Sex-Based Differences in Prevalence and Outcomes of Common Acute Conditions Associated With Type 2 Myocardial Infarction

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Little is known about the association between acute prevalent conditions in patients with type 2 Myocardial Infarction (T2MI) and clinical outcomes, particularly between genders. Using the Nationwide Inpatient Sample (2017), we examined outcomes of T2MI in patients stratified by prevalent associated conditions (renal failure, decompensated heart failure, infection, acute respiratory failure, cardiac arrhythmias, bleeding) and gender. Multivariable logistic regression was performed to assess the odds ratios (OR) of in-hospital all-cause mortality in each of the study groups. A total of 38,715 T2MI patients were included in the analysis, of which 47.9% (n = 18,540) were females. Renal failure was the most common prevalent condition in both genders (males: 60%; females: 52.6%). Acute respiratory failure was associated with the greatest odds of mortality (OR 5.46, 95% confidence interval (CI) 5.02 to 5.94) when compared with other conditions: renal failure (OR 2.20 95% CI 2.01 to 2.40), infections (OR 2.96 95% CI 2.72 to 3.21), major bleeding (OR 1.71 95% CI 1.52 to 1.93), arrhythmias (OR 1.30 95% CI 1.19 to 1.43) and decompensated heart failure (OR 0.71, 95% CI 0.65 to 0.77). However, there was no difference in mortality between genders for all acute conditions except renal failure (females OR: 1.02, 95% CI 1.02 to 1.02, p = 0.011). In conclusion, in-hospital mortality after T2MI differs according to the underlying acute condition, with acute respiratory failure being associated with the highest rate of mortality. No significant differences in mortality were observed between genders amongst all prevalent acute conditions, with the exception of renal failure which was marginally higher in females. **(Am J Cardiol 2021;147:8−15)**

Acute myocardial infarction (AMI) affects more than 700,000 patients in the United States (US) annually.[1] Myocardial injury in the absence of acute coronary atherosclerotic plaque rupture or thrombosis is usually due to demand-supply mismatch of myocardial oxygenation, and is classed as type 2 myocardial infarction (T2MI).[2] It is believed that up to 58% of all AMI events are classed as T2MI,[3] which is often associated with worse prognosis compared with type 1 myocardial infarction (T1MI).[4,5] Several factors have been previously described as physiological stressors that could lead to T2MI, primarily through two mechanisms: decreased myocardial supply and increased myocardial oxygen demand, often in the presence of underlying renal or heart disease.[5,6] Although there have been previous reports on the frequency of such conditions amongst patients with T2MI, there are limited data on the association between common acute conditions and in-hospital outcomes in the context of T2MI. Furthermore, while there is data to suggest that females are more likely to present with T2MI compared with males, little is known about sex differences in the distribution of acute conditions and subsequent outcomes after T2MI.[7-9] The present study was designed to examine the association between prevalent acute conditions and clinical outcomes, stratified by sex, using a nationally representative sample of T2MI hospitalizations in the United States.

Methods

The National Inpatient Sample (NIS) is the largest publicly available all-payer database of hospitalized patients in the US and is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project (HCUP).[10] NIS includes anonymized data on discharge diagnoses and procedures from more than 7 million hospitalizations annually. The NIS dataset constitutes a 20% stratified sample of US community hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population.

All adult (≥18 years) hospitalizations for T2MI in 2017 were included, as identified using the International

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Classification of Diseases, tenth revision (ICD-10 I21.A1). Patient characteristics and procedural data were extracted using the ICD-10 codes provided in Table S1 (Supplemental Material) Records with missing data (1.6% of original cohort, n = 630) on the following variables were excluded: elective admission, primary expected payer, death and median household income as illustrated in Figure S1 (Supplemental Material). There were no other inclusion or exclusion criteria.

The primary outcome of interest was in-hospital all-cause mortality. The secondary outcome was in-hospital receipt of invasive management, in the form of coronary angiography or PCI.

For exploratory analyses, the prevalence acute conditions associated with T2MI were compared between genders, as were in-hospital mortality and receipt of invasive management. Continuous variables are summarized using medians and interquartile range (IQR) for non-parametric data and were compared using the Kruskal-Wallis test. Categorical variables are summarized as percentages and were analyzed using the chi squared (X^2) test.

Several multivariable logistic regression models were constructed to examine the odds ratios (OR) of in-hospital mortality in both genders for each of the most prevalent acute conditions. Covariate selection was a-priori based and included those based on clinical significance and those that may directly influence in-hospital outcomes. All multivariable models also adjusted for the following covariates: age, weekend admission, elective admission, primary expected payer, median household income, hospital bed size, region and teaching status, year of admission, all-cause shock (excluding cardiogenic shock), cardiogenic shock, dyslipidemia, thrombocytopenia, smoking status, previous MI, previous PCI, prior coronary artery bypass grafting (CABG), previous cerebrovascular accident (CVA; stroke or transient ischemic attack), anemia, chronic lung disease, atrial fibrillation (AF), coagulopathies, diabetes, hypertension, liver disease, solid tumors hematological malignancy, metastatic disease, peripheral vascular disease (PVD),valvular heart disease, dementia, . All statistical analyses were performed using SPSS version 26 (IBM Corp, Armonk, New York).

Results

A total of 38,715 patients with an index diagnosis of T2MI were included in the analysis of which 47.9% (n=18,540) were females. Females were more likely to be older (Median age 75 vs 71 years), Medicare-insured (77.9% vs 70.5%), and have a lower median household income (0-25th quartile (32.4% vs 30.5 %). (Table 1) Females also had a higher prevalence of previous CVA (9.1% vs 8.4%), hypertension (24.5% vs 20.2%), chronic pulmonary disease (34% vs 31%), valvular heart disease (12.5% vs 10.4%) and dementia (14.8% vs 10.5%). In contrast, males were more likely to be White (73% vs 70.8%), with a history of previous MI (13.8% vs 9.9%) and previous CABG (22.1% vs 12.2%), and PVD (5.9% vs 4.9%). Males also had a higher prevalence of diabetes (42.8% vs 38.7%), liver disease (6.5% vs 4.5%), thrombocytopenia (10.9% vs 8.8%), coagulopathy (14.7% vs 12.6%) and malignancies (hematological malignancies [2.9% vs 2.1%], metastatic cancer [3.5% vs 3%], and solid tumors 6.9% vs 5.4%]).

Overall, renal failure was the most common associated condition (56.5%), followed by infection (47.4%), acute respiratory failure (35.2%), decompensated heart failure (32.1%), arrhythmias (17.2%), and major bleeding (7.2%). (Figure 1) Females experienced higher rates of acute respiratory failure (36.7% vs 33.9%) and infection (51.3% vs 43.8%) compared with males, while major bleeding (7.8% vs 6.6%), arrhythmias (18.1% vs 16.2%), decompensated heart failure (33.7% vs 30.4%) and renal failure (60% vs 52.6%) were proportionately more common in males compared with females. In many cases, more than one associated condition was present, and the types as well as degree of overlap are illustrated in Figure 2 with the frequencies of different combinations provided in Table S2.

The rates of coronary angiography and PCI in the total cohort were 11% and 1.8%, respectively, and these were both higher in males compared with females (coronary angiography: 11.8% vs 10.1%; PCI: 2.3% PCI, vs 1.3%). (Table 2)

Overall mortality rate was 8.9%, with no clinically significant difference between males and females (p = 0.066). (Table 2) The rate of in-hospital mortality was highest amongst those with acute respiratory failure (18.3%), followed by major bleeding (16.6%), infection (13.8%), renal failure (11.8%), arrhythmias (11%), and decompensated heart failure (8%). When stratified by condition, the rate of in-hospital mortality was higher in females compared with males in the major bleeding and renal failure groups (19.6% vs 14.3% and 12.6% vs 11.2%, respectively). There was no difference in crude mortality between genders for all other conditions (Table 2). After adjustment for baseline differences, there was no difference in the adjusted rates of in-hospital mortality between genders except in the renal failure group in which the mortality was higher in females than males (11.3% vs 10.8%, p = 0.026, Figure 3).

Overall, there was no difference in mortality between genders in the total cohort (females OR 1.07, 95% CI 0.99-1.16). (Table 3**,** Figure 4**)** The condition with the highest mortality was acute respiratory failure (OR 5.46, CI 5.02 to5.94) followed by infection (OR 2.96, CI 2.72 to 3.21), renal failure (OR 2.20, CI 2.01 to 2.40), major bleeding (OR 1.71, CI 1.5 to 1.93) and arrhythmias (OR 1.30, CI 1.19 to 1.43). In contrast to the other acute conditions, type 2 MI associated with reduced odds of in-hospital mortality amongst those with decompensated heart (OR 0.71, CI 0.65 to 0.77). After adjustment for baseline differences, there was no difference in mortality between genders for all of the associated conditions except renal failure, which was higher in females compared with males (acute respiratory failure: OR 1.05, 95% CI 0.97 to 1.14; infections: OR 1.00, 95% CI 0.93 to 1.08; major bleeding: OR 1.07; 95% CI 0.99 to 1.15; arrhythmias: OR 1.07, 95% CI 0.99 to 1.15; decompensated heart failure: OR 1.05, CI 0.98 to 1.14; OR 1.02, 95% CI 1.02 to 1.02). (Figure 4)

Discussion

This is the first study to examine the sex-based differences in the distribution and outcomes of prevalent acute

Table 1
Patient characteristics of Type 2 MI patients according to sex

Variable	Male (52.1%)	Female (47.9%)	Total	p-value
Number of weighted discharges	20175	18540	38715	
Age (years), median (IQR)	71 (61,82)	75 (64,85)	73 (62,83)	<0.001
Ethnicity				<0.001
White	73.0%	70.8%	72.0%	
Black	15.5%	17.3%	16.3%	
Hispanic	6.7%	6.9%	6.8%	
Asian/Pacific Islander	2.2%	2.1%	2.2%	
Native American	0.6%	1.0%	0.8%	
Other	2.0%	2.0%	2.0%	
Weekend admission	25.9%	26.2%	26.1%	0.552
Primary expected payer				<0.001
Medicare	70.5%	77.9%	74.1%	
Medicaid	9.6%	9.0%	9.3%	
Private Insurance	14.3%	10.1%	12.3%	
Self-pay	2.7%	1.6%	2.2%	
No charge	0.3%	0.1%	0.2%	
other	2.6%	1.3%	2.0%	
Median Household Income (quartile)				<0.001
0-25th	30.5%	32.4%	31.4%	
26-50th	28.2%	28.2%	28.2%	
51-75th	23.3%	22.1%	22.7%	
76-100th	17.9%	17.3%	17.6%	
All-cause Shock	6.0%	5.4%	5.7%	0.007
Cardiogenic Shock	2.9%	2.8%	2.8%	0.914
Co-morbidities				
Dyslipidaemia	47.1%	46.6%	46.9%	0.341
Thrombocytopenia	10.9%	8.8%	9.9%	<0.001
Previous MI	13.8%	9.9%	11.9%	<0.001
Previous PCI	12.5%	8.1%	10.4%	<0.001
Previous CABG	22.1%	12.2%	17.3%	<0.001
Previous CVA	8.4%	9.1%	8.7%	0.008
Anaemia	31.9%	32.3%	32.1%	0.482
Chronic pulmonary disease	31.0%	34.0%	32.4%	<0.001
Atrial fibrillation	27.2%	27.5%	27.4%	0.514
Coagulopathy	14.7%	12.6%	13.7%	<0.001
Diabetes	42.8%	38.7%	40.8%	<0.001
Hypertension	20.2%	24.5%	22.2%	<0.001
Liver disease	6.5%	4.5%	5.5%	<0.001
Solid tumours	6.9%	5.4%	6.2%	<0.001
Haematological malignancies	2.9%	2.1%	2.5%	<0.001
Metastatic cancer	3.5%	3.0%	3.3%	0.004
Peripheral vascular disease	5.9%	4.9%	5.4%	<0.001
Valvular heart disease	10.4%	12.5%	11.4%	<0.001
Dementia	10.5%	14.8%	12.6%	<0.001
Hospital bed size				0.483
Small	18.6%	19.1%	18.8%	
Medium	26.0%	25.9%	26.0%	
Large	55.4%	55.0%	55.2%	
Hospital Region				0.235
Northeast	24.9%	24.8%	24.9%	
Midwest	26.8%	27.3%	27.1%	
South	31.6%	31.9%	31.8%	
West	16.6%	15.9%	16.3%	
Location/ Teaching status				0.014
Rural	8.9%	9.0%	9.0%	
Urban non-teaching	17.9%	19.0%	18.4%	
Urban- teaching	73.2%	72.0%	72.6%	

MI = myocardial infarction; CABG = coronary artery bypass graft; CVA = cerebrovascular accident (stroke or transient ischemic attack); IQR = interquartile range; PCI = percutaneous coronary intervention.

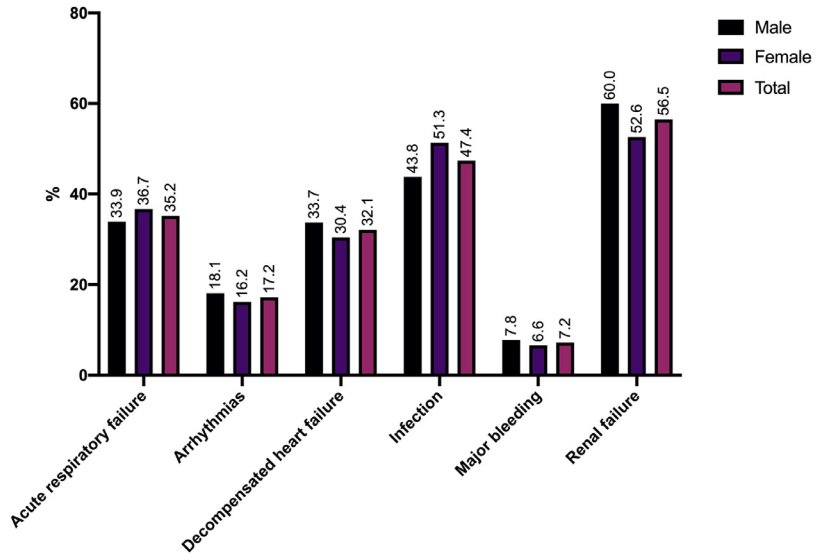

Figure 1. Prevalence of T2MI associated conditions according to sex.**Legend:** T2MI: Type 2 myocardial infarction.

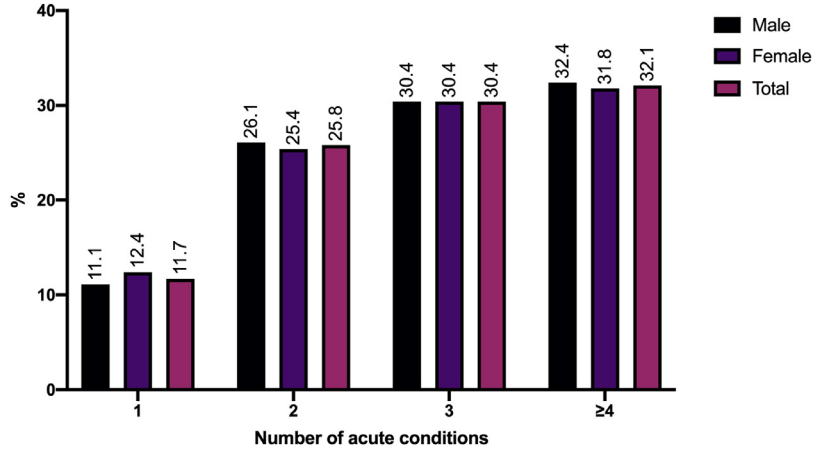

Figure 2. Number of major conditions associated with T2MI.Legend: T2MI: Type 2 myocardial infarction; Males vs Females: p = 0.341.

conditions amongst those with T2MI in a national cohort of hospitalizations. We observe that renal failure was the most prevalent condition amongst those with T2MI, followed by infections, acute respiratory failure, and heart failure, with similar rates in both genders. Our analysis suggests differences in mortality after T2MI between different acute conditions, with the highest mortality associated with acute respiratory failure, followed by

Table 2
In-hospital management and mortality

Variable	Male (52.1%)	Female (47.9%)	Total	p-value
Number of weighted discharges	20175	18540	38715	-
Coronary angiography	11.8%	10.1%	11.0%	<0.001
PCI	2.3%	1.3%	1.8%	<0.001
CABG	0.5%	0.1%	0.3%	<0.001
Mortality				
All conditions	8.6%	9.1%	8.9%	0.066
Acute respiratory failure	17.9%	18.7%	18.3%	0.230
Arrhythmias	11.3%	10.7%	11.0%	0.439
Decompensated heart failure	7.7%	8.3%	8.0%	0.224
Infection	13.9%	13.8%	13.8%	0.836
Major bleeding	14.3%	19.6%	16.6%	<0.0001
Renal failure	11.2%	12.6%	11.8%	0.003

CABG = Coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

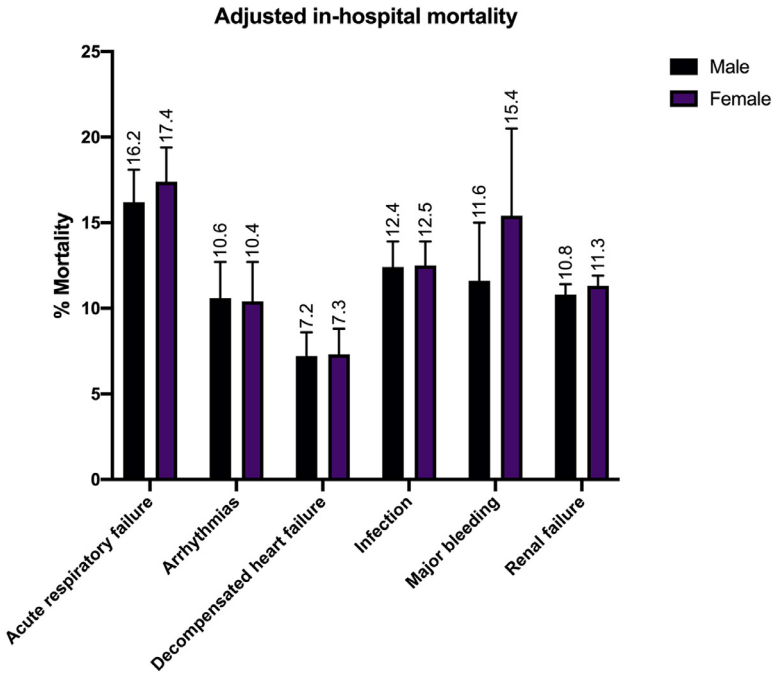

Figure 3. Adjusted in-hospital mortality according to T2MI associated condition in both sexes. Legend: T2MI: Type 2 myocardial infarction.

Table 3
Odds ratios (OR) of in-hospital mortality according to associated condition*

Outcome	OR [95 CI]	p-value
Female vs Male (Any condition)	1.07 [0.99, 1.16]	0.208
Acute respiratory failure		
Overall	5.46 [5.02, 5.94]	<0.001
Female	6.39 [5.63, 7.25]	<0.001
Male	5.03 [4.47, 5.66]	<0.001
Female vs Male	1.05 [0.97, 1.14]	0.297
Infections		
Overall	2.96 [2.72, 3.21]	<0.001
Female	3.15 [2.78, 3.56]	<0.001
Male	2.92 [2.60, 3.27]	<0.001
Female vs Male	1.00 [0.93, 1.08]	0.99
Major bleeding		
Overall	1.71 [1.52, 1.93]	<0.001
Female	2.20 [1.85, 2.60]	<0.001
Male	1.41 [1.18, 1.67]	<0.001
Female vs Male	1.07 [0.99, 1.15]	0.087
Arrhythmias		
Overall	1.30 [1.19, 1.43]	<0.001
Female	1.25 [1.09, 1.43]	0.001
Male	1.41 [1.24, 1.61]	<0.001
Female vs Male	1.07 [0.99, 1.15]	0.088
Decompensated heart failure		
Overall	0.71 [0.65, 0.77]	<0.001
Female	0.71 [0.63, 0.81]	<0.001
Male	0.70 [0.62, 0.79]	<0.001
Female vs Male	1.05 [0.98, 1.14]	0.176
Renal failure		
Overall	2.20 [2.01, 2.40]	<0.001
Female	2.13 [1.89, 2.40]	<0.001
Male	2.21 [1.94, 2.52]	<0.001
Female vs Male	1.02 [1.02, 1.02]	0.011

* reference is the absence of that condition in each category.

infections. Finally, we find no clinically relevant differences in mortality after between genders for all acute conditions associated with T2MI.

T2MI is defined as the presence of cardiac biomarker elevation with one or more symptoms or signs of ischemia, without evidence of atherosclerotic thrombotic occlusion.[2] The proportion of patients with T2MI amongst patients presenting with AMI has varied between 2-58% in various studies.[3,11] and prognosis is known be worse in T2MI compared with T1MI.[4,5] In an analysis of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel - Thrombolysis In Myocardial Infarction 38) trial, patients with T2MI demonstrated 3-fold higher rate of cardiovascular death.[12] As such, there has been limited data on the impact of sex and associated conditions on differences in T2MI outcomes. In this first large-scale analysis of T2MI outcomes based on sex, we found no difference in overall mortality for males versus females, in keeping with findings from a prior smaller analysis.[8] The utilization of coronary angiography was remarkably low in this population (11%) but similar to a recent study (9 to 15%),[8] suggesting that a clinical diagnosis based on non-invasive studies is made in the vast majority of cases. Although there were differences in utilization of coronary angiography and PCI (higher proportion in males compared with females), this was small and is in keeping with the historical pattern of higher utilization of invasive management of AMI in males previously demonstrated in previous studies.[13]

Several acute conditions are linked to T2MI, however, there is limited information on their prevalence from a national perspective with the majority of studies to date isolated to case series or small cohorts. In our nationwide analysis we find that renal failure was the most prevalent acute condition in both genders, with a prevalence of more than

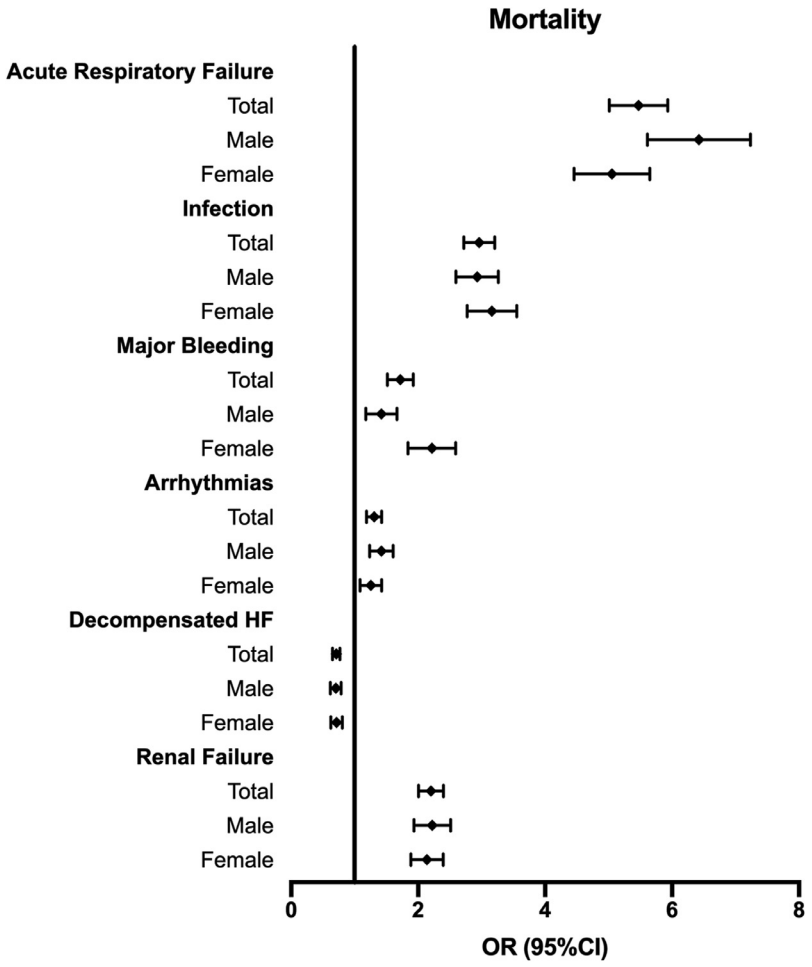

Figure 4. Odds ratios (OR) and 95% confidence interval (CI) of mortality according to associated condition and sex. Legend: HF: heart failure.

50%, while major bleeding was the least common, affecting less than 10% of T2MI patients. Renal failure has a significant association with underlying epicardial atherosclerotic disease,[14] as well as microvascular disease,[15] with decreased clearance of cardiac troponins.[16] Any perturbation in myocardial oxygen supply or demand can thus easily result in troponin elevation with symptoms and/or signs of ischemia in this cohort. Renal failure was the only condition that had overlap in some patients with each of the other conditions, including infection, respiratory failure, infection, decompensated heart failure, cardiac arrhythmias, and bleeding, reflective of its degree of prevalence.

To date, there has been no analysis of T2MI outcomes according to type of prevalent acute condition. This is important for risk stratification and prognostication of T2MI patients, whose outcomes largely vary depending on the management of underlying condition as opposed to the standard management offered to T1MI patients (e.g. antiplatelet therapy, secondary preventative therapy and PCI).[4] In our analysis we identify important differences in outcomes based on type of prevalent condition. Patients with acute respiratory failure had the worst mortality, likely due to the acuity and extent of decrease in myocardial oxygen supply with this condition when compared with patients with renal failure, infection or bleeding. On the other hand, the supply-demand mismatch from a tachy-arrhythmia is commonly short-lived due to defibrillation or rate control, explaining the relatively lower odds of mortality in the arrhythmia sub-group when compared with other associated conditions. These differences in outcomes based on associated conditions emphasizes the importance of treating T2MI as a group of phenotypic clusters based on mechanism of mismatch rather than a homogenous population.[17,18] Although there were differences in prognosis of each prevalent acute condition, we did not find any major differences based on sex, except for a modest increase in risk of mortality in females of the renal failure subgroup compared with males.

We also found that mortality was lower in patients with decompensated heart failure compared with other associated conditions. Decompensated heart failure patients often have cardiac symptoms (that can be difficult to differentiate from new ischemic symptoms), pre-existent electrocardiographic changes, chronically elevated troponin levels as well as echocardiographic wall motion abnormalities that can make the differentiation between T1MI, T2MI, acute nonischemic MI and chronic

MI very difficult. Further, heart failure patients, in general, are more likely to be on appropriate preventative therapy including beta-blockers, angiotensin receptor blockers, antiplatelets and statin therapy (in those with ischemic cardiomyopathy), and the upstream use of these medications could have contributed to the observed favorable outcomes with T2MI.

There are several limitations to the present study. First, although the utilization of administrative datasets has been previously validated for the purpose of cardiovascular studies, they are reliant on the quality of coding inputted by trained professionals, which may be subject to inaccuracies.[19-21] Second, certain laboratory (e.g. cardiac biomarkers) and pharmacological data (e.g. antithrombotic therapy) are not captured by NIS, although the latter is likely to alter the prognosis of T2MI compared with T1MI. Third, a diagnosis of T2MI requires the rise and fall of cardiac biomarkers, with associated signs or symptoms of ischemia; in the absence of the latter, this would be classified as chronic myocardial injury (in absence of acute rise of biomarkers) or silent myocardial infarction. Without access to patient case notes, it is difficult to ascertain whether all patients were correctly classified as T2MI in such a situation. It is also possible that some T2MI patients were misclassified as T1MI or vice versa, although this reflects real-world practice where it is not always possible to ascertain the exact etiology of AMI in a proportion of cases. However, the low rates of revascularization in the T2MI cohort are reassuring that there is no significant "contamination" of this cohort with T1MI patients. Furthermore, it is possible that certain events may have precipitated T2MI prior to admission such as recent surgery, which is not captured in our database. Finally, there is a degree of overlap between prevalent conditions, meaning that further differences could be observed as a result of the combined impact of multiple co-existent conditions in a proportion of patients.

In a national cohort of T2MI hospitalizations we demonstrate differences in in-hospital mortality between acute prevalent conditions, with acute respiratory failure being associated with the highest mortality. However, there were no significant differences in mortality between genders amongst all prevalent acute conditions. These present findings highlight the importance of risk stratifying patients with T2MI according to their associated acute conditions for a more reliable prognostication of their in-hospital survival.

Credit Author Statement

Mohamed O. Mohamed: Methodology, Data curation, Formal Analysis, Writing- Original draft preparation, Visualization; **Tahmeed Contractor**: Writing- Original draft preparation, Visualization, **Dmitry Abramov**: Writing- Reviewing and Editing, **Purvi Parwani**: Writing- Reviewing and Editing, **Erin D. Michos**: Writing- Reviewing and Editing, **David Fischman**: Writing- Reviewing and Editing, **M Chadi Alraies**: Writing- Reviewing and Editing, **Rodrigo Bagur**: Writing- Reviewing and Editing; **Mamas A. Mamas:** Conceptualization; Supervision; Writing- Reviewing and Editing.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.02.011.

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