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ORIGINAL RESEARCH

Impact of Sex- and Gender-Related Factors on Length of Stay Following Non–ST-Segment–Elevation Myocardial Infarction: A Multicountry Analysis

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BACKGROUND: Gender-related factors are psycho-socio-cultural characteristics and are associated with adverse clinical outcomes in acute myocardial infarction, independent of sex. Whether sex- and gender-related factors contribute to the substantial heterogeneity in hospital length of stay (LOS) among patients with non–ST-segment–elevation myocardial infarction remains unknown.

METHODS AND RESULTS: This observational cohort study combined and analyzed data from the GENESIS-PRAXY (Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary Syndrome study), EVA (Endocrine Vascular Disease Approach study), and VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI [Acute Myocardial Infarction] Patients study) cohorts of adults hospitalized across Canada, the United States, Switzerland, Italy, Spain, and Australia for non–ST-segment–elevation myocardial infarction. In total, 5219 participants were assessed for eligibility. Sixty-three patients were excluded for missing LOS, and 2938 were excluded because of no non–ST-segment–elevation myocardial infarction diagnosis. In total, 2218 participants were analyzed (66% women; mean±SD age, 48.5±7.9 years; 67.8% in the United States). Individuals with longer LOS (51%) were more likely to be White race, were more likely to have diabetes, hypertension, and a lower income, and were less likely to be employed and have completed secondary education. No univariate association between sex and LOS was observed. In the adjusted multivariable model, age (0.62 d/10 y; $P<0.001$), unemployment (0.63 days; $P=0.01$), and some of countries included relative to Canada (Italy, 4.1 days; Spain, 1.7 days; and the United States, –1.0 days; all $P<0.001$) were independently associated with longer LOS. Medical history mediated the effect of employment on LOS. No interaction between sex and employment was observed. Longer LOS was associated with increased 12-month all-cause mortality.

CONCLUSIONS: Older age, unemployment, and country of hospitalization were independent predictors of LOS, regardless of sex. Individuals employed with non–ST-segment–elevation myocardial infarction were more likely to experience shorter LOS. Sociocultural factors represent a potential target for improvement in health care expenditure and resource allocation.

Key Words: acute myocardial infarction ■ employment ■ gender ■ length of stay ■ sex

In-hospital length of stay (LOS) has surfaced as an important cost-sensitive outcome in acute myocardial infarction (AMI) as it relates to the severity of illness and serves as a target for resource allocation and optimization of cost expenditure.[1,2] Whether sex differences exist in LOS remains uncertain because of varying reports.

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CLINICAL PERSPECTIVE

What Is New?

- Clinical research has yet to address whether sex- and gender-related factors impact length of stay (LOS) in non–ST-segment–elevation myocardial infarction.
- Prior studies reporting LOS in acute myocardial infarction have consisted of largely older male participants, whereas our cohort is composed of mostly younger women pooled from across various countries.
- This study performed inclusion and analysis of multiple psycho-socio-cultural (gender)–related factors, including their prevalence and associated impact on LOS.

What Are the Clinical Implications?

- Identification of comorbidities/risk factors associated with longer LOS may improve risk stratification in hospital.
- Identification of psycho-socio-cultural (gender)–related factors shown to influence LOS may provide targets for upstream social determinant of health interventions.
- Comparison of the impact of country on LOS may provide insight into further avenues of research for optimization.

Nonstandard Abbreviations and Acronyms

EVA	Endocrine Vascular Disease Approach study
GENESIS-PRAXY	Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary Syndrome study
VIRGO	Variation in Recovery: Role of Gender on Outcomes of Young AMI [Acute Myocardial Infarction] Patients study

Overall, longer LOS has been shown in women compared with men, with women being reported to be older and to have higher severity of disease.[3–5] Participants in these studies tend to be older and men, with less inclusion of younger adults and women, who tend to be underrepresented. Previous studies have also not assessed whether the factors attributed to the psycho-socio-cultural environment of men and women, referred to as gender-related factors, play a role in LOS following AMI in conjunction with sex assigned at birth. Current evidence has established the impact of gender-related factors on outcomes in AMI, increasing their relevance in this regard.[6]

Although the incidence of AMI has considerably decreased in both Canada and the United States,[7,8] AMI remains a leading cause of global morbidity and mortality, with 8.9 million deaths worldwide in 2015 alone, whereas Europe reported 6.1 million new cases of cardiovascular disease (CVD).[9] The impact of LOS in AMI on health care system expenditure has been quantified with number of in-hospital days and related costs.[10] For example, the mean index hospital cost for patients receiving percutaneous coronary intervention for AMI between 2010 and 2013 in the United States averaged $18 931, which comprised $19 327 for ST-segment elevation–myocardial infarction and $18 465 for non–ST-segment–elevation myocardial infarction (NSTEMI), with a mean LOS of 3.1 days.[10] Although LOS has globally decreased following the implementation of percutaneous coronary intervention and pharmacological advances,[2] it remains an important cost-sensitive outcome for health care systems and therefore identifying predictors of LOS is necessary to further increase hospital efficiency and decrease health care costs. Furthermore, the variability in LOS within the population with NSTEMI is higher than in their counterparts with ST-segment elevation–myocardial infarction (most receive percutaneous coronary intervention immediately), whereas heterogeneity in case-specific care is more frequent. Hence, further research is needed to identify determinants of LOS in the population with NSTEMI.

Previously identified predictors of prolonged LOS in AMI include comorbidity burden, Killip class, timely access to percutaneous coronary intervention, and hypertension, diabetes, or stroke.[11–15] Yet, both sex- and gender-related factors must be explored to potentially identify predictors of longer LOS in patients with AMI toward sparing resources.

Although sex assigned at birth describes the biological aspect of men and women, gender refers to the psycho-socio-cultural characteristics attributed to men and women in society, including 4 distinct dimensions: institutionalized gender (ie, the distribution of power between sexes in society), roles (ie, the behavioral norms applied to men and women in society), relations (ie, the experience in interaction with others based on sex), and identity (ie, one's self-perception based on sex).[16,17]

With the harmonization of data from 3 different, mostly female, prospective longitudinal cohorts of young adults with ischemic heart disease, we examined the impact of sex- and gender-related factors on LOS in individuals with NSTEMI. We hypothesized that women would experience longer LOS following an

NSTEMI compared with men, and that this difference could be partially explained by a clustering of unfavorable gender-related factors.

METHODS

This study received institutional review board approval MP-CUSM-GEN-08-018-Biobank. All subjects included provided informed consent. The data that support the findings of this study are available from the corresponding author on reasonable request.

Cohort Selection and Data Sources

This observational cohort study comprised 3 independent preexisting prospective cohorts whose study design has been previously described.[6,18,19] Briefly, in the GENESIS-PRAXY (Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary Syndrome study; n=1117), young adults (aged 18–55 years) with acute coronary syndrome were prospectively recruited across 24 sites in Canada, 1 site in United States, and 1 site in Switzerland, between January 2009 and April 2013.[6] In the EVA (Endocrine Vascular Disease Approach study; n=530), adults (aged >18 years) who were hospitalized and underwent cardiac catheterization in Italy for suspected ischemic heart disease were recruited between 2016 and 2019.[19] In the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients study; n=3572), young adults (aged 18–55 years) with AMI were prospectively recruited between 2008 and 2012 across 103 hospitals in the United States, 24 hospitals in Spain, and 3 hospitals in Australia.[20] These cohorts were chosen because of their collection of gender-related variables that are hypothesized to influence CVD outcomes, including LOS. Informed consent was acquired from each patient at the time of enrollment, and ethics approval was obtained for each respective study. Eligibility criteria for inclusion in each respective cohort can be found in Table S1.

For inclusion in this study, participants were aged >18 years, admitted for an NSTEMI, and had recorded LOS. Data harmonization method was applied to ensure comparability of variables, achieve reliable combination of data, and reduce any potential sources for deviation in measurement across the studies (Data S1 and Figure S1).

Baseline Clinical and Gender-Related Characteristics

Baseline sociodemographic and clinical characteristics included age, self-reported sex, self-reported race, country of hospitalization, medical/cardiovascular comorbidities (ie, diabetes, hypertension, and dyslipidemia), history of AMI, family history of CVD, and smoking status. Gender-related variables were assembled by the gender domains recognized by the Institute of Gender and Health/Canadian Institutes of Health Research. This included employment status for gender roles, education level and personal income for institutionalized gender, and marital status and social support for gender relations.[21] Unemployment was defined as the absence of full-time employment of the individual at the time of their NSTEMI. Level of education was categorized into 3 distinct groups: individuals who never completed high school, those who completed high school, or those who completed any additional educational training following high school. Household income was defined as high, intermediate, or low based on the respective countries' standards.

Finally, low social support was categorized into 2 categories, including low social support and acceptable social support, based on the ENRICHD (Enhancing Recovery in Coronary Heart Disease) Social Support Scale. The ENRICHD Social Support Scale is a 7-item self-administered questionnaire that was developed for the ENRICHD study to evaluate social support variables found to increase mortality risk following AMI. Items identified in the questionnaire belong to the following 3 groups: structural (partner), instrumental (tangible support), and emotional (caring). The choices for response range from 1 (none of the time) to 5 (all of the time), with item 7 (living with spouse) being given a score of 4 for "yes" and 2 for "no." Scores of <3 on at least 2 items or an overall score of <18 indicates low social support.[22,23] A table of harmonized variables and associated definitions may be found in Table S2.

Outcomes

The primary outcome was LOS, defined as the number of in-hospital days from admission to discharge or occurrence of a fatal event during the in-hospital stay.

Statistical Analysis

Descriptive statistics were calculated for the overall population using frequencies for categorical variables and means (SDs) or medians (interquartile ranges) for continuous and count variables. Descriptive analyses included comparing baseline and gender-related characteristics, as well as the outcomes, between patients hospitalized for <4 and ≥4 days. An LOS of 4 days in duration was chosen as the cutoff solely for the purpose of descriptive statistics as it represented the median LOS based on the distribution of the data. A χ^2 test was performed for comparison of qualitative variables, and a 2-tailed *t* test was performed for comparison of quantitative variables. Patients with missing admission or discharge dates were excluded (n=63 patients total).

Linear regression models were used to evaluate the independent association between sex, gender-related factors, and LOS. The final linear regression was chosen for its lowest Akaike Information Criterion using an

incremental analytic approach, with forward stepwise addition of available harmonized gender variables grouped by gender domains, as listed above. Two-way interaction analysis between sex- and gender-related variables significantly associated with LOS. Mediation analysis was conducted on gender-related variables found to be associated with LOS together with all the available clinical characteristics to identify what might drive the association. Statistical significance was defined as $P<0.05$. All analyses were performed using RStudio version 1.2.1335.

RESULTS

In total, 2218 hospitalized participants with NSTEMI were included in the present analysis (Figure 1). In the overall cohort, the median LOS was 4 days (minimum, 0 days; maximum, 66 days). The mean LOS within the shorter stay group was 2.4 days, compared with 8.0 days in the longer group.

The distribution of LOS was similar in both sexes (Figure 2). Patients in the longer LOS group were significantly more likely to be White race (78.9% versus 74.8%) and had a higher prevalence of diabetes (40.3% versus 26.0%) and hypertension (69.2% versus 62.9%) (Table 1). Individuals in the longer LOS group were less likely to be employed (53.6% versus 65.0%), were less likely to have completed education following high school (47.3% versus 55.4%), and were more likely to have a lower income (41.5% versus 36.0%) (Table 2).

In the multivariable model with the best fit that included sex- and gender-related factors, age (0.62 d/10 y; $P<0.001$), being employed (–0.63 days in workers; $P=0.01$), and country (Canada as reference) (Italy, 4.1 days; Spain, 1.7 days; and the United States, –1.0 days; all $P<0.001$) were significant independent predictors of LOS (Table 3 and Figure 3).

Further explorative analyses revealed that unemployed individuals were more likely to be women (74.1% versus 42.0%) and to have diabetes (42.4% versus 27.0%), hypertension (75.4% versus 59.6%), a history of AMI (29.7% versus 16.5%), a family history of CVD (58.8% versus 44.9%), and a history of depression/anxiety (58.8% versus 44.9%). Adjustment for these comorbidities and history of cardiovascular events in the best model decreased the estimate and association for employment status from –0.63 to –0.38 days ($P=0.13$).

To further explore if employment had a different effect on LOS in men and women, we tested a

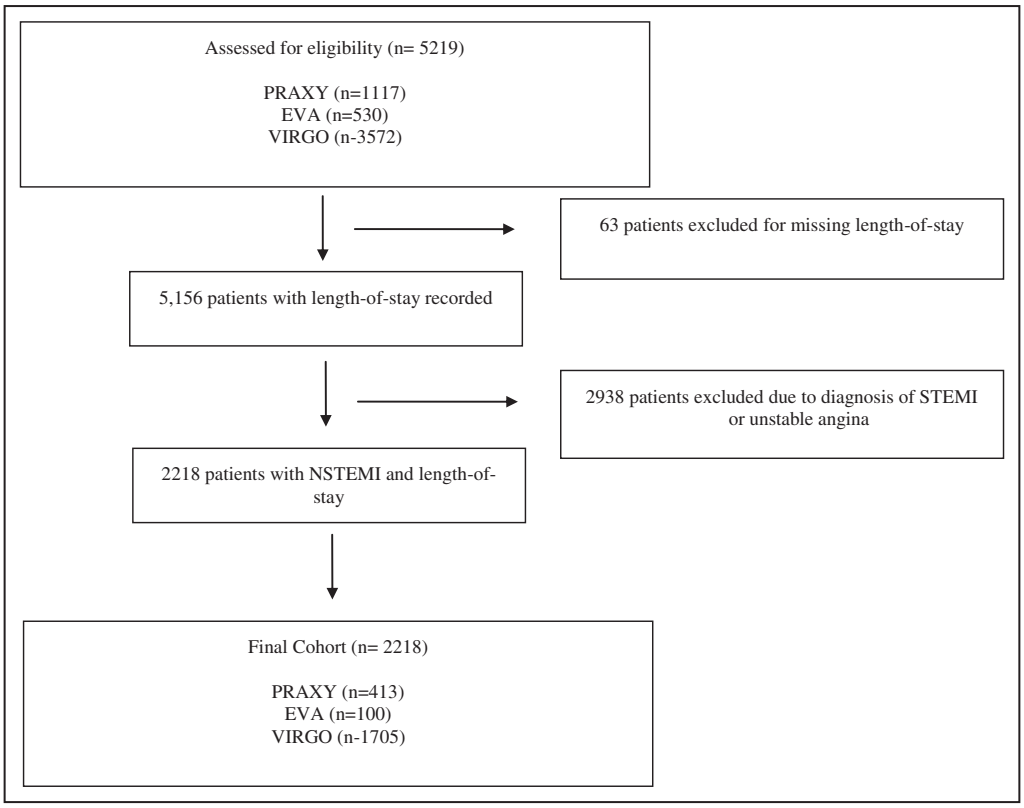

Figure 1. Flowchart of cohort selection for patients with non–ST-segment–elevation myocardial infarction (NSTEMI) and recorded length of stay.
EVA indicates Endocrine Vascular Disease Approach study; GENESIS-PRAXY, Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary Syndrome study; STEMI, ST-segment–elevation myocardial infarction; and VIRGO, Variation in Recovery: Role of Gender on Outcomes of Young AMI [Acute Myocardial Infarction] Patients study.

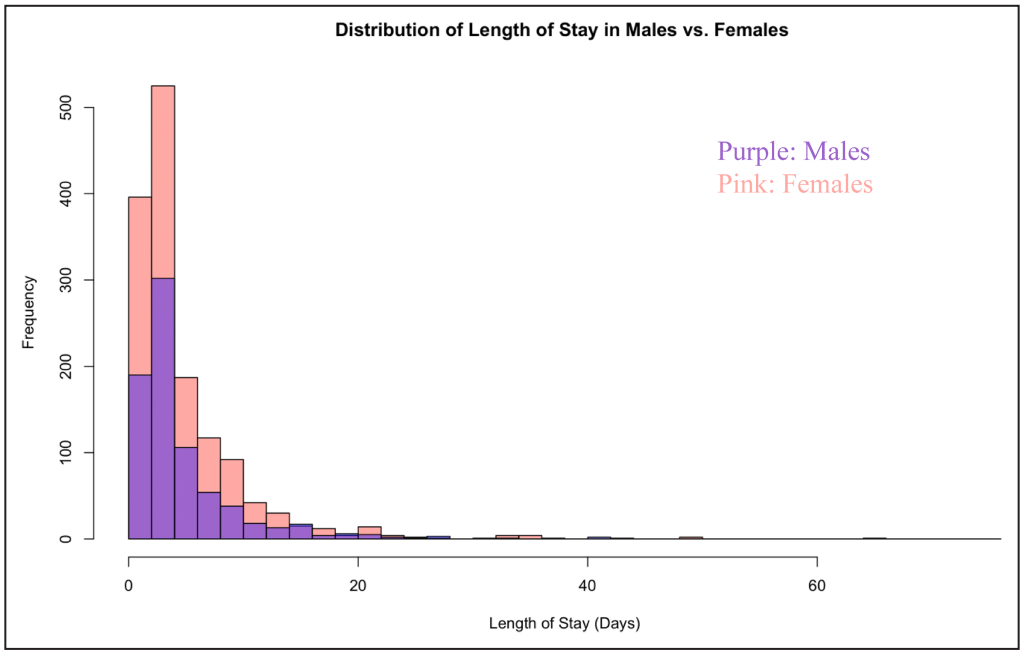

Figure 2. Distribution of length of stay overall and by sex in patients with non–ST-segment–elevation myocardial infarction.

sex-by-employment interaction within the multivariate analysis that was not statistically significant (*P*=0.74).

DISCUSSION

The main finding of this multicountry analysis of adults with NSTEMI is that older age, being unemployed, and the country where a patient is treated are contributors to their LOS, regardless of sex assigned at birth. In terms of gender-related factors, unemployment was the only factor associated with a longer LOS in patients hospitalized for NSTEMI. Female sex, diabetes, hypertension, a history of myocardial infarction, a family history of CVD, and a history of depression/anxiety appear to partially mediate the effect of unemployment. Furthermore, this relationship persists independently of the country where the patient was treated for AMI.

A reduction in LOS following NSTEMI remains a focus for health care cost optimization. Several studies have identified female sex as a predictor of longer LOS compared with male sex.[24-28] The reasons behind such findings have been ascribed mainly to a result of delayed presentation, atypical clinical presentation, and exceeding established benchmarks of reperfusion strategies. This may be further attributed to an elevated prevalence of CVD in women and related increased mortality rate compared with their male counterparts, signifying asymmetric burden of disease.[29-31] These observations are postulated to result from inherent pathophysiological differences in coronary disease obstruction, as well as lower revascularization rates and higher comorbidity burden and presenting age in women.[25,26,31-33] Nevertheless, other studies[33] have reported no sex differences in LOS. Such conflicting results suggest that other patient- or structural-level features of individuals beyond sex contribute to the duration of in-hospital stay among individuals with NSTEMI.

Interestingly, in our cohort, the proportion of women in the long and short LOS groups was similar. These results differ from previous research as they were derived from a younger, international, and mostly female cohort, whereas to date most NSTEMI cohorts analyzed have been composed of older, mostly male participants. As such, we are uniquely positioned to offer insight into the LOS following NSTEMI in younger age groups. Furthermore, the absence of sex differences in LOS following an NSTEMI may result from more rigorously applied treatment algorithms in these younger patients.

A novel finding of the study was that although sex was not a predictor of LOS, we found that among the gender-related variables included (ie, roles, relations, and institutionalized gender), only gender role, captured by employment status, was associated with LOS independent of sex assigned at birth. More specifically, in the final multivariate model, being unemployed (a surrogate marker of gender roles) was independently associated with 0.63-day longer LOS compared with their employed counterparts; this difference is not negligible and represents a 15% longer LOS based on

Table 1. Baseline Characteristics of Patients With NSTEMI According to LOS

Variables	LOS <4 d (N=1094)	LOS ≥4 d (N=1124)	*P* value
Age, mean±SD, y	47.3±6.5*	49.8±8.9*	<0.0001
Female sex	710 (64.9)	743 (66.1)	0.56
White race	818 (74.8)*	887 (78.9)*	0.02
Country			
Canada	168 (15.4)	208 (18.5)	0.054
United States	869 (79.4)*	635 (56.5)*	<0.0001
Switzerland	8 (0.7)	19 (1.7)	0.051
Spain	30 (2.7)*	159 (14.1)*	<0.0001
Australia	10 (0.9)	12 (1.1)	0.83
Italy	9 (8.2)	91 (8.1)	<0.0001
Cardiovascular risk factors			
Diabetes	284 (26.0)*	453 (40.3)*	<0.0001
Hypertension	688 (62.9)*	778 (69.2)*	0.0017
Dyslipidemia	877 (80.2)	875 (77.8)	0.19
Prior myocardial infarction	223 (20.4)	264 (23.5)	0.081
Family history of cardiovascular disease	600 (54.8)	622 (55.3)	0.82
Depression/anxiety	529 (48.4)*	589 (52.4)*	0.02
Currently smoking	350 (32.0)	358 (31.9)	0.97

All data are presented as number (percentage) of participants unless otherwise specified. LOS indicates length of stay; and NSTEMI, non–ST-segment–elevation myocardial infarction.

*$P<0.05$.

employment status alone. Although unemployment status is known to adversely impact the risk for CVD, the impact of unemployment on LOS in NSTEMI has not been previously reported.[34] Albeit, the studies that included gender-related measures were limited to socioeconomic status and found longer LOS in patients with lower socioeconomic status.[35,36]

To explore the potential mechanism through which unemployment resulted in longer LOS, potential mediators of the effect of unemployment on LOS were identified through further subgroup analysis. Unemployed individuals were more likely to be women and have diabetes, hypertension, a history of myocardial infarction, a family history of CVD, and/

Table 2. Presence of Gender-Related Variables in Patients with NSTEMI According to LOS

Variables	LOS <4 d (N=1094)	LOS ≥4 d (N=1124)	*P* value
Employed*	711 (65.0)† 59.8	602 (53.6)† 59.8	<0.0001
More than high school education‡	606 (55.4)† 64.7	532 (47.3)† 65.4	0.0002
Low income§	394 (36.0)† 74.9	466 (41.5)† 76.6	0.009
Married¶	635 (58.0) 60.9	649 (57.7) 63.2	0.90
Low social support‖	214 (19.6) 66.8	239 (21.3) 65.3	0.34

All data are presented as number (percentage) of participants. Percentage female sex is presented under each number. LOS indicates length of stay; and NSTEMI, non–ST-segment–elevation myocardial infarction.

*Employed: employment status.

†$P<0.05$.

‡More than high school education: individuals having completed high school and pursued either trade school or further academia.

§Low income: household income of <$30 000/year if living in the United States, Canada, and Australia, <500 euro/month if living in Italy or Spain, or <2300 franks/month if living in Switzerland.

¶Married: marital status.

‖Low social support: as defined by a score of <3 on at least 2 items or an overall score of <18 on the ENRICHD Social Support Scale.

Table 3. Bivariate and Multivariate Linear Regression Models of Sex- and Gender-Related Factors on LOS

Variables	Univariate	Model 1	Model 2	Model 3	Model 4
Female sex	0.036 (−0.41 to 0.49)	−0.14 (−0.57 to 0.29)	−0.19 (−0.64 to 0.26)	−0.13 (−0.58 to 0.32)	−0.17 (−0.62 to 0.28)
Age, y		0.077 (0.046 to 0.108)‡	0.068 (0.037 to 0.099)‡	0.065 (0.034 to 0.096)‡	0.062 (0.029 to 0.095)‡
Country relative to Canada					
United States		−0.78 (−1.35 to −0.21)†	−1.11 (−1.72 to −0.5)‡	−1.15 (−1.76 to −0.54)†	−1.06 (−1.69 to −0.43)‡
Switzerland		−0.58 (−2.46 to 1.3)	−1.27 (−3.41 to 0.87)	−1.36 (−3.50 to 0.78)	−1.18 (−3.32 to 0.96)
Spain		1.82 (0.96 to 2.68)‡	1.53 (0.59 to 2.47)‡	1.61 (0.67 to 2.55)‡	1.69 (0.73 to 2.65)‡
Australia		1.07 (−1.01 to 3.15)	1.32 (−0.82 to 3.46)	1.32 (−0.82 to 3.46)	1.45 (−0.69 to 3.59)
Italy		5.84 (4.59 to 7.09)‡	4.09 (2.72 to 5.46)‡	3.87 (2.50 to 5.24)‡	4.14 (2.71 to 5.57)‡
Education level higher than high school			−0.037 (−0.39 to 0.31)	0.010 (−0.34 to 0.36)	0.016 (−0.33 to 0.37)
Low income			−0.26 (0.51 to 0.01)†	−0.092 (−0.36 to 0.18)	−0.12 (−0.41 to 0.17)
Being employed				−0.74 (−1.21 to −0.27)†	−0.63 (−1.12 to −0.14)*
Low social support					0.38 (−0.13 to 0.89)
Being married					0.057 (−0.39 to 0.51)
AIC	13571	13256	11553	11546	11290

Coefficient estimates are reported as the first number, followed by 95% CI in parentheses. The final model was chosen for its lowest AIC of 11 290. Model 1: adjusted for sex, age, and country. Model 2: model 1 plus institutionalized gender variables. Model 3: model 2 plus gender roles variables. Model 4: model 3 plus gender relations variables. AIC indicates Akaike Information Criterion; and LOS, length of stay.

*$P<0.05$.
†$P<0.001$.
‡$P<0.01$.

or a history of depression/anxiety, which have been identified as predictors of prolonged LOS and were found to mediate the effect of employment on LOS in our cohort.[12,13,35,37] One suggested explanation for this relationship is that the prolonged LOS observed in unemployed individuals, mostly women, is the result of the severity of NSTEMI and/or comorbidity burden and that being unemployed promotes a social environment that increases the likelihood for acquiring these health risk factors. Another postulated mechanism may be that unemployment delays disposition because of a lack of social support, leading to difficult discharge planning. Although no sex difference in LOS was observed, unemployed individuals were far more likely to be women. Because the social environment of the individual is known to impact CVD and AMI outcomes, our analysis highlights that in addition to sex, the need to evaluate the roles of psycho-socio-cultural characteristics on clinical outcomes in patients with NSTEMI remains paramount.

Finally, in our analysis, both age and country of hospitalization were independently associated with LOS in the final multivariate model. The relationship between age and longer LOS in AMI has been previously explored, whereas country-based variations present a new avenue for potential improvement of LOS in NSTEMI.[15] Postulated mechanisms for shorter hospitalizations in the United States in contrast with longer hospitalizations in Spain and Italy relative to Canada include differences in institutional-level policy, health care organization, and discharge protocol among the various locations and institutions included. In addition, possible differences in distribution of gender-related variables across countries may exist and signify an interaction between gender-related variables and country of residence. In addition, although our study incorporated measures belonging to 3 gender dimensions, other gender-related variables not recorded in our cohort may contribute to the observed relationship.

Strengths and Limitations

The main strengths of our analysis include the younger and mostly female cohort used, the availability of a well-represented set of gender-related variables to include in the analysis, as well as the unprecedented multi-country representation addressing LOS in NSTEMI.

Several important limitations of the present study must be addressed. As this is an observational cohort study, variables not recorded or included in the analysis may influence the final multivariate model. Recruitment for the EVA cohort occurred 6 years following completion of the GENESIS-PRAXY and VIRGO cohort studies, and although the management of acute coronary syndrome has remained similar, this represents a potential limitation to our study. Furthermore, although appropriate data harmonization method was used in the merger of these 3 cohorts, variables were often grouped and reduced to include data from each respective cohort. As such, valuable information may have been lost in the creation of the

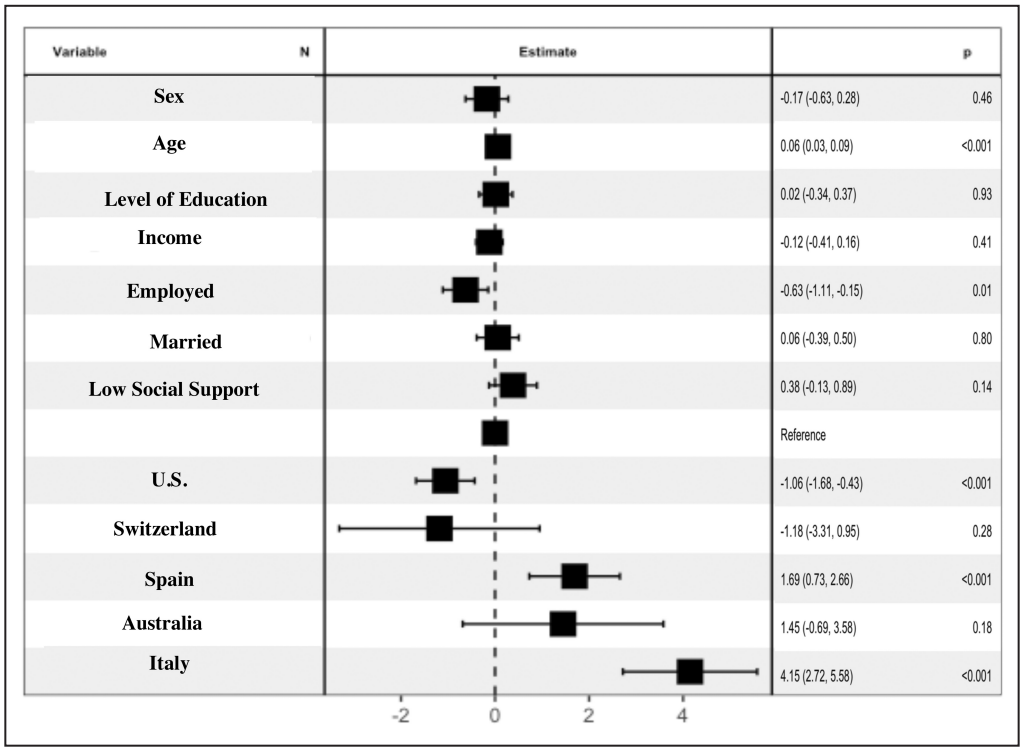

Figure 3. Forest plot of the multivariate linear regression model, including sex- and gender-related factors.
All CIs are indicated on the right-hand side with associated *P* values. Sex is reported as "female sex," age in years, level of education as "education level higher than high school," income as "low income," employment as "being employed," low social as "low social support," married as "being married," and country as "country relative to Canada." Gender-related factors include level of education, income, employed, and married. Sex refers to sex assigned at birth.

final harmonized variables, which may have impacted the associations observed in the regression models. In addition, we recorded employment status as the individual's state of employment at the time of hospitalization because of the availability of data; however, further categorization of employment trends as well as specific types of employment may be more relevant for future analysis. Finally, country-specific sample sizes varied significantly and may limit the power and generalizability of association between country of hospitalization and LOS in NSTEMI. Variation in health care system between countries may limit analysis as well. Nevertheless, our findings remain relevant and provide a different and unique perspective on the influence of gender/the social environment on the trajectory of LOS in NSTEMI.

Our cohort did not measure variables pertaining to gender identity and only included binary categorization of sex assigned at birth. Gender identity concerns the individual's self-perception and is often conflated with sex assigned at birth in biomedical research. Further studies should aim to collect data on gender identity for further stratification.

CONCLUSIONS

Being unemployed, older age, and the country of hospitalization were independent predictors of LOS following NSTEMI regardless of sex. Individuals employed at the time of hospitalization were more likely to experience a shorter LOS following an NSTEMI. A history of diabetes, hypertension, prior myocardial infarction, and depression/anxiety, and a family history of CVD, mediated the effect of unemployment on LOS. Variation in LOS exists across different countries, likely attributable to institutional policy, resource allocation, and distribution of gendered factors. Occupation represents a modifiable target for gender-sensitive intervention to improve screening, risk stratification, and discharge planning and therefore warrants further research. Our findings offer promising insight into the impact that the sociocultural gender may have on LOS, as well as highlight a significant target for improvement in health care expenditure and resource allocation.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S2
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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Data Harmonization

Data harmonization methodology was employed in order to facilitate pooling large-data analysis across these three independently recruited patient cohorts. The methodology used was based on the established framework published by the Maelstrom group at the McGill University Health Centre (39). Data harmonization for the present study consisted of the following four steps and is summarized in **Figure S1**: ***Step 1 (Data Exploration)*****:** The presence of the gender-related factors baseline characteristics, and clinical variables of interest was assessed across all three cohorts. ***Step 2 (Variable Definitions)*****:** Variable definitions within each cohort were evaluated for harmonization potential, as definitions commonly differed between cohorts. ***Step 3 (Creation of Harmonized Variables):*** Harmonized variable names and definitions were merged across the four cohorts using a reductionist approach in order to maximize inclusiveness. Missing data was assessed on a case-by-case basis. ***Step 4 (Extraction Code)*****:** An extraction/conversion code was created to extract the data from the cohort-specific datasets into the final harmonized dataset under the new harmonized variables and variable definitions. ***Step 5 (Analysis)*** Retrospective analysis was conducted in order to determine the influence of sex assigned at birth and gender-related factors, on length-of-stay in subjects with NSTEMI. Merging these cohorts allowed for an increased study population size with increased statistical power. Benefits resulting from proper data harmonization include processing large amounts of data with the elimination of deviations in data measurement, which is a possible risk in meta-analytical methodology (40, 41). Given our local access to each of the datasets used in this study, data harmonization was applied and an analysis on the final harmonized dataset was performed.

Table S1. Eligibility Criteria Across Individual Cohorts.

	GENESIS-PRAXY	EVA	VIRGO
Inclusion	• 18-55 years • Fluent in English or French • Able to provide written consent • Admitted to the hospital with a diagnosis of ACS	• Patients with ischemic heart disease (acute or chronic) undergoing percutaneous coronary intervention (urgent or elective) • Written informed consent • Both sexes • Age > 18 years	**1.** 18-55 years **2. AMI Criteria (must meet both the following criteria – 2.1 and 2.2):** **2.1 Need at least one of the following elevated markers of myocardial necrosis:** • Troponin I or T level greater than 99th percentile of upper reference limit • CK level > twice the upper reference limit with CK-MB activity level > 10% total • CK value on the same draw or CK-MB mass greater than the 99th percentile of upper reference limit **2.2 Supporting evidence of myocardial ischemia with <u>at least one</u> of the following:** • Symptoms of ischemia • ECG changes indicative of new ischemia • Other evidence of myocardial necrosis (imaging, pathology) **3. Presentation: must meet one of the following:** • Patient initially presented at this facility • Patient was transferred here from another facility within 24h of original presentation
Exclusion	• Did not meet any of above	• Patients with life expectancy < 12 months • Active cancer • Pregnancy	• Previously enrolled in VIRGO • Non-English/Spanish speaking • Inability to provide informed consent • Inability to contact for follow-up • Acute MI due to chest trauma • Currently a prisoner

Inclusion and exclusion criteria present in each of the three cohorts used in this study: GENESIS-PRAXY, EVA, VIRGO.

Table S2. Harmonized Variables with Variable Definitions.

Variable	Definition
Sex	Male or female
Age	Numeric
Race	Black/African American, White/Caucasian, American Indian/Alaska Native, Asian/Pacific Islander/East Indian, Other, Don't know
Country of Origin	Canada, U.S., Switzerland, Spain, Australia, Italy
Type of Ischemic Heart Disease	STEMI, NSTEMI; only NSTEMI included
Diabetes	Diagnosis of diabetes
Hypertension	Diagnosis of hypertension
Hyperlipidemia	Diagnosis of hyperlipidemia
Family History of CVD	Presence of family history of CVD
Previous History of CAD	Prior personal history of CAD
Smoking	Active smoking status
Alcohol Consumption	Alcohol consumption of more than 2 drinks per day
Depression	Diagnosis of depression as per DSM IV criteria
Anxiety	Diagnosis of anxiety as per DSM IV criteria
Employment Status	Employment status at the time of admission to hospital
Low social support	based on the ENRICHD Social Support Scale (ESSI). Scores of less than 3 on at least 2 items or an overall score a score of less than 18 indicate low social support
Marital status	Marital status at the time of admission to hospital
Education Level	No high school, high school, or more than high school
Low Personal Income	Income of less thank 30,000$/year if living in the U.S., Canada, Australia, less than 500 euro/month if Italian or from Spain, or less than 2300 franks/month if Swiss
Length of in-hospital stay	Numeric; total number of days admitted to hospital

Variables harmonized across the three included studies for inclusion in the final cohort.

Figure S1. Overview of data harmonization methodology employed in the construction of the present cohort.