Current Research in Medical Sciences
p ISSN: 3116-0298
Student Research Committee
Babol University of Medical Sciences

Original Article

Association Between Influenza-like Illness and Acute Myocardial Infarction: A Case-control Study

Seyed Morteza Mohseni[1], Soheil Ebrahimpour[2], Mohammad Barary[3], Ghasem Faghanzadeh Ganji[4], Arefeh Babazadeh[2], Kamyar Amin[5], Ali Tavakoli Pirzaman[1], Malihe Esmailzadeh[4], Hossein Nazari Rostami[6], Mehran Shokri[2,*]

[1]Student Research Committee, Babol University of Medical Sciences, Babol, Iran
[2]Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
[3] Student Research Committee, Department of Pharmacology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Clinical Research Development Center, Ayatollah Rohani Hospital, Babol University of Medical Sciences, Babol, Iran
[5]Department of Cardiology, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran.
[6]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Article Info.

Received: 10 Jun 2025
Accepted: 31 Dec 2025

*** Corresponding Author:**

Mehran Shokri (MD)
E-mail:
mshokri2015@yahoo.com
Tel: +989111149309

Cite this article
Mohseni SM, Ebrahimpour S, Barary M, Faghanzadeh Ganji Gh,Babazadeh, Amin K,Tavakoli Pirzaman A, Esmailzadeh M, Nazari Rostami H, Shokri M . Association between Influenza-like illness and acute myocardial infarction: A case-control study Curr Res Med Sci. 2025;9(2): 30-37.
DOI:10.22088/crms.9.2.30

Abstract

Background: Acute myocardial infarction (AMI) is a leading cause of death worldwide. Seasonal influenza can lead to cardiovascular complications. Thus, the association between influenza and cardiovascular events has recently attracted considerable interest. This study aimed to investigate recent influenza-like illness (ILI) among AMI patients compared with other hospitalized patients (control group) during the cold season in northern Iran.

Methods: This retrospective case-control study included 300 patients (150 AMI patients and 150 controls) aged ≥ 50 years who were hospitalized for AMI or other conditions between September 22, 2019, and March 15, 2020. Patients in each group were frequency-matched for gender and age range. The primary exposure was recent ILI (fever ≥ 37.8°C, cough, and sore throat) during the past month.

Results: Fifty-two females with a mean age of 40.23 ± 16.31 years were included. The mean hemoglobin level before treatment was 12.40 ± 1.08 g/dL, increasing to 13.04 ± 1.04 g/dL after treatment ($p < 0.001$). The mean serum ferritin level increased from 27.51 µg/L before treatment to 51.81 µg/L after treatment ($p < 0.001$). Hemoglobin increments were also observed in two subgroups: those with ferritin levels of 15–30 µg/L ($p < 0.001$) and those with levels of 30–50 µg/L ($p = 0.001$).

Conclusion: The patients' mean age was 64.42 ± 9.47 years, ranging from 50 to 94 years. Overall, 150 (50%) patients reported ILI, with a significantly higher prevalence in the AMI group (111 cases, 74%) than in controls (39 cases, 26%). Patients in the AMI group reported ILI significantly more often than controls (adjusted OR: 3.04, 95% CI: 1.02-9.09, $p < 0.001$). On the other hand, patients who received the influenza vaccine were significantly less likely to have an acute myocardial infarction than those who did not (adjusted OR: 0.02, 95% CI: 0.001-0.38, $p = 0.006$).
Keywords: Influenza-like disease, Acute myocardial infarction, Vaccination, Cardiovascular diseases

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Introduction

Acute myocardial infarction (AMI) is a leading cause of death and disability [1]. Previous studies have demonstrated the association between influenza and cardiovascular events [2-4]. Seasonal influenza can lead to cardiovascular complications in vulnerable individuals, especially the elderly and those with underlying medical conditions (including diabetes, hypertension, cardiovascular disease, and chronic obstructive pulmonary disease (COPD)) [5, 6]. First described in a series of observational studies in the 1930s, evidence supports the hypothesis that seasonal influenza may trigger AMI. Research indicates that respiratory pathogens, including influenza and S. pneumoniae, can induce myocarditis and hypercoagulability, thereby increasing the risk of thrombotic events. New findings suggest that infection with the mentioned organisms increases the risk of a heart attack one week after the infection and a stroke one month later [7-10]. Moreover, a previous study has shown that cardiovascular complications occurred in approximately 18% of patients hospitalized for pneumonia [11].

Confirming the link between influenza and AMI is crucial, as influenza-induced cardiovascular events can be effectively prevented by vaccination. More evidence on influenza-induced cardiovascular events may lead to a change in the clinical approach that improves vaccine coverage in patients at high risk for AMI [12, 13]. Given that the association between AMI and influenza-like illness (ILI) has been less studied in our country and that risk factors can inform preventive interventions, it is necessary to examine this association. Therefore, this study investigated the association between influenza-like illness and acute myocardial infarction.

Methods

Study Design and Population

This observational case-control study was conducted among hospitalized patients at Ayatollah Rohani Hospital in Babol, Northern Iran, during the 2019-2020 influenza season (September 22, 2019, to March 15, 2020). According to previous studies, the influenza season in Iran has been defined as the period between late November and April, which can peak in the winter months (especially January and February). However, we considered the period from September 22, 2019, to March 15, 2020 as the influenza season [14, 15]. Patients in both study groups (AMI and control) were matched for gender and age. The age range of the participants was 50-94 years. The AMI group consisted of 150 patients who had experienced an AMI, including both ST-elevation MI (STEMI) and non-ST-elevation MI (NSTEMI) (defined as a rise in troponin T with ischemic symptoms, typical ECG changes, or angiographic evidence of acute coronary artery thrombosis during primary percutaneous coronary intervention) [16]. The control group comprised 150 cases chosen from different hospital wards, e.g., patients with appendicitis, gastrointestinal bleeding, and urinary tract infection, with no AMI history within the past month. These patients were selected as controls because their admissions were unlikely to have been influenced by recent ILI [16]. The primary exposure was recent ILI (fever $\geq$ 37.8°C, cough, and sore throat) during the past month. It should be noted that in this study, the diagnosis of ILI was defined solely by clinical manifestations such as fever, cough, and sore throat.

Procedure

Data on recent ILI, demographic characteristics, past medical history, and influenza vaccination status in the past year were collected using a data collection checklist. This self-reported checklist for recent respiratory illnesses is subject to recall bias. However, because recall bias may be associated with self-declaration forms, we reviewed the electronic medical records of all patients and found no history of ILI. Nevertheless, as shown in previous studies, the self-reported checklist had higher sensitivity in detecting recent respiratory symptoms than the documented medical history of the participants [16, 17]. Finally, it should be noted that we assumed only the current year's vaccination was sufficiently effective; therefore, we treated all other categories (i.e., last year's immunization and vaccination from > two years ago) as unvaccinated.

Data analysis

The data were analyzed using SPSS Statistics version 16.0 (IBM Inc., Chicago, IL, USA). Continuous and categorical variables were presented as median (IQR) and n (%). The paired t-test, Spearman's rank-order correlation, chi-square test, and Fisher's exact test were used to compare continuous and categorical variables as appropriate. We used multivariable logistic regression analysis to investigate associations between recent ILI exposure and case/control status, controlling for the frequency-matching factors (age group, gender, and month of admission), influenza vaccination status as an a priori confounder (in all models), and other potential

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confounding factors. P-values < 0.05 were considered statistically significant.

Results

In this study, of the 300 patients included, 150 were hospitalized in Ayatollah Rouhani Hospital's cardiovascular ward for AMI, and the remaining 150 were selected from other hospital wards without a history of AMI in the past month. The mean age of patients was 64.42 ± 9.47 years (range: 50–94 years). After analyzing the demographic variables, a history of smoking, recreational drug addiction, and the presence of underlying diseases (including diabetes, hypertension, cardiovascular disease, and COPD) were found to be significantly associated with AMI occurrence ($p < 0.001$ for each). However, age, gender, and location of residence were not associated with AMI occurrence ($p = 0.33$, $p = 0.29$, and $p = 0.08$, respectively) (Table 1). The frequency of influenza-like symptoms among the study participants was as follows: muscle pain (120, 40%), muscle pain and chills (n=105, 35%), chills alone (n=33, 11%), fever and chills (n=18, 6%), sore throat (n=12, 4%), and muscle pain and diarrhea (n=12, 4%).

There was a significant association between ILI history and AMI occurrence ($p < 0.001$). Furthermore, examining the association between influenza vaccination and AMI risk revealed a considerable association: receipt of the influenza vaccine was associated with a lower risk of AMI ($p = 0.006$). Moreover, patients in the AMI group were more likely to report ILI than controls (adjusted OR: 3.04, 95% CI: 1.02-9.09, $p < 0.001$). The logistic regression analysis results summarized in Table 2 indicated that in the analysis of unadjusted variables, age (unadjusted OR: 1.13, 95% CI: 0.75-2.23), gender (unadjusted OR: 1.27, 95% CI: 0.68-2.00), and location of residence (unadjusted OR: 1.49, 95% CI: 0.94-2.19) did not affect the risk of AMI occurrence. These findings were also confirmed in the adjusted analysis. Specifically, age (adjusted OR: 1.28, 95% CI: 0.58-2.82, $p = 0.33$), gender (adjusted OR: 1.52, 95% CI: 0.78-2.95, $p = 0.29$), and location of residence (adjusted OR: 1.17, 95% CI: 0.60-2.28, $p = 0.08$) did not affect the risk of AMI occurrence.

Table 1: Demographic variables in all patients with and without acute myocardial infarction (overall 300 cases, of which 150 cases are dedicated to AMI group and 150 cases to control group)

Variables	Total frequency n (%)	AMI group n (%)	Control group n (%)	p-value
Age (years)				
50-70	231 (77%)	112 (74.7%)	119 (79.3%)	0.33
≥71	69 (23%)	38 (25.3%)	31 (20.7%)	
Gender				
Men	159 (53%)	75 (50%)	84 (56%)	0.29
Women	141 (47%)	75 (50%)	66 (44%)	
Location of residence				
Urban	161 (53.7%)	73 (48.7%)	88 (58.7%)	0.08
Rural	139 (46.3%)	77 (51.3%)	62 (41.3%)	
History of smoking				
No	255 (85%)	108 (72%)	147 (98%)	< 0.001
Yes	45 (15%)	42 (28%)	3 (2%)	
History of recreational drug addiction				
No	265 (88.3%)	118 (78.7%)	147 (98%)	< 0.001
Yes	35 (11.7%)	32 (21.3%)	3 (2%)	
Underlying diseases				
No	174 (58%)	46 (30.7%)	128 (85.3%)	< 0.001
Yes	126 (42%)	104 (69.3%)	22 (14.7%)	
Influenza vaccination				
Vaccinated	150 (50%)	2 (1.3%)	148 (98.7%)	0.006
Not vaccinated	150 (50%)	148 (98.7%)	2 (1.3%)	

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Table 2: Unadjusted and adjusted odds ratios (ORs) for the association between acute myocardial infarction and influenza-like illnesses exposure variables (overall 300 cases, of which 150 cases are dedicated to AMI group and 150 cases to control group)

Exposure variable	AMI group n (%)	Control group n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Age (50-70 years)	112 (74.7%)	119 (79.3%)	1.130 (0.75-2.23)	1.28 (0.58-2.82)	0.33
Gender (male)	75 (50%)	84 (56%)	1.27 (0.68-2.00)	1.52 (0.78-2.95)	0.29
Location of residence (urban)	73 (48.7%)	88 (58.7%)	1.49 (0.94-2.19)	1.17 (0.60-2.28)	0.08
History of smoking	42 (28%)	3 (2%)	19.05 (5.75-63.09)	15.72 (3.87-63.83)	< 0.001
History of recreational drug addiction	32 (21.3%)	3 (2%)	13.28 (3.97-44.47)	5.70 (1.29-25.11)	< 0.001
Influenza-like illnesses	111 (74%)	39 (26%)	8.43 (3.44-20.62)	3.04 (1.02-9.09)	< 0.001
Influenza vaccination	2 (0.3%)	148 (98.7%)	0.15 (0.03-0.70)	0.02 (0.001-0.38)	0.006

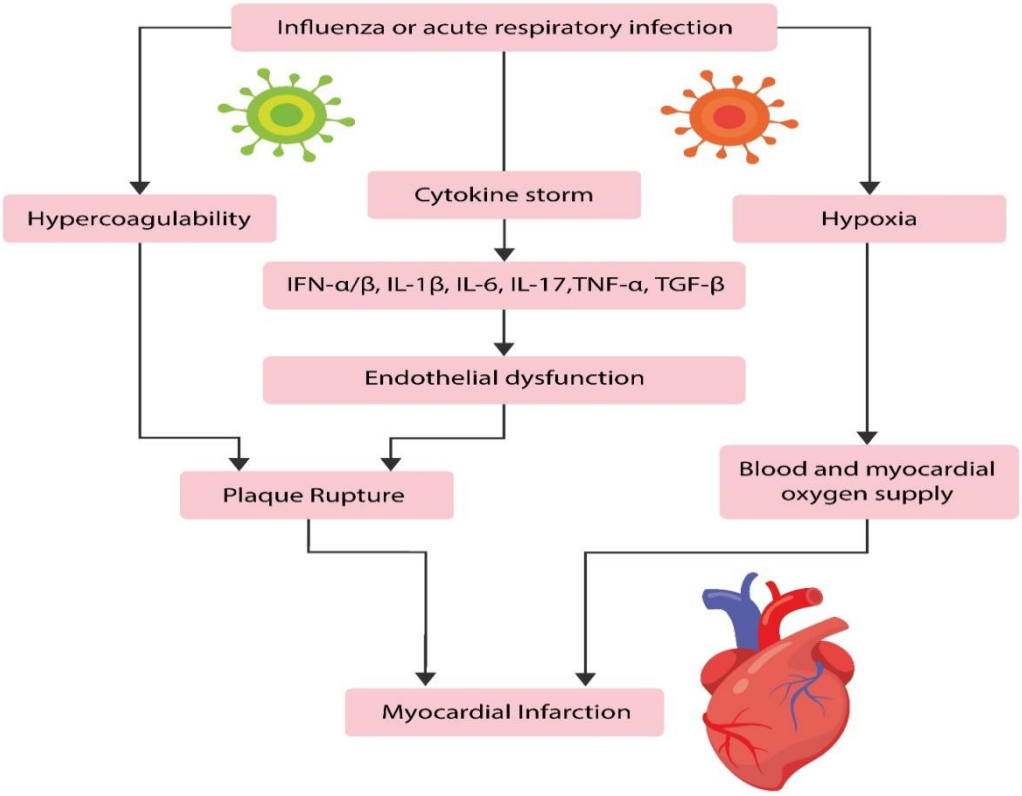

Figure 1: A summary of influenza- or other acute respiratory infection-induced myocardial infarction. Influenza virus and other acute respiratory infections can trigger three distinct yet highly interconnected mechanisms: hypoxia, hypercoagulability, and a cytokine storm. During a cytokine storm, interferons alpha and beta, interleukins 6 and 17, tumor necrosis factor alpha, and transforming growth factor beta can be released in high amounts, causing endothelial damage. Together with the hypercoagulability state, this damage may cause plaque rupture, causing a myocardial infarction. On the other hand, the induced hypoxia by those pathogens can compromise the blood and myocardial oxygen supply, leading to myocardial infarction. Abbreviations: IFN-α, Interferon-alpha; IFN-β, Interferon-beta; IL-6, Interleukin-6; IL-17, Interleukin-17; TNF-α, Tumor necrosis factor-alpha; TGF-β, Transforming growth factor-beta

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Discussion

This retrospective case-control study investigated the association between ILI and AMI and whether influenza vaccination reduces the risk of AMI among 300 patients in Babol, Northern Iran. Since our study was conducted in Northern Iran, it may help authorities gain a clearer understanding of the association between ILI and AMI in the local population, given that ILI is a common disorder in this area. The most important finding of the present study was that patients with a history of ILI were at increased risk of AMI, with the highest risk observed during the most severe influenza season. A previous study by Warren-Gash et al. (2009) found that influenza could cause AMI or cardiovascular mortality. [10]. Several observational studies in different settings with various methods have also reported a continuing association between ILI and AMI [10, 18-20]. Based on the present study's findings, a history of smoking, recreational drug addiction, and ILI were identified as risk factors for AMI, which can significantly increase the chance of occurrence ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). As for smoking, its role in boosting cardiovascular events was also confirmed by other studies [21-23]. Other renowned risk factors for cardiovascular events are increased economic power of industrial societies, excessive well-being in life, excessive consumption of fats, meat, sugar, and salt, and increased tobacco consumption [24, 25].

The prevalence of ILI among our patients was 50% (150 patients), of which 111 patients (74%) were in the AMI group. The most common symptoms of ILI in this study were muscle pain (120, 40%), followed by muscle pain (105, 35%) and chills, chills alone (33, 11%), fever, and chills (18, 6%), sore throat (12, 4%), and muscle pain and diarrhea (12, 4%). Nevertheless, a previous study reported that the most common ILI symptoms were headaches, fever, coughing, and muscle aches [26]. Another study by Sullivan et al. demonstrated that fever, headache, sore throat, chest pain, and cough were the most prevalent ILI symptoms [27]. Furthermore, half of the patients were administered the influenza vaccine within the last year, of which 148 (98.7%) were in the control group, similar to a previous study in which 49% of patients with ischemic heart disease were vaccinated for influenza [28]. This finding underscores the importance of vaccination in reducing cardiovascular events. Another significant result of this study is that receiving the flu vaccine can significantly lower the chances of AMI, which was consistent with other studies in different parts of the world (adjusted OR: 0.02, 95% CI: 0.001 to 0.38, $p = 0.006$) [10, 16, 28-30]. ILI is one of the most common infectious diseases of the respiratory system, infecting many people and causing morbidity and mortality. Genetic changes in this virus are more numerous than in any other virus. Humans will need to produce a vaccine against the virus annually. Determining how vaccines and antivirals are protected in patients with cardiovascular disease is necessary. Therefore, a robust public health effort is essential to increase influenza vaccination among patients at high risk of cardiovascular disease. Figure 1 illustrates the proposed mechanisms behind ILI-induced MI.

The current study is limited by a small sample size. Thus, it may lack generalizability. Therefore, subsequent clinical studies with larger sample sizes and more extended follow-up periods should be conducted to confirm our findings. Additionally, because the method for collecting data on the history of ILI in study participants relied on a self-reported checklist, it may be susceptible to recall bias. Nevertheless, as shown in previous studies, this method is more sensitive than searching patients' medical history documents. The extremely low odds ratio for vaccination should be interpreted with caution because the number of vaccinated individuals in the AMI group ($n = 2$) and unvaccinated individuals in the control group ($n = 2$) is small, which may lead to statistical instability.

Conclusion

The present study results show an association between ILI and AMI. According to this study, ILI, smoking, and recreational drug addiction are among the risk factors for AMI, and receiving the flu vaccine is associated with a lower risk of AMI.

Acknowledgment

The authors thank the Department of Infectious Diseases of Babol University of Medical Sciences.

Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Author's contribution

SMM, GFG, and MS contributed to methodology. SMM, SE, MB, AB, ATP, and PS contributed to data curation. KA contributed to validation. SE and MS contributed to supervision. ME contributed to project administration and resources. SMM, SE, MB, GFG, AB, KA, ATP, PS, and MS contributed to writing – original

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draft preparation. MB contributed to writing – review and editing.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding

Not funding supported the study was not funded.

Ethical Statement

This study protocol was approved by the ethics committee of Babol University of Medical Sciences (IR.MUBABOL.REC.1399.031).

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