



Frequency of troponin elevations in patients with influenza infection during the 2017–2018 influenza season

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ARTICLE INFO

Article history:

Received 28 August 2018

Received in revised form 17 December 2018

Accepted 21 December 2018

Available online 30 January 2019

Keywords:

Troponin elevations

Influenza

2017–2018 influenza season

Myocardial infarction

ABSTRACT

Background: With the increased number of influenza cases observed during the 2017 – 2018 season, patients may be at a greater risk of cardiac related complications as a sequela of viral illness. We described the frequency of troponin elevations in patients with influenza infection during the 2017 – 2018 influenza season.

Methods: This was a retrospective, single-center observational study. All patients aged 18 years or older and had laboratory confirmed influenza viral infection were included in the study. Troponins were considered elevated if greater than 0.3 ng/mL. Electronic health records were reviewed for demographics, laboratory values, coronary artery disease history, electrocardiography, echocardiography results, and incidence of inpatient mortality.

Results: A total of 1,131 patients had lab confirmed influenza infection. Majority of the influenza strains were influenza A, 76.2% (n = 863), and the rest of the influenza strains comprised of influenza B, 23.8% (n = 270). Thirty three (2.9%) patients had elevation of troponin levels greater than 0.3 ng/mL. Most of the patients with elevated troponin levels had influenza A infection (90.9%, n = 30), of which H3 subtype was the most common (48.5%, n = 16). Fifteen patients (45.5%) had a myocardial infarction, 20 (60.6%) had left ventricular abnormalities visualized on echocardiogram, and four (12.1%) died while inpatient.

Conclusions: Our results describe the frequency of troponin elevations in patients with influenza infection at our institution during the 2017 – 2018 influenza season.

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1. Introduction

Reports by the Centers for Disease Control and Prevention (CDC) have stated that the 2017–2018 influenza season witnessed the highest number of patients with influenza like illness in the United States since the 2009 pandemic [1]. By the close of week 40 in the season, influenza A strains encompassed 73.4% of laboratory confirmed influenza cases with H3N2 accounting for 84.3% of these type A strains [2]. Historically, influenza A(H3N2) strains have been associated with more deaths and hospitalizations among individuals over 65 compared to other strains [2]. Interim estimates of the 2017–2018 season have estimated the vaccine effectiveness to be 25% against illnesses caused by influenza A (H3N2) virus [3].

Troponin elevations may occur as the result of several inflammatory inducing insults to the heart, one of which is viral illness, including influenza [4]. Viral replication within the myocardium may lead to a cascade of inflammatory processes that causes fibrosis and ultimately cardiac necrosis. While there are several mechanisms that are proposed to explain the cardiac effects as a sequelae of viral infection, the exact mechanism has not been fully elucidated.

Although rare, current literature describes that acute myocarditis has been associated with influenza viral infection in up to 10% of patients, depending on diagnostic criteria [5–9]. However, these studies have had various limitations such as nonspecific measures of influenza infection, study designs subject to bias, and nonspecific techniques of varying sensitivities for the detection of myocyte injury [9,10]. With an increase in the observed cases of influenza infections during the 2017–2018 season, compared to previous years [1], the potential for cardiac complications secondary to influenza infection may have also increased. The aim of this study is to describe the frequency of troponin elevations in patients with laboratory confirmed influenza infection at Houston Methodist Sugar Land Hospital (HMSL) from August 2017–March 2018.

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Table 1
Characteristics of 33 patients with influenza infection and troponinI elevations.

Variable	Patients (n = 33)
Age, mean $\pm$ SD	71.2 $\pm$ 12.3
Male, n (%)	13 (39.4%)
Influenza diagnostic test, n (%)	
Respiratory pathogen panel by polymerase chain reaction	21 (63.6%)
Fluorescent immunoassay influenza antigen detection	12 (36.4%)
Influenza virus type, n (%)	
Unspecified type A	12 (36.4%)
A/H3	16 (48.5%)
A/H1	2 (6.1%)
B	3 (9.1%)
History of coronary artery disease, n (%)	
PCI	4 (12.1%)
CABG	6 (18.2%)
CABG and PCI	3 (9.1%)
CAD	2 (6.1%)
NSTEMI	1 (3.0%)
None	17 (51.5%)
Interval between influenza detection and elevated troponinI, n (%)	
1st day and 3rd day	32 (97.0%)
TroponinI elevation peak, n (%)	
0.3 to 1.5 ng/mL	23 (69.7%)
>than 1.5 ng/mL	10 (30.3%)
Myocardial infarction, n (%)	
STEMI	1 (3.0%)
NSTEMI	14 (42.4%)
Ejection fraction performed, n (%)	
<40%	10 (34.5%)
41%–49%	2 (6.9%)
>50%	17 (58.6%)
Treatment	
Neuraminidase inhibitors, n (%)	33 (100%)
Duration of treatment, days, mean $\pm$ SD	4.0 $\pm$ 2.0
Length of stay days, mean $\pm$ SD	7.2 $\pm$ 5.9
Mortality, n (%)	4 (12.1%)

SD = standard deviation; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; CAD = coronary artery disease; ECG = electrocardiogram; NSTEMI = non-ST segment elevation myocardial infarction; STEMI = ST segment elevation myocardial infarction.

2. Methods

This was a retrospective, single-center observational study at a 305 bed community hospital. All patients aged 18 years or older and had laboratory confirmed influenza viral infection documented within 48 h of admission were included in the study. TroponinI isoforms were measured and considered elevated if >0.3 ng/mL.

The data sources utilized in this study included Vigilanz™ and institutional electronic health records (EHR). Vigilanz™ provided patient demographics and identification of patients with laboratory confirmed influenza viral infection with troponinI levels >0.3 ng/mL. From the EHR, the study investigators obtained clinical measures such as laboratory results, cardiac history, cardiac related imaging, and the timing of these events. Outcome measures included peak troponinI levels, changes in T waves observed during ECG, in-patient mortality, and length of stay. Patients were determined to have a STEMI or NSTEMI during the current admission based on documentation from physician progress notes. Additionally, we compared the frequency of troponinI elevation between influenza A and B virus, and between influenza A subtype H3 and H1 strains as an exploratory, hypothesis generating

endpoint. Fisher's exact test was used to calculate the *p*-values for categorical variables. A two-sided *p* value of <0.05 was considered statistically significant. We also calculated odds ratio of troponinI elevations between infections caused by influenza A and B, and between influenza A H1 and H3 subtypes respectively. Data analysis was performed using GraphPad Prism 7 software (GraphPad Software, Inc., La Jolla, CA)©.

3. Results

A total of 1131 patients from August 2017–March 2018 were positive for the influenza virus. Diagnosis of influenza was confirmed via respiratory pathogen panel (RPP) by polymerase chain reaction and via fluorescent immunoassay (FIA). Because of the rapid turnaround time, our emergency department utilizes FIA as the diagnostic test of choice for influenza infections. Two patients had a mixed infection with influenza A and B (i.e. these two patients had both influenza A and B strains detected by RPP). Majority of the influenza strains were influenza A, 76.2% (*n* = 863), and the rest of the influenza strains comprised of influenza B, 23.8% (*n* = 270). Most of the influenza A strains were not typed because they were detected by FIA (48.5%, *n* = 549). Similar to the CDC's 2017–2018 influenza activity interim analysis, influenza A subtype H3 strains (21.8%, *n* = 247) were more frequently isolated compared to the H1 subtype (5.9%, *n* = 67).

Of the patients with influenza infection, 33 (2.9%) patients had troponinI levels >0.3 ng/mL. 1096 patients were excluded because they had troponinI levels <0.3 ng/mL, and 2 patients were excluded because influenza was detected >48 h after admission. The mean age was 71.2 years ($\pm$ 12.3) and majority were females (60.6%). Over half of the patients (51.5%) had no history of coronary artery disease. Majority of the patients with elevated troponinI levels had influenza A infection (90.9%, *n* = 30), of which H3 subtype was the most common (48.5%, *n* = 16). Since the FIA test for influenza antigen detection does not result the subtypes of influenza A, 12 of the influenza A infections (detected by FIA) that led to troponinI elevations >0.3 ng/mL were not typed. Antiviral therapy was initiated in all patients who were included in this study. At HMSL, the neuraminidase inhibitor oseltamivir is prescribed exclusively. Doses were adjusted based on individual's renal function and continued until discharge or completion of therapy.

Following initial detected elevations in troponinI levels, 10 patients (34.5%) had a peak troponinI level >1.5 ng/mL, 14 (42.4%) had a non-ST-elevation myocardial infarction (NSTEMI), and 1 (5.0%) patient had a ST-elevation myocardial infarction (STEMI). The mean length of stay was 7.2 days ($\pm$ 5.9). There were 4 (12.1%) in-patient mortality events that occurred during the study time frame. All patients who expired while inpatient had no previous documented cardiac history. Two of the four patients who expired experienced NSTEMI events while inpatient, one patient went into sudden cardiac arrest, and one patient expired within 16 h of admission secondary to an intracranial hemorrhage. Additionally, all patients who expired were infected with the influenza A, subtype H3 strain. Baseline demographics, medical history and outcomes are included in Table 1 for the patients with influenza infections and elevated troponinI levels.

Patients who were infected with the influenza A strain had an increased incidence of elevated troponins when compared to those infected with influenza B strain (OR 3.20, 95% CI 0.97–10.59; *p* = 0.054) see Table 2. Among patients who were infected with the influenza A strains, those who had A/H3 subtype had an increased incidence of elevated

Table 2
Comparison of troponin elevations among influenza A and influenza B strains.

Variable	Influenza A (n = 863)	Influenza B (n = 270)	OR	95% CI	<i>p</i> -value
Positive troponin level n, (%)	30 (3.48)	3 (1.11)	3.20	0.97–10.59	0.054

OR = odds ratio; CI = confidence interval.

Table 3

Comparison of troponin elevations among influenza A H3 and H1 subtypes.

Variable	Influenza A/H3 (n = 247)	Influenza A/H1 (n = 67)	OR	95% CI	p-value
Positive troponin level n, (%)	16 (6.48)	2 (2.99)	2.25	0.50–10.04	0.29

OR = odds ratio; CI = confidence interval.

troponins when compared to those infected with A/H1 subtype [odds ratio (OR) 2.25, 95% confidence interval (CI) 0.50–10.04; $p = 0.29$] see Table 3.

4. Discussion

Several studies have evaluated the impact of influenza viral illness on cardiac function with various diagnostic criteria such as laboratory values, T wave changes on ECG, as well as echocardiography findings [11–15]. Biological markers such as troponin can provide insight to myocardial injury.

Consistent with the CDC's interim report, majority of our influenza cases for the 2017–2018 influenza season were influenza A. Of those that could be typed, subtype H3 was the most common. Our frequency of elevated troponins was 2.9% ($n = 33$). Majority of the patients with elevated troponins had influenza A (90.9%, $n = 30$), of which H3 subtype was the predominant strain ($n = 16$, 53.3%). During the 2017–2018 influenza season, patients infected with influenza A H3 subtype had >2 times the odds of troponin elevations compared to patients infected with influenza A H1 subtype. However, these results were not statistically significant likely because of a small sample size. The findings are hypothesis generating and paves the way for future research on the differences between the various influenza strains and their impact on cardiac function. Patients without history of CAD are also at risk for cardiac complications; 51.5% of the patients with influenza infection and elevated troponins had no previous history of CAD.

Although previous studies have shown that viral myocarditis is often mild to moderate, there remains a potential for myocardial infarction [10,16]. One recently published article found that there was up to a six fold increase in the incidence of acute myocardial infarction during the seven days after laboratory confirmed influenza infection [10]. Of the 33 patients with elevated troponins, 15 patients (45.5%) in our study were diagnosed with myocardial infarction within their admission. Most of these patients ($n = 14$) had a NSTEMI and 1 patient had a STEMI. Of the patients that had a myocardial infarction, 5 (33.3%) patients had no previous history of coronary artery disease, and 4 of these patients expired during their hospital stay.

This study had several limitations. Firstly, approximately 64% of our influenza A strains were not typed because of the use of FIA as a diagnostic tool. Having information on the subtypes of influenza A strains are useful in identifying which strains were prevalent and contributed to elevated troponins during the 2017–2018 influenza season. However, the use of the FIA test is common place in emergency departments because of its rapid turnaround. Secondly, vaccine history was not captured. Vaccinations can theoretically lead to an attenuated severity of symptoms. Published literature has shown that influenza vaccination reduces cardiovascular events and mortality [10], and vaccinations may have impacted outcomes of this study. Thirdly, prior admission ECGs were not available for the majority of patients to assist in differentiating acute from pre-existing cardiac conduction abnormalities. Lastly, because of the single center design, our sample size of patients with influenza and elevated troponins was small leading to potential type II error when comparing the subtypes of influenza A associated with troponin elevations.

5. Conclusion

Among patients with laboratory confirmed influenza infections during the 2017–2018 season at our institution, 2.9% of all patients experienced elevated troponins with 45.5% of these experiencing myocardial infarctions. Our results describe the frequency of troponin elevations in patients with influenza infection at our institution during the 2017–2018 influenza season. Patients without history of CAD are also at risk for cardiac complications. Early recognition is crucial to identify patients who may be at risk for poor outcomes related to changes in cardiac function as a consequence of influenza infection.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Funding source

None to declare.

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