Influence of Influenza Infection on In-Hospital Acute Myocardial Infarction Outcomes

Byomesh Tripathi, MD[a], Varun Kumar, MD[b], Ankur Kalra, MD[c], Tanush Gupta, MD[d], Abhishek C. Sawant, MD, MPH[a], Purnima Sharma, MD[a], Shilpkumar Arora, MD, MPH[e], Muhammad S. Panhwar, MD[f], Radha Gopalan, MD[a], Abhishek Deshmukh, MD[g], Ashish Pershad, MD[a], Martha Gulati, MD, MS[a], and Deepak L. Bhatt, MD, MPH, FACC, FAHA, FSCAI, FESC[h,*]

Influenza is associated with significant morbidity in the United States but its influence on in-hospital outcomes in patients with AMI has not been well studied. The Nationwide Readmission Database (NRD) from 2010 to 2014 was queried using the International Classification of Diseases-Ninth edition, Clinical Modification (ICD-9-CM) codes to identify all patients ≥18 years who were admitted for AMI with and without concurrent influenza. Propensity score matching was used to adjust patients' baseline characteristics and comorbidities. In-hospital mortality, 30-day readmission rates, in-hospital complications, and resource utilization were analyzed. We identified a total of 2,428,361 patients admitted with AMI, of whom 3,006 (0.12%) had coexisting influenza. We noted significantly higher in-hospital mortality (7.7% vs 5.6%, p <0.01) and 30-day readmission rates (15.8% vs 14.1%, p <0.01) in patients with influenza compared with those without it. After propensity matching, the differences in in-hospital mortality and 30-day readmission were no longer statistically significant between the groups. Patients with influenza had a higher incidence of acute kidney injury (30.9% vs 24.6%, p <0.01), acute respiratory failure (50.2% vs 32.2%, p <0.01), need for mechanical ventilation (13.9% vs 9.2%, p <0.01), and sepsis (10% vs 3.8%, p <0.01) in the matched cohort. Patients with influenza had longer hospital stays (8.4 days vs 6.4 days, p <0.01) and mean costs of care (26,200USD vs 23,400USD, p <0.01). In conclusion, AMI patients with concomitant influenza infection had higher in-hospital mortality, 30-day readmission, in-hospital complications, and higher resource utilization compared with those without influenza. **(Am J Cardiol 2020;130:7−14)**

Influenza infection has been recognized as a major contributor to the increased mortality and morbidity in the United States and worldwide.[1−3] Influenza infection has a large socioeconomic impact due to loss of workdays, frequent influenza-related complications, questionable clinical efficacy and cost effectiveness of antiviral medications, and inappropriate prescription of antibiotics.[4,5] An association of influenza infection with cardiac and cerebrovascular diseases has long been recognized, especially in the older population[6] which is a concerning issue because they are at particularly high risk of influenza infection and cardiac diseases. Previously published studies found an increased incidence of AMI after influenza infection[7−9] and lower incidence of cardiovascular events with influenza immunization[10] but there is a paucity of data related to effect of influenza on in-hospital outcomes in patients admitted with a primary diagnosis of AMI. In this context, we extend the work of previous investigators by studying the in-hospital outcomes in patients with concomitant influenza and AMI from a large, nationally representative database.

[a]University of Arizona College of Medicine, Phoenix, Arizona; [b]University of South Florida, Tampa, Florida; [c]Cleveland Clinic, Cleveland, Ohio; [d]New York Presbyterian Hospital/Columbia University Medical Center, New York, New York; [e]Case Western Reserve University, Cleveland Ohio; [f]Tulane University, New Orleans, Louisiana; [g]Mayo Clinic, Rochester, Minnesota; and [h]Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, Massachusetts. Manuscript received April 24, 2020; revised manuscript received and accepted May 27, 2020.

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See page 13 for disclosure information.

*Corresponding author: Deepak L. Bhatt, MD, MPH, FACC, FAHA, FSCAI, FESC, Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, 75 Francis Street, Boston, MA 02115.

E-mail address: dlbhattmd@post.harvard.edu (D.L. Bhatt).

Method

The Healthcare Cost and Utilization Project's National Readmission Database (NRD) is sponsored by the Agency for Healthcare Research and Quality. Data from 2010 to 2014 were analyzed. The NRD is a de-identified database and was deemed exempt from ethical review at institutional review board at the University of Arizona, Phoenix, AZ. NRD is one of the largest publicly available all-payer inpatient care databases in the United States and represents approximately 50% of total US hospitalizations. NRD includes data on approximately 15 million discharges in the years 2010 to 2014, estimating roughly 35 million discharges from 22 states with reliable, verified linkage numbers. Patients were tracked during the same year using variable "NRD_visitlink," and time between 2 admissions was calculated by subtracting variable

"NRD_DaysToEvent". Time to readmission was calculated by subtracting length of stay (LOS) of index admissions to time between 2 admissions. Sampling weights provided by the sponsor were used to produce national estimates.[11] The design of NRD is available online.[12]

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for AMI (410.xx) in primary diagnosis field and influenza (487.0, 487.1, 487.8, 488.01, 488.02, 488.09, 488.11, 488.12, 488.19, 488.81, 488.82, and 488.89) in secondary diagnosis fields were used to extract the study population. Only patients with age ≥18 years were included in the final study. Exclusion criteria for our study were patients with missing data on age, sex, or mortality as well as those admitted in the month of December to allow for 30-day follow-up, as NRD does not allow follow-up of the patients in consecutive years. We identified in total 2,428,361 index admissions. Similar methodology for data extraction from NRD has been used and validated in previously published studies.[13−17] Primary end points of our study were in-hospital mortality and 30-day readmissions. Secondary end points were in-hospital complications, length of stay, and cost of hospitalization.

NRD-provided variables were utilized to compare hospital characteristics (bed size and teaching status) as well as patient-specific characteristics (age, gender, insurance provider, admission type, admission day, and discharge disposition). Coexisting medical conditions such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, coagulopathy, anemia, fluid and electrolyte disturbance, collagen vascular diseases, and depression were identified by "CM_" variables provided in NRD, which uses ICD-9 CM diagnoses and the diagnosis-related group in effect on the discharge date. Additional co-morbidities were identified by ICD9-CM codes in the secondary diagnosis field, including chronic kidney disease, previous myocardial infarction, previous stroke/TIA, atrial fibrillation, atrial flutter, and smoking history (Supplementary Table 1). We also evaluated length of stay provided by NRD. Cost of index hospitalization was calculated by merging cost to charge ratio provided by HCUP to the main dataset and after adjusting for inflation.[18]

SAS 9.4 (SAS Institute Inc., Cary, NC) was utilized for analyses. The Wilcoxon rank sum test was performed to test differences in continuous variables between comparison groups as data were not normally distributed. The chi-square test of independence was used for testing the difference between the 2 groups with respect to categorical variables.

A propensity score, which was assigned to each principal hospitalization, was based on a multivariable logistic regression model that examined the impact of patient demographics, co-morbidities, and hospital characteristics on the likelihood of treatment assignment. We selected all variables from baseline tables with statistically significant differences ($p < 0.05$) between the 2 treatment groups. Patients with nearest propensity scores in 2 treatment groups (influenza and no influenza) were matched 1 to 100 without replacement using a greedy algorithm (Figure 1). Maximum propensity score difference (caliper width) of 0.05 was permitted between matched observations.

Results

We identified a total of 2,428,361 patients who were admitted with a primary diagnosis of AMI of whom 3,006 (0.12%) had concomitant influenza infection. Patients with influenza were older (mean age 72.5 years vs 67.7 years, $p < 0.01$) and more likely to be female (44.2% vs 38.6%, $p < 0.01$). A greater proportion of patients with influenza were covered by Medicare (72.2% vs 57.9%, $p < 0.01$), admitted over the weekend (29.4% vs 26.9%, $p < 0.01$), and treated emergently (97.2% vs 95.4%, $p < 0.01$). The most common coexisting conditions were hypertension, diabetes mellitus, fluid and electrolyte disorders, atrial fibrillation or flutter, and chronic kidney disease. The influenza group had significantly higher co-morbidity burden compared with the noninfluenza group (Table 1).

The prevalence of non-ST elevation myocardial infarction (NSTEMI) was higher among the influenza cohort (86.1% vs 67.9%, $p < 0.01$). Patients with influenza had lower utilization of PCI (46.5% vs 75.0%, $p < 0.01$ in STEMI group; 19.0% vs 38.8%, $p < 0.01$ in NSTEMI group), and coronary angiography (67.3% vs 87.7%, $p < 0.01$ in STEMI group; 45.0% vs 70.5%, $p < 0.01$ in NSTEMI group) than noninfluenza patients. There was no difference in CABG rates among STEMI patients with and without influenza ($p = 0.57$) but NSTEMI patients with influenza had lower utilization of CABG compared with those without it (6.4% vs 10.4%, $p < 0.01$). Influenza patients required circulatory support more frequently than those without influenza (9.2% vs 20.5%, $p < 0.01$ in STEMI group and 2.9% vs 4.0%, $p < 0.01$ in NSTEMI group; Table 2). Compared with AMI patients without influenza, those with influenza had significantly higher in-hospital mortality (7.7% vs 5.6%, $p < 0.01$) and 30-day readmission rate (15.8% vs 14.1, $p < 0.01$) in analysis involving unmatched data. In the propensity-matched cohort, difference in in-hospital mortality (9.4% vs 8.7%, $p = 0.24$) or 30-day readmissions (9.3% vs 8.6%, $p = 0.36$) did not reach statistical significance among patients with and without influenza.

Patients with influenza had a higher incidence of acute kidney injury, acute respiratory failure, ventilator use, and sepsis in both unmatched and propensity-matched cohorts. Patients with influenza were less likely to get percutaneous coronary intervention and coronary artery bypass grafting. Higher incidence of cardiogenic shock and major bleeding was noted in influenza group compared with noninfluenza group, but difference was not statistically significant after propensity match analysis (Table 3).

In STEMI subgroup, we noted a significantly higher 30-day readmission rate (14.1% vs 11.2%, $p = 0.048$) and in-hospital mortality (13.9% vs 8.7%, $p < 0.01$) in patients with influenza compared to those without it. Significantly longer hospital stays (9.6 days vs 4.7 days, $p < 0.01$) and cost of care (37,842USD vs 24,778USD, $p < 0.01$) was noted in influenza group as well (Figure 2).

We compared difference in outcomes based on age and sex of patients with influenza. Female patients in age group

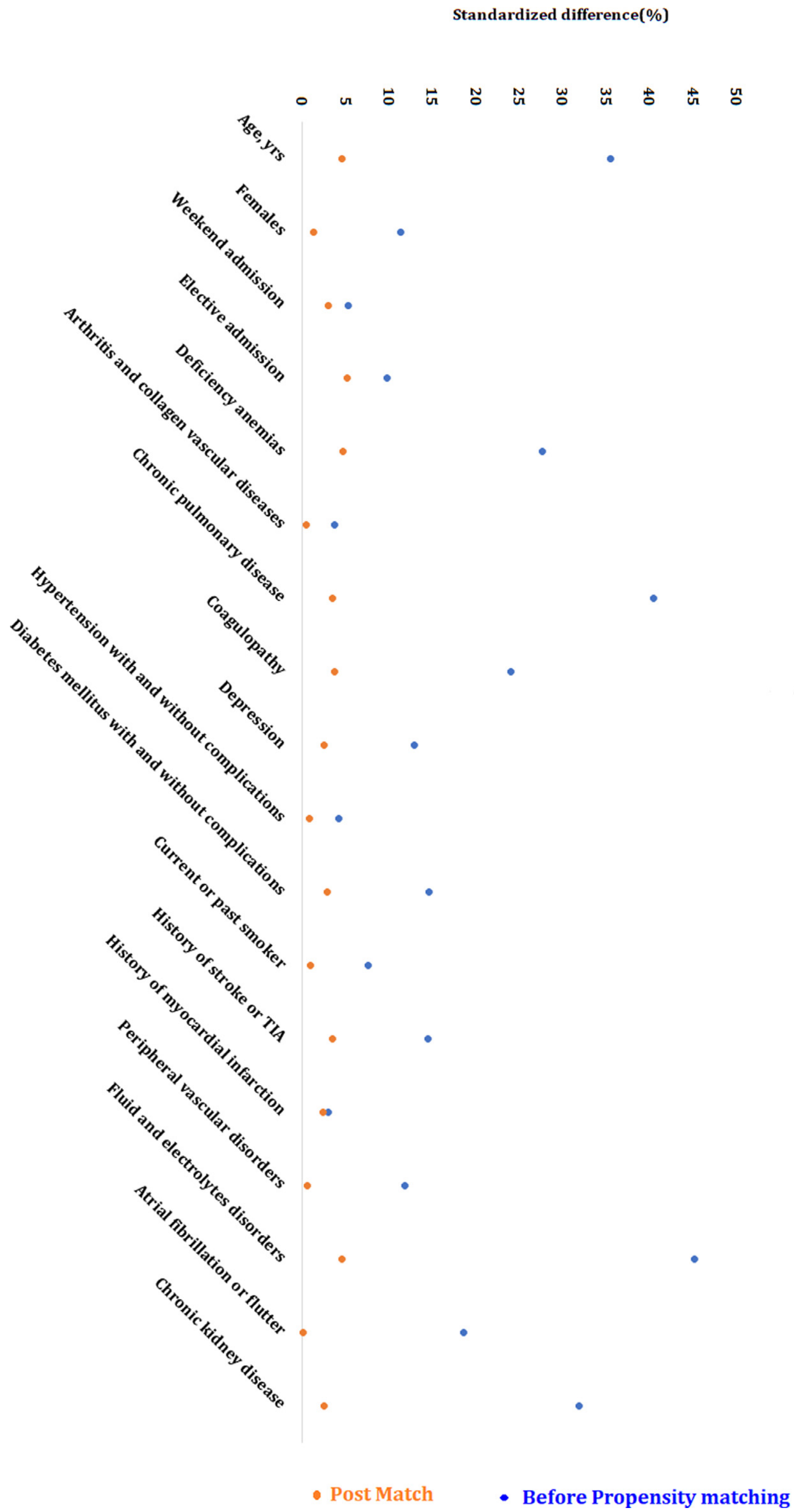

Figure 1. Standardized difference between influenza and noninfluenza groups pre- and postpropensity matching.

18 to 54 years had higher 30-day readmission (29.7% vs 18.6%, p = 0.02) without any significant difference in in-hospital mortality or resource utilization compared with male counterparts in same age group. No statistical difference in any of the end points was noted based on sex in patients ≥55 years of age (Figure 3).

AMI patients with influenza admitted during influenza season (October to May) had lower cost of care compared with the counterparts admitted during noninfluenza season (26,621USD vs 34,039USD, p = 0.02). No differences in 30-day readmission, in-hospital mortality, and length of stay were noted based on month of admission (Figure 4).

Table 1
Baseline characteristics of acute myocardial patients with and without influenza

	Prematching				Postmatching (1:100)			
	No influenza	Influenza	Overall	p Value	No influenza	Influenza	Overall	p Value
Index hospitalization	2,425,355	3006 (0.12%)	2,428,361	<0.01	133,900	1,339	135,239	<0.01
Age (years ± Std dev)	67.7 ± 14	72.5 ± 13	67.7 ± 14	<0.01	73.3 ± 12.5	72.7 ± 13.3	73.3 ± 12.5	0.20
Women	38.6 %	44.2 %	38.6 %	<0.01	44.2 %	44.9 %	44.2 %	0.62
Insurance status				<0.01				
Medicare	57.9 %	72.2 %	57.9 %		74.7 %	72.8 %	74.7 %	0.06
Medicaid	6.6 %	6.7 %	6.6 %		8.0 %	7.0 %	8.0 %	
Private including HMO	25.2 %	15.0 %	25.2 %		13.1 %	15.3 %	13.1 %	
Self	6.0 %	3.4 %	6.0 %		2.6 %	2.9 %	2.6 %	
Other/no charge	4.0 %	1.9 %	4.0 %		1.6 %	2.1 %	1.6 %	
Weekend admission	26.9 %	29.4 %	27.0 %	<0.01	28.0 %	29.4 %	28.0 %	0.29
Emergent admission	95.4 %	97.2 %	96.3 %	<0.01	3.1 %	2.3 %	3.1 %	0.09
Hospital teaching status*				0.70				1.00
Non-Teaching	48.0 %	47.7 %	48.0 %		47.1 %	47.1 %	47.1 %	
Teaching	52.0 %	52.3 %	52.0 %		52.9 %	52.9 %	52.9 %	
Hospital bed size†				<0.01				0.54
Small	8.8 %	10.5 %	8.8 %		9.1 %	8.6 %	9.1 %	
Medium	22.3 %	22.1 %	22.3 %		22.4 %	23.6 %	22.4 %	
Large	68.9 %	67.4 %	68.9 %		68.6 %	67.9 %	68.6 %	
Comorbidities								
Deficiency anemias‡	16.4 %	27.8 %	16.4 %	<0.01	26.2 %	28.3 %	26.3 %	0.10
Arthritis and collagen vascular diseases‡	2.5 %	3.1 %	2.5 %	0.03	3.2 %	3.1 %	3.2 %	0.85
Chronic pulmonary disease‡	20.7 %	38.9 %	20.7 %	<0.01	36.8 %	38.6 %	36.9 %	0.21
Coagulopathy‡	5.4 %	12.2 %	5.4 %	<0.01	10.9 %	12.2 %	10.9 %	0.17
Depression‡	7.8 %	11.6 %	7.8 %	<0.01	9.1 %	9.9 %	9.1 %	0.35
Hypertension with and without complications‡	71.9 %	73.8 %	71.9 %	0.02	73.3 %	73.7 %	73.3 %	0.75
Diabetes mellitus with and without complications‡	36.0 %	43.1 %	36.0 %	<0.01	43.4 %	44.9 %	43.4 %	0.30
Current or past smoker§	40.2 %	36.4 %	40.2 %	<0.01	34.4 %	34.9 %	34.4 %	0.72
History of stroke or TIA§	2.3 %	5.0 %	2.3 %	<0.01	3.9 %	4.7 %	3.9 %	0.20
History of myocardial infarction§	11.6 %	12.6 %	11.6 %	0.09	12.0 %	12.8 %	12.0 %	0.39
Peripheral vascular disorders‡	12.1 %	16.3 %	12.1 %	<0.01	16.0 %	16.2 %	16.0 %	0.84
Fluid and electrolytes disorders‡	22.1 %	42.8 %	22.1 %	<0.01	40.2 %	42.4 %	40.2 %	0.09
Atrial fibrillation or flutter§	18.0 %	25.7 %	18.0 %	<0.01	25.5 %	25.5 %	25.5 %	0.98
Chronic kidney disease§	20.1 %	34.2 %	20.1 %	<0.01	33.3 %	34.5 %	33.3 %	0.34

HMO = Health Maintenance Organization.

* A hospital is considered to be a teaching hospital if it has an AMA-approved residency program, is a member of the Council of Teaching Hospitals (COTH) or has a ratio of full-time equivalent interns and residents to beds of 0.25 or higher. https://www.hcup-us.ahrq.gov/db/vars/hosp_ur_teach/nrdnote.jsp

† The bed size cut-off points divided into small, medium, and large have been done so that approximately one-third of the hospitals in a given region, location, and teaching status combination would fall within each bed size category. https://www.hcup-us.ahrq.gov/db/vars/hosp_bedsize/nrdnote.jsp

‡ Variables are AHRQ co-morbidity measures.

§ Co-morbidities derived from appropriate ICD 9CM codes as shown in supplementary Table 1.

Patients with influenza had overall higher length of stay (8.4 days vs 6.4 days, p <0.01) and cost of care (26,200USD vs 23,400USD, p <0.01). Patients with influenza were more likely to be discharged to nursing facilities compared with those who did not have influenza (24.0% vs 20.3%, p <0.01).

Discussion

Using data from a large nationally representative cohort involving 2,428,361 AMI-related hospitalizations, we noted substantially higher in-hospital mortality, 30-day readmission, in-hospital complications, length of stay, and overall cost in patients with concomitant influenza compared with those without it.

Previous reports have established the increased incidence of AMI after influenza infection[8,19] but data on its impact on in-hospital outcomes in AMI patients are limited. Our study highlighted that concomitant influenza infection is associated with an increased risk of in-hospital mortality and 30-day readmission among AMI patients, although after propensity matching, the difference was no longer statistically significant. This may relate to older age and higher co-morbidity burden in patients with concomitant influenza as well as reduction in sample volume on propensity matching. As expected, influenza with AMI was more likely in older patients, women and in those with a greater co-morbidity burden. In those presenting with an AMI with influenza, there was an increased risk of in-hospital complications such as acute kidney injury, acute respiratory failure requiring mechanical ventilation, and sepsis in those with influenza. They are more likely to have a NSTEMI and less likely to undergo any cardiovascular intervention and yet more likely to have bleeding complications. These patients

Table 2
Treatment strategies stratified by type of myocardial infarction

	No influenza	Influenza	Overall	p Value
STEMI overall	32.1 %	13.9 %	32.05 %	<0.01
NSTEMI overall	67.9 %	86.1 %	68.0 %	<0.01
STEMI subgroup				
Percutaneous coronary intervention	75.0 %	46.5 %	75.0	<0.01
Coronary artery bypass grafting	6.7 %	7.4 %	6.7 %	0.57
Coronary angiography	87.7 %	67.3 %	87.7%	<0.01
Mechanical circulatory support*	9.2 %	20.5 %	9.2 %	<0.01
NSTEMI subgroup				
Percutaneous coronary intervention	38.8 %	19.0 %	38.8 %	<0.01
Coronary artery bypass grafting	10.4 %	6.4 %	10.4 %	<0.01
Coronary angiography	70.5 %	45.0 %	70.5 %	<0.01
Mechanical circulatory support*	2.9 %	4.0 %	2.9 %	<0.01

STEMI = ST segment elevation myocardial infarction; NSTEMI = non-ST segment elevation myocardial infarction.

* Mechanical circulatory support = Intra-aortic balloon pump or Impella or Tandem Heart.

are therefore high-risk cohorts and appropriate resources should be allocated to them in a timely fashion to prevent adverse events. Our study calls for incorporating routine influenza vaccination into clinical practices, particularly in older patients or those at high risk for atherosclerotic cardiovascular disease. Lower revascularization rates among influenza patients noted in our study may be due to a higher prevalence of type 2 myocardial infarction in this population or may represent reluctance to do procedures on patients with an acute infectious illness.

Our study demonstrated STEMI patients had higher 30-day readmission, in-hospital mortality cost of care, and longer hospital stay if they had concomitant influenza. This supports the compounding effect of influenza infection on AMI unrelated to its inflammatory state leading to demand supply mismatch (type 2 MI). Additionally, female patients in age group 18 to 54 years had higher 30-day readmission rates compared with males of same age group. Likely explanation for this sex-based difference in outcomes in young patients appears to be prehospital delays, resource underutilization, lower rate of referral to cardiac rehab, and higher dropouts in female patients as reported by Chandrasekhar et al.[20] Last, we noted higher cost utilization in AMI patients with nonseasonal influenza compared with seasonal influenza. Explanation for these findings is unclear and needs to be investigated but it may be related to the high virulence of influenza in nonseasonal outbreaks as well as lower cohort immunity.

An important aspect of our study was relation of influenza infection on resource utilization. We noted significantly higher cost of care in AMI patients with influenza infection in both unmatched and propensity-matched data. Higher expenditure in this subgroup appears to be secondary to longer hospital stays and higher in-hospital complications, and increased deconditioning requiring placement to nursing facilities. Our observation on cost burden in AMI patients with influenza differs from data published by Panhwar et al[21] involving heart failure patients who reported no difference in cost of care in patients with and without influenza infection. This is notable as it suggests a greater opportunity for cost savings by influenza vaccination among AMI patients compared with non-AMI cardiac patients.

It was not possible to delineate the temporal association of influenza with AMI in our study; as a result, it is not possible to know if the influenza virus resulted in the AMI, just that the admitting principal diagnosis was an AMI. Certainly, it was noted there was more NSTEMI in those with influenza compared with those without. With this data, it is difficult to determine if the MI was actually a type 2 MI or a type 1 MI. Being an observational analysis, there is always some possibility of residual confounding, but

Table 3
Comparison of in-hospital outcomes in acute myocardial patients with and without influenza

Outcomes	Prematching				Postmatching (1:100)			
	No influenza	Influenza	Overall	p Value	No influenza	Influenza	Overall	p Value
30-day readmission	14.1 %	15.8 %	14.1 %	0.01	9.3 %	8.6 %	9.3 %	0.36
Overall, in hospital mortality	5.6 %	7.7 %	5.6 %	<0.01	9.4 %	8.7 %	9.4 %	0.24
In-hospital complications								
Acute kidney injury	15.1 %	31.7 %	15.2 %	<0.01	24.6 %	30.9 %	24.6 %	<0.01
Blood product transfusion	7.9 %	11.4 %	8.0 %	<0.01	12.3 %	11.8 %	12.3 %	0.54
Acute respiratory failure	22.3 %	50.0 %	22.3 %	<0.01	32.5 %	50.2 %	32.7 %	<0.01
Mechanical ventilation	6.1 %	12.2 %	6.1 %	<0.01	9.2 %	13.9 %	9.3 %	<0.01
Cardiopulmonary resuscitation	1.8 %	2.6 %	1.8 %	<0.01	2.6 %	2.7 %	2.6 %	0.77
Cardiogenic shock	5.6 %	8.2 %	5.6 %	<0.01	7.9 %	8.4 %	7.9 %	0.53
Sepsis	2.3 %	9.1 %	2.3 %	<0.01	3.8 %	10.0 %	3.9 %	<0.01
Gastrointestinal bleeding	1.8 %	4.0 %	1.8 %	<0.01	2.7 %	2.9 %	2.7 %	0.55
Major bleeding event	3.6 %	4.9 %	3.6 %	<0.01	5.6 %	4.3 %	5.5 %	0.06
Disposition								
Home	79.1 %	66.0 %	79.1 %	<0.01	69.4 %	66.8 %	69.4 %	<0.01
Facility/others	14.3 %	25.3 %	14.3 %	<0.01	20.3 %	24.0 %	20.3 %	<0.01
Length of stay (Mean, Std Err)	5.2 ± 0.01	8.3 ± 0.20	5.2 ± 0.01	<0.01	6.4 ± 0.02	8.4 ± 0.2	6.4 ± 0.02	<0.01
Cost (Mean, Std Err), Thousand USD	21.2 ± 21.3	25.5 ± 770.7	21.2 ± 21.3	<0.01	23.4 ± 76	26.2 ± 856	23.4 ± 76	<0.01

USD = United States dollar.

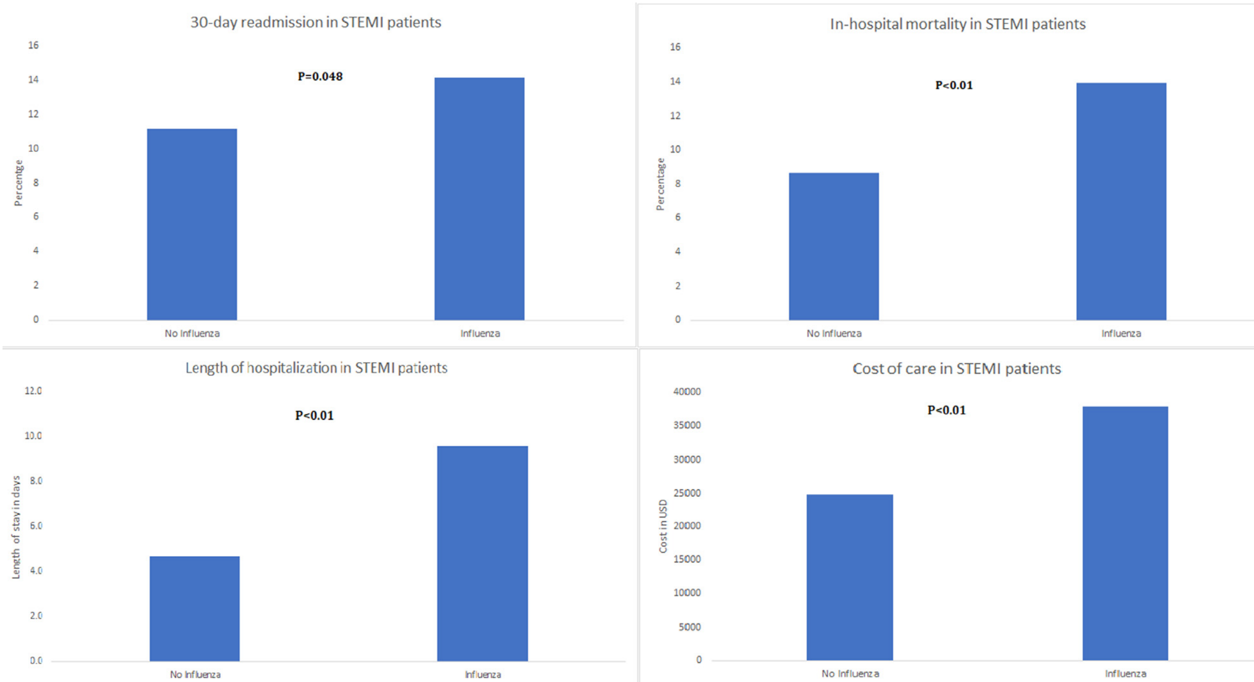

Figure 2. Outcome difference among ST-elevation myocardial infarction patients with and without influenza.

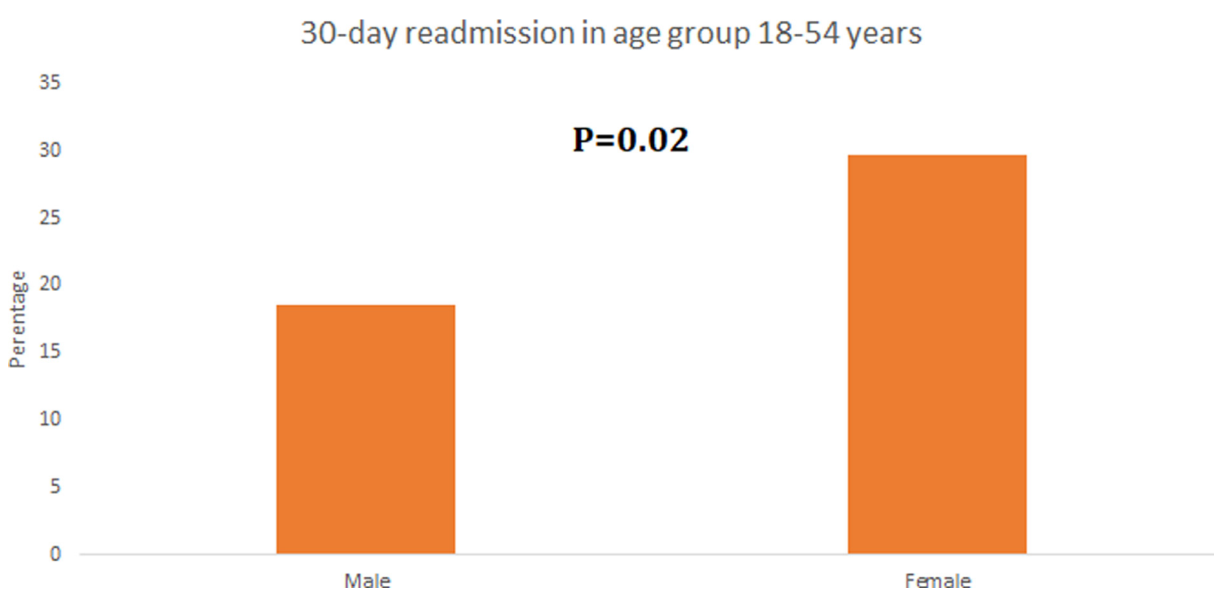

Figure 3. Age- and gender-stratified outcome differences in patient with acute myocardial infarction and influenza.

propensity matching was done to limit this as much as possible. Additionally, only inpatient data are provided by NRD so long-term outcomes could not be assessed. Last, we do not have any data on those who received the influenza vaccine and cannot demonstrate protection based on vaccination status.

In conclusion, our study highlights effects of influenza infection in AMI patients. Increased in-hospital mortality, 30-day readmission, in-hospital complications, and cost of care were noted in influenza positive patients. However, mortality and readmission did not reach statistical significance in the matched cohort. These findings have important public health implications and emphasize the need for focused efforts on education and delivering influenza vaccination for those at greatest risk of AMI, particularly in the older and high-risk populations. Significant cost savings for our health system could be seen by a simple preventive measure.

Author Contribution

Byomesh Tripathi: Conceptualization, Writing-Original draft preparation

Varun Kumar: Methodology, Software

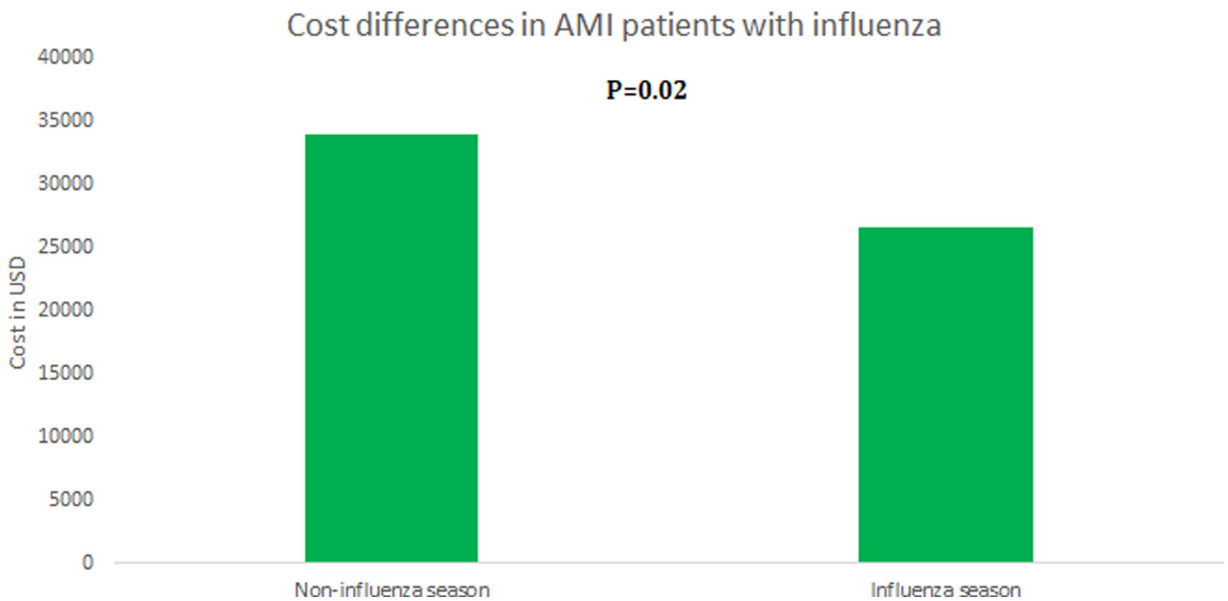

Figure 4. Outcome differences based on admission during month of admission in patients with influenza.

Ankur Kalra: Writing-Reviewing and Editing
Tanush Gupta: Writing-Reviewing and Editing
Abhishek C. Sawant: Writing-Reviewing and Editing
Purnima Sharma: Conceptualization, Methodology
Shilpkumar Arora: Software
Muhammad S. Panhwar: Writing-Reviewing and Editing
Radha Gopalan: Supervision
Abhishek Deshmukh: Supervision
Ashish Pershad: Supervision
Martha Gulati: Supervision
Deepak L. Bhatt: Supervision; Writing-Reviewing and Editing

Disclosures

The authors report following relations:

1. Dr. Tripathi, Dr. Kumar, Dr. Sharma, Dr. Gupta, Dr. Arora, Dr. Panhwar, Dr. Gopalan, Dr. Sawant, Dr. Pershad, and Dr. Gulati report no relevant disclosures pertaining to the current work.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.05.045.

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