Original Contribution

Gender-based outcome differences for emergency department presentation ofnon-STEMI acute coronary syndrome

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A B S T R A C T

Background: It is known that women generally have worse mortality outcomes than men with regards to ST-segment elevation myocardial infarction. However, less is known about contemporary gender differences in non-STEMI acute coronary syndrome, particularly those presenting to emergency departments within a regionalized system of care with standardized protocols.
Methods: Retrospective registry data from 2010 to 2016 were examined from the North Texas Mission: Lifeline system of care, representing 33 hospitals around the Dallas Texas metropolitan area. We explored gender-based differences using multivariate logistic regression model, controlling for patient's age, baseline condition, and hospital factors.
Results: There were 16,861 patients who presented directly to emergency departments with NSTEMI, and 6513 (38.6%) were women. At baseline, women were older (68.04 vs. 63.7 years, $p < 0.001$) and presented with history of prior cardiovascular disease more often than men. Women had higher unadjusted in-hospital mortality rates than men (4.8% vs. 3.9%, $p < 0.001$), which persisted after controlling for patient age, comorbidities, and hospital factors. Women also had 23 min longer ED lengths of stay ($p < 0.001$) and were much less likely to receive an early invasive strategy (diagnostic coronary angiography within 24 h of arrival) than men (47.0% vs 54.4%, $p < 0.001$).
Conclusion: Emergency department NSTEMI protocols should consider potential gender disparities that exist for women. Overall, women had worse outcomes, which persist even in an urban system of care with standardized protocols.

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1. Introduction

Cardiovascular disease is the leading cause of death in the United States, and acute coronary syndromes (ACS) represent a substantial percentage of these deaths [1]. The majority of ACS patients are initially treated in the emergency department (ED). Nearly two-thirds of patients experiencing an ACS in the US each year have a non-ST-segment elevation myocardial infarction (NSTEMI), and that proportion is increasing [2]. There is sparse and conflicting evidence about whether gender is a factor in NSTEMI mortality and other outcomes [3]. A very recent retrospective analysis of NSTEMI found that women had higher in-hospital mortality rates, but these differences were mitigated entirely after controlling for age and comorbidity [4]. We attempt to refine the understanding of NSTEMI gender differences by focusing on hospital emergency departments that participate in a regionalized system of care, as well as including other variables of interest to the emergency community.

Treatment protocols vary based on admitting emergency physicians and cardiologists, but contemporary evidence and class I recommendations support an early invasive management strategy incorporating coronary catheterization within 24 h to reduce in-hospital mortality [5,6]. The emergency department plays a critical role in the management of NSTEMI patients, since time and early management are predictors of long-term mortality [7].

Standardized protocols in coordinated, regional systems of care—which incorporate emergency medical services, emergency departments, and cardiologists—have been found to improve overall outcomes and mitigate gender disparities [8]. However, there is no prior study that has examined contemporary gender disparities for NSTEMI specifically in a large regional system of care. Our objectives were to evaluate if gender-related differences persist for mortality, ED length of stay, and use of an early invasive management strategy for patients with NSTEMI in an urban, regionalized system of care with standardized protocols.

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2. Materials and methods

2.1. Study design and setting

This retrospective study was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston.

2.2. Study setting

NSTEMI patient data were gathered from the six counties participating in the American Heart Association's North Texas Mission: Lifeline Program. This system of care developed standardized protocols for STEMI and NSTEMI recognition and treatment across all hospitals and EMS agencies in the region. Thirty-three (33) interventional hospitals (i.e., those with percutaneous coronary intervention capabilities) treated ASC patients, abstracting patient data in the National Cardiovascular Data Registry (NCDR) Action Registry, Get With The Guidelines (GWTG). Demographic data (including sex and age), in-hospital procedures, medications, mortality, and time-based process metrics were recorded for all ACS from January 2010–December 2016, while we focus specifically on NSTEMI for this analysis.

2.3. Outcome variables

The primary outcome variable was in-hospital mortality. In addition, we examined rates of use of an early invasive strategy (cardiac catheterization <24 h from ED arrival), median patient delays (measured as difference in time between symptom onset and arrival at the ED), and ED length of stay (measured as time in the ED before transfer or discharge).

2.4. Covariates

The primary independent variable is gender (with male as the reference). We adjusted for a number of covariates, include age (continuous), race (categorical), medical history (including diabetes, dyslipidemia, prior stroke, prior MI, prior cardiovascular disease), and patient condition upon hospital presentation (those in cardiogenic shock or cardiac arrest). We further controlled for hospital characteristics including bed size and teaching status.

2.5. Statistical analysis

Baseline characteristics of the study population by sex were examined using proportions for categorical variables, and medians (with interquartile ranges) for continuous data. We examined differences between frequencies and proportions using chi-square tests for categorical data, and Kruskal-Wallis medians tests for nonparametric data. Univariate tests were first used to examine differences between sex and the outcome variables. We evaluated the effect of gender using logistic regression for mortality, adjusting for multiple covariates. All analyses were performed using SPSS version 25 (IBM, Armonk NY), with a 2-sided test and a significance level of 0.05.

3. Results

3.1. Patient demographics

There were 16,861 patients who presented to an emergency department with NSTEMI during the six-year study period. Women represented 38.6% of the sample and were 4.3 years older on average than men. The majority of patients were Caucasian/white (71%) and women more frequently had a history of diabetes and previous cardiovascular disease, but lower rates of prior MI and stroke and were less likely to have cardiac arrest (Table 1).

Table 1
NSTEMI patient characteristics.

	Total (N = 16,861)	Men (N = 10,348)	Women (N = 6513)	p-Value
Demographics				
Age, years, mean ± SD	65.4 (13.8)	63.7 (13.2)	68.0 (14.2)	0.001
Race				0.100
White	11,802 (70.0)	7170 (69.3)	4632 (71.2)	
African American	2545 (15.1)	1542 (14.9)	1003 (15.4)	
Asian	371 (2.2)	238 (2.3)	133 (2.0)	
Hispanic	2023 (12.0)	1325 (12.8)	699 (10.7)	
Other	120 (0.7)	73 (0.7)	46 (0.7)	
Baseline characteristics				
Diabetes, (%)	6842 (40.6)	4082 (39.4)	2760 (42.4)	0.001
Dyslipidemia, (%)	10,784 (64.0)	6671 (64.5)	4113 (63.2)	0.084
Prior MI, %	4950 (29.4)	3253 (31.4)	1697 (26.1)	0.001
History of CVD, %	2362 (14.0)	1298 (12.5)	1064 (16.3)	0.001
Prior stroke, %	1641 (9.7)	906 (8.8)	735 (11.3)	0.070
Condition upon presentation				
Cardiogenic shock, %	271 (1.6)	176 (1.7)	95 (1.5)	0.223
Cardiac arrest, %	245 (1.5)	174 (1.7)	71 (1.1)	0.030

The overall unadjusted in-hospital mortality rate was 4.2% and was higher in women (4.8% vs. 3.9%, $p < 0.001$). Women had approximately a 47 min (0.79 h) longer patient delay in seeking emergency care (time of onset of symptoms until their arrival at the ED) and longer median ED lengths of stay (253 vs. 230 min, $p < 0.001$). Early invasive strategy was employed 42.2% of the time, but significantly less often in women than men (35.7% versus 46.2%, $p < 0.001$) (Table 2).

After controlling for patient baseline and hospital factors, gender persisted as a significant predictor of mortality (OR = 1.27; CI = 1.087–1.484, $p < 0.001$). Mortality was significantly lower in teaching hospitals (i.e., those hospitals who provide substantial graduate medical education) than community hospitals (OR = 0.803; CI = 0.684–0.944, $p < 0.01$). Although an early invasive strategy and length of stay were different in univariate tests, they were not independent predictors in the final regression model (Table 3).

4. Discussion

In this large regional cohort with over 16,000 patients, we report several primary findings. First, even after adjustments, women had significantly (1.27×) worse overall odds of in-hospital death than men. Second, women had approximately 47 min longer delay in seeking treatment after their symptom onset, as well as 23 min longer ED lengths of stay. Third, women were far less likely to receive the recommended early invasive approach. Fourth, while women had higher prevalence of prior cardiovascular disease, diabetes, and prior stroke—they had significantly lower prevalence of prior MI, dyslipidemia, and were less likely to present in cardiac arrest than men. Differences in baseline condition and age were not sufficient to mitigate the differences in mortality for women. In addition, the differences in treatment delays did not appear to be significant predictors in the mortality differences.

Crude in-hospital mortality rates were higher in women with NSTEMI. This finding is similar to some studies, but contradictory to others. Hochman et al. reported in their clinical trial that the adjusted risk for death or reinfarction at 30 days after NSTEMI was nearly similar between women and men (OR 0.93, 95% CI 0.72 to 1.21) [9]. They conclude that baseline characteristics alone between sexes do not entirely account for differences in ACS outcomes, suggesting either anatomical or pathophysiologic differences might be potential causes. Valero-Masa found age adjustments tend to mitigate any mortality outcome differences, and that sex alone is not an independent prognostic factor [3]. Wei et al. [8] found regionalized systems of care with standardized protocols for AMI eliminate treatment and mortality disparities, although they did not report on NSTEMI specifically [8]. Many others

Table 2
Outcome differences by gender.

Outcomes	Total ($N = 18,539$)	Men ($N = 12,874$)	Women ($N = 5692$)	p-Value
Mortality, %	714 (4.2)	401 (3.9)	313 (4.8)	0.003
Patient delay, hours, median (IQR)	4.45 (11.9)	4.18 (11.6)	4.97 (12.4)	0.001
ED LOS, minutes, median (IQR)	238 (178)	230 (170)	253 (185)	0.001
Use of early invasive strategy	7107 (42.2)	4782 (46.2)	2325 (35.7)	0.001

noted differences but concluded that age was the primary confounding determinant [10-12]. Lloyd-Jones et al. discovered in their retrospective analysis that men had a worse prognosis after adjustment for age [13]. In our study however, we did not find evidence that age and other baseline and hospital characteristics were sufficient to explain the mortality differences in women with NSTEMI.

Women with NSTEMI who presented to the ED were less likely to receive an early invasive strategy within 24 h of arrival. The American Heart Association/American College of Cardiology guidelines for treatment of NSTEMI recommend a class 1 level of evidence (LOE) for early coronary angiography [14], based on strong evidence [15-17]. NSTEMI treatment guidelines generally have similar criteria for men and women, encouraging an early invasive strategy. One exception to this is low-risk women with troponin-negative results, which should follow an ischemia-guided strategy, versus an invasive one. In one longitudinal study spanning five years, researchers found that women underwent significantly lower cardiac catheterization and revascularization than men [18]. It is impossible to measure bias, but we did observe differences that could not be explained by age, risk and hospital factors. Other factors such as ED crowding, lack of cardiac lab capacity, or disease processes (e.g., Takotsubo, spontaneous coronary artery dissection, and coronary spasm) that impact women more than men are potential factors that may impact treatment strategies, but should not explain gender differences using our definition of early invasive strategy (cardiac catheterization within 24 h) [14].

Prior studies have suggested that reasons women present to the ED slower than men from first symptom of onset are due to patient-related delays [19-21]. We confirmed this in our study, perhaps suggesting a reluctance in women seeking care earlier or lack of symptom recognition. Finally the differences in time to treatment in combination with age and baseline comorbidities still did not mitigate the significance difference in mortality between men and women.

This study has several limitations. Because this registry comes from a region of Texas, our data may be not representative of other states or regionalized systems of care. Second, since this was a retrospective observational study, the lack of randomization could lead to potential confounding factors which we did not identify or control for. Third, we were unable to determine patient outcomes after hospital discharge that could be used to assess all-cause, long-term mortality or other major adverse cardiac events (MACE).

5. Conclusion

In our cohort of NSTEMI patients, we found that women with NSTEMI present later, have longer ED length of stay, are less likely to receive an early invasive management approach than men, and have higher in hospital mortality. These differences persist even in an urban system of care using standardized protocols. The results should guide future focus on NSTEMI algorithms and protocols to ensure health equity for women. Further investigations are needed to determine the underlying causes of these disparities, as well as protocol changes to eliminate outcome and treatment variations for women.

Table 3
NSTEMI regression model results.

	Mortality	
	OR (CI)	p-Value
Variables		
Women (reference men)	1.270 (1.087–1.484)	0.003
Early invasive strategy	0.940 (0.800–1.104)	0.453
ED length of stay	1.000 (1.000–1.000)	0.665
Patient delay (onset to ED arrival)	1.001 (0.993–1.008)	0.853
Patient comorbidities/characteristics		
Age	1.000 (1.000–1.000)	0.927
Race	1.000 (1.000–1.000)	0.897
Diabetes	1.019 (0.866–1.196)	0.819
Dyslipidemia	0.727 (0.617–0.857)	0.000
History of CVD	1.167 (0.815–1.669)	0.399
Prior MI	1.086 (0.911–1.296)	0.360
Prior stroke	0.767 (0.499–1.180)	0.227
Shock on arrival	0.936 (0.487–1.798)	0.842
Cardiac arrest on arrival	1.077 (0.560–1.280)	0.825
Hospital characteristics		
Teaching hospital	0.803 (0.684–0.944)	0.008
Bed size	1.000 (1.000–1.000)	0.010

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