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Prognostic impact of high sensitive troponin in predicting 30-day mortality among patients admitted to hospital with influenza

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A R T I C L E   I N F O

A B S T R A C T

Background: Worldwide, seasonal influenza causes significant mortality and severe infections may cause cardiac injury. High-sensitive-troponins (hsTnT) are sensitive and specific markers of myocardial damage. This study investigated the prognostic impact of hsTnT on 30-day mortality in hospitalised influenza patients.

Methods: This retrospective study included influenza patients ≥ 18 years, who had hsTnT performed during admission in two tertiary-hospitals in South Australia. Diagnosis of influenza was confirmed by polymerase–chain-reaction (PCR) test and hsTnT > 14 ng/L with a change of > 20% during admission was considered to be indicative of acute-cardiac injury. Clinical characteristics, complications and 30-day mortality were compared among four groups of patients: hsTnT unavailable, hsTnT negative, chronically elevated hsTnT and acutely elevated hsTnT. Cox-proportional hazard regression determined the hazard of death at 30-days following hospital discharge after adjustment for co-variates.

Results: Between January 2016 -March 2020, 1828 influenza patients, mean age 66.4 years, were hospitalised. Troponin results were available for 617 (47.7%) patients, of whom, 62 (10%) had acute myocardial injury and 232 (37.6%) had chronic hsTnT elevation. Both inpatient and 30-day mortality were significantly higher among patients with acute (P < 0.001) and chronic hsTnT (P < 0.001) when compared to other groups. When compared to patients with negative hsTnT, acute but not chronic hsTnT elevation was significantly associated with 30-day mortality after adjustment for various co-variates (HR 8.30, 1.80–17.84, P value = 0.013).

Conclusions: This is the largest available analysis of cardiac-specific biomarker hsTnT in patients with influenza. An acutely elevated hsTnT was associated with 30-day mortality among hospitalised influenza patients.

1. Introduction

Influenza most often causes a self-limited respiratory illness but, in some instances, may be severe enough to require hospitalisation and may even lead to death. Worldwide, more than 1 million deaths may be associated with an influenza pandemic with some strains of avian influenza having a case fatality rate of as high as 60% [1,2]. In 2017, there were 29,000 influenza related hospital-isations and 745 deaths were reported due to influenza in Australia [3].

The most common complication associated with influenza is pneumonia, although, influenza may also lead to exacerbation of other underlying chronic medical problems (e.g. congestive heart failure (CHF), atrial fibrillation etc.) [4,5]. In addition, influenza may lead to cardiac injury which may manifest as myocardial infarction (MI), myocarditis and CHF [6,7]. Observational studies have suggested that influenza may be associated with an increased cardiovascular morbidity and mortality especially in older people (>85 years) during winter months [8,9]. Case control studies indicate an increased risk of hospital admissions for acute MI and CHF during influenza season and have also suggested that there is a protective role of influenza vaccination and reduced risk of vas-

cular events with use of antivirals for influenza infection among patients with a history of cardiovascular disease [10–12].

Although influenza poses a significant burden to the health of the global population, there are still gaps in the understanding of precise magnitude of this burden measured in terms of long-term outcomes, complications and costs, especially in patients with severe infection. Cardiac troponins have emerged as sensitive and specific markers of myocardial injury and elevated levels may indicate myocardial involvement during acute influenza infection [13]. Studies [14,15] indicate higher immediate mortality among influenza patients who have elevated troponin levels. The impact of troponin levels in predicting long term clinical outcomes among patients with influenza is unknown. Therefore, the aim of the present study was to retrospectively analyse hsTnT serum levels as a marker of 30-day mortality among patients who needed hospitalisation for severe influenza.

2. Methods

We retrospectively analysed data obtained by reviewing the electronic medical records of all patients ≥ 18 years who had an admission with a confirmed influenza infection at two tertiary teaching hospitals (Flinders Medical Centre (FMC) and Royal Adelaide Hospital (RAH)) in Adelaide, between January 2016 to March 2020. Patients were classified as having a confirmed influenza infection in the presence of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) [16] diagnosis code of influenza (ICD-10-AM J9 or J10) and a laboratory confirmed influenza infection, which was defined as occurring in a patient in whom influenza virus was detected in a respiratory sample on the basis of a positive reverse-transcription polymerase chain reaction (RT-PCR) test.

Cardiac injury was identified through analysis of electronic laboratory records of patients who had confirmed influenza infection. A case of acute cardiac injury was defined as a rise or fall of hsTnT with at least one value above 99th percentile upper reference limit (URL) [17]. Troponins were measured with the Roche hsTnT assay (Roche Elecsys Troponin T level of > 14 ng/L corresponds to 99th percentile URL) and > 20% rise or fall in hsTnT was regarded as a significant change to indicate an acute cardiac injury [18]. Ethical approval was granted by the Southern Adelaide Human Clinical Research Ethics Committee (SA HREC) and this study was registered with the Australia and New Zealand Clinical Trial Registry (ANZCR) no 12618000451202.

From the EMR, we abstracted the following variables for all patients who had had a hospital admission with laboratory confirmed influenza infection: age, sex, Charlson Comorbidity Index (CCI) [19], smoking status, history of diabetes, ischaemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), bronchial asthma, interstitial lung disease (ILD), chronic kidney disease (CKD), malignancy and immunosuppression. Serum creatinine and c-reactive protein (CRP) levels available during admission were recorded. We also recorded complications during hospital admission: pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock. Patients were determined to have an acute coronary syndrome (ST-elevation MI (STEMI), non-ST-elevation MI (NSTEMI) or unstable angina) during the index admission based on documentation in the discharge summaries or physician progress notes. The severity of influenza related illness was described by the number of medical emergency response team (MET) calls during admission, proportion of patients having multiple (≥2) MET calls, proportion of patients who went to the intensive care unit (ICU), time spent in hours in the ICU and in hospital mortality. The length of hospital

stay (LOS) was adjusted for inpatient mortality. We also recorded mortality and unplanned hospital readmissions within 30 days following discharge.

3. Statistical analyses

Data were analysed for normality using histograms and continuous variables were analysed using one-way analysis of variance (ANOVA) or Kruskal-Wallis H test, while categorical variables were analysed using chi squared or Fisher's exact test, where appropriate. For this study, patients who had an elevated hsTnT (>99th percentile URL) along with a significant rise or fall (>20%) during admission were determined to have an acute cardiac injury and were classified as acutely elevated hsTnT group, while those with elevated hsTnT with no significant rise or fall during admission were classified as chronically elevated hsTnT group. We compared clinical characteristics, complications and outcomes between four groups: patients where hsTnT results were unavailable, hsTnT negative, chronic hsTnT elevation and acute hsTnT elevation. We used cox proportional hazard model to determine the impact of acutely elevated hsTnT during admission on 30-day mortality after adjustment for the following confounding variables: age, sex, CCI, creatinine levels and severity of illness as determined by C-RP levels, presence of sepsis, number of MET calls during admission and time spent in the ICU. Logistic regression was used with 30-day mortality as an outcome variable and hsTnT as continuous variable after adjustment for the above mentioned co-variates. We computed mortality risk over time by using the Nelson-Aalen cumulative hazard estimate [20] and risk curves were compared among four groups. The log-rank test was used to compare survival difference between patients with or without acute hsTnT elevation. All tests were two-sided and a P value < 0.05 indicated statistical significance. All statistical analyses were performed using STATA vs16.0 (StataCorp., Texas).

4. Results

A total of 1828 hospitalised patients ≥ 18 years tested positive for influenza between January 2016 to March 2020. Of these, 1616 (88.4%) patients were identified as having influenza A and 212 (11.6%) as influenza B infection. High sensitive TnT results were available for 741 (40.5%) patients, of whom, 124 (16.7%) patients were excluded because the reported hsTnT assay detection limits were > 20 ng/L, while 1087 (59.5%) did not have hsTnT performed during admission (Fig. 1). Among 617 patients where hsTnT results were available and were included in the analyses, 294 (47.7%) patients had a positive hsTnT while 323 (52.3%) had negative hsTnT. Of 294 patients who had positive hsTnT, 62 (21.1%) patients had an evidence of acute myocardial injury, as reflected by an elevation of troponin levels (>14 ng/L) along with a significant rise or fall during admission, while 232 (78.9%) patients had chronically elevated hsTnT without significant change during admission (Fig. 1). One hundred and fifty five (46.9%) patients had more than two hsTnT results available during admission. The mean (SD) hsTnT levels were 9.4 (3.3) ng/L among patients who had negative hsTnT as compared to 135.2 (621.2) ng/L among patients who were in chronically elevated hsTnT group and 170.5 (265.1) ng/L in those with acutely elevated hsTnT group.

The mean age was 66.4 years (SD 20.1; range 18–101) and majority were females (52.3%). More than two-thirds of patients had no previous history of coronary artery disease and less than half were smokers. Diagnosis of ACS was made in 23 (37.7%) patients who were in acutely elevated hsTnT group, of whom, 3 patients (13%) died during admission in comparison to 1(3.8%) death among patients who were in chronically elevated hsTnT
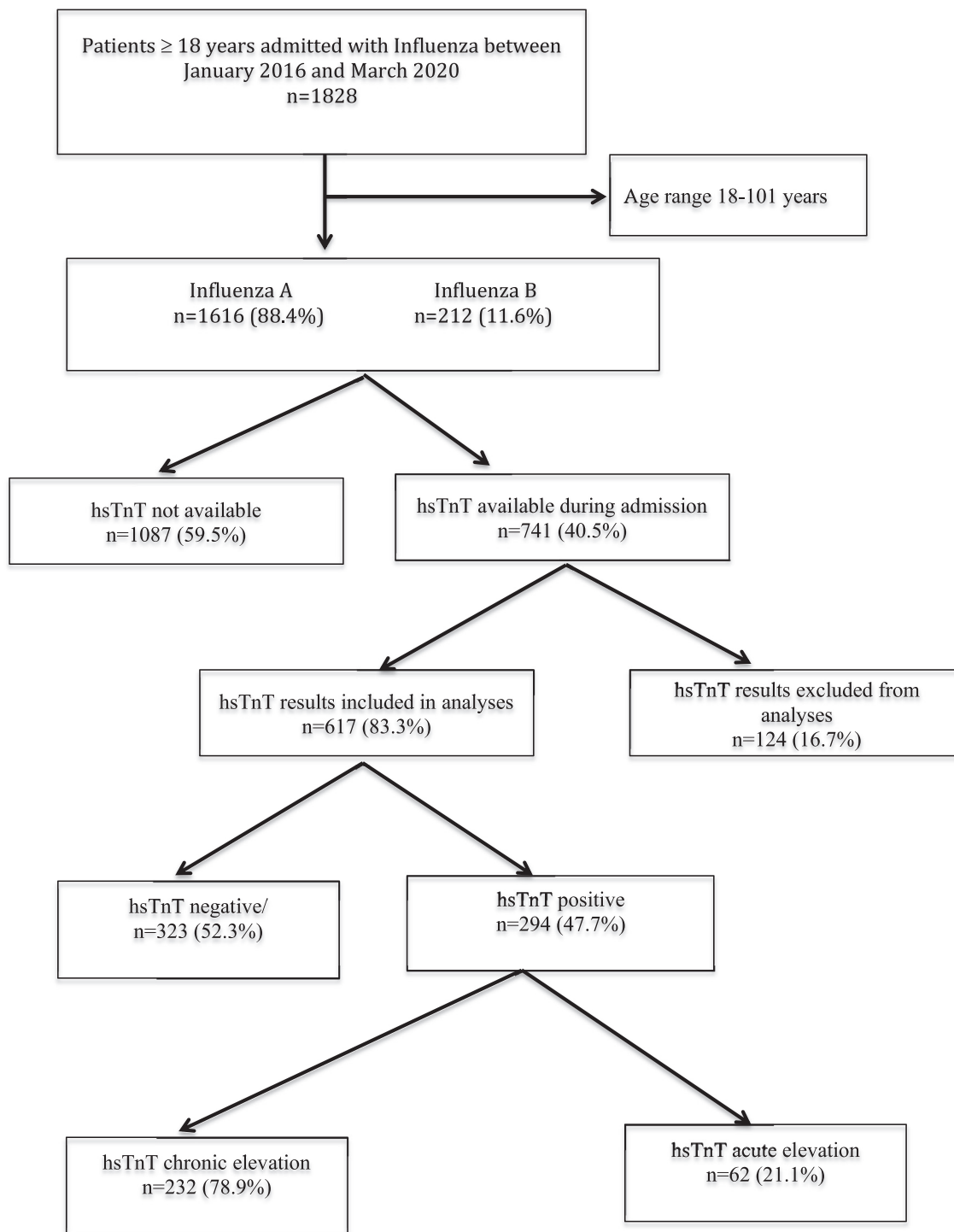
Fig. 1. Study flow diagram (hsTnT, high sensitive troponin).

group. Among 23 patients who developed ACS, NSTEMI was diagnosed in 22 (96%) patients and 1(4%) patient developed STEMI. Echocardiogram results were available for 41 patients and mean ejection fraction (EF) was not significantly different between the two groups (P < 0.05).

Table 1 shows differences in the baseline characteristics of influenza patients among four groups of influenza patients according to hsTnT results: hsTnT unavailable, hsTnT negative, chronic hsTnT elevation and acute hsTnT elevation. Influenza patients who had an acute or chronic hsTnT elevation were more likely to

be older with a history of IHD, diabetes, COPD, asthma, CKD and had a significantly higher CCI when compared to other groups. Similarly, when compared to other groups patients with acute or chronic hsTnT elevation were more likely to have a higher creatinine and C-RP levels. However, no differences were observed in regard to the degree of immunosuppression or influenza subtypes between various groups (Table 1).

Influenza patients who had an acute or chronic hsTnT elevation had a higher incidence of sepsis, septic shock, and respiratory failure, however, other complications such as pneumonia, ARDS and

Table 1
Baseline characteristics of patients.

Variable	hsTnT not available (n = 1087)	hsTnT negative (n = 323)	Chronically elevated hsTnT (n = 232)	Acutely elevated hsTnT (n = 62)	P value
Age mean (SD)	62.7 (21.1)	66.4 (18.5)	79.7 (12.1)	78.3 (13.7)	<0.001
Age group n (%)					
< 40	214 (84.9)	35 (13.9)	1(0.4)	2 (0.8)	<0.001
40–59	202 (69.9)	67 (23.2)	17 (5.9)	3 (1.0)	
60–79	384 (63.3)	133 (21.9)	69 (11.4)	21 (3.4)	
> 80	287 (51.6)	88 (15.8)	145 (26.1)	36 (6.5)	
Sex male n (%)	473 (46.4)	132 (42.7)	125 (54.4)	31 (50.8)	0.050
Influenza type n (%)					0.252
Influenza A	958 (88.1)	281 (87.0)	213 (91.8)	57 (91.9)	
Influenza B	129 (11.9)	42 (13.0)	19 (8.2)	5 (8.1)	
CCI mean (SD)	1.1 (1.5)	0.9 (1.3)	2.2 (2.1)	2.9 (1.8)	<0.001
Smoking history n (%)	481 (44.3)	162 (50.2)	124 (53.5)	30 (48.4)	0.057
IHD n (%)	155 (14.3)	49 (15.2)	74 (31.9)	24 (38.7)	<0.001
Diabetes n (%)	237 (21.8)	63 (19.5)	86 (37.1))	26 (41.9)	<0.001
COPD n (%)	241 (22.2)	82 (25.4)	94 (40.5)	23 (37.1)	<0.001
Asthma n (%)	79 (7.3)	31 (9.6)	7 (3.0)	0	0.003
ILD n (%)	13 (1.2)	0	5 (2.1)	2 (3.2)	0.047
CKD n (%)	8 (0.7)	2 (0.6)	5 (2.1)	3 (4.8)	0.005
Malignancy n (%)	124 (11.4)	33 (10.2)	32 (13.8)	10 (16.1)	0.401
Immunosuppressed n (%)	6 (0.5)	1 (0.3)	2 (0.8)	1 (1.6)	0.600
hsTnT mean (SD) (ng/L)			135.2 (621.2))	170.5 (265.1)	<0.001
EF mean (SD)			52.4 (13.2)	48.8(11.2)	0.354
Creatinine mean (SD) (μmol/L)	106.4 (111.4)	82.7 (31.5)	143.2 (143.9)	149.3 (126.3)	<0.001
CRP mean (SD) (mg/L)	55.7 (67.5)	59.5 (76.4)	68.0 (73.5)	65.8 (65.5)	0.032

hsTnT, (high sensitive troponin); SD, (standard deviation); CCI, (charlson comorbidity index); IHD, (ischaemic heart disease); COPD, (chronic obstructive lung disease), ILD, (interstitial lung disease), CKD, (chronic kidney disease); EF, (ejection fraction).

myocarditis were not significantly different when compared to those who had negative hsTnT or where hsTnT results were unavailable (Table 2). When compared to patients with negative hsTnT, patients in the acutely elevated or chronically elevated hsTnT group had a greater severity of illness as reflected by the higher number of MET calls, a higher proportion of patients who had multiple (>2 MET calls), proportion of patients who needed ICU admission and time spent in the ICU (Table 2). Median length of hospital stay was significantly longer (P < 0.001) and inpatient mortality was significantly higher (9.7% vs 5.6% vs 1.6% vs 1.3%, P value < 0.001) in patients with acute or chronic hsTnT elevation when compared to those where hsTnT was negative or unavailable. HsTnT levels had a significant but weak positive correlation with

LOS (r = 0.14, P < 0.05) and time spent in the ICU (r = 0.20, P < 0.05) but had no correlation with the number of MET calls. At 30 days following hospital discharge, 10 (16.1%) patients who had an acute hsTnT elevation during admission died as compared to 23 (9.9%) deaths among patients who had chronic hsTnT elevation and 5 (1.6%) deaths in the group who had negative hsTnT (P < 0.001), but there was no difference in the number of unplanned hospital readmissions between different groups (Table 2). The hazard of death at 30 days following hospital discharge among patients who had acute hsTnT elevation was 8.3 times higher when compared to those who had negative hsTnT, even after adjustment for factors such as age, sex, creatinine, CCI and the severity of illness as assessed by factors such as CRP levels,

Table 2
Complications and outcomes.

Variable	hsTnT not available (n = 1087)	hsTnT negative (n = 323)	Chronically elevated hsTnT (n = 232)	Acutely elevated hsTnT (n = 62)	P value
In hospital mortality n (%)	15 (1.3)	4 (1.2)	13 (5.6)	6 (9.7)	< 0.001
30-day mortality n (%)	35 (3.2)	5 (1.6)	23 (9.9)	10 (16.1)	< 0.001
30-day readmissions n (%)	139 (12.8)	37 (11.5)	45 (19.4)	6 (9.9)	0.046
LOS median (IQR)	3 (5)	4 (5)	6 (9)	8 (17)	< 0.001
MET calls n (%)	27 (4.8)	16 (6.3)	29 (16.4)	15 (36.6)	< 0.001
Number of MET calls mean (SD)	0.1 (0.4)	0.1 (0.3)	0.3 (0.8)	0.8 (1.1)	< 0.001
Patients with multiple MET calls n (%)	7 (1.3)	2 (0.8)	13 (7.3)	9 (21.9)	< 0.001
ICU admission n (%)	50 (4.6)	32 (9.9)	31 (13.4)	20 (32.3)	< 0.001
ICU hours mean (SD)	6.8 (56.1)	13.6 (93.8)	22.2 (87.9)	91.7 (234.6)	<0.001
Pneumonia mean (SD)	67 (6.6)	21 (6.8)	22 (9.6)	10 (16.4)	0.020
Sepsis n (%)	39 (3.8)	10 (3.2)	22 (9.6)	11 (18.0)	<0.001
Septic shock n (%)	4 (0.3)	2 (0.6)	7 (3.0)	1 (1.6)	<0.001
Respiratory failure n (%)	73 (7.2)	34 (11.0)	33 (14.4)	10 (16.4)	0.001
ARDS n (%)	6 (0.6)	3 (1.0)	3 (1.3)	1 (1.6)	0.581
Myocarditis n (%)	0	0	1 (0.4)	1 (1.6)	0.282
Pericarditis n (%)	0	0	0	1 (1.6)	0.035

*Multiple MET calls ≥ 2.
hsTnT, (high sensitive troponin); LOS, (length of hospital stay); MET, (medical emergency response team); SD, standard deviation; ICU (intensive care unit), ARDS, (adult respiratory distress syndrome).

Table 3

Multivariable cox proportional hazard model comparing acute hsTnT and chronic hsTnT with negative hsTnT as baseline.

Variable	Hazards ratio	CI	P value
Acute hsTnT elevation	8.30	1.80–17.84	0.013
Chronic hsTnT elevation	5.2	0.61–45.59	0.131
Age	1.11	1.04–1.18	<0.001
Male sex	0.56	0.20–1.53	0.262
CCI	1.41	1.15–1.71	0.001
Creatinine	0.99	0.98–0.99	0.043
CRP	1.00	0.99–1.01	0.630
Sepsis	4.00	0.98–16.33	0.053
ICU admission	1.10	0.03–2.14	0.428
MET calls	1.04	0.27–3.93	0.953

CI, confidence interval; hsTnT, high sensitive troponins; CCI, charlson comorbidity index; CRP, C-reactive protein; ICU, intensive care admission; MET, medical emergency response team.

presence of sepsis, MET calls and need for an ICU admission (HR 8.30, 95% CI 1.80–17.84, P value = 0.013) (Table 3). Nelson-Aalen curve showed significant survival difference between two groups (Fig. 2) and log rank test was statistically significant (χ^2 27.10, P < 0.001). Logistic regression showed that hsTnT levels during admission were significantly associated with 30-day mortality after adjustment for various co-variates (coefficient 0.003, 95% CI 0.0010–0.0057, P = 0.005). However, the hazard of death at 30-days following hospital discharge was not significantly different for patients who had chronic hsTnT elevation when compared to those with negative hsTnT group (HR 5.2, 95% 0.61–45.51, P = 0.131) Table 3.

5. Discussion

This study suggests that influenza patients who have an evidence of acute cardiac injury as reflected by elevated and significant change in cardiac biomarkers have significantly higher number of complications during hospital admission with a consequent longer LOS and higher inpatient mortality. Mortality remained significantly higher even after 1 month following hospital discharge only in patients who had an acute and significant troponin elevation during admission even after adjustment for various confounders including comorbidities and severity of illness during index admission.

A previous large study [21] among U.S. veterans, which included over 4000 influenza patients over a period of 2 years, of which, cardiac biomarkers were available for 14% patients, found that 24% of influenza patients had elevated cardiac biomarkers and 25% of these patients developed ACS. In comparison, in our study a higher number of patients (39.7%) were found to have elevated cardiac biomarkers with slightly higher (37.7%) rates of ACS. These differences could be related to the higher sensitivity of the troponin assay used in our population [22]. Furthermore, higher rates of ACS in our study are probably related to the differences in cardio vascular disease (CVD) risk factor profile because patients in our study were older (median age 82 years vs. 77 years in the US study). In addition, these differences in rates of ACS may be related to the virulence of circulating influenza strains in respective epidemiological season [23]. Another study [15], which included 264 influenza patients admitted over a period of 5 years where hsTnT results were available, found that 31.8% of patients had elevated cardiac biomarkers and 7.6% of these patients developed ACS, however, patients in this study were much younger (68.7 vs. 82 years) as compared to our population.

Several studies [13–15,24] have previously evaluated the impact of influenza viral infection on cardiac function and immediate mortality but only limited studies have determined the long term clinical consequences of severe influenza infection who require hospitalisation. These studies have indicated an increased incidence of arrhythmias, presence of regional wall motion abnormalities and a reduction in ejection fraction along with increased mortality during acute phase of viral illness. A recent study [25] suggests six-fold increased incidence of acute myocardial infarction within one week of laboratory confirmed influenza infection. Of 62 patients with significantly elevated troponins, 23 (37.1%) patients in our study were diagnosed with an ACS and 3 (13%) died during their hospital stay. Interestingly, 14 (60.9%) of our patients
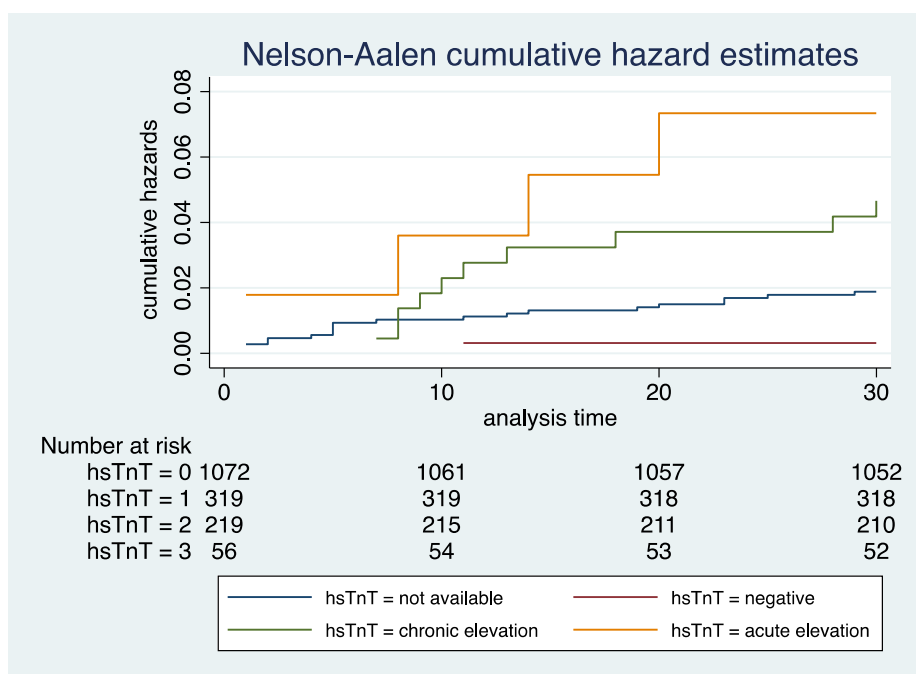
Fig. 2. Nelson Aalen hazard curve.

who developed ACS had no previous history of CAD. These findings are in contrast to a study by Harris et al, [14] who found that among 33 patients (mean age of 71.2 years) who had elevated troponins, only 33.3% had no previous history of coronary artery disease. This difference might be related to fewer risk factors for CAD in our population because less than half of the patients in our study were smokers or had a history of diabetes.

The present study suggests that influenza patients are at a significantly higher risk of dying during (9.7%) and after one month of hospital discharge (16.1%) and this risk was especially higher among patients who had an acute elevation and significant change in cardiac biomarkers during their admission. These results are similar to a study by Ludwig et al [21] who found that 13% patients with elevated cardiac biomarkers died within 30 days of laboratory-confirmed influenza infection and 61% received diagnosis of NSTEMI or probable NSTEMI. A systematic review [26] suggests that 0.4% to 13% patients hospitalised with influenza may have an associated myocarditis and are more likely to develop CHF. In this review, among 44 patients who developed pericardial effusions 23 patients required advanced cardiac life support with mortality of 22%. The prevalence of influenza associated myocarditis was only 0.12% in our study and thus does not explain higher mortality. However, patients in our study were at a higher risk of death because they were significantly older and had a higher number of comorbidities than those included in this review. Another aspect of cardiac involvement by influenza viral infection may be through exacerbation of pre-existing CAD [4,27]. Systemic inflammation has been recognised as an important driver of atherosclerosis. Influenza infection promotes inflammation and is associated with a pro-coagulant state, which can destabilise atherosclerotic plaques and can cause vascular occlusion [28,29]. Recent studies have described an increased risk of myocardial infarction with laboratory confirmed influenza and to a lesser extent with other viral infections [26,30].

Another possible reason for a higher late mortality among influenza patients could be related to an increased risk of bacterial superinfections, such as pneumonia [31]. In recent decades there has been a high incidence of staphylococcus aureus superinfections, especially during influenza A pandemics [32]. This occurs because influenza viral replication leads to cytopathic effects in the cells and dysregulates cytokine production [31]. This in turn alters the host's immune response to clear bacteria and achieve an appropriate modulation of the inflammatory cascade to fight infection [33]. A previous study [34] suggests that factors associated with a high 60-day mortality was Asian race, admission to ICU and immunosuppression (patients with human immunodeficiency virus (HIV) or immune dysfunction). In our study, 30-day mortality was significantly higher among patients who had spent longer time in the ICU but was not increased in patients who were immunosuppressed. It is quite possible that elevated cardiac biomarkers in patients with influenza are just a marker of severe viral illness and, as a consequence of immune dysfunction, patients becomes susceptible to new infections with a resultant higher mortality.

A major limitation of this study is that due to the retrospective design, there could have been a selection bias among patients who got evaluated for cardiac injury at the time of admission, as such, the findings of this study cannot be used to triage patients for admission according to the troponin levels. We were unable to get data on antiviral treatment received during admission, as previous studies [34,35] suggest mortality benefits among patients who receive early antiviral treatment. Vaccination status of the participants was not captured. Evidence [25] suggests that influenza vaccination reduces cardiovascular events and mortality and it is possible that vaccination may have impacted mortality in this study. Another limitation of this study is that there is a pos-

sibility that some of the outcome events were not captured by our central computer database, as the data were only available for patients who presented to the hospitals specified and there were no data available for patients who had sought treatment elsewhere e.g. in private hospitals.

6. Conclusions

An acute and significant change in hsTnT among patients with influenza is not only associated with an immediate increased mortality but is also associated with an increased 30-day mortality after discharge. Troponins were elevated in many who lacked a documented history of ischaemic heart disease. As such a finding of acute cardiac troponin elevation among patients with influenza patients should prompt a search for underlying predisposing conditions or risk factors for CAD and these should be meticulously managed according to the current guidelines to improve clinical outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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