Original Article

Impact of concomitant respiratory infections in the management and outcomes acute myocardial infarction-cardiogenic shock

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A R T I C L E   I N F O

A B S T R A C T

Objective: To evaluate the prevalence and impact of respiratory infections in cardiogenic shock complicating acute myocardial infarction (AMI-CS).
Methods: Using the National Inpatient Sample (2000–2017), this study identified adult (≥ 18 years) admitted with AMI-CS complicated by respiratory infections. Outcomes of interest included in-hospital mortality of AMI-CS admissions with and without respiratory infections, hospitalization costs, hospital length of stay, and discharge disposition. Temporal trends of prevalence, in-hospital mortality and cardiac procedures were evaluated.
Results: Among 557,974 AMI-CS admissions, concomitant respiratory infections were identified in 84,684 (15.2%). Temporal trends revealed a relatively stable trend in prevalence of respiratory infections over the 18-year period. Admissions with respiratory infections were on average older, less likely to be female, with greater comorbidity, had significantly higher rates of NSTEMI presentation, and acute non-cardiac organ failure compared to those without respiratory infections (all $p < 0.001$). These admissions received lower rates of coronary angiography (66.8% vs 69.4%, $p < 0.001$) and percutaneous coronary interventions (44.8% vs 49.5%, $p < 0.001$), with higher rates of mechanical circulatory support, pulmonary artery catheterization, and invasive mechanical ventilation compared to AMI-CS admissions without respiratory infections (all $p < 0.001$). The in-hospital mortality was lower among AMI-CS admissions with respiratory infections (31.6% vs 38.4%, adjusted OR 0.58 [95% CI 0.57–0.59], $p < 0.001$). Admissions with respiratory infections had longer lengths of hospital stay (12^{7-20} vs 6^{3-11} days, $p < 0.001$), higher hospitalization costs and less frequent discharges to home (27.1% vs 44.7%, $p < 0.001$).
Conclusions: Respiratory infections in AMI-CS admissions were associated with higher resource utilization but lower in-hospital mortality.
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1. Introduction

Despite increase in early revascularization with percutaneous coronary interventions (PCI), acute myocardial infarction with cardiogenic shock (AMI-CS) continues to be associated with high inpatient mortality of around 30–45%.[1] Patients with AMI-CS have associated hemodynamic instability, fluid overload, and respiratory compromise with a greater need for mechanical circulatory support (MCS), invasive therapies, and mechanical ventilation.[2,3] However, these management strategies confer risk of infections in these patients.[4,5] In addition to ventilator-associated respiratory infections, the use of cardiopulmonary resuscitation and hypothermia in these critically ill patients further increases risk of infections like pneumonia.[5,6] The inflammatory and immune response due to respiratory infections has been shown to have a role in pathogenesis of acute cardiovascular events including AMI.[7,8] The recent COVID-19 pandemic has shown a similar cardiac dysfunction together with

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Abbreviations

AMI	acute myocardial infarction
CI	confidence interval
CS	cardiogenic shock
HCUP	Healthcare Cost and Utilization Project
ICD-9CM	International Classification of Diseases-9 Clinical Modification
ICD-10CM	International Classification of Diseases-10 Clinical Modification
NIS	National/Nationwide Inpatient Sample
NSTEMI	non-ST-segment elevation myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction

inflammatory state resulting in cardiogenic and vasodilatory shock.[9]

Available data have shown increased in-hospital mortality due to pneumonia and influenza in patients with AMI.[8,10,11] However, no accurate data is reported on the role of concomitant pneumonia and influenza in patients with AMI-CS. Hence, using a large national database, we sought to assess the prevalence and impact of these respiratory infections on outcomes in AMI-CS. We also sought to evaluate the demographics, clinical characteristics, management strategies and resource utilization of AMI-CS stratified by the presence of respiratory infections to better inform clinical care for these patients.

2. Material and methods

2.1. Study population, variables and outcomes

The National (Nationwide) Inpatient Sample (NIS) contains discharge data from a 20% stratified sample of community hospitals and is the largest all-payer database of hospital inpatient stays in the United States. It is a part of the Healthcare Quality and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality.[12] The HCUP-NIS does not capture individual patients but captures all information for a given admission. Information regarding each discharge includes patient demographics, primary payer, hospital characteristics, principal diagnosis, up to 29 secondary diagnoses, and procedural diagnoses. Institutional Review Board approval was not sought due to the publicly available nature of this de-identified database. These data are available to other authors via the HCUP-NIS database with the Agency for Healthcare Research and Quality.[12]

Using the HCUP-NIS data from January 1, 2000 through December 31, 2017, a retrospective cohort of adult admissions (>18 years) with AMI in the primary diagnosis field (International Classification of Diseases 9.0 Clinical Modification [ICD-9CM] 410. x and ICD-10 CM I21. x-22. x) and a secondary diagnosis of CS (ICD-9 CM 785.51, ICD-10 CM R57.0) were identified.[1,13,14] The administrative codes for CS have been noted to have high positive predictive value (>90%) and specificity (>95%) but low sensitivity (>50%).[15,16] Concomitant respiratory infections including pneumococcal and other bacterial pneumonia, interstitial pneumonia due to organisms like mycoplasma and chlamydia, unspecified pneumonia, influenza due to avian virus, H1n1 and novel influenza A virus were all identified using ICD-9 CM 481–488 and ICD-10 CM J09-18. The Deyo's modification of the Charlson Comorbidity Index was used to identify the burden of co-morbid diseases.[17] The

admissions month was used to identify the season of admission. Similar to prior literature, we defined the seasons based on the meteorological classification of the Northern Hemisphere as—Spring (March—May), Summer (June—August), Fall (September—November) and Winter (December-February).[18,19] Chronic lung disease was identified using Charlson Comorbidity Index codes ICD-9CM 416.8, 416.9, 490. x-505. x, 506.4, 508.1, 508.8 and ICD-10 CM I27.8, I27.9, J40. x-J47. x, J60. x-J67. x, J68.4, J70.1, J70.3. Demographic characteristics including age, sex, race, hospital characteristics, acute organ failure, MCS, cardiac procedures, and non-cardiac organ support therapies were identified for all admissions using previously used methodologies from our group (Supplementary Table 1).[1–3,13,14,19–35]

The primary outcome of interest was differences in the in-hospital mortality of AMI-CS admissions with and without respiratory infections. The secondary outcomes included use of coronary angiography, PCI, MCS, hospitalization costs, hospital length of stay, and discharge disposition. Sub-group analyses were performed to confirm the results of the primary analysis stratifying the population by age (<or ≥ 75 years), sex (male/female), type of AMI (ST-segment elevation [STEMI] vs. non-ST-segment elevation [NSTEMI]), admission season (winter/other seasons), and presence of chronic lung disease.

2.2. Statistical analysis

In accordance with HCUP-NIS recommendations, survey procedures using discharge weights provided with the HCUP-NIS database were used to generate national estimates.[36] Trend weights were used for samples from 2000 to 2011 to account for the 2012 HCUP-NIS re-design. The inherent restrictions of the HCUP-NIS database related to research design, data interpretation, and data analysis were reviewed and addressed.[36] Pertinent considerations include not assessing individual hospital-level volumes, treating each entry as an 'admission' as opposed to individual patients, restricting the study details to inpatient factors since the HCUP-NIS does not include outpatient data, and limiting administrative codes to those previously validated and used for similar studies. Chi-square and *t*-tests were used to compare categorical and continuous variables, respectively. Trends over time were analyzed using multivariable logistic regression (referent year 2000). Univariable analysis for trends and outcomes was performed and was represented as odds ratio (OR) with 95% confidence interval (CI). Multivariable logistic regression analysis incorporating age, sex, race, comorbidity, primary payer, socio-economic stratum, hospital characteristics, comorbidities, admission season, admission year, AMI type, acute organ failure, cardiac arrest, cardiac and non-cardiac procedures was performed for assessing temporal trends analyses and in-hospital mortality. For the multivariable modeling, regression analysis with purposeful selection of statistically (liberal threshold of $p < 0.20$ in univariate analysis) and clinically relevant variables was conducted. Two-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS v25.0 (IBM Corp, Armonk NY).

3. Results

Between January 1, 2000 and December 31, 2017, a total of 11, 622, 528 admissions for AMI were identified of which CS was noted in 557,974 (4.8%). Concomitant respiratory infections were identified in 84,684 (15.2%) admissions, with pneumonia in 84,027 (15.1%) and influenza in 908 (0.2%). Unadjusted temporal trends showed a slight increase in the prevalence of respiratory infections over the study period with a greater prevalence in NSTEMI compared to STEMI AMI-CS admissions (Fig. 1A). Adjusted analyses,

however, revealed a relatively stable trend and comparable prevalence in both STEMI and NSTEMI admissions over the 18-year period (Fig. 1B). Both adjusted and unadjusted analysis showed a significantly higher proportion of respiratory infections between 2008 and 2009. Admissions with respiratory infections were on average older, less likely to be female, belonged to the lowest income quartile, with greater comorbidity, more often admitted during winter, and were more likely to receive care at large urban hospitals compared to those without respiratory infections (Table 1).

Admissions with respiratory infections had significantly higher rates of NSTEMI presentation (42.7% vs 32.3%), respiratory, renal, hepatic, hematologic, and neurologic organ failure compared to those without respiratory infections (all $p < 0.001$) (Table 1). Compared to AMI-CS admissions without respiratory infections, those with respiratory infections received lower rates of coronary angiography (66.8% vs 69.4%, $p < 0.001$) and PCI (44.8% vs 49.5%, $p < 0.001$) (Table 1). Over the 18-year study period, a steady increase in the use of both procedures was seen in STEMI and NSTEMI admissions with a consistently lower utilization of both in STEMI admissions with respiratory infections compared to STEMI

admissions without respiratory infections (Fig. 2A–B). The utilization rates of coronary angiography and PCI were comparable in NSTEMI admissions with and without respiratory infections over the study period (Fig. 2A–B). Higher rates of mechanical circulatory support (MCS), pulmonary artery catheterization, invasive mechanical ventilation and hemodialysis was seen in AMI-CS admissions with respiratory infections (all $p < 0.001$) (Table 1). There was a trend toward increasing utilization of MCS during the study period with STEMI admissions with respiratory infections having a greater utilization than STEMI admissions without infections while MCS utilization was comparable among both groups of NSTEMI admissions (Fig. 2C). Utilization of pulmonary artery catheterization declined among all groups over the study period (Fig. 2D).

The in-hospital mortality was lower among AMI-CS admissions with respiratory infections in both unadjusted (31.6% vs 38.4%, $p < 0.001$) and adjusted analyses (OR 0.58 [95% CI 0.57–0.59], $p < 0.001$) compared to those without. During the study period, a declining trend in in-hospital mortality across the overall population was noted, which was consistent in those with respiratory infections too (Fig. 1C and D). AMI-CS admissions with respiratory infections had significantly longer length of hospital stays (12[7–20]
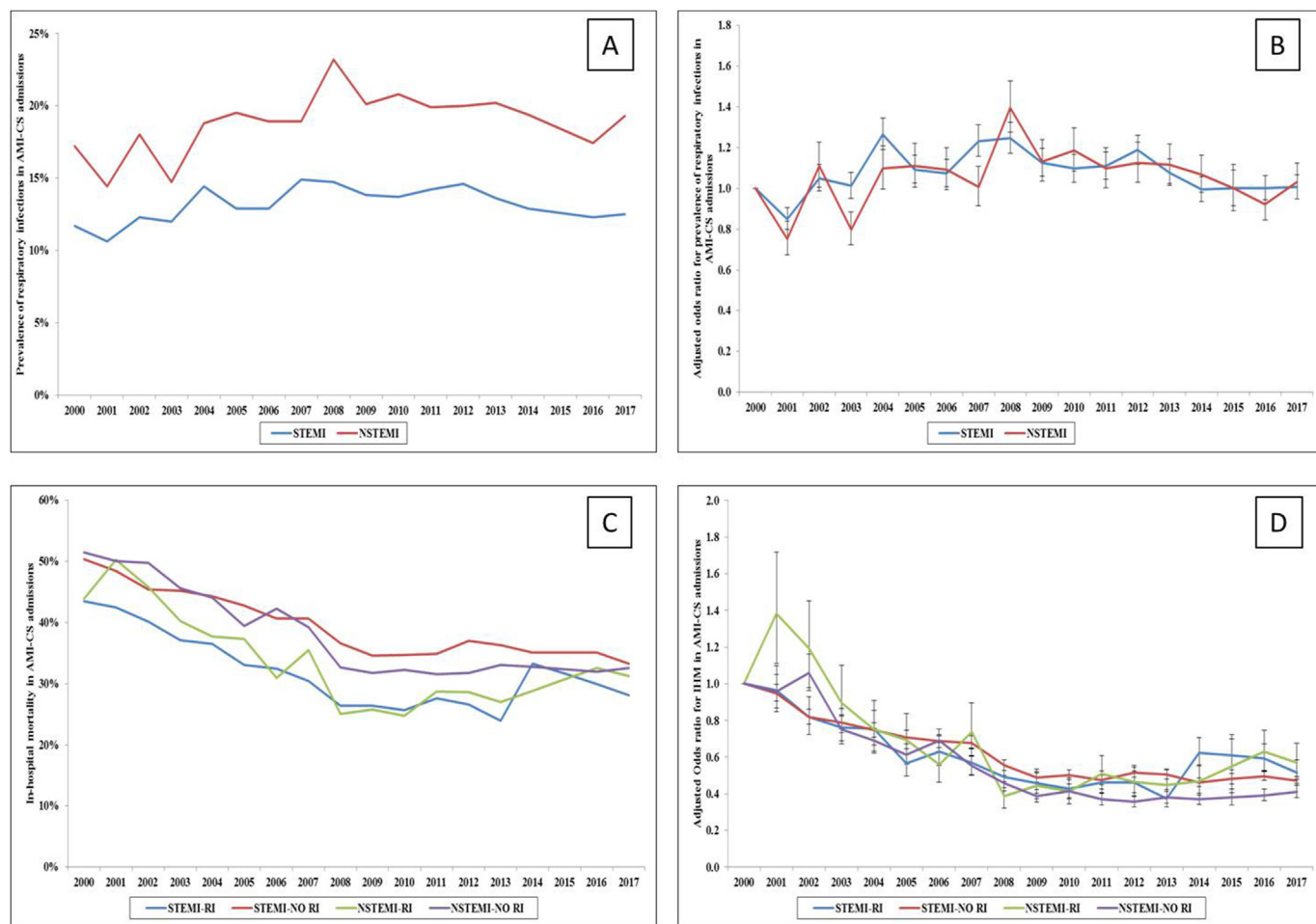
Fig. 1. Temporal trends in the prevalence of respiratory infections in AMI-CS admissions. Legend: A: Unadjusted temporal trends in the prevalence of respiratory infections in AMI-CS stratified by AMI type (all $p < 0.001$ for trends over time); B: Adjusted multivariate logistic regression for the prevalence of respiratory infections in AMI-CS stratified by AMI type (referent year 2000); adjusted for age, sex, race, comorbidity, primary payer, socio-economic status, hospital characteristics, and admission season (all $p < 0.001$ for trends over time); C: Unadjusted in-hospital mortality in AMI-CS admissions with and without respiratory infections stratified by AMI type (all $p < 0.001$ for trends over time); D: Adjusted multivariate logistic regression for in-hospital mortality temporal trends in AMI-CS admissions with and without respiratory infections stratified by AMI type (referent year 2000); adjusted for age, sex, race, comorbidity, primary payer, socio-economic stratum, hospital characteristics, comorbidities, admission season, admission year, AMI type, acute organ failure, cardiac arrest, cardiac and non-cardiac procedures (all $p < 0.001$ for trends over time).Abbreviations: AMI: acute myocardial infarction; CS: cardiogenic shock; NSTEMI: non-ST-segment elevation myocardial infarction; RI: respiratory infections; STEMI: ST-segment elevation myocardial infarction.

Table 1
Baseline and in-hospital characteristics of AMI-CS admissions with and without respiratory infections.

Characteristic		Respiratory infections (N = 84,684)	No respiratory infections (N = 473,291)	P
Age (years)		69.4 ± 12.6	68.9 ± 13.0	<0.001
Female sex		35.4	38.9	<0.001
Race	White	64.2	64.6	0.02
	Black	6.3	6.3	
	Others[a]	29.5	29.1	
Primary payer	Medicare	63.1	60.9	<0.001
	Medicaid	7.7	6.7	
	Private	21.6	24.1	
	Others[b]	7.6	8.3	
Quartile of median household income for zip code	0–25th	26.4	24.3	<0.001
	26th-50th	26.0	26.6	
	51st-75th	24.2	24.8	
	75th-100th	23.4	24.2	
Charlson Comorbidity Index	0–3	22.5	28.8	<0.001
	4–6	52.9	51.6	
	≥7	24.6	19.6	
Hospital teaching status and location	Rural	6.5	7.0	<0.001
	Urban non-teaching	35.9	37.3	
	Urban teaching	57.7	55.6	
Hospital bed-size	Small	8.2	8.8	<0.001
	Medium	23.4	23.3	
	Large	68.4	67.8	
Hospital region	Northeast	17.4	18.2	<0.001
	Midwest	22.2	22.8	
	South	38.8	38.7	
	West	21.6	20.3	
Tertile of admission years	2000–2005	26.2	30.0	<0.001
	2006–2011	33.8	31.4	
	2012–2017	40.0	38.6	
Admission Season	Spring	25.7	26.1	<0.001
	Summer	22.6	24.5	
	Fall	23.1	23.7	
	Winter	28.6	25.7	
AMI type	STEMI	57.3	67.7	<0.001
	NSTEMI	42.7	32.3	
Acute non-cardiac organ failure	Respiratory	65.3	43.6	<0.001
	Renal	51.1	35.6	<0.001
	Hepatic	12.5	8.6	<0.001
	Hematologic	16.3	11.5	<0.001
	Neurologic	20.8	14.0	<0.001
Cardiac arrest		27.2	28.9	<0.001
Coronary angiography		66.8	69.4	<0.001
Percutaneous coronary intervention		44.8	49.5	<0.001
Pulmonary artery catheterization		9.6	6.8	<0.001
Mechanical circulatory support	Total	46.8	44.5	<0.001
	IABP	43.9	41.8	<0.001
	PLVAD	3.0	2.9	0.002
	ECMO	1.2	0.8	<0.001
Invasive mechanical ventilation		58.2	40.1	<0.001
Hemodialysis		4.6	2.4	<0.001

Legend: Represented as percentage or median (interquartile range).
Abbreviations: AMI: acute myocardial infarction; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; NSTEMI: non-ST-segment-elevation myocardial infarction; pLVAD: percutaneous left ventricular assist device; STEMI: ST-segment-elevation myocardial infarction.

vs 6[3–11] days), higher hospitalization costs and were less likely to be discharged home (27.1% vs 44.7%) compared to admissions without respiratory infections (Table 2). Sensitivity analyses revealed similarly lower in-hospital mortality for admissions with respiratory infections across all sub-groups of interest (Supplementary Figure 1).

4. Discussion

In this large study spanning over 18 years, we identified that respiratory infections complicate 15.2% of AMI-CS admissions. Admissions with AMI-CS complicated by respiratory infections had lower utilization of coronary angiography and PCI, and higher rates of MCS use and invasive mechanical ventilation. Admissions with respiratory infections had longer length of in-hospital stays, higher

hospitalizations costs, less frequent discharges to home and lower in-hospital mortality compared to those without.

The association of respiratory infections and acute cardiac conditions like AMI has been well documented.[7,8,10] But the impact of infections like pneumonia and influenza on the subset of AMI patients complicated with CS has not been properly evaluated. Although some studies have evaluated the trends and burden associated with healthcare associated infections in CS patients, these lack data specific to respiratory infections.[37,38] The reported prevalence of pneumonia in these studies was 5–8%. These reports included either all patients with CS or only patients with STEMI-CS.[37,38] In contrast, our analysis included only admissions with AMI-CS and we identified a higher prevalence of pneumonia (15%). Further these earlier studies focused on hospital acquired and/or ventilator acquired pneumonia with specific administrative
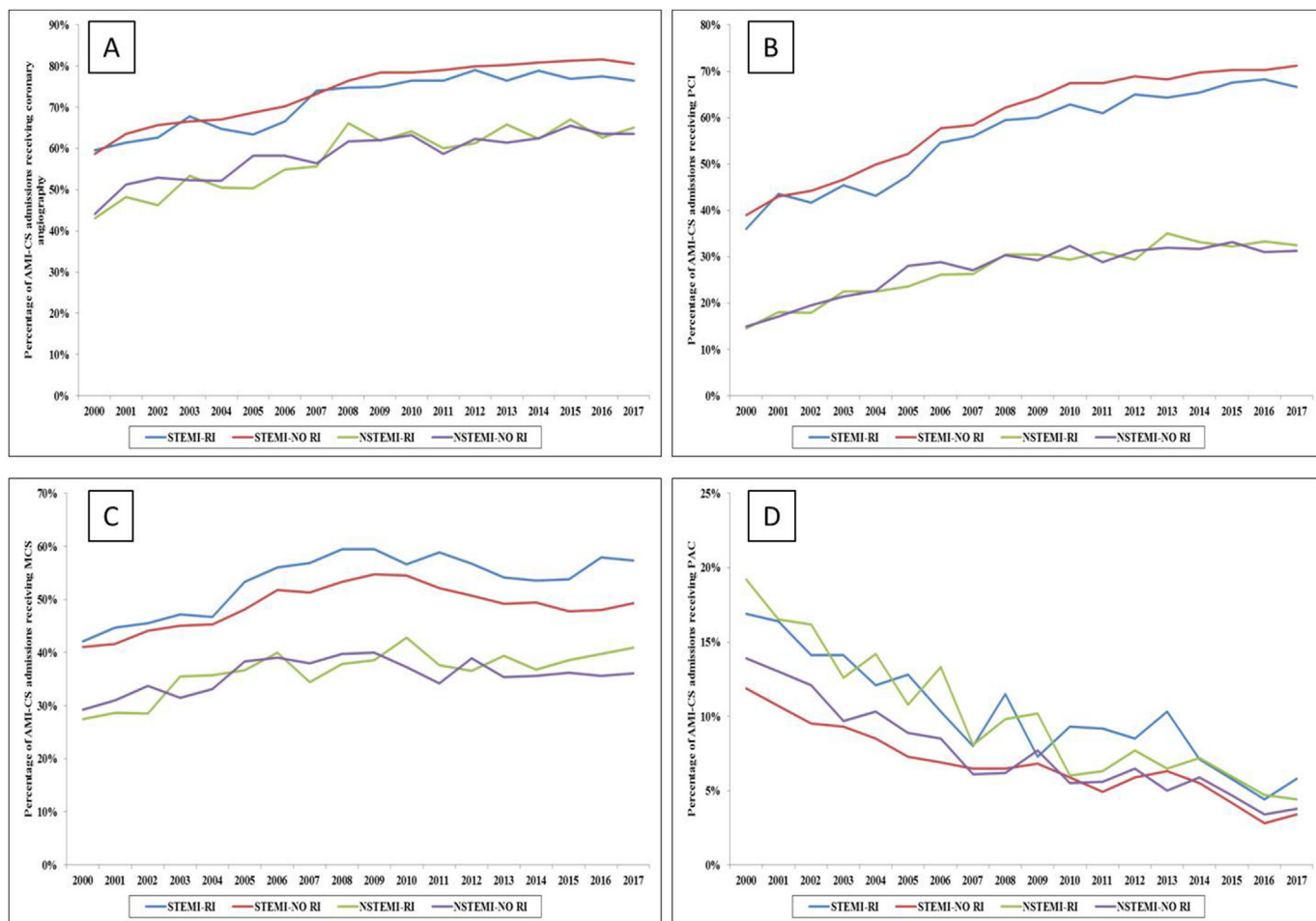
Fig. 2. Temporal trends in the use of coronary angiography, PCI, MCS and PAC stratified by presence of respiratory infections. Legend: A: Temporal trends in the use of coronary angiography (A), PCI (B), MCS (C) and PAC (D) in AMI-CS admissions with and without respiratory infections (all *p* < 0.001 for trend over time). Abbreviations: AMI: acute myocardial infarction; MCS: mechanical circulatory support; NSTEMI: non-ST-segment elevation myocardial infarction; PAC: pulmonary artery catheterization; PCI: percutaneous coronary intervention; RI: respiratory infections; STEMI: ST-segment elevation myocardial infarction.

Table 2
Clinical outcomes of AMI-CS admissions with and without respiratory infections.

Characteristic		Respiratory infections (N = 84,684)	No respiratory infections (N = 473,291)	P
In-hospital mortality		31.6	38.4	<0.001
Length of stay (days)		12 (7–20)	6 (3–11)	<0.001
Hospitalization costs (×1000 USD)		150.4 (72.5–282.6)	83.4 (39.8–159.4)	<0.001
Discharge disposition	Home	27.1	44.7	<0.001
	Transfer	9.5	11.8	
	Skilled nursing facility	45.6	26.4	
	Home with HHC	17.2	16.7	
	Against medical advice	0.5	0.5	

Legend: Represented as percentage or median (interquartile range).
Abbreviations: AMI: acute myocardial infarction; CS: cardiogenic shock; HHC: home health care; USD: United States Dollars.

codes.[37,38] Unlike these, our study identified admissions with any diagnosis of pneumonia and this together with differences in patient population explain the differences in prevalence. Using the HCUP-NIS database, Miller et al showed a temporal increase in all infections in cardiogenic shock hospitalizations,[38] whereas Chehab and colleagues reported a decline in nosocomial infections in STEMI-CS hospitalizations.[37] In our analysis specific to respiratory infections, we identified a relatively stable trend in prevalence among both STEMI-CS and NSTEMI-CS admissions. However, a spike in respiratory infections was seen around 2008–2009

coinciding with the H1n1 pandemic. Influenza together with pneumonia as a secondary manifestation may have contributed to this observed increase.[39]

Older patients are more susceptible to respiratory infections and also reportedly have higher rates of NSTEMI.[40,41] Understandably, respiratory infections were more common in older admissions and in those with NSTEMI-CS presentation in our study. Further, the possibility of greater prevalence of type 2 AMI in patients with respiratory infections,[7,40] could also explain the observed higher rates of NSTEMI-CS in these patients. A similarly greater association

of pneumonia and influenza with NSTEMI has been reported in studies of AMI patients.[8,11] The higher rates of NSTEMI-CS and lower rates of STEMI-CS in admissions with respiratory infections compared to those without could have also resulted in the observed lower utilization of coronary angiography and PCI in admissions with infections. However, in the subset of STEMI-CS admissions, those with respiratory infections continued to have lower rates of these procedures compared to those without. This could be due to the greater acuity in patients with infections evidenced by significantly higher rates of acute organ failure and comorbidity index scores in our study consistent with earlier reports.[11,37,42] In the subgroup of AMI-CS admissions with infections, those with STEMI are expected to have higher use of angiography and PCI compared to NSTEMI due to the respective management protocols and this was apparent in our study.

The observed higher rates of organ failure in admissions with respiratory infections also correlate with the observed greater use of MCS and pulmonary artery catheterization in this group. Earlier reports have shown a similarly greater use of MCS devices and invasive hemodynamic monitoring in AMI-CS admissions with acute organ failure.[1] In turn, as previously alluded to, use of these procedures including mechanical ventilation, multiple access sites for circulatory support could contribute to the development of nosocomial infections.[5,43] Indeed, a prospective study of AMI-CS patients identified that nearly 46% developed infections during hospitalization with the majority being respiratory infections.[5] On the other hand the enhanced inflammatory response triggered by respiratory infections can lead to myocardial damage. Higher levels of inflammatory biomarkers are also known to have negative ionotropic effect contributing to initiation or further progression of cardiogenic shock.[44,45] While we are unable to establish the temporal sequence of respiratory infections in relation to AMI-CS due to the limitations of an administrative database, based on the above reports a bidirectional relationship can be assumed that can play a major role in associated outcomes. Further mechanistic studies evaluating the interplay of nosocomial infections on the management and outcomes of AMI-CS are urgently warranted.

Earlier reports have shown that concomitant presence of respiratory infections and acute cardiac events including AMI increase mortality.[8,11] Interestingly however, in our analysis of AMI-CS admissions, we did not find any increased risk of in-hospital mortality among those with respiratory infections. In fact, admissions with respiratory infections had lower in-hospital mortality compared to those without after adjusting for comorbidity, organ failure and other clinical factors. This could potentially be due to the critically-ill status of AMI-CS patients and respiratory infections may not have further additive mortality burden. Despite the lack of direct comparative data, results from previous studies on burden of infections in AMI-CS patients may help understand this observation. Parenica and associates in their prospective study of AMI-CS patients showed no differences in survival of patients with and without hospital infections (68% of which were respiratory infections).[5] In contrast, a study of STEMI-CS admissions from NIS data demonstrated increased in-hospital mortality among those with nosocomial infections. However, mortality was lower in patients on MCS compared to those without.[37] This and another study also reported that sepsis and/or septic shock had a greater impact on mortality in patients with CS irrespective of MCS use.[37,46] Taken together with findings from our study, it appears that severity of illness, circulatory support, sepsis and organ failure are more important determinants of in-hospital outcomes in patients with AMI-CS than respiratory infections. Further, the lower use of interventions in admissions with respiratory infections may have resulted in lower procedural complications contributing to the observed lower in-hospital mortality. We did however identify

longer lengths of in-hospital stays and higher hospitalization costs in admissions with respiratory infections. The presence of these infections may require longer care or it is possible that patients staying longer in hospitals are at greater risk of respiratory infections as previously reported.[37,47]

4.1. Limitations

Despite the HCUP-NIS database's attempts to mitigate potential errors by using internal and external quality control measures, this study has several limitations. Prior validation of administrative codes for AMI and CS reduces the inherent errors in the study.[15,16] Echocardiographic data, angiographic variables, and hemodynamic parameters were unavailable in this database which limits physiological assessments of disease severity. Angiographic data, such PCI location, lesion classification, presence of multi-vessel disease, and revascularization failure, that may significantly influence outcomes, were not available in this database. The temporality of AMI-CS and respiratory infections cannot be established in this database. Despite best attempts at controlling for confounders by a multivariate analysis it is possible that observed results could be due to residual confounding. Finally, the study has limitations inherent to a retrospective design and our data are only reflective of in-hospital outcomes. We cannot comment on the long-term outcomes of these admissions. Despite these limitations, this study addresses an important knowledge gap highlighting the impact of respiratory infections in AMI-CS in a contemporary population.

5. Conclusions

Respiratory infections in AMI-CS admissions were associated with lower in-hospital mortality but had significantly higher resource utilization. While the prolonged length of in-hospital stay and frequent discharges to skilled nursing facilities reflect the added burden of respiratory infections, they do not appear to worsen mortality in this population. In light of the limitations of our study, further evaluation using granular datasets is essential to confirm the study findings and assess the long-term sequelae of concomitant respiratory infections in AMI-CS population.

Declaration of competing interest

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Author contributions

Sources of funding

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2021.07.004.

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