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Prevalence of influenza and other acute respiratory illnesses in patients with acute myocardial infarction in Bangladesh: A cross-sectional study

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Abstract

Background and Aims: Several studies imply that influenza and other respiratory illnesses could lead to acute myocardial infarction (AMI), but data from low-income countries are scarce. We investigated the prevalence of recent respiratory illnesses and confirmed influenza in AMI patients, while also exploring their relationship with infarction severity as defined by ST-elevation MI (STEMI) or high troponin levels.

Methods: This cross-sectional study, held at a Dhaka tertiary hospital from May 2017 to October 2018, involved AMI inpatients. The study examined self-reported clinical respiratory illnesses (CRI) in the week before AMI onset and confirmed influenza using baseline real-time reverse transcription polymerase chain reaction (qRT-PCR).

Results: Of 744 patients, 11.3% reported a recent CRI, most prominently during the 2017 influenza season (35.7%). qRT-PCR testing found evidence of influenza in 1.5% of 546 patients, with all positives among STEMI cases. Frequencies of CRI were higher in patients with STEMI and in those with high troponin levels, although these relationships were not statistically significant after adjusting for other variables. The risk of STEMI was significantly greater during influenza seasons in the unadjusted analysis (relative risk: 1.09, 95% confidence interval [CI]: 1.02–1.18), however, this relationship was not significant in the adjusted analysis (adjusted relative risk: 1.03, 95% CI: 0.91–1.16).

Conclusion: In Bangladesh, many AMI patients had a recent respiratory illness history, with some showing evidence of influenza. However, these illnesses showed no significant relationship to AMI severity. Further research is needed to understand these relationships better and to investigate the potential benefits of infection control measures and influenza vaccinations in reducing AMI incidence.

KEYWORDS

acute myocardial infarction, acute respiratory illness, influenza, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction

1 | INTRODUCTION

Influenza-associated acute respiratory illness (ARI) accounts for millions of severe cases and more than half a million deaths worldwide every year.[1,2] Adults with comorbid illness and those aged more than 65 years are at higher risk of severe influenza outcomes[1] such as intensive care unit admissions.[3] The 2009 pandemic H1N1 influenza is thought to have contributed to more than 80,000 additional cardiovascular deaths globally indicating an unrecognized burden of severe influenza.[4] Furthermore, adverse cardiovascular incidents such as acute myocardial infarction (AMI) and stroke contribute to almost one-third of all deaths worldwide, and the majority of the global burden of AMI is currently observed in low- and middle-income countries, such as Bangladesh, where it is on a yearly rise.[5–7]

An AMI may be precipitated from a vulnerable atherosclerotic plaque rupture after short-term exposure of certain triggering factors such as acute respiratory infection.[8] An increase in the incidence of acute cardiovascular events such as AMI and stroke during winter months has been attributed to ARI, along with other determinants over the past years.[9] Temporal variations in acute cardiovascular events were reported as early as 1937[10] and several time-series analyzes showed correlations of seasonal peaks of influenza-associated mortality with cardiovascular deaths.[11–15] Meta-analysis of multiple case-control studies revealed that AMI cases were associated with greater incidence rates of recent acute respiratory illness, influenza-like illness, and laboratory-confirmed influenza compared to control groups (pooled odds ratio: 2.01; 95% confidence interval [CI]: 1.47–2.76),[16] which suggests that recent ARI and influenza may significantly contribute to the occurrence of AMI events. Furthermore, self-controlled case-series investigations have reported a heightened risk of AMI in the immediate aftermath of acute respiratory illness and laboratory-confirmed influenza.[17–20] Influenza and ARI have also been known to exacerbate myocardial injury, as indicated by troponin levels.[21] Although influenza-associated AMI may go unnoticed, it can be prevented through influenza-specific preventive measures, such as influenza vaccination, which has been proven effective in various large-scale randomized controlled trials (RCTs)[22] as well as several smaller RCTs.[23–25]

Like other low- to middle-income countries, an inadequately investigated double burden of communicable illnesses such as ARIs and non-communicable diseases such as adverse acute cardiovascular events like AMI prevails in Bangladesh.[26] National surveillance data confirms annual seasonal influenza prevalent among hospitalized patients throughout Bangladesh with unimodal peak during rainy season and may be associated with deaths among older adults and elderly.[27,28] Despite the existing burden of incidences of AMI, as well as the concomitant evidence of circulating influenza among the population there is lack of data and awareness on the prevalence of influenza as well as recent ARI exclusively among AMI patients in Bangladesh, which incited the current investigation. Therefore, the primary research question was about the prevalence of recent ARI and laboratory evidence of influenza among patients with AMI in Bangladesh. This information is crucial for understanding the extent of the impact of these illnesses on the cardiovascular health of the population and for developing targeted interventions. To address the gap, the current exploratory study aimed to estimate the prevalence of recent respiratory illness and laboratory-confirmed influenza among patients hospitalized with AMI. A secondary aim was to explore the relationship of recent respiratory illness with severity of infarction. As an initiative, we opted for a cross-sectional design without a control group for its time efficiency, simplicity and ability to include a larger population.

2 | METHODS

2.1 | Study design and study population

A cross-sectional study was conducted on patients aged ≥18 years hospitalized with AMI to the cardiology unit of National Institute of Cardiovascular Diseases in Dhaka, Bangladesh (NICVD). The patients were enrolled during the study period between 1st May 2017 and 31st October 2018 which included the 2017 annual influenza season (rainy season; between 1st May and 31st October) and the 2018 annual influenza seasons (rainy season; between 1st May and 31st October) and non-influenza season (winter; November 1, 2017 to April 30, 2018). The description of annual influenza seasons for Bangladesh based on national surveillance data is discussed in detail by Zaman et al.[27] Bangladesh is the eighth-most populous country in the world, with a population exceeding 165 million, and also among the most densely populated countries in the world.[29] The NICVD is the largest government-operated tertiary-level acute care teaching hospital in Bangladesh specialized exclusively in management of cardiovascular patients traveling from all regions of the country. Project staff followed a standardized protocol to identify and recruit cases with AMI, diagnosed on electrocardiogram (ECG) findings (ST-segment elevation or depression, pathological Q waves) and ischemic symptoms (chest or arm pain, nausea or vomiting, sweating, shortness of breath), with either a change in blood level of cardiac biomarkers of myocardial necrosis (typical rise and gradual fall in Troponin or more rapid rise and fall in Creatine Kinase MB) or coronary artery intervention.[30] To minimize the potential misclassification bias, after reviewing the criteria for case definition of AMI from hospital records, staff consulted with attending cardiologist to further ensure the diagnosis of AMI. Cases with previous history of cardiovascular event were eligible. Cases with self-reported history of chronic liver impairment, chronic renal impairment, malignancy, and autoimmune disorders or those not providing consent were excluded from the study. These conditions and their treatments could independently affect inflammatory markers and cardiovascular risk, complicating the interpretation of the relationship between influenza and AMI.

2.2 | Sample size

We projected that 15%[27] of patients with AMI would have a history of recent respiratory illness, and therefore we required a minimum

sample size of 396 patients to estimate this proportion with an absolute precision of 5% points and a 95% level of confidence at 80% power. The 5% absolute precision for sample size calculation was chosen to balance accuracy in prevalence estimates with resource limitations, allowing significant differences to be detected within the 10%–20% expected prevalence range while maintaining practical feasibility. To calculate the sample size, we utilized the power and sample size function in STATA 13 for Windows. The formula used was "sampsi 0.15 0.10, power(0.80) onesample." This approach enabled us to determine the minimum sample size required to achieve our desired level of precision and confidence in the estimation of the proportion of recent respiratory illness among AMI patients. However, we enrolled 744 participants instead of the initially planned 396 to enhance robustness and reliability. This increase accounted for potential dropouts and ensured sufficient statistical power for detailed subgroup and stratified analyzes by influenza and non-influenza seasons among AMI patients.

2.3 | Data collection

On a daily basis staff reviewed medical records and interviewed recruited AMI patients using a structured interviewer-administered questionnaire to record sociodemographic data, self-reported history of recent respiratory symptoms including fever, cough, sore throat, runny nose, and difficulty breathing within the past week of AMI onset, information on lifestyle and co-morbid illness and conducted clinical examination as well as anthropometric measurements of the participants. The blood cardiac troponin results were obtained from hospital records measured at baseline in nanograms per milliliter (ng/mL).

2.4 | Specimen collection and laboratory analysis

Trained staff collected nasopharyngeal and oropharyngeal swabs at recruitment within 72 h of the date and time of AMI onset. Specimen collection within the aforementioned timeframe was conducted to maximize the sensitivity of the study to detect influenza RNA in the swabs before the cessation of viral shedding. The specimens were transported daily in Viral Transport Medium (VTM) at 2–8°C to the virology laboratory of International Centre for Diarrheal Disease Research, Bangladesh (icddr,b), in Dhaka. The specimens were aliquoted in a BSL-2 (bio-safety level-2) safety cabinet and were stored in freezers at or below −70°C until analysis. Viral RNA was extracted from the swab specimen and real-time reverse transcription polymerase chain reaction (qRT-PCR) was performed using primers and probes specific for influenza A and B viruses provided by the Influenza Division at CDC. Hemagglutinin subtyping of types A and B viruses was performed to detect subtypes, A/H3, A/H1N1pdm09, B/Victoria, and B/Yamagata. The laboratory used validated protocols[31] and followed standard quality control procedures.

2.5 | Exposure and outcome measures

The primary exposure was clinical respiratory illness (CRI) defined as self-reported history of ≥2 respiratory symptoms (fever, cough, sore throat, runny nose, and difficulty breathing) within the prior 7 days of the date of onset of AMI.[32,33] The secondary exposure was baseline qRT-PCR confirmed influenza A or B. In the current study, the main predictor variables of interest were CRI and laboratory evidence of Influenza, and the outcome variables were AMI and AMI sub-types.

2.6 | Data analysis

Categorical data were expressed as frequencies and percentages, while continuous data was expressed as mean ± standard deviation (SD).

2.6.1 | Prevalence of CRI among all AMI cases and sub-groups of AMI cases

Descriptive analysis was performed to determine the prevalence (frequencies and percentages) of CRI and qRT-PCR-confirmed influenza among all AMI cases as well as among various sub-groups of AMI cases. The prevalence of CRI and influenza among the enrolled patients was estimated by study seasons: during 2017 annual influenza season (1st May to 31st October, 2017), 2017/2018 non-influenza season (November 1, 2017 to April 30, 2018) and 2018 annual influenza season (1st May to 31st October, 2018). The sub-groups of AMI cases included the binary variables created for non-ST-Elevation Myocardial Infarction (NSTEMI) or, ST-Elevation Myocardial Infarction (STEMI), for blood troponin level (high or low) and for new onset or recurrent onset AMI. The STEMI and NSTEMI were classified by the presence or absence of ST-elevation findings in ECG. High-troponin was defined as the upper 4th quartile of the blood cardiac troponin level ≥24.3 ng/mL. STEMI and high-troponin were measures of more severe myocardial damage among AMI cases. The Pearson χ^2 test[34] was conducted to compare the proportions of CRI and influenza across AMI subgroups and also between influenza and non-influenza seasons. For the differences between groups, a $p \leq 0.05$ was considered as statistically significant.

2.6.2 | Relationship of recent clinical respiratory illness with STEMI and high-troponin level in blood among AMI patients

Multivariable log-binomial regression[35] analyzes were performed to investigate the relationships of CRI with the occurrence of STEMI and high blood troponin among AMI patients, controlling for potential confounders. All variables deemed clinically relevant as well as having potential confounding effect and also based on *p*-value were entered in the base model and sequentially removed using a backward stepwise approach whereby variables with *p*-values ≤0.25 remained in the final model. Additionally, the variables altering the exposure-outcome

TABLE 1 Demography, lifestyle, and clinical characteristics of enrolled patients with acute myocardial infarction.

Characteristics	*N* = 744; *n* (%)
Mean (*SD*) age in years	51.7 (10.4)
Male	677 (91)
Marital status	
Never married	20 (2.7)
Married	695 (93.4)
Divorced/widow/other	29 (3.9%)
Location	
Rural	351 (47.2)
Urban	393 (52.8)
Education	
≤primary level	538 (72.3)
Primary to HSC	143 (19.2)
Completed graduation	63 (8.5)
Lifestyle	
Ever used tobacco	551 (74.1)
Doing moderate to heavy physical activity every week	383 (51.5)
Family history of cardiovascular diseases	469 (63)
Self-reported chronic illnesses or past illnesses	
At least one chronic illness	442 (59.4)
Hypertension	285 (38.3)
Diabetes	187 (25.1)
High blood cholesterol	63 (8.5)
Stroke	23 (3.1)
Coronary heart disease	68 (9.1)
Heart failure	16 (2.2)
Structural heart disease	2 (0.3)
History of percutaneous coronary intervention (PCI)	9 (1.2)
History of coronary artery bypass graft (CABG)	2 (0.3)
Onset of AMI	
New	678 (91.1)
Recurrent	66 (8.9)
Type of AMI	
NSTEMI	143 (19.2)
STEMI	601 (80.8)
Subtype of STEMI	
Anterior STEMI	189 (25.4)
Anteroseptal STEMI	106 (14.2)
Inferior STEMI	308 (41.4)
Lateral STEMI	11 (1.5)
Other subtypes of STEMI	71 (9.5)
Mean (*SD*) BMI	25.4 (13.8)

Abbreviations: AMI, acute myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; *SD*, standard deviation; STEMI, ST-segment elevation myocardial infarction.

association, in the multivariable model, by 10% were considered confounders. We investigated the aforementioned relationships for, (1) entire study period and (2) independently for either the influenza or non-influenza seasons. The magnitudes of relationships were expressed as relative risk (RR) and adjusted relative risk (aRR) with 95% CI in unadjusted and adjusted analyzes, respectively.

2.6.3 | Risk of occurrence of STEMI during influenza season compared to non-influenza season

We compared proportion of STEMI over NSTEMI among all AMI cases between influenza and non-influenza seasons. The purpose was to examine if exposure to influenza season as opposed non-influenza season had any significant impact on the frequency of events of STEMI compared to that of NSTEMI. Univariate and multivariable Log binomial regression analyzes were performed to measure the unadjusted and adjusted RRs of occurrence of STEMI during influenza versus non-influenza season. The steps for building the multivariable regression model followed the previously mentioned process.

All of the statistical tests conducted in the current work was two-tailed. The SAS statistical software version 9.4 (SAS institute, USA) was used to run all the analyzes.

2.7 | Ethical approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Enrollment of the participants started after approval of the study by the icddr,b Institutional Review Board (PR-17039) and UNSW Human Research Ethics Committee (HC 17861). Informed written consent to participate in the study was obtained.

3 | RESULTS

A total of 744 AMI patients were enrolled during the study period (Table 1). The mean age of participants was 51.7 years. The majority were male (91%) and more than three-fourth of the participants reported tobacco use. Sixty-three percent had family history of CVD.

TABLE 2 Prevalence of self-reported clinical respiratory illness and laboratory-confirmed influenza among the patients with acute myocardial infarction by study seasons.

Patients	Proportion, *n/N* (%)			
	2017 Influenza season	Non-influenza season	2018 Influenza season	All seasons
Clinical respiratory illness				
All AMI	20/56 (35.7)	27/210 (12.9)	37/478 (7.7)	84/744 (11.3)
New onset AMI	18/44 (40.9)	27/198 (13.6)	32/436 (7.3)	77/678 (11.4)
Recurrent onset AMI	2/12 (16.7)	0/12 (0)	5/42 (11.9)	7/66 (10.6)
NSTEMI	6/18 (33.3)	3/41 (7.3)	3/46 (6.5)	12/105 (11.4)
STEMI	14/38 (36.8)	24/169 (14.2)	34/432 (7.9)	72/639 (11.3)
Low-troponin AMI	7/20 (35.0)	9/78 (11.5)	11/127 (8.7)	27/225 (12.0)
High-troponin AMI	3/8 (37.5)	1/32 (3.1)	4/35 (11.0)	8/75 (10.7)
Laboratory-confirmed influenza				
All AMI	1/56 (1.8)	0/12 (0)	7/478 (1.5)	8/546 (1.5)
New onset AMI	1/44 (2.3)	0/11 (0)	5/436 (1.1)	6/491 (1.2)
Recurrent AMI	0/12 (0)	0/1 (0)	2/42 (4.8)	2/55 (3.6)
NSTEMI	0/18 (0)	0/4 (0)	0/46 (0)	0/68 (0)
STEMI	1/38 (2.6)	0/8 (0)	7/432 (1.6)	8/478 (1.7)
Low-troponin AMI	1/20 (5)	0/3 (0)	2/127 (1.6)	3/150 (2)
High troponin AMI	0/8 (0)	0/2 (0)	1/35 (2.9)	1/45 (2.2)

Note: 2017 annual influenza season: rainy season; during 1st May to 31st October, 2017. Non-influenza season: winter; November 1, 2017 to April 30, 2018. 2018 annual influenza seasons: rainy season; during 1st May to 31st October, 2018.

Abbreviations: AMI, acute myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

The most commonly reported chronic illness was hypertension (38.3%) followed by diabetes (25.1%). Among the cases, 91.1% were of new-onset AMI and 80.8% were STEMI. The majority of the STEMI cases were inferior STEMI (41.4%).

3.1 | Proportion of CRI among patients with AMI

Out of the 744 AMI patients enrolled during the entire study duration, 84 (11.3%) had reported having CRI during the week before AMI onset (Table 2). The majority of participants reporting CRI (77/84; 91.7%) had developed CRI within 3 days of AMI onset. The most common respiratory symptoms reported during the week preceding AMI were fever (17.9%), cough (16.5%), and runny nose (10.6%). The prevalence of CRI among AMI cases and subgroups varied between influenza and non-influenza seasons, with the highest prevalence observed during the 2017 influenza season (35.7%). During the 2018 influenza season, CRI was more common in recurrent than new onset AMI cases (11.9% vs. 7.3%; $p = 0.36$). Furthermore, during the 2017 influenza season, the prevalence of CRI was higher among STEMI cases than NSTEMI cases (36.8% vs. 33.3%; $p = 0.79$), and prevalence of CRI was higher in STEMI than in NSTEMI cases during the non-influenza season (14.2% vs. 7.3%; $p = 0.24$) and during the 2018 influenza season (7.9% vs. 6.5%; $p = 0.74$). The high-troponin AMI cases had higher rates of CRI compared to low-troponin cases during 2017 (37.5% vs. 35.0%; $p = 0.90$) and during 2018 influenza season (11% vs. 8.7%; $p = 0.62$). Last, the percentage of CRI within 3 days of onset of AMI was higher in recurrent than new onset AMI cases ($p = 0.15$), in high-troponin than low-troponin AMI cases ($p = 0.62$) during 2018 influenza season and higher in STEMI than NSTEMI cases during both non-influenza ($p = 0.31$) and 2018 influenza season ($p = 0.50$).

3.2 | Proportions of laboratory-confirmed influenza

Out of 744 participants enrolled in the study, 546 (73.4%) were tested for influenza by qRT-PCR, and among them only 8 (1.5%) were positive (Table 2). Of the positive cases, one was confirmed during the 2017 influenza season and seven during the 2018 influenza season. The identified influenza subtypes were one influenza B/Yamagata during October 2017, four A/H3

TABLE 3 Relationship of clinical respiratory illness with ST-elevation myocardial infarction by study seasons.

Clinical respiratory illness status	Total	NSTEMI *n* (%)	STEMI *n* (%)	RR[a] (95% CI)	aRR[b] (95% CI)
All seasons					
No	660	93 (14.1)	567 (85.9)	**Ref.**	**Ref.**
Yes	84	12 (14.3)	72 (85.7)	0.99 (0.91–1.09)	1.03 (0.87–1.22)
2017 influenza season					
No	36	12 (33.3)	24 (66.7)	**Ref.**	**Ref.**
Yes	20	6 (30.0)	14 (70.0)	1.05 (0.73–1.52)	1.03 (0.60–1.75)
During 2017/2018 non-influenza season					
No	183	38 (20.8)	145 (79.2)	**Ref.**	**Ref.**
Yes	27	3 (11.1)	24 (88.9)	1.12 (0.96–1.31)	1.05 (0.82–1.34)
During 2018 influenza season					
No	441	43 (9.8)	398 (90.2)	**Ref.**	**Ref.**
Yes	37	3 (8.1)	34 (91.9)	1.02 (0.92–1.13)	1.01 (0.87–1.19)
During all influenza seasons[c]					
No	477	55 (11.5)	422 (88.5)	**Ref.**	**Ref.**
Yes	57	9 (15.8)	48 (84.2)	0.95 (0.85–1.06)	0.92 (0.29–2.87)

Abbreviations: aRR, adjusted relative risk; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; NSTEMI, non-ST-segment elevation myocardial infarction; RR, relative risk; STEMI, ST-segment elevation myocardial infarction.

[a]RR: unadjusted relative risk.

[b]aRR: adjusted relative risk; adjusted for age, sex, tobacco use, hypertension, diabetes, high blood cholesterol, heart failure, exercise level, previous history of CHD, family history of CVD and BMI.

[c]Includes both annual influenza seasons of 2017 and 2018.

during July, one A/H3 during August, and two A/H1N1pdm09 during July 2018 influenza season. Influenza virus was detected exclusively among STEMI cases. Influenza was more prevalent among recurrent AMI cases than new AMI cases during the overall study period (3.6% vs. 1.2%; 0 = 0.16) and the 2018 influenza season (4.8% vs. 1.1%; $p = 0.06$). Influenza positivity was higher among AMI cases with high troponin levels than those with low troponin levels during the 2018 influenza season (2.9% vs. 1.6%; $p = 0.62$).

3.3 | Proportion of CRI compared between 2017/2018 non-influenza season and all influenza seasons

We compared the proportions of AMI cases and also sub-groups of AMI cases reporting recent CRI during the combined duration of annual influenza seasons to that during the 2017/2018 non-influenza season. Among AMI patients with high blood level of troponin, proportion of CRI was higher during influenza seasons (16.3%) compared to non-influenza season (3.1%) with $p = 0.07$. Similarly, NSTEMI patients had a higher proportion of CRI during influenza season (14.1%) compared to non-influenza season (7.3%) with a p value of $p = 0.3$.

3.4 | Log binomial regression

3.4.1 | Relationship of CRI with STEMI by study seasons

Overall, the proportions of STEMI were similar between AMI cases with or without CRI during either non-influenza and influenza seasons. However, STEMI proportion was slightly higher among patients with CRI than patients without CRI during 2017-influenza season and during non-influenza season (Table 3). Nevertheless, the aRRs for relationship of CRI with STEMI were around 1 during different study seasons which was statistically not significant.

3.4.2 | Relationship of CRI with high blood level of troponin among AMI patients by study seasons

Overall, the results demonstrate that there was no significant relationship between recent CRI (Table 4) and high blood levels of troponin among patients with AMI, during different study seasons. However, there was a positive trend in the relationship between CRI and high-troponin AMI, especially during the 2018 influenza season where the RR is 1.26 and the aRR is 1.79. However, these estimates were not statistically significant. Similarly, during all influenza seasons, there was a slight positive trend in

TABLE 4 Relationship of clinical respiratory illness with high level of troponin in blood among patients with myocardial infarction by study seasons.

Respiratory illness	Total	Low troponin *n* (%)	High troponin *n* (%)	RR[a] (95% CI)	aRR[b] (95% CI)
During all seasons					
No	265	198 (74.7)	67 (25.3)	**Ref.**	**Ref.**
Yes	35	27 (77.1)	8 (22.9)	0.90 (0.47–1.72)	0.89 (0.42–1.87)
During 2017 influenza season					
No	18	13 (72.2)	5 (27.8)	**Ref.**	**Ref.**
Yes	10	7 (70.0)	3 (30.0)	1.08 (0.70–1.67)	1.03 (0.46–2.31)
During 2017/2018 non-influenza season					
No	100	69 (69)	31 (31)	**Ref.**	**Ref.**
Yes	10	9 (90)	1 (10)	0.32 (0.05–2.12)	0.36 (0.08–1.61)
During 2018 influenza season					
No	147	116 (78.9)	31 (21.1)	**Ref.**	**Ref.**
Yes	15	11 (73.3)	4 (26.7)	1.26 (0.52–3.1)	1.79 (0.58–5.48)
During all influenza seasons[c]					
No	165	129 (78.2)	36 (21.8)	**Ref.**	**Ref.**
Yes	25	18 (72.0)	7 (28.0)	1.28 (0.79–2.09)	1.12 (0.53–2.35)

Abbreviations: aRR, adjusted relative risk; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; RR, relative risk.

[a]RR: unadjusted relative risk.

[b]aRR: adjusted relative risk; adjusted for age, sex, tobacco use, hypertension, diabetes, high blood cholesterol, heart failure, exercise level, previous history of CHD, family history of CVD and BMI.

[c]Includes both annual influenza seasons of 2017 and 2018.

TABLE 5 Relationship of influenza seasons with ST-elevation myocardial infarction.

Seasons	Total	NSTEMI *n* (%)	STEMI *n/N* (%)	RR[b] (95% CI)	aRR[c] (95% CI)*
Non-influenza season	210	41 (19.5)	169 (80.5)	**Ref.**	**Ref.**
Influenza seasons[a]	534	64 (12.0)	470 (88.0)	1.09 (1.02–1.18)	1.03 (0.91–1.16)

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; NSTEMI, non-ST-segment elevation myocardial infarction; RR, relative risk; STEMI, ST-segment elevation myocardial infarction.

[a]Includes both annual influenza seasons of 2017 and 2018.

[b]RR: unadjusted relative risk.

[c]aRR: adjusted relative risk; adjusted for age, sex, tobacco use, exercise level, hypertension, diabetes, high blood cholesterol, heart failure, previous history of CHD and BMI.

*$p = 0.67$.

the RR of 1.28 and the aRR of 1.12, but again, the results were not statistically significant.

3.4.3 | Risk of STEMI during influenza season compared to non-influenza season

Table 5 shows the regression analysis for the risk of experiencing a STEMI over NTEMI during the influenza season compared to the non-influenza season. In the univariate analysis, onset of STEMI was significantly more likely during influenza compared to non-influenza season, with a risk of RR: 1.09, 95% CI: 1.02–1.18, but this relationship was not found significant after adjusting for confounders in the multivariate analysis (aRR: 1.03, 95% CI: 0.91–1.16).

4 | DISCUSSION

To the best of our knowledge, this is the first study in Bangladesh to investigate the prevalence of recent CRI and laboratory-confirmed influenza among patients with AMI. The results of this study indicate that a significant proportion of the participants had a history of CRI

within a week of AMI onset and that qRT-PCR-confirmed influenza was present, suggesting that recent acute respiratory illness and influenza may potentially contribute to triggering AMI. Notably, the self-reported CRI among AMI patients was prevalent during both influenza and non-influenza seasons, indicating that the circulation of non-influenza respiratory viral pathogens could also potentially play a role in triggering the onset of AMI.[36–38] These findings highlight the need for further investigation into the potential association between recent respiratory illnesses and AMI, including the identification of specific viral pathogens and mechanisms underlying this association. About one-third of the enrolled AMI patients during the 2017 influenza season reported a history of CRI which was much more frequent than that reported during 2018 influenza season. This could be validated in the context of report by the national hospital-based influenza surveillance program in Bangladesh indicating a relatively more severe influenza epidemic and upward surge in severe acute respiratory illness (SARI) admissions occurred in the country during 2017 compared to the 2018 influenza season[39] suggesting that there could be a potential link between the intensity of the influenza season and the number of AMI cases associated with influenza. The current study did not find a statistically significant relationship between recent CRI and the severity of myocardial damage, as defined by STEMI or high blood troponin. However, in general, the proportion of STEMI cases over NSTEMI was higher during the influenza season compared to the non-influenza season, and this difference was statistically significant in the unadjusted but not in adjusted regression analysis. It is possible that unrecognized recent influenza infection may play a role in triggering STEMI, however, further research is needed to establish a definitive relationship. Although our findings imply a potential link between recent acute respiratory illnesses and influenza with the occurrence of AMI, it is crucial to acknowledge that our study's cross-sectional design does not allow us to establish a definitive association between the exposures and the outcome and hence recommend further validation. Further studies, including case-control studies or prospective cohort studies, are needed to confirm an association and elucidate the mechanisms underlying this association. However, these results do highlight the importance of considering the potential impact of respiratory illness, including seasonal influenza, on cardiovascular health among population in Bangladesh. Importance of further research and analysis of the potential benefits of robust infection control measures and influenza vaccination programs for AMI prevention cannot be overstated.

Previous studies have reported a wide range of frequencies of recent respiratory illness among AMI cases, ranging from 2.8% to 60.3%.[16] The overall frequency of recent CRI in this study (11.3%) is comparable to previous reports,[16] from London (14.3%) and Finland (12.2%), and the frequency of CRI during the 2017 influenza season in this study (36%) is comparable to reports,[16] from Sydney, Australia (31.1%), Massachusetts (28%), London (24.3%), Finland (28%) and lastly from Karachi, Pakistan[37] (36.2%). However, it is possible that the differences in reported frequency of acute respiratory illness among AMI cases across studies may be attributed to various factors, such as demographic variations among participants and discrepancies in the criteria used to define recent acute respiratory illness. Most of the previous studies were conducted in high-income countries where the average age of recruited AMI patients was over 60 years old, which was significantly older than the average age of participants in our study (52 years). While Warren et al.[40] defined recent acute respiratory illness for AMI cases as having both respiratory and systemic symptoms with an onset of illness within the past month, our criteria for CRI did not include systemic symptoms. This difference in criteria may be an important limiting factor in appropriately classifying cases with recent acute respiratory illness, as including systemic symptoms in the criteria for recent acute respiratory illness may be crucial in accurately identifying cases that have truly had a recent acute respiratory infection. Our study's definition for CRI[32,33] only included respiratory symptoms that developed within a week of AMI to minimize recall bias. We believe that major cardiovascular events following an acute respiratory infection are more clinically plausible during this timeframe than a longer period of time after the infection. Despite the lack of systemic symptoms in our case definition, we still believe that our definition for recent respiratory illness in the current study is clinically sensitive enough to increase the likelihood of capturing cases with recent respiratory infection preceding onset of AMI. However, we acknowledge that our definition may have lower specificity, potentially leading to the inclusion of false positive cases for CRI. Another potential contributing factor to the differing frequencies across previous studies is that some were restricted to only influenza seasons while others were conducted during both influenza[30,40] and non-influenza seasons.[41]

Due to cross-sectional study design, we were unable to show a direct association between recent CRI and AMI. However, several previous case-control studies showed an association of recent respiratory illness with AMI. A case-control study based on large general practice database in Europe showed risk of AMI incidence twofold within 7 days after respiratory infection.[41,42] Another longitudinal population-based cohort study performed in the United States indicated risk of acute cardiovascular events including AMI, stroke and death highest during the first month of hospitalization for pneumonia.[41,42] In general AMI cases could be as much as twice more likely than controls to report history of recent respiratory illness occurring within 7 days of AMI onset and the strength of this association is lesser for respiratory illness occurring >7 days of onset of AMI and fell over time.[30,40,41] There is high double burden of both acute respiratory infections as well as acute cardiovascular events[26] in Bangladesh and despite evidence in other countries there is no data for Bangladesh about prevalence of recent respiratory illness preceding onset of AMI.

We reported a low frequency of influenza positivity in AMI cases. In the previous studies, the frequency of influenza detection by real-time PCR, paired serum influenza antibodies and single baseline influenza antibody titer among AMI patients ranged from 14% to 86.3%.[16] The detection rates may considerably vary due to study-specific laboratory methods applied, pattern as well as intensity of

influenza strains during study period, and study conducted during both or either influenza and/or non-influenza seasons. The most confirmatory standard test method to diagnose influenza is the RT-PCR test of respiratory swabs as recommended by the World Health Organization (WHO). Most of the previous studies identified low numbers of influenza by PCR alone.[30,40,43] Nevertheless, investigators considered using baseline serology[43] and analysis of paired serums[30] for immunoglobulin G or baseline serology for immunoglobulin A[40] to report additional influenza with or without PCR. The WHO recommends swabbing patients within 10 days of onset of respiratory symptoms to increase the likelihood of detecting influenza RNA by PCR before diminution of viral shedding.[44] There is still limited clarity on the exact timeline of onset of AMI after influenza infection, hence PCR test will likely have lower sensitivity if viral shedding diminishes before swabbing AMI patients. However, to maximize sensitivity to detect viral shedding, all participants in our study were swabbed within 72 h of the onset of AMI. Serological analysis of convalescent serum in addition to PCR could have enhanced the sensitivity to detect more influenza-positive AMI patients which is limitation of the current study. Moreover, due to administrative delays, we enrolled and tested only a minimal number of AMI cases during the peak influenza months May-September in 2017 influenza season when sequentially A(H1N1)pdm09, A/H3, and influenza B were the predominant strains circulating nationally.[39]

During the current study, all cases of qRT-PCR-confirmed influenza among AMI patients were identified only within the influenza seasons. The influenza subtypes that were identified fully corresponded to the month-specific circulating influenza strains identified through the national influenza surveillance scheme in the country[39] signifying typical influenza strains were also circulating among AMI patients in Bangladesh during the 2017 and 2018 influenza seasons. Interestingly, our study found a higher frequency of real-time PCR-confirmed influenza in AMI patients compared to similar studies conducted in high-income countries, where only 0/70 and 1/275 AMI cases tested positive for influenza nucleic acid.[30,40] It is possible that the population in Bangladesh has a higher susceptibility to influenza-associated AMI due to factors such as low vaccination rates, or high prevalence of cardiovascular co-morbidities. Nevertheless, our study design was cross-sectional and did not have a control group, therefore not specifically designed to investigate the association between laboratory-confirmed influenza and AMI. However, very few previous case-control studies were able to reveal a direct association between laboratory-confirmed influenza and AMI,[43] perhaps due to the fact that influenza may be less common in the particular age group where AMI usually occurs. Conversely, more case-control studies have reported significant effectiveness of influenza vaccine against AMI[16,30] which could be an indirect evidence of influenza's association with AMI.

When we explored the relationship between recent CRI and the severity of myocardial damage, particularly during influenza seasons, our findings indicated that recent CRI frequencies were generally higher among STEMI patients compared to NSTEMI patients. Similarly, the analysis showed a positive trend in the relation between CRI and high troponin levels- up to 80% higher during the 2018 influenza season. However, none of these findings had statistical significance. Therefore, caution should be exercised in interpreting these trends, as they do not necessarily indicate a definitive association. Furthermore, while all of the identified influenza strains were exclusive to STEMI cases, it is important to interpret these findings with caution in patient evaluations, as this observation may not represent a genuine relationship. Both STEMI and high troponin level are related to severe myocardial damage. We believe that the analyzes conducted during influenza seasons were underpowered because the sample sizes were too small within the AMI subgroups categorized by myocardial damage severity. This small sample size likely prevented us from detecting statistically significant results, even if a genuine relationship between CRI and infarction severity existed. Nevertheless, there is previous evidence that influenza infection may increase the risk while the influenza vaccine is effective against large-size infarcts, high troponin or CK-MB levels in patients with AMI.[45] Potential connection between seasonal fluctuations in the occurrence of severe acute respiratory infections, such as influenza, and AMI events with significant myocardial damage in high-risk, unvaccinated individuals could benefit from more detailed investigation. This investigation should involve robust analytical studies carried out over multiple seasons to enhance the clarity and reliability of the findings. It seems plausible that the magnitude and direction of such relationships might be influenced by the intensity and pattern of circulating seasonal influenza strains embedded within climatic factors[37,46] and perhaps additionally and importantly, on clinically unrecognized respiratory viral infections.[11,13,36] For example, five out of seven influenza-positive cases in the current study did not report recent CRI which may imply that the link between influenza and AMI may be more complex than our current understanding. This may also suggest that there may be other mechanisms by which influenza increases the risk of AMI, even in the absence of an acute respiratory illness. For example, influenza may cause changes in the immune system, blood clotting, or cardiac function increasing the risk of AMI. Alternatively, it may be that the individuals in the study who tested positive for influenza but did not report recent acute respiratory illness had underlying conditions predisposing them to AMI, and the influenza infection simply acted as a trigger.[47] Accordingly, further analysis in the current study showed a higher prevalence of STEMI over NSTEMI among participants during influenza season than during non-influenza season. The univariate analysis showed there was a significant 9% increase in the risk of STEMI during influenza than during non-influenza season suggesting that acute respiratory illnesses could potentially intensify STEMI events during periods of influenza.

The underlying pathophysiology of STEMI is complete blockage of the coronary artery by atherothrombosis causing transmural cardiac myonecrosis. This is primarily driven by an acute end stage of a chronic inflammatory atherosclerotic lesion characterized by abrupt rupturing of the de-stabilized atherosclerotic plaque due to short-term exposure of certain triggering factors that may differ from the

number of known cardiovascular risk factors.[48] Such triggers of plaque rupture can include respiratory viral infections including influenza along with smoking, excessive alcohol, hypertension, heavy physical exertion or any kind of stressful events.[49,50] One study showed respiratory viral infections can precipitate both STEMI and NSTEMI and were positively associated with risk of mortality among NSTEMI, but not among STEMI.[51] Nevertheless, patients after STEMI have a higher in-hospital mortality rate and worse short-term outcomes while NSTEMI patients have poorer long-term prognosis.[52] Blood troponin levels are well correlated to the extent of infarction in both STEMI and NSTEMI but more impressive in STEMI.[53,54] In the current study, age at onset of STEMI was significantly lower than NSTEMI, suggesting that these different subtypes of AMI may have different risk factors and underlying mechanisms. Further research is needed to explore the relationship between influenza and different subtypes of AMI, as well as any factors influencing the association between influenza and STEMI. Preventing early onset STEMI is crucial in Bangladesh, where the age of onset for AMI is much earlier than in high-income countries. A simple yet effective measure to combat this issue could be the administration of the influenza vaccine. This could not only help curb the early onset of STEMI but also significantly lower in-hospital mortality among young individuals in Bangladesh.

The immune system plays a critical role in both the pathophysiology of AMI and the physiological mechanisms behind the protection offered by the influenza vaccine against AMI. This interplay between the immune system and AMI highlights the vital importance of understanding the intricacies of this relationship to effectively prevent and treat AMI. Dominant pro-inflammatory over the anti-inflammatory component of the immune system may favor sudden atherosclerosis progression leading to acute cardiovascular events like AMI.[55] Influenza virus can induce significant acute changes in pro-inflammatory cytokine levels in blood and pro-inflammatory as well as prothrombotic effects in atherosclerotic plaques which can trigger AMI onset through plaque destabilization.[56] However, there are interindividual differences in the intensity of a rapid pro-inflammatory response which may explain the difference in the level of risk of AMI among individuals in response to an acute stimulus such as influenza.[57] Investigations continue globally to understand the relationship between influenza and AMI, with the goal of using influenza vaccination to prevent AMI in high-risk individuals. Several observational studies,[16,30,58] small scale[59,60] and large scale[22] randomized clinical trials reported protective efficacy of influenza vaccine against adverse cardiovascular events including hospitalization or death due to AMI. Animal study showed influenza vaccine stabilized atherosclerotic plaque through promoting anti-inflammatory atheroprotective immune response[61] implying possibly a greater protection against underlying pathophysiology of onset of STEMI than NSTEMI. Influenza vaccine has been shown to blunt pro-inflammatory and enhance anti-inflammatory mediators after coronary artery bypass surgery.[62]

5 | STRENGTHS AND LIMITATIONS

The study's large sample size improves the generalizability of findings on CRI/influenza prevalence among AMI patients. Conducted in a specialized tertiary-level cardiac hospital, it strengthens the applicability of our findings to similar settings. By spanning both influenza and non-influenza seasons, the study compares the impact of respiratory illnesses on AMI patients across different seasons. A standardized protocol and verification by attending cardiologists minimized misclassification bias. The clear case definition for recent acute respiratory illness and qRT-PCR testing for influenza enhanced exposure sensitivity. Multivariate regression analysis controlled for confounders, further reducing bias in assessing the relationship between recent respiratory illness and AMI severity. However, it's crucial to acknowledge certain limitations in the present study. First of all, the cross-sectional design of our study did not allow us to investigate the association of CRI and influenza with onset of AMI. For this inaugural Bangladeshi study, we favored a cross-sectional design, lacking a control group, over a case-control approach due to time sensitivity, the need for rapid data collection, its efficiency, cost-effectiveness, and capability to study a larger population. Therefore, in our recommendation for future research, we recognize that a case-control design would be the appropriate method to enable statistical investigation of the association of CRI and influenza with AMI. Second, any clinical definition for acute respiratory illness has inherent limitations including subjectivity, limited specificity, and variability of respiratory symptoms depending on the patient's age and individual experiences, compounded by the lack of standardization. This could lead to potential bias in our prevalence estimates. Our case definition of CRI excluded systemic symptoms like body ache, likely compromising sensitivity and underestimating the prevalence of AMI patients with recent CRI. Consequently, individuals with systemic symptoms might have been missed, leading to a reported prevalence lower than the actual prevalence. A more standardized and objective measures of respiratory illness may improve the reliability and generatability of the findings. Third, we were unable to further confirm every AMI diagnosis through angiogram findings of coronary artery blockage and echocardiogram findings of regional wall motion abnormalities. Fourth, due to delay in initiation of the field implementation we had not enrolled participants during peak influenza months June–July of 2017 which might significantly affect our overall estimates for frequencies of CRI and influenza. Our study only investigated two annual influenza seasons, which may not fully reflect the broader trends of influenza prevalence among AMI patients. As influenza activity varies significantly year to year, a longer study period would yield a more comprehensive understanding of these patterns and their impact on AMI. Fifth, we utilized only qRT-PCR to identify influenza among participants which had limited sensitivity due to diminution of viral shedding. We believe addition of influenza serology would have significantly enhanced the sensitivity of the current study to identify additional influenza-positive participants. Lastly as our study was conducted in a single center in Bangladesh, our results are limited due

lack of generalizability and hence may not represent the broader population of the country.

6 | CONCLUSION

The present study results indicate that recent influenza and other acute respiratory illnesses may commonly occur before onset of AMI among Bangladeshi patients. Additionally, the study has generated some data regarding the relationship between recent respiratory illness and influenza with severity of myocardial infarction across different study seasons in Bangladesh which, however, were statistically not significant. Nevertheless, our results emphasize the importance of increased awareness among patients with heart conditions as well as among healthcare providers in Bangladesh about the possible risk of seasonal outbreaks of influenza and other acute respiratory illnesses. This may lead to improved timeliness of early interventions and hence better patient outcomes. Our results indicate the need for further studies, using prospective cohort or case-control design, and in particular conducted over multiple seasons and multiple centers across the country to investigate the association between recent respiratory illness and influenza with onset of AMI in Bangladeshi context. Given the known high prevalence of both acute cardiovascular events like AMI as well as seasonal influenza[27] in Bangladesh, and potential efficacy of influenza vaccination against incidence of AMI, as revealed through recently completed large scale clinical trial[22] and other observational studies, benefits of influenza vaccination program as well as infection prevention and control practices in Bangladesh deserve further exploration. Our study may provide valuable insights about the latent risk of acute respiratory illness and influenza for cardiovascular patients in Bangladesh, but our results should be cautiously considered in the context of their limitations and potential biases.

There is currently no acute respiratory illness surveillance exclusively among patients hospitalized with adverse cardiovascular events in Bangladesh highlighting a gap in the healthcare system in Bangladesh. Without dedicated surveillance, there is limited understanding of respiratory illness's impact among patients with cardiovascular diseases. The current study findings emphasized the relevance of dedicated respiratory illness surveillance among hospitalized individuals with adverse cardiovascular events. A dedicated surveillance would improve our understanding of the impact of respiratory illnesses among these groups of patients, provide data for health planning, and mitigate missed opportunities for early detection and intervention.

AUTHOR CONTRIBUTIONS

Mohammad Abdul Aleem: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; validation; writing—original draft; writing—review & editing. **Abrar Ahmad Chughtai**: Formal analysis; supervision; writing—original draft; writing—review & editing. **Bayzid Rahman**: Formal analysis; methodology; supervision; writing—review & editing. **Zubair Akhtar**: Investigation; project administration; writing—review & editing. **Fahmida Chowdhury**: Investigation; project administration; resources; writing—review & editing. **Firdausi Qadri**: Conceptualization; investigation; methodology; project administration; resources; supervision; writing—review & editing. **C Raina Macintyre**: Conceptualization; investigation; methodology; project administration; supervision; writing—review & editing. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No additional data are available. Mohammad Abdul Aleem, the lead and corresponding author, had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. Data generated during the study are subject to a data access policy of icddr,b and are available from icddrb's research administration on reasonable request through the corresponding author.

TRANSPARENCY STATEMENT

The lead author Mohammad Abdul Aleem affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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