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Sex Differences in Symptom Phenotypes Among Older Patients with Acute Myocardial Infarction

John E. Brush Jr., MD[1,*], **Alexandra M. Hajduk, PhD, MPH**[2], **Erich J. Greene, PhD**[4], **Rachel P. Dreyer, PhD**[3,5], **Harlan M. Krumholz, MD, SM**[3,4,5], **Sarwat I. Chaudhry, MD**[6]

[1]Sentara Healthcare and Eastern Virginia Medical School, Norfolk, VA

[2]Section of Geriatrics, Department of Internal Medicine, Yale School of Medicine

[3]Section of Cardiovascular Medicine, Department of Internal Medicine and Department of Emergency Medicine

[4]Yale School of Medicine; Department of Health Policy and Management and Department of Biostatistics

[5]Yale School of Public Health; Center for Outcomes Research and Evaluation, Yale-New Haven Hospital

[6]Section of General Internal Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, CT

Abstract

Background: Clinicians make a medical diagnosis by recognizing diagnostic possibilities, often using memories of prior examples. These memories, called exemplars, reflect specific symptom combinations in individual patients, yet most clinical studies report how symptoms aggregate in populations. We studied how symptoms of acute myocardial infarction combine in individuals as symptom phenotypes and how symptom phenotypes are distributed in women and men.

Methods: In this analysis of the SILVER-AMI Study, we studied 3041 patients (1346 women and 1645 men) 75 years old with acute myocardial infarction. Each patient had a standardized in-person interview during the acute myocardial infarction admission to document the presenting symptoms, which enabled a thorough examination of symptom combinations in individuals. Specific symptom combinations defined symptom phenotypes and distributions of symptom phenotypes were compared in women and men using Monte Carlo permutation testing and repeated subsampling.

Results: There were 1469 unique symptom phenotypes in the entire SILVER-AMI cohort of acute myocardial infarction patients. There were 831 unique symptom phenotypes in women, as

*Corresponding Author. John E. Brush, Jr., MD, Sentara Healthcare and Eastern, Virginia Medical School, 835 Glenrock Road, Suite 220, Norfolk, VA 23502, Telephone: (757) 261-0700, Fax: (757) 261-0701, jebrush@mac.com.

compared with 819 in men, which was highly significant, given the larger number of men than women in the study (p<0.0001). Women had significantly more symptom phenotypes than men in almost all acute myocardial infarction subgroups.

Conclusions: Older patients with acute myocardial infarction have enormous variation in symptom phenotypes. Women reported more symptoms and had significantly more symptom phenotypes than men. Appreciation of the diversity of symptom phenotypes may help clinicians recognize the less common phenotypes that occur more often in women.

Keywords

Gender disparities; diagnostic reasoning; acute myocardial infarction

Introduction

Making a diagnosis for an individual patient typically starts with a clinician using pattern recognition to generate a list of diagnostic possibilities.[1–4] Novice students, lacking clinical experience, use causal knowledge of diseases to recognize diagnostic possibilities, whereas expert diagnosticians rely more on clinical experience including memories of specific clinical instances. [5,6] When an instance such as a diagnostic encounter is stored in long-term memory, it is remembered using a knowledge structure called an exemplar.[7,8]

Because exemplars are memories of patients with specific feature combinations, it may be important to study how symptoms combine in patients as symptom phenotypes. Most clinical reports of a diagnosis describe how symptoms aggregate at the population level and not how symptoms combine at the individual patient level as symptom phenotypes.

The Comprehensive Evaluation of Risk Factors in Older Patients with Acute Myocardial Infarction (SILVER-AMI) study was a cohort study that enrolled older patients (75 years old) hospitalized with acute myocardial infarction.[9] This study provided an opportunity to examine symptom phenotypes in patients with acute myocardial infarction because all study participants underwent structured interviews that systematically recorded patient's symptoms. Accordingly, our objective was to examine symptom phenotypes in older acute myocardial infarction patients in SILVER-AMI, to study the variation in symptom phenotypes and to compare the variation and distribution of symptom phenotypes in women and men.

Methods

Study Population.

The SILVER-AMI study prospectively collected information on 3041 participants from 94 hospitals in the United States.[10–12] Institutional Review Boards at each institution approved the study and all participants provided informed consent. Eligible participants were patients   75 years old who met the criteria for the Third Universal Definition of acute myocardial infarction.[13] Patients were enrolled in the study at the time of hospitalization and underwent a comprehensive, face-to-face, structured interview at baseline by a local research coordinator. Further abstraction of medical records was performed by the Yale Coordinating

Center for in-depth chart review of medications, cardiac procedures, and adverse events. A primary objective of the SILVER-AMI study was to assess functional impairments, including those in mobility, activities of daily living, and cognition. Mobility impairment was assessed using the Timed UP and Go (TUG) test, and activities of daily living were assessed by asking about pre-hospital function.[14] Cognitive status was assessed as part of the face-to-face baseline interview using the telephone interview for cognitive status (TICS). Cognitive impairment was defined by a TICS score of <27.[15]

Symptoms.

Each patient had a standardized in-person interview by a trained, local research coordinator during the acute myocardial infarction admission. Patients were specifically asked if they experienced chest pain, neck or throat pain, jaw, teeth, or mouth pain, shoulder or arm pain, back pain between the shoulder blades, sweating or diaphoresis, lightheadedness, confusion, numbness or tingling, blurry vision, shortness of breath, cough, indigestion or heartburn, stomach or epigastric pain or pressure, nausea, vomiting, belching, anxiety, stress or agitation, ankle swelling, weakness or fatigue, a fall, or other symptoms not listed. Thus, there were 22 symptoms that could combine in individual patients as unique symptom phenotypes.

Statistical Analysis.

Symptoms obtained by the standardized interviews were analyzed by combining the symptoms in individual patients into combinations that defined symptom phenotypes and by creating subsets of patients with unique symptom phenotypes. The distribution of symptom phenotypes was compared in women and men and stratified by subgroups that might affect presenting symptoms: acute myocardial infarction type (ST-segment-elevation myocardial infarction [STEMI] or non-ST-segment-elevation myocardial infarction [NSTEMI]), receipt of emergent or urgent percutaneous coronary intervention (PCI) or no PCI, presentation time of 6 hours from onset of symptoms or <6 hours, presence or absence of diabetes, presence or absence of chest pain as a presenting symptom, and presence or absence of cognitive, mobility, or activities of daily living impairment.

The variation and distributions of symptom phenotypes were analyzed using SAS/STAT Version 14.3 (SAS, Cary, NC). The SILVER-AMI population had unequal numbers of female (44.2%) and male (55.8%) patients. This imbalance could bias the comparison of the number of symptom phenotypes in women and men because different sample sizes could randomly affect the ability to detect rare symptom phenotype in a smaller group of patients. Therefore, two analytical approaches were used to compare women and men: Monte Carlo permutation tests[16] and repeated subsampling,[17] as described previously.[18] Monte Carlo permutation testing was the primary method for analyzing the differences in the numbers of symptom phenotypes between women and men because it compared the observed differences to that which would have been expected if the differences in the number of phenotypes were simply due to the different sample sizes. Repeated subsampling allowed further analysis of the overlap in symptom phenotypes between women and men.

For the Monte Carlo permutation analysis, patients' sexes were randomly permuted to generate 99,999 data sets reflecting the null hypothesis that any difference in the number of phenotypes was due to the unequal sample sizes for female and male patients rather than due to the effect of sex. These datasets plus the dataset that was actually observed in SILVER-AMI resulted in an ensemble of 100,000 datasets, a number that was deemed adequate for analysis. This analysis created an empirical distribution of the differences in phenotypes for significance testing. The median of the empirical distribution was interpreted as an estimate of the difference in the number of phenotypes between women and men that would have been expected due to the differences in sample sizes alone and the p-value was the proportion of the empirical distribution showing a difference as large or larger than the difference between sexes observed in the original SILVER-AMI data.

For the repeated subsampling analysis, 100,000 subsamples of 500 women and 500 men were randomly generated. The numbers of distinct phenotypes in each subsample of women and men were compared with Student t-test (with Satterthwaite correction for unequal variances). Logistic regression was performed on the repeated sub-samples to determine if the number of symptoms in the phenotype predicted if a phenotype was unique to either women or men.

Distributions of patients in subgroups were compared in women and men using chi-square analysis. Symptom counts in women and men were compared using the Wilcoxon-Mann-Whitney rank-sum test.

Results

There were 3041 patients in the SILVER-AMI study; 1346 (44.2%) were women. The average age was 82.1 years in women and 81.1 years in men ($p < 0.0001$). Of the women, 1134 (84.2%) were White, 162 (12.0%) were Black, and 50 (3.7%) were other race, as compared with men where 1534 (90.5%) were White, 88 (5.2%) were Black, and 73 (4.3%) were other race ($p < 0.0001$). Of the women, 46 (3.4%) were Hispanic, as compared with 41 (2.4%) of the men.

The average number of symptoms per patient was 4.2±2.8 in women and 3.6±2.5 in men ($p < 0.0001$). The frequencies for individual symptoms at the population level are listed in Table 1. Chest pain was more commonly reported in men, whereas pain in other areas including the neck, jaw, arm, and back were more commonly reported in women. Indigestion, nausea and vomiting were also more commonly reported in women. Frequencies of other individual symptoms were not different between women and men.

Examination of how symptoms combine at the individual level revealed that there were 1469 unique symptom phenotypes in the entire SILVER-AMI cohort of patients. There were 831 unique symptom phenotypes in women, as compared with 819 in men. The observed difference of 12 greater phenotypes in women was highly statistically significant because men would have been expected to have 158 more phenotypes than women under the null that the difference was due to different sample sizes rather than sex (permutation $p < 0.0001$).

The differences between women and men in the number of symptom phenotypes in subgroups are listed in Table 2. Women had significantly more symptom phenotypes than men in all subgroups except Hispanic patients, and patients with cognitive impairment and activities of daily living impairment. Chest pain was the most frequently reported symptom in both women and men but was not a reported symptom significantly more often women than men (Table 1). Women had significantly more symptom phenotypes than men regardless of whether chest pain was one of the reported symptoms (Table 2).

Women were more broadly distributed in the symptom phenotype subgroups than men. Among women, 279 (21%) were in one of the top 10 symptom phenotype subgroups, as compared with 517 (31%) of men (p<0.0001). Only 5% of women had the most common symptom phenotype of chest pain alone, as compared with 11% of men. The top 10 symptom phenotypes are listed in Table 3. The top two phenotypes (chest pain and chest pain plus dyspnea) were the same in both women and men. Two of the top ten phenotypes occurred in only women or men and the remaining 6 of the top ten phenotypes occurred in both women and men but in different order of frequency.

The top 4 symptoms reported by both women and men were chest pain, shoulder or arm pain, dyspnea, and weakness. In women, 91.2% of the patients had one or more of those 4 symptoms and 92.9% of the phenotypes included one or more of those 4 symptoms, as compared with 92.1% of the patients and 93.8% of the phenotypes in men (NS).

Repeated subsample analysis also showed significantly more symptom phenotypes in women than men, as shown in Figure 1. The average number of phenotypes in repeated subsampling was 353.6±8.1 in women and 299.3±8.8 in men (p<0.0001). Repeated subsample analysis showed that 82.4±1.4% of the symptom phenotypes constituting 62.1±2.0% of women were present only in women and not in men, and 79.2±1.7% of symptom phenotypes constituting 51.8±2.2% of men were present only in men and not in women (Figure 2). Logistic regression showed that the probability of overlap in symptom phenotypes in women and men decreased with the number of symptoms in the phenotype. The odds ratios accompanying a one-symptom increase were 0.398 (95% CI=0.398–0.399) for women (p<0.001) and 0.401 (95% CI=0.401–0.402) for men (p<0.001).

Discussion

The SILVER-AMI study provided an opportunity to analyze how symptoms combine as symptom phenotypes in individual patients with acute myocardial infarction. Our analysis revealed marked variation with a total of 1469 unique symptom phenotypes among older acute myocardial infarction patients and significantly more symptom phenotypes in women than men. A larger number of symptom phenotypes was seen in women in all the subgroups of acute myocardial infarction that were analyzed, except Hispanic patients, and patients with cognitive impairment and activities of daily living impairment where the smaller subgroups may have lacked sufficient numbers to capture the enough phenotypes to show a significant difference between women and men. These results echo the findings in younger patients in the VIRGO Study analysis[18] and extends the findings to a cohort of older patients with acute myocardial infarction.

At the population level, the top reported symptoms by both women and men were chest pain, shoulder or arm pain, dyspnea, and weakness. Over 90% of both women and men and over 90% of the phenotypes in both women and men had one or more of these symptoms. The difference in women and men, appeared to be primarily explained by the other reported symptoms. Women were more likely than men to report 8 other symptoms, as compared with men who only reported chest pain more commonly than women (Table 1). As a result of reporting additional symptoms, women showed greater diversity of symptom combinations.

Clinicians make medical diagnoses using a process of hypothesis generation and hypothesis testing and the process evolves and improves as clinicians gain experience.[1–4] This process is usually informed by population-level statistics about the most common symptoms, but how symptoms combine at the individual level may be more informative and may provide insights that could help clinicians better navigate the diagnostic process and improve diagnostic accuracy. To our knowledge, this study and the prior VIRGO analysis[18] are the first studies to analyze how symptoms combine in individuals as symptom phenotypes.

Analysis of symptom phenotypes may have implications for understanding diagnostic error. The higher number of symptom phenotypes observed in women in SILVER-AMI, as well as in VIRGO, may be a source of error for diagnosticians. Rare phenotypes may be more difficult to recognize, and because they occur more commonly in women, this could lead to more missed diagnoses in women. Although missed diagnosis rates are hard to calculate because of difficulty establishing a denominator representing all patients under consideration for a specific diagnosis, one prior study suggested that women have a higher rate of missed diagnosis,[19] which could lead to worse outcomes that have been observed in women with acute myocardial infarction.[20] The increased variability in symptom phenotypes in women might provide an explanation for the higher rates of missed diagnoses in women with acute myocardial infarction.

Analysis of symptom phenotypes may also have implications for understanding the diagnostic process. With experience, clinicians store memories of individual diagnostic instances in episodic memory as exemplars.[7,21–24] Episodic memory encodes direct memories of experiences (in contrast to semantic memory which encodes abstracted knowledge about concepts and meaning).[25] Accumulated memories of exemplars give clinicians an implicit sense of the range of variation within a diagnostic category and the relative prevalence of a diagnosis.[26] Diagnostic exemplars are retrieved from memory quickly and intuitively.[27–29] The ease of retrieval depends on the strength of the association, the number of common features, and the recency or vividness of the memory.[30,31]

Other frameworks for knowledge representation in addition to exemplars have also been proposed including semantic networks and prototypes.[7,21,22] Prototypical or classic descriptions of diagnoses are often discussed and presented as textbook examples. For acute myocardial infarction, the prototype might be a patient with chest pain, radiating to the arm, with shortness of breath and diaphoresis. Interestingly, that specific combination of symptoms occurred in less than 1% of the SILVER-AMI and VIRGO patients.[18] The SILVER-AMI data indicate that the prototype for older acute myocardial infarction patients

would include weakness rather than diaphoresis as one of the four most common symptoms. This combination of symptoms also was very uncommon, occurring in less than 1% of the SILVER-AMI patients. Although our analysis shows that the classic prototype for acute myocardial infarction is not a common phenotype, one or more of the prototypical symptoms occurred in over 90% of patients and phenotypes in both women and men, suggesting that looking for phenotypes that contain one or more of the prototypical symptoms would be a better diagnostic strategy than looking for the specific phenotype that matches the prototype.

These findings may have implications for how we teach and for how we might improve the diagnostic process.[33–38] Teachers and clinicians should acknowledge that there is enormous variation in the patterns of presenting symptoms for acute myocardial infarction and the variation is greater in women. Knowledge of exemplar theory may help learners make the most of their experience by encouraging them to intentionally focus on categorizing each diagnostic encounter to make each encounter more memorable. Cognitive psychology studies have emphasized the importance of numerous examples for learning.[39,40] The large number of symptom phenotypes suggest that extensive experience may be necessary to assure expertise in the diagnosis of acute myocardial infarction.[41,42] Finally, there may be opportunities to apply computerized alerts or decision-support tools to help clinicians recognize rare and complex phenotypes.[43–45]

This study has several limitations. The available data only provide the ability to analyze patients with the established diagnosis of acute myocardial infarction. It would be intriguing to also analyze patients with suspected acute myocardial infarction where the diagnosis was missed to determine whether there are specific symptom combinations that might obscure the diagnosis of acute myocardial infarction. As noted above, defining a representative sample of all possible diagnostic encounters is difficult, so designing a study that compared the symptom phenotypes in patients with and without a documented diagnosis would be very difficult. Although this study may lack a "control group" of patients with suspected acute myocardial infarction who had an alternate diagnosis, the study does provide a robust opportunity to evaluate variation of symptom combinations in patients with established acute myocardial infarction. Finally, our study does not provide a mechanism to explain the observed differences in the number of symptom phenotypes between women and men. The differences could be due to biologic sex differences in acute myocardial infarction pathophysiology or pain perception or social differences in how symptoms are reported, and this is an interesting area for further study.

In summary, by analyzing how symptoms combine at the individual level, we have demonstrated that there is enormous variation in symptom phenotypes in acute myocardial infarction and women have significantly more symptom phenotypes than men. Examining how symptoms combine as symptom phenotypes provides important insights into how clinicians recognize diagnoses in individual patients and how individual diagnostic encounters add to a clinician's experiential knowledge. These findings may have important implications for clinicians, learners, and teachers, which may ultimately improve diagnostic accuracy and help address gender disparities in the diagnosis of acute myocardial infarction.

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Declaration of Competing Interest

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Clinical Significance

- Clinical studies usually report how symptoms aggregate in populations, not how symptoms combine in individuals, yet clinicians observe symptom combinations in individuals as symptom phenotypes.

- In the Silver-AMI registry of 3041 AMI patients, there were 1469 symptom phenotypes of AMI, demonstrating enormous variability.

- There were significantly more symptom phenotypes in women.

- These findings have implications that could improve diagnostic accuracy and gender disparities in the diagnosis of AMI.
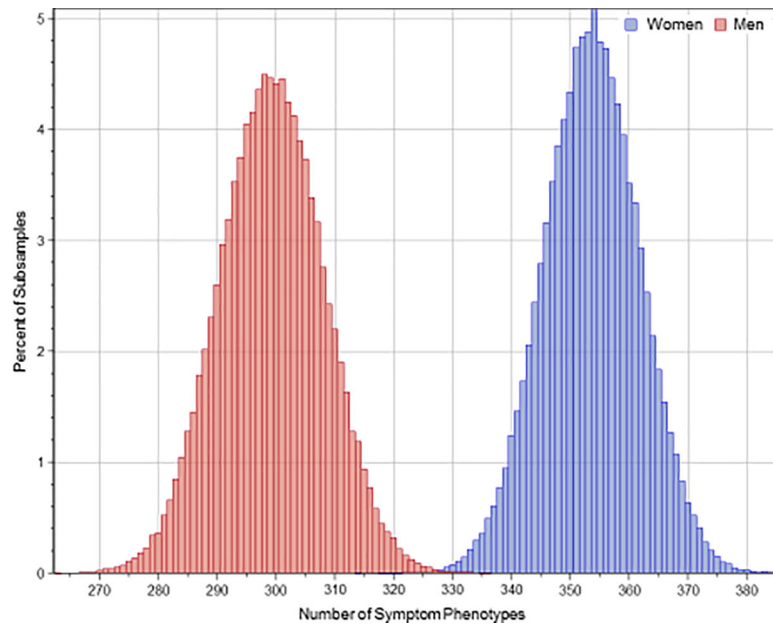
Figure 1.
Distribution of the number of symptom phenotypes in women and men with 100,000 subsamples with a bootstrap size of 500.
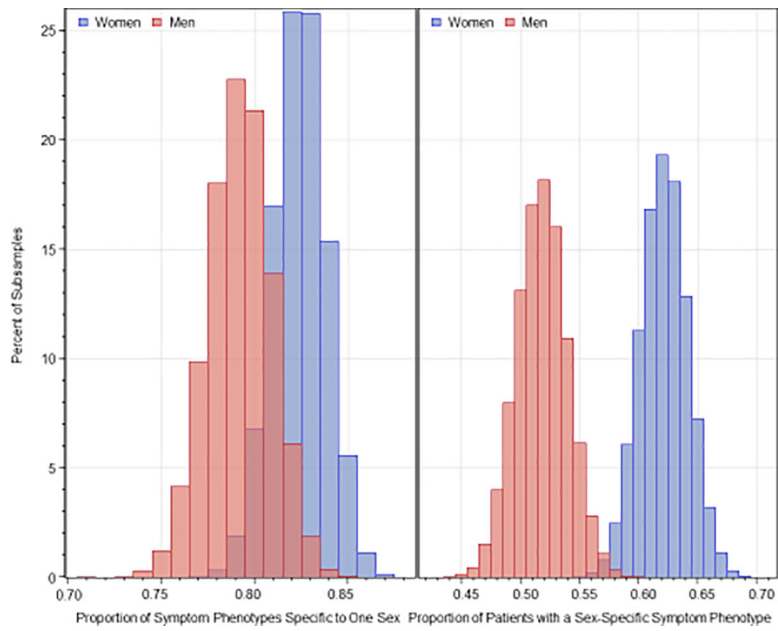
Figure 2.
Distributions of the proportion of phenotypes specific to one sex in the left panel and proportion of patients with a sex-specific phenotype in the right panel.

Table 1.

Frequencies of Symptoms at the Population Level in Women and Men.

Symptom	Women	Men	p value
Chest Pain	72.8	78.2	0.0006
Neck/Throat Pain	17.4	9.6	<0.0001
Jaw Pain	13.5	7.9	<0.0001
Shoulder/Arm Pain	34.8	28	<0.0001
Interscapular Pain	22	11.9	<0.0001
Diaphoresis	22.3	21.7	0.6914
Lightheaded	19.5	16.6	0.0455
Confusion	6.3	5.8	0.5928
Numbness/Tingling	7.5	6.7	0.3919
Blurred Vision	3.5	4.2	0.3015
Dyspnea	45.5	44.8	0.7413
Cough	11.1	10.0	0.3716
Indigestion	19.6	16.4	0.0221
Epigastric Pain	11.1	10.1	0.4050
Nausea	25.0	15.1	<0.0001
Vomiting	11.5	6.2	<0.0001
Belching	7.1	7.1	1.0000
Anxiety, stress, agitation	19.7	18.2	0.3273
Ankle Edema	6.5	5.4	0.2158
Weakness/Fatigue	28.9	26.7	0.1781
Fall	2.5	3.1	0.3810
Other symptom not listed	10	8.1	0.0739

Table 2.

Distribution of Women and Men in Subgroups and Results of the Monte Carlo Permutation Analysis.

Subgroup	Distribution of Patients		Monte Carlo Permutation Tests		
	Women	Men	Observed Difference	Difference under the null	p value
Overall (n=3041)	1346 (44%)	1695 (56%)	12	158	.00001
White (n=2668, 89%)	1134 (43%)	1534 (57%)	−46	−183	.00001
Non-white (n=325, 11%)	194 (60%)	131 (40%)	64	45	.00483
Hispanic (n=87, 3%)	46 (53%)	41 (47%)	0	4	.91014
NSTEMI (n=2244, 74%)	968 (43%)	1276 (57%)	−25	−143	.00001
STEMI (n=797, 26%)	378 (47%)	419 (53%)	19	−25	.00018
Delay (n=1289, 43%)	580 (45%)	709 (55%)	9	−68	.00002
No Delay (n=1736, 57%)	761 (44%)	975 (56%)	−19	−107	.00001
PCI (n=1738, 57%)	758 (44%)	980 (56%)	−7	−118	.00001
No PCI (n=1303, 43%)	588 (45)	715 (55%)	0	−62	.00009
DM (n=1128, 37%)	495 (44%)	632 (56%)	−16	−73	.00013
No DM (n=1913, 63%)	850 (44%)	1063 (56%)	7	−105	.00001
Chest Pain (n=2306, 76%)	980 (42%)	1326 (58%)	−17	−152	.00001
No Chest Pain (n=735, 24%)	366 (50%)	369 (50%)	29	−2	.00842
Cognitive Impairment (n=512, 17%)	277 (54%)	235 (46%)	36	26	.17871
No Cognitive Impairment (n=2479, 82%)	1037 (42%)	1442 (58%)	−40	−189	.00001
Mobility Impairment (n=1064, 35%)	580 (55%)	484 (45%)	101	54	.00092
No Mobility Impairment (n=1493, 49%)	550 (37%)	943 (63%)	−128	−200	.00002
ADL Impairment (n=420, 14%)	247 (59%)	173 (41%)	67	53	.05246
No ADL Impairment (n=2620, 86%)	1099 (42%)	1521 (58%)	−57	−191	.00001

NSTEMI=non-ST elevation myocardial infarction, STEMI=ST-elevation myocardial infarction, PCI=emergent or urgent percutaneous coronary intervention, DM=diabetes mellitus, ADL=activities of daily living.

Table 3.

Rates of the Top 10 Symptom Phenotypes in Women and Men.

Women		Men	
Symptom	**Rate**	**Symptom**	**Rate**
Chest pain	5%	Chest pain	11%
Chest pain, dyspnea	3%	Chest pain, dyspnea	6%
None	3%	Chest pain, arm pain	3%
Dyspnea	3%	None	3%
Chest pain, arm pain	2%	Dyspnea	2%
Chest pain, interscapular pain	1%	Chest pain, diaphoresis	2%
Chest pain, arm pain, interscapular pain	1%	Chest pian, dyspnea, weakness	1%
Arm pain	1%	Chest pain, indigestion	1%
Chest pain, dyspnea, weakness	1%	Chest pain, arm pain, dyspnea	1%
Chest pain, arm pain, dyspnea	1%	Chest pain, interscapular pain	1%
Top 10 phenotypes [*]	21%	Top 10 phenotypes	31%

[*]
p<0.0001