H1N1) in pericardial and myocardial tissues of influenza patients (35–37). These studies suggest the potential of direct viral invasion as the cause of infection-associated cardiac injury (38). Alternatively, severe influenza infection may trigger an exaggerated immune response, with many individuals with severe influenza infection showing increased serum cytokines (38–42). The activation or enhanced release of various inflammatory cytokines, or transient hypoxia-induced mitochondrial dysfunction, may aggravate the impairment of intracellular calcium function, which may result in abnormal electrocardiography and echocardiography (6, 20, 43). In the present study, the proportion of patients with detectable viral RNA until discharge or death was significantly higher among patients with cardiac injury than among uninjured patients. Because influenza A (H7N9) virus can cause severe infection, we hypothesize that it promotes cardiac injury by up-regulating pro-inflammatory cytokines (44, 45), but this needs to be further explored.

Studies have shown that during influenza epidemics, cardiac injury was associated with increased mortality (13, 14) and was more prevalent among infected individuals who died (15). Study of a cohort from the severe H1N1 pandemic in 2009 showed that elevated TNI and left ventricular systolic dysfunction (EF < 50%) were associated with high mortality (9). Autopsies of influenza-infected patients who experienced sudden death show typical inflammatory infiltration and myocardial necrosis that occurred before death (4, 5). Consistent with this result, 69% of patients who died of influenza B viral infection in one study showed pathologic evidence of cardiac

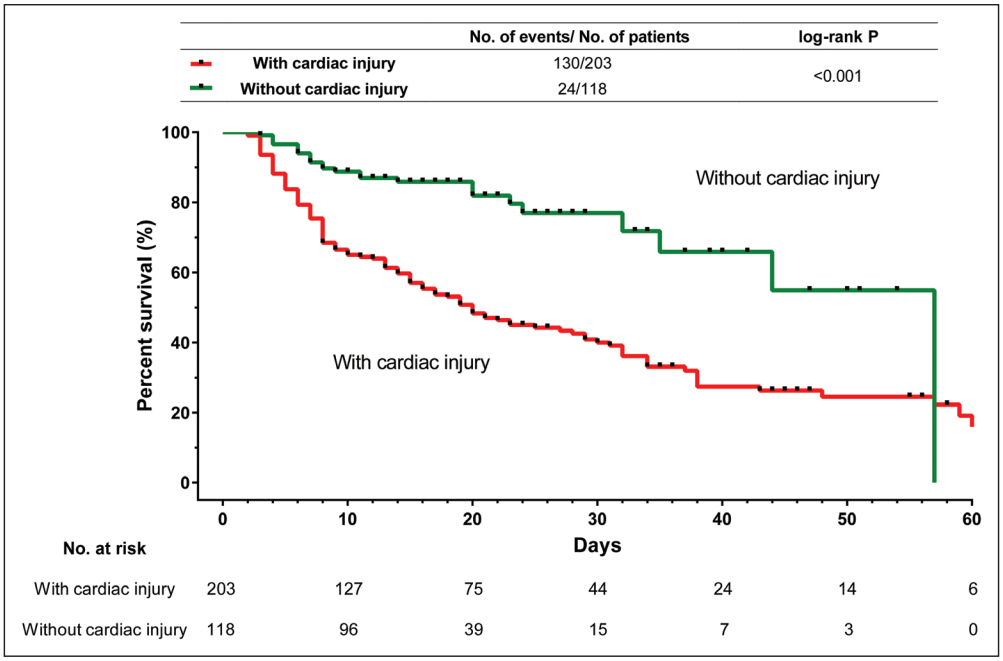

Figure 1. Kaplan-Meier survival curves for mortality during hospitalization. The numbers under the graph represent the number of hospitalized patients with or without cardiac injury at risk of death on the indicated day.

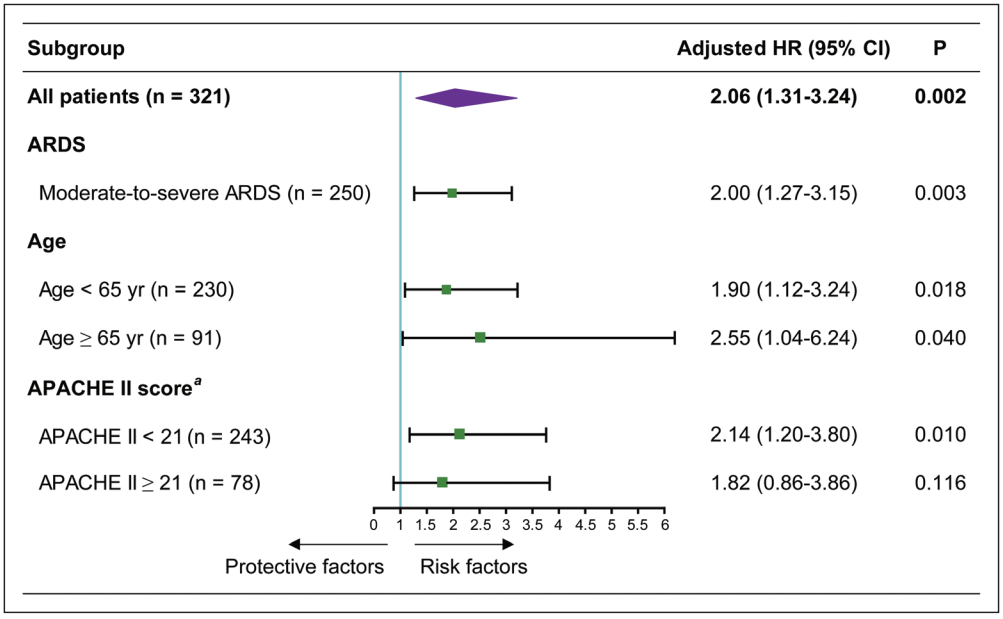

Figure 2. Multivariate Cox regression analysis of cardiac injury associated with mortality in influenza A (H7N9) virus–infected hospitalized patients. [a]Acute Physiology and Chronic Health Evaluation (APACHE) II score was assessed within 24 hr of admission to hospital. The potential confounding variables including age (< 65 yr, ≥ 65 yr), APACHE II score at admission (< 21, ≥ 21), Pao_2/Fio_2 (≤ 200 mm Hg, > 200 mm Hg), acute kidney injury, and preexisting cardiac conditions were used to adjust for the association between cardiac injury and mortality. ARDS = acute respiratory distress syndrome, HR = hazard ratio.

injury (46). Our study is the first to identify cardiac injury as an independent risk factor for in-hospital mortality. Cardiac injury in influenza-infected patients may contribute to mortality in part by causing hemodynamic deterioration. Indeed, many of our patients with cardiac injury were on vasopressor therapy. This deterioration may be due to cytokines released after severe infection. Cytokines can suppress cardiac output, and cytokine storms inhibit oxygen use by mitochondria, and contribute to the occurrence of acute heart failure in patients with severe infection (45, 47).

Our study is limited by its retrospective nature, and by the fact that we could not include all patients in mainland China with laboratory-confirmed influenza A (H7N9) viral infection. Nevertheless, we included patients from 17 provinces, autonomous regions, and municipalities, and the characteristics of our patients were similar to those for the general population of patients with H7N9 viral infection, based on data from the China Center for Disease Control and Prevention. Second, because patients varied between when they had their first cardiac examination and when infection manifested, we were not able to find the risk interval between H7N9 viral infection and cardiac injury.

CONCLUSIONS

Cardiac injury is a frequent condition among hospitalized patients infected with influenza A (H7N9) virus, and it is associated with higher risk of in-hospital mortality. The association between H7N9 virus and cardiac injury needs further exploration, and clinicians should be aware of the potential of cardiac injury in H7N9 virus–infected patients. Such patients should require more extensive and frequent monitoring.

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