Association of influenza infection and vaccination with cardiac biomarkers and left ventricular ejection fraction in patients with acute myocardial infarction

Abrar Ahmad Chughtai [a,*], Timothy C. Tan [b,c], Eleanor M. Hitchen [c], Mohana Kunasekaran [d], Chandini Raina MacIntyre [d,e]

[a] School of Public Health and Community Medicine, UNSW Medicine, The University of New South Wales, Sydney, New South Wales, Australia
[b] School of Medical Sciences, UNSW Medicine, The University of New South Wales, Sydney, New South Wales, Australia
[c] Sydney Medical School, The University of Sydney, Department of Medicine, Westmead Hospital, Australia
[d] Biosecurity Program, Kirby Institute, University of New South Wales, Sydney, NSW, 2052, Australia
[e] College of Public Service & Community Solutions, Arizona State University, Phoenix, AZ, USA

A B S T R A C T

Aims: The aim of this study was to examine the association of influenza infection and vaccination with extent of cardiac damage during acute myocardial infarctions (AMIs) as measured by serum biomarkers and left ventricular ejection function (LVEF) in patients.

Methods: Post-hoc analysis was performed on data from a prospective case-control study of influenza and AMI, conducted in a tertiary care hospital in Sydney, Australia. We included 275 cases of AMI, aged ≥ 40 years admitted to the cardiology during the study period.

Results: Mean and median CK-MB levels were significantly higher among unvaccinated group compared to vaccinated group (p value < 0.05). Troponin levels were also higher among unvaccinated group compared to vaccinated group; although not statistically significant. Troponin and CKMB values were not statistically different among influenza positive cases and influenza negative cases. Large size infarcts were less frequent among vaccinated cases compared to unvaccinated cases (25% vs 35.5%) and were more frequent among influenza positive cases compared to influenza negative cases (35.3% vs 31.5%), however differences were not statistically significant. LVEF was lower among vaccinated cases compared to unvaccinated cases (62.5% vs. 52.8%) and influenza positive cases compared to influenza negative cases (58.8% vs 55.4), however differences were not significant.

Conclusion: Lower CKMB levels among vaccinated groups showed that influenza vaccine may have a protective effect against large infarcts, therefore influenza vaccination should be recommended for high risk groups. The study suggests an association of larger infarcts with influenza infection, but larger studies are required to confirm this.

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1. Introduction

Worldwide, the annual influenza seasonal epidemic is estimated to result in approximately three to five million severe infections, and 290 000 to 650 000 respiratory deaths [1]. Similarly, ischaemic heart disease represents a significant disease burden, responsible for around 31% deaths globally. In the United States, an estimated 18.2 million people (6.7%) that are over 20 years of age have ischaemic heart disease [2]. Approximately 430,000 Australians are believed to have had a myocardial infarction in their lifetime, with the majority of these (>90%) being over the age of

55 [3], and an estimated 0.5 up to 45% being associated with influenza infection [4–8]. It has long been recognised that respiratory illness, in particular influenza virus infection [9], increases the risk of heart failure, acute clinical and subclinical myocarditis [10], cardiac arrhythmias [11], pericarditis [10], stress induced cardiomyopathy [12,13] and myocardial infarction [9,14,15] and associated mortality [16,17]. Acute cardiac injury, measured in the form of elevated cardiac biomarkers (Troponin T or creatinine kinase isoenzyme MB) is known to occur most commonly within the first three days after laboratory confirmation of influenza, with type 1 myocardial infarction conferring a worse prognosis than type 2. Despite this, there is some evidence that this effect may persist for up to twelve months after respiratory tract infection.

* Corresponding author.

In addition, lengths of hospital stay, shock, respiratory failure and acute kidney injury rates are all increased, and these patients are less likely to be considered for or offered invasive coronary revascularisation.

The pathophysiological mechanisms surrounding the co-development of myocardial infarction in the context of influenza are not fully understood. It is known that influenza has a weak affinity for cardiac myocytes when compared with the high affinity coxsackie B virus which commonly results in the development of myocarditis or myocardial infarction via disruption of dystrophin in cardiac myocytes.

It is common to observe an elevated troponin in patients infected with influenza, particularly if they are elderly or have other comorbidities. In one study the majority of patients (90.9%) with elevated troponin had influenza A [4]. Approximately 50% of these patients were later diagnosed with myocardial infarction despite being treated with antiviral therapy as per local guidelines [4]. Measurement of cardiac enzymes, is not only important for diagnostic purposes, but also as an indication of extent of myocardial damage, which gives valuable information regarding prognosis in terms of changes in left ventricular ejection fraction (LVEF) and mortality following a myocardial infarct. Cardiac troponins (I and T), creatinine kinase (CK) and creatinine kinase isoenzyme MB (CKMB) are all used as surrogate markers for the measurement of infarct size and are more accessible and less expensive in day to day clinical practice than the more accurate imaging modalities available to measure this such as MRI. Evidence is mounting that influenza vaccine can prevent AMI, and it is recommended for at-risk groups such as people who suffer from chronic conditions such as diabetes, respiratory and cardiovascular diseases. The aim of this study was to examine the association of influenza infection and vaccination with cardiac function as measured by biomarkers and LVEF in patients with acute myocardial infarction.

2. Methodology

We conducted a post-hoc analysis using data from a prospective case-control study of influenza and AMI [18]. This case-control study was conducted in a tertiary care hospital in Sydney, Australia during 2008 to 2010 (from late June to October in 2008 and 2010 and late May to October in 2009). The main aim of this study was to examine association of influenza and AMI. Cases (n = 275) included patients aged $\geq$ 40 years admitted to the cardiology unit with an AMI, during the study period. Diagnosis of AMI was based on biochemical markers of myocardial necrosis (rise and fall in troponin or CK-MB), with one or more of the following: ischaemic symptoms (chest or arm pain, nausea/vomiting, sweating, or shortness of breath); development of pathological Q waves on ECG; ECG changes indicative of ischemia (ST segment elevation or depression); coronary artery intervention; or pathological findings of an AMI. Details of the participants have been published previously [18]. Samples for cardiac biomarkers were collected from all cases within 72 h of the AMI event.

Structured interviews were conducted at the time of recruitment, to collect sociodemographic and health data, including age, gender, smoking and alcohol use, pre-existing medical illnesses, drug intake, vaccination uptake and self-reported respiratory illnesses (2009–10 only). Influenza vaccination records were validated from GP records. Nasal and pharyngeal viral swabs and blood samples were collected at the time of recruitment and blood samples were collected during the follow-up at 4–6 weeks for convalescent influenza serology. Primary outcome measure was laboratory evidence of influenza, defined as a positive Nucleic acid testing (NAT) or serological evidence of influenza A or B (defined as either a fourfold rise in titre between baseline and follow-up

in any individual, or a single titre of $\geq$ 64 at baseline in an unvaccinated individual). Details of testing methods have been previously published [18].

2.1. Data analysis

There were 275 AMI cases. Frequencies were calculated for categorical variables and means were calculated for continuous variables. First means and medians of troponin and CKMB were calculated among vaccinated and unvaccinated participants and influenza positive and influenza negative participant. Nonparametric independent sample test (Mann-Whitney U Test and Median test) were used to test significance and calculate p-values. Troponin and CKMB values were also stratified by STEMI and non-STEMI cases.

We used troponin [19–22] and CKMB [23] as measures of infarct size [21–24]. Plasma concentrations of cardiac troponin and CK-MB were described as mean and median values with the corresponding interquartile range (IQR). A categorical variable "infarct size" was created and large infarct was defined as troponin higher than 4.25 or CKMB higher than 2204 (i.e. upper 4th quantile). Of 275 cases, 88 had troponin or CKMB in upper 4th quantile and 187 had Troponin or CK-MB in lower 3 quantiles. Cardiac function was assessed as a categorical variable based on a cut-off LVEF of 50% - "low ejection fraction" if LVEF is $\leq$ 50% and high ejection fraction" if LVEF > 50. The Pearson $\chi2$ and logistic regression were used to test the association of influenza and vaccination status with infarct size and ejection fraction, with p $\leq$ 0.05 considered statistically significant. Potential confounders, including age, sex, smoking status, hypertension, high cholesterol and diabetes, were adjusted in multivariate regression model. The study protocol was approved by the Human Research Ethics Committee of the Sydney West Area Health Service (Westmead), New South Wales, Australia – HREC2007/2/4.8 (2533).

3. Results

Mean age of participants was 62 years and more than two thirds were male. Around one third received influenza vaccination (92/275, 33%) and 12% (34/275) tested positive for influenza. Demographic and health characteristics of vaccinated and unvaccinated AMI cases included in the study are in Table 1. Mean age of vaccinated participants was significantly higher compared to unvaccinated participants (p value < 0.001). The proportion of males and smokers was also higher among the unvaccinated group.

Table 2 shows mean and median troponin and CKMB values according to influenza vaccination status and influenza positivity. The mean and median troponin values were higher among unvaccinated participants and influenza negative participants; however, differences were not statistically significant. The mean (P value 0.023) and median (P value 0.033) CKMB values were significantly higher among unvaccinated group compared to vaccinated group. Both Troponin and CKMB values were generally higher in STEMI cases, compared to non-STEMI cases. CK-MB values were similar among influenza positive cases and influenza negative cases.

Large size infarcts were less frequent among vaccinated cases (23/92, 25%), compared to unvaccinated cases (65/182, 35.5%), however the difference was not statistically significant (OR 0.60 95% CI 0.34–1.05 and AOR 0.72, 95% CI 0.35–1.49). Among influenza positive cases, 12 (35.3%) had large size infarct and among influenza negative cases 76 (31.5%) had large size infarct (OR 1.77, 95% CI 0.55–2.50 and AOR 1.09, 95% CI 0.44–2.73). Table 3.

LVEF was lower among vaccinated and influenza positive cases. The rate of "low ejection fraction" (defined as LVEF $\leq$ 50%) was higher among vaccinated cases (62.5%, 25/40) compared to

Table 1

Demographic and health characteristics of participants.

Variable	Vaccinated		Unvaccinated		P value
	Number	Percent/mean SD	Number	Percent/mean SD	
Age (mean SD)	92	69.72 (±10.55 SD)	183	58.09 (±9.97 SD)	<0.001
Gender					
Male	63/216	68.5%	153/216	83.6%	0.004
Female	29/59	31.5%	30/59	16.4%	
Smoking status					
Current/ex-smoker	12/76	13.3%	64/76	35.2%	<0.001
No	78/196	86.7%	118/196	64.8%	
High blood pressure					
Yes	59/148	64.1%	89/148	48.6%	0.015
No	33/127	35.9%	94/127	51.4%	
High cholesterol					
Yes	54/150	58.7%	96/150	52.5%	0.327
No	38/125	41.3%	87/125	47.5%	
Diabetes					
Yes	22/68	23.9%	46/68	25.1%	0.824
No	70/207	76.1%	137/207	74.9%	
Large infarct					
Yes	23/88	25%	65/88	35.7%	0.073
No	69/186	75%	117/186	64.3%	
Low ejection fraction (LVEF ≤ 50%)					
Yes	25/72	62.5%	47/72	52.8%	0.305
No	15/57	37.5%	42/57	47.2%	
STEMI					
Yes	53/164	82.6%	111/164	76.6%	0.310
No	11/45	17.2%	34/45	23.4%	

*Missing 66 ** missing 112.

Table 2

Means and medians troponin and CKMB values according to influenza vaccination status and influenza positivity.

	Troponin			CKMB		
	Influenza vaccination	No vaccination		Influenza vaccination	No vaccination	
Mean	13.62	129.04	0.083	1144.43	1694.50	**0.023**
Mean STEMI	22.67	151.35	0.024	1396.92	2211.35	**0.012**
Mean nonSTEMI	2.15	197.61	0.516	1071.73	1219.44	0.907
Median	0.86	1.71	0.056	413.50	724.00	**0.033**
Mean STEMI	1.04	2.96	0.152	455	1177	**0.045**
Mean nonSTEMI	1.10	0.80	0.719	372	620.50	0.542
	Influenza	No influenza	P value	Influenza	No influenza	P value
Mean	22.12	100.38	0.361	1528.20	1506.42	0.687
Mean STEMI	5.91	123.26	0.303	2327.63	1889.43	0.672
Mean nonStemi	119.37	157.53	0.366	492.57	1269.68	0.280
Median	1.26	1.11	0.833	560.50	602.00	0.873
Mean STEMI	2.10	2.38	0.956	1304	964	0.626
Mean nonSTEMI	1.74	0.88	1.00	227	601.50	0.958

Table 3

Association of influenza vaccine and influenza positivity with infarct size in AMI patients.

	Infarct size*		OR and 95% CI	**AOR and 95% CI
	Large # (%)	Small # (%)		
Influenza vaccination				
Yes	23 (25)	69 (75)	0.60 (0.34–1.05)	0.72 (0.35–1.49)
No	65 (35.7)	117 (64.3)	Ref	Ref
Influenza positivity				
Yes	12 (35.3)	22 (64.7)	1.77 (0.55–2.50)	1.09 (0.44–2.73)
No	76 (31.5)	164 (68.3)	Ref	Ref

* Infarct size defined by Troponin or CKMB in upper 4th quartile.
** Adjusted by age, gender, smoking, high BP, high cholesterol and STEMI.

unvaccinated cases (52.8%, 47/89), however the difference was not significant (OR 1.49, 95% CI 0.69–3.20, AOR OR 1.23, 95% CI 0.46–3.31). Although most of the influenza positive cases had lower ejection fraction (58.8%) compared to influenza negative cases (55.4%), the difference was not statistically significant (OR 1.15, 95% 0.41–3.24 and AOR 1.20, 95% CI 0.39–3.68). Table 4.

4. Discussion

In this study we examined the relationship between influenza infection and vaccination with cardiac biomarkers and LVEF in patients with AMI, using data from a case-control study. Lower CKMB levels among vaccinated groups showed that influenza

Table 4
Association of influenza vaccine and influenza positivity with ejection fraction in AMI patients.

	Left ventricular ejection fraction (LVEF)		OR and 95% CI	AOR and 95% CI
	Low $\leq$ 50%# (%)	High > 50%# (%)		
Influenza vaccination				
Yes	25 (62.5)	15 (37.5)	1.49 (0.69–3.20)	1.23 (0.46–3.31)
No	47 (52.8)	42 (47.2)	Ref	Ref
Influenza positivity				
Yes	10 (58.8)	7 (41.2)	1.15 (0.41–3.24)	1.20 (0.39–3.68)
No	62 (55.4)	50 (44.6)	Ref	Ref

**Adjusted by age, gender, smoking, high BP, high cholesterol and stemi.

vaccine may have a protective effect against large infarcts. Influenza vaccines should be given to high risk cardiac patients to reduce morbidity and mortality associated with influenza-related cardiovascular events. Large scale studies are warranted to determine the association of influenza infection and vaccination with cardiac biomarkers and infarct size in patients with AMI.

Cardiac biomarkers are not only used for early diagnosis of AMI but may also be used to assess the extent of the myocardial necrosis and thus infarct size [19–21]. Troponin is a protein complex of three subunits (I, C and T) and of them troponin I and troponin T are heart-specific biomarkers. Steen et al. found significant correlation between cardiac troponin measurements 96 h after onset of ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation myocardial Infarction (NSTEMI) and infarct size measured by magnetic resonance imaging (MRI) [25]. A strong correlation has been observed between cardiac troponin I levels and infarct size in STEMI patients at 24, 48, 72, and 96 h after onset of symptoms [19]. Another study showed that 72-h troponin I is strongly correlated with 5-day and 30-day infarct size [26]. In this study we used troponin T and CKMB to estimate the infarct size. In this study only CKMB levels were significantly higher in the unvaccinated group compared with the vaccinated group. This may be due to a difference in kinetics of CK-MB release compared with troponin. Hedström et al. estimated the time-to-peak for CKMB and cardiac troponin T in AMI patients after reperfusion and infarct through percutaneous coronary intervention [21]. An earlier peak was seen for CK-MB (7.69 ± 3.6 h) compared to troponin T (8.19 ± 3.4 h). CKMB levels became normal for more than half of the cases after 48 h, while troponin T levels remained high in all patients [21]. However, both CKMB and troponin T levels were correlated with infarct size [21].

Influenza can potentially increase the risk of myocardial infarction through multiple mechanisms, including through hypoxia, tachycardia, release of cytokines and by causing a pro-thrombotic state. Influenza virus infection results in a rapid and aggressive cellular immune activation and resultant cytokine/chemokine response. Influenza has also been shown to cause increased destruction, permeability and disruption of cellular junctions by invading the endothelium [27], and there is a risk of influenza-associated thromboses and hypercoagulability. This is postulated to be caused by prothrombotic cytokines, endothelial dysfunction resulting in activation of the endothelium, upregulation of adhesion molecules and an increase in platelet aggregation [27]. These, combined with other influenza-induced pro-thrombotic and hypoxic effects as well as platelet activation via direct infection [27], may contribute to the increased myocardial infarction risk in influenza patients. However, there are some challenges to using cardiac biomarkers as a measure of infarct size [20,28]. First, timing of blood sample collection is important as some markers rise immediately after cardiac injury, while others peak at the later stage. Secondly, serial blood collection is required in order to identify the peak of marker release. Finally, the distribution and concentration of troponin in cardiac tissue is not consistent. Cardiac

troponin mass, measured as per gram wet weight tissue and per gram of protein, is generally lower in the atria compared to the ventricles [20,28]. Despite these limitations, cardiac markers are still widely used to identify high risk cases and also to determine infarct size.

Many studies have identified an association between influenza infection and AMI. Clinically, electrocardiographic changes have been noted in individuals infected with influenza, particularly if they already have underlying cardiac disease. In a study of healthy young adults (aged 18–40 years), experimentally infected with influenza B, various electrocardiographic changes were noted in just over 50% of patients. However, these were generally transient in nature and did not correlate with echocardiographic or cardiac biomarker abnormalities [29]. Two small studies demonstrated some structural and functional cardiac changes with influenza infection. One small prospective study identified regional wall motion abnormalities in patients clinically suspected of having influenza-associated myocarditis [30] and a smaller study of 28 patients infected with the influenza A H1N1 strain, showed enlarged left ventricular end systolic diameter (LVESD) and a significantly higher global myocardial performance index (MPI) [31]. However, the clinical significance of these findings was unclear. Most other studies looking at identifying echocardiographic changes in patients infected with influenza have not shown any significant change in standard echocardiographic parameters of cardiac structure and function [10].

Elevation of troponin [4] and CK [32] have also been demonstrated with influenza infection. Harris et al reported troponin levels in 1,131 laboratory confirmed influenza cases and 33 (2.9%) of them had elevated troponin levels>0.3 ng/mL [4]. In this study mean troponin levels were lower among influenza positive participants; however median troponin levels were higher among influenza positive cases. High rates of large size infarct and low LVEF among influenza positive cases provide an indirect evidence of association between influenza and AMI.

Current evidence suggests that influenza vaccine is protective against AMI and other acute cardiovascular events, therefore influenza vaccine is strongly recommended for high risk patients. The exact mechanism of this protection is not clear. Possible hypotheses include the prevention of influenza infections which have been shown to trigger AMI, and the prevention of the associated cytokine and inflammatory responses, which maintain stability atherosclerotic plaques [33]. There are also direct effects of influenza vaccine on bradykinin receptors [34]. Although there is evidence of elevation of cardiac biomarkers [4,32] in influenza infection, there has not been any direct studies examining the impact of influenza infection or influenza vaccination on infarct size. In this study CKMB levels were significantly higher among unvaccinated cases compared to vaccinated cases. Although troponin levels were also higher among unvaccinated cases compared to vaccinated cases, the difference was not statistically significant. This may be due to a greater variability in serum troponin levels as a result of different sampling times. This also suggests that the

current study is not adequately powered to detect a significant difference in the troponin levels. Large size infarcts were less frequent among vaccinated cases, which may be indirect evidence of influenza vaccine effectiveness against severe AMI.

Influenza viruses also can result in impairment of left ventricular function as a result of direct ischemic injury to the cardiac muscles, although left ventricular dysfunction have been reported without the presence of any ischemic injury. A review of 123 patients hospitalized with pandemic A(H1N1) in the United States reported 4.9% (6/123) had new or worsened left ventricular dysfunction [35]. In this study, infarct size correlated with left ventricular function [36] justifying the use of left ventricular ejection fraction as a surrogate measure of left ventricular damage in the case of influenza infection. This study demonstrated lower LVEF among influenza positive cases compared to those without infection. Further studies are clearly required to characterise the association of influenza infection and the impact of influenza vaccination with on LVEF in acute coronary syndromes.

There are a number of limitations of the study. The sample size was small, and hence underpowered to demonstrate a clear association between influenza infection, influenza vaccination and infarct size. However, the current study clearly demonstrates lower CKMB and troponin levels in vaccinated cases, which shows that influenza vaccine may have a protective effect against large infarcts. The other limitation relates to the large variability in the troponin levels which relate to sampling times and frequency which is generally strong after 3 days (i.e. 72 h [26]. In this study samples were collected at the time of recruitment, and were not adjusted for sample collection day. Quantification of infarct size using advanced imaging techniques such as cardiac MRI was not routinely performed due to the prohibitive cost and lack of availability of these imaging modalities at the time the study was carried out.

In summary, this study suggests that an influenza infection may result in larger infarct sizes and that influenza vaccination may have a cardioprotective effect. Influenza vaccination is a cheap and effective secondary preventive measure which may reduce the risks associated with AMI. Larger studies are required to further characterise and validate this relationship.

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Authors' contributions

CRM conceived the study. AAC, TCT and CRM designed the study. AAC and CRM performed the analyses. AAC, EMH and MK wrote the first draft of the manuscript, and all authors critically revised the manuscript and provided final approval of the manuscript.

Declaration of Competing Interest

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