The Impact of Sex and Gender-Related Factors on Length-of-Stay Following NSTEMI: A Multicountry Analysis

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Table of Contents

Abstract

Background: Gender-related factors refer to psycho-socio-cultural characteristics and are associated with adverse clinical outcomes in acute myocardial infarction (AMI) independent of sex. Substantial heterogeneity in hospital length of stay (LOS) exists among patients admitted with non-ST-segment elevation myocardial infarction (NSTEMI). Whether sex and gender-related factors predict length-of-stay (LOS) among patients with NSTEMI remains unknown.

Methods: To examine the relationship between sex, gender-related factors and LOS in adults hospitalized for NSTEMI, data from the GENESIS-PRAXY (n=1210, Canada, U.S. and Switzerland), EVA (n=430, Italy) and VIRGO (n=3572, U.S., Spain and Australia) cohort studies of adults hospitalized for AMI were combined and analyzed. Baseline demographics and clinical characteristics including gender-related factors were pooled and descriptive analyses were conducted on groups with shorter (<4 days) and longer (>/=4 days) LOS based on the median LOS in the overall cohort. A best-fit linear regression model was selected through incremental analysis by stepwise addition of gender-related variables.

Results: Among the overall cohort (n=5212), 2218 participants with a diagnosis of NSTEMI and recorded LOS were included in the final cohort (66% females, mean age = 48.5 years +/- 7.9, 67.8% U.S.). Patients with a LOS longer than 4 days (n=1124) were more likely to be white and have diabetes and hypertension in comparison to those with shorter LOS. Individuals in the longer LOS group were less likely to be employed (53.6% vs 65.0%), to have completed education

following high school (47.3% vs 55.4%), were more likely to have a lower income (41.5% vs 36.0%) and reported higher stress levels (53.4% vs 47.9%) than the shorter LOS group. No association between sex and LOS was observed in the bivariate analysis (p=0.88). In the multivariable model adjusted for sex, age, country of hospitalization, level of education, marital status, employment status, income, and social support, age (0.62 days/10 years, p=0.0002), being unemployed (0.63 days in non-workers, p=0.01) and country relative to Canada (Italy=4.1 days; Spain=1.7 days; and the U.S.=-1.0 days, all p-value<0.001) were associated with a longer LOS. A history of diabetes, hypertension, depression, family history of cardiovascular disease and prior MI were found to mediate the effect of employment on LOS. No interaction between sex and employment status was observed.

Conclusion: Age, employment status and the country where a patient with NSTEMI is treated were independent predictors of LOS regardless of sex. Individuals employed at the time of hospitalization were more likely to experience a shorter LOS following a NSTEMI. Variation in LOS across different countries is likely due to institutional policy, resource allocation, and distribution of gendered factors.

Résumé

Contexte : Les facteurs relatifs au genre renvoient à des caractéristiques psychosocioculturelles et sont liés à des résultats cliniques indésirables en cas d'infarctus aigu du myocarde (IAM), quel que soit le sexe. Il existe une grande hétérogénéité dans la durée de séjour à l'hôpital parmi les patients admis pour un infarctus du myocarde sans sus-décalage du segment ST (IDM non ST+). On ne sait toujours pas si les facteurs liés au sexe et au genre influencent la durée du séjour chez les patients présentant un IDM non ST+.

Méthodes : Pour étudier la corrélation entre le sexe, les facteurs liés au genre et la durée du séjour chez les adultes hospitalisés pour un IDM non ST+, les données des études des cohortes GENESIS-PRAXY (n=1210, Canada, États-Unis et Suisse), EVA (n=430, Italie) et VIRGO (n=3572, États-Unis, Espagne et Australie) menées auprès d'adultes hospitalisés pour un IAM ont été regroupées et analysées. Les données démographiques de base et les caractéristiques des patients, y compris les facteurs liés au genre, ont été regroupées et des analyses descriptives ont été effectuées sur les groupes dont la durée de séjour était la plus courte (<4 jours) et la plus longue (>/=4 jours), en fonction de la durée médiane du séjour de l'ensemble de la cohorte. Un modèle de régression linéaire mieux adapté a été choisi grâce à une analyse différentielle en ajoutant progressivement des variables liées au genre.

Résultats : Sur l'ensemble de la cohorte (n=5212), 2218 participants présentant un diagnostic de IDM non ST+ et une durée de séjour comptabilisée ont été intégrés à la cohorte finale (66 % de femmes, âge moyen = 48,5 ans +/— 7,9, 67,8 % des États-Unis). Les patients présentant une durée de séjour supérieure à 4 jours (n=1124) étaient plus souvent blancs, diabétiques et atteints d'hypertension, par rapport aux patients dont la durée de séjour était plus courte. Ils étaient moins

souvent actifs professionnellement (53,6 % contre 65,0 %), étaient moins souvent diplômés d'un établissement d'enseignement supérieur (47,3 % contre 55,4 %), avaient plus souvent de faibles revenus (41,5 % contre 36,0 %) et ont déclaré des niveaux de stress plus élevés (53,4 % contre 47,9 %) que les patients du groupe dont la durée de séjour était plus courte. Aucune corrélation entre le sexe et la durée de séjour n'a été observée dans l'analyse bivariée (p=0,88). Dans le modèle multivariable ajusté en fonction du sexe, de l'âge, du pays d'hospitalisation, du niveau d'éducation, de l'état civil, de la situation professionnelle, du revenu et du soutien social, l'âge (0,62 jour/10 ans, p=0,0002), le fait d'être sans emploi (0,63 jour chez les personnes sans emploi, p=0,01) et le pays par rapport au Canada (Italie=4,1 jours ; Espagne=1,7 jour ; et États-Unis=-1,0 jour, toutes les valeurs p<0,001) ont été associées à une durée de séjour plus longue. On a constaté que les antécédents de diabète, d'hypertension, de dépression, les antécédents familiaux de maladies cardiovasculaires et les antécédents d'infarctus du myocarde pouvaient atténuer l'effet de l'emploi sur la durée de séjour. Aucune corrélation n'a été observée entre le sexe et la situation professionnelle.

Conclusion : L'âge, la situation professionnelle et le pays où est soigné un patient atteint d'un infarctus du myocarde sans sus-décalage persistant du segment ST étaient des facteurs prédictifs indépendants de la durée de séjour, et ce, sans tenir compte du sexe. Les patients qui occupaient un emploi au moment de l'hospitalisation étaient plus disposés à avoir une durée de séjour plus courte à la suite d'un IDM non ST+. Les écarts en matière de durée de séjour entre les pays sont probablement dus à la politique institutionnelle, à l'allocation des ressources et à la répartition des facteurs spécifiques au sexe.

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Contribution of Authors

I am first author of the manuscript presented and have been involved in all aspects of this research, including the conceptual design of the study, literature review, statistical modelling and analysis, and interpretation and presentation of results.

As my thesis supervisor, Dr. Pilote has contributed to, as well as supervised, all components of the research conducted, in addition to providing me with access to the GENESIS-PRAXY cohort. Dr. Norris and Dr. Raparelli are both members of my thesis committee and have also contributed to all aspects of this work. Dr. Raparelli has also provided me with access to the EVA cohort. As a colleague and post-doctoral fellow in our lab, Dr. Christina Tadiri has guided me throughout and provided insight into the statistical modelling. As the statistician of group, Dr. Hassan Behlouli educated me and provided ongoing counsel for the statistical modelling and and application. Finally, Dr. Rachel Dreyer has provided me with access to the VIRGO cohort. All of the listed authors have uniquely contributed to the review of the work.

Introduction

Acute Myocardial Infarction (AMI) is a subset of cardiovascular disease (CVD) and is a leading cause of global morbidity and mortality. Despite continuous improvements in the management of cardiac risk factors, North America has experienced an increase in the prevalence of Ischemic Heart Disease (IHD) and it remains a significant source of resource allocation and healthcare expenditure (1, 2). Specifically, length-of-stay (LOS) in-hospital following non-ST-elevation myocardial infarction (NSTEMI), a subgroup of AMI with traditionally longer and more deviation in duration of hospital admissions, represents a potential source for optimization as decreasing LOS would reduce cost and be beneficial to the healthcare system. Therefore, identifying predictors of LOS following NSTEMI would enable earlier targeted intervention for at-risk individuals with the aim of decreasing LOS.

Numerous predictors of prolonged LOS have been identified and include the presence of cardiovascular comorbidities, such as diabetes and hypertension, and a history of prior AMI, among others. While females are at higher risk of NSTEMI, there is conflicting evidence regarding the role of sex in LOS following NSTEMI, with some reports of prolonged LOS in females and others reporting no difference between sexes. Furthermore, previous groups have failed to incorporated measures of gender, the psycho-socio-cultural environment surrounding the individual, in model construction and analysis. Since many of these gendered variables are social determinants of health that either vary in presence or impact between males and females, it stands to reason that the gender of an individual would impact the development and severity of NSTEMI, in addition to LOS. By assessing the impact of sex and gender-related variables on LOS following

NSTEMI, we hoped to identify targets for early identification and intervention in order to decrease LOS among patients hospitalized for NSTEMI.

Literature Review

1. Acute Myocardial Infarction

Acute myocardial infarction (AMI) is a subset of acute coronary syndrome (ACS) and is defined by cardiac injury with resultant myocardial cell necrosis in the setting of myocardial ischemia (3). AMI is further categorized by the extent to which the heart muscle is affected; infarction with characteristic ST-segment elevations (STEMI) on electrocardiogram represent transmural cardiac involvement, whereas non-ST-segment elevation (NSTEMI) infarction typically result from non-transmural or subendocardial involvement of infarcted cardiac tissue and are characterised by ST-segment depressions on electrocardiogram (4). **Figure 1** demonstrates the stated difference between extent of cardiac wall involvement during AMI (5).

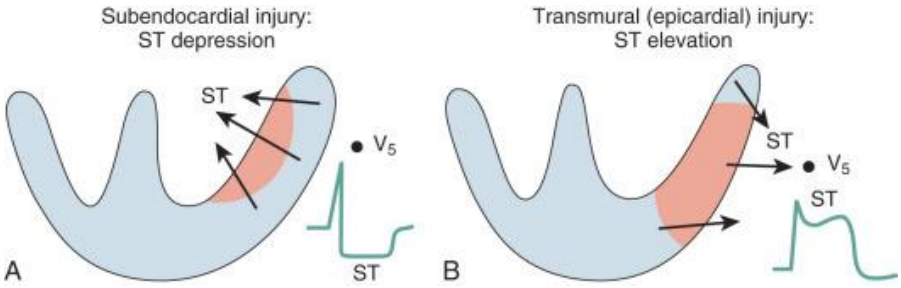


Figure 1. Current of injury patterns with acute ischemia. (A) With predominant subendocardial ischemia the resultant ST-segment vector is directed toward the inner layer of the affected ventricle and the ventricular cavity. Overlying leads therefore record ST-segment depression. (B) With ischemia involving the outer ventricular layer (transmural or epicardial injury), the ST-segment vector is directed outward. Overlying leads record ST-segment elevation. Reciprocal ST-segment depression can appear in contralateral leads. Adapted from Kaplan's Essentials of Cardiac Anesthesia (5).

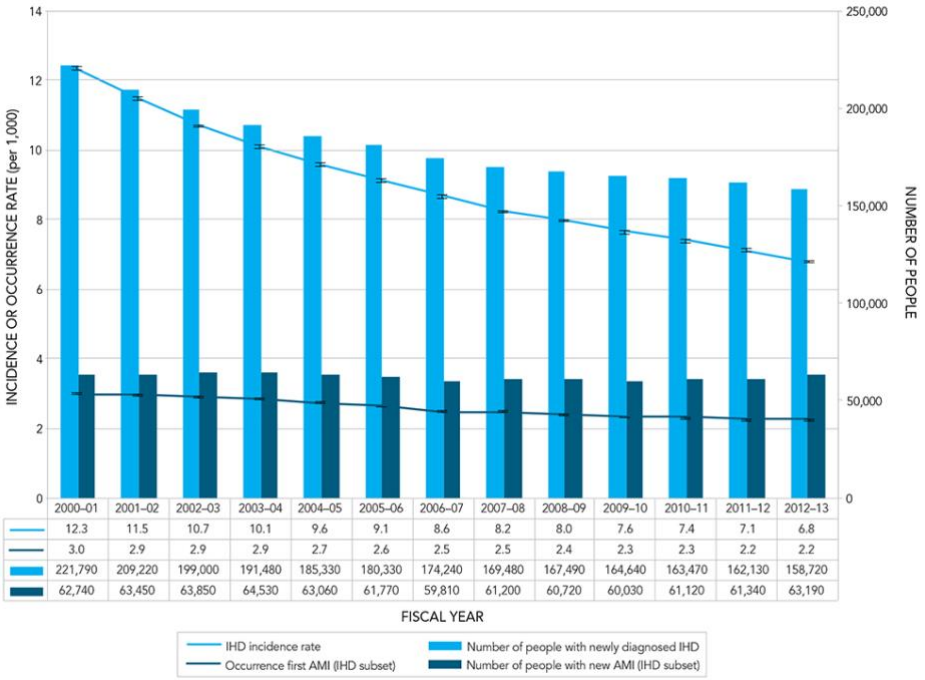
The etiology for AMI consists of a decrease in coronary blood flow that leads to a mismatch between cardiac oxygen demand and coronary oxygen supply. In the adult population, decreased coronary blood flow is most commonly due to the rupture of an atherosclerotic plaque in the coronary arteries secondary to coronary artery disease (CAD). Other less common etiologies include coronary artery embolism, drug-induced ischemia, coronary artery dissection, coronary vaspospasm and coronary microvascular dysfunction, the latter being more prevalent in females than in males (6, 7).

The treatment for NSTEMI is similar to that of STEMI. In STEMI, immediate reperfusion is achieved through percutaneous coronary intervention (PCI), with the addition of dual antiplatelet therapy. In NSTEMI, high-risk/symptomatic patients may be treated with dual antiplatelet therapy and immediate reperfusion through PCI, whereas stable/asymptomatic patients may not benefit from PCI and are therefore treated with dual antiplatelet therapy only (8).

2. Evolution of Disease Burden Over Time

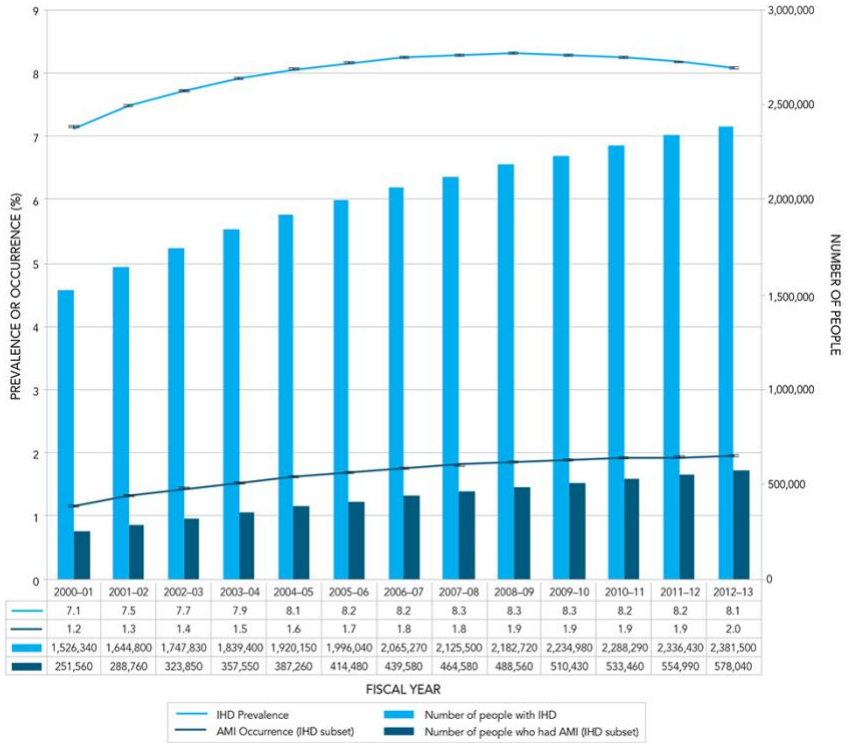
There has been considerable evolution in AMI burden over the last several decades. Although the heterogeneity present in different geographical regions and treatment centers make it difficult to obtain accurate estimates, the United States has seen a significant decline in the incidence of AMI over time, with an expected incidence of 1 million coronary events in 2019 (1). In addition, the prevalence of CAD, a precursor and major risk factor for AMI, has declined from 3.9 to 2.2 per 1000 person-years in people without diabetes, and from 11.4 to 5.4 person-years in those with diabetes from 1987-2009 (9). Canada has experienced a similar trend, with a 45% decrease in incidence of ischemic heart disease (IHD) and a 17% decrease in incidence of AMI

from 2000-2013, as illustrated in **Figure 2**, coupled with an increase in prevalence of IHD as a result of lower case-fatality viewed in **Figure 3** (2). Despite these local improvements, IHD remains a leading cause of death worldwide, with 8.9 million deaths in 2015 alone. This is largely due to the demands of an ever-growing and aging population, especially in underdeveloped countries, as well as increasing rates of obesity with related hypertension and diabetes (10).



	2000–01	2001–02	2002–03	2003–04	2004–05	2005–06	2006–07	2007–08	2008–09	2009–10	2010–11	2011–12	2012–13
IHD incidence rate	12.3	11.5	10.7	10.1	9.6	9.1	8.6	8.2	8.0	7.6	7.4	7.1	6.8
Occurrence first AMI (IHD subset)	3.0	2.9	2.9	2.9	2.7	2.6	2.5	2.5	2.4	2.3	2.3	2.2	2.2
Number of people with newly diagnosed IHD	221,790	209,220	199,000	191,480	185,330	180,330	174,240	169,480	167,490	164,640	163,470	162,130	158,720
Number of people with new AMI (IHD subset)	62,740	63,450	63,850	64,530	63,060	61,770	59,810	61,200	60,720	60,030	61,120	61,340	63,190

Figure 2. Incidence of diagnosed ischemic heart disease (IHD) and occurrence of first acute myocardial infarction (AMI) among Canadians aged 20 years and older, Canada, 2000–2001 to 2012–2013 (2).



	2000–01	2001–02	2002–03	2003–04	2004–05	2005–06	2006–07	2007–08	2008–09	2009–10	2010–11	2011–12	2012–13
IHD Prevalence	7.1	7.5	7.7	7.9	8.1	8.2	8.2	8.3	8.3	8.3	8.2	8.2	8.1
AMI Occurrence (IHD subset)	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.8	1.9	1.9	1.9	1.9	2.0
Number of people with IHD	1,526,340	1,644,800	1,747,830	1,839,400	1,920,150	1,996,040	2,065,270	2,125,500	2,182,720	2,234,980	2,288,290	2,336,430	2,381,500
Number of people who had AMI (IHD subset)	251,560	288,760	323,850	357,550	387,260	414,480	439,580	464,580	488,560	510,430	533,460	554,990	578,040

Figure 3. Prevalence of diagnosed ischemic heart disease (IHD) and occurrence of acute myocardial infarction (AMI) among Canadians aged 20 years and older, Canada 2000–2001 to 2012–2013 (2).

Temporal improvements in incidence of and outcomes related to AMI, such as mortality, length-of-stay, and readmission, are attributed to the development and implementation of evidence-based therapies: routine use of statins for prevention, high-sensitivity cardiac biomarkers for diagnosis, and novel antiplatelet medications and PCI for immediate treatment (11).

3. Evolution of Length-of-stay in AMI

Prior to the implementation of PCI and current pharmacological advancements, AMI was treated using the "armchair" technique. In the 1950s, this consisted of immobilization and a hospital length admission of 4-6 weeks (12). Considerable reduction in hospital length-of-stay has occurred since. In the 1980s, the mean duration of hospitalization for patients with AMI decreased to slightly more than 10 days, followed by further reduction to 6-8 days in the 1990s (13). In one study conducted at the Mayo Clinic, trends in length-of-stay were analyzed over the 1988-1997 period. The authors demonstrated that the median length-of-stay decreased from 9 to 5 days, with significant reductions caused by primary reperfusion, use of beta-blockers, and use of aspirin (14). During the same time period, Canada experienced a reduction in length-of-stay following AMI as well (15).

More recently, length-of-stay has continued to decrease in duration. From 2001-2011, one group in Massachusetts reported a further decrease in mean length-of-stay from 4.1 to 2.9 days in patients with a first uncomplicated AMI, with no increased risk for post-discharge adverse events (16). In patients with STEMI, a similar trend is apparent in the National Inpatient Sample Database: mean length-of-stay decreased from 3.3 to 2.7 days from 2005-2011 with a pronounced decrease in length-of-stay greater than 3 days. This reduction is postulated to result from improved

procedural techniques and algorithm-driven care (17, 18). Other countries have also exhibited similar relationships with decrease in length-of-stay following AMI over the last two decades (19, 20). With the ever-decreasing length-of-stay following AMI, multiple studies have sought to identify predictors of increased length-of-stay as sources for targeted intervention and further reduction of hospitalization duration.

4. Relevance of Length-of-Stay for AMI in Healthcare

Length of in-hospital stay represents an important outcome in AMI for multiple reasons. In addition to signifying the severity of illness, length-of-stay presents a target for improvement of resource allocation and maximal cost-expenditure efficiency. As mentioned prior, AMI prevalence continues to increase, necessarily implicating high cost and burden on the healthcare system worldwide. NSTEMI alone is responsible for up to 1.2 million hospitalizations and $75.2 billion per year in the United States (21). A recent literature review conducted by Sharkawi et al. on early discharge following primary PCI for STEMI concluded that implementing a structured discharge planning strategy could reduce hospital costs, resource utilization and improve patient satisfaction without impacting outcomes (22). As such, multiple groups have studied the cost-effectiveness of interventions to reduce length-of-stay following AMI as a potential source for cost and care optimization.

In order to quantify the cost of length-of-stay in AMI, Cowper et al. prospectively studied ~12,000 patients undergoing PCI in United States from 2010-2013. They found that mean index hospital costs for AMI was $18,931 ($19,327 for STEMI, $18,465 for NSTEMI), with a mean length-of-stay of 3.1 days. They reported that 20% of this cost was allocated to post-

procedural stay, with potential for cost reduction (23). Similar results were reported stating that hospitalization of patients with uncomplicated AMI beyond 3 days following thrombolysis is economically unattractive, even when controlling for the potential for rehospitalization given earlier discharge (24).

AMI also impacts societal economy at the employment level. In Canada, mean reduction in annual salary following AMI was $3,834 and persisted for up to 3 years following the initial event, with consequences for both patients and the government. Given the burden of AMI in healthcare, optimization of length-of-stay constitutes an avenue for reduction of cost.

5. Predictors of Length-of-stay in AMI

The evidence presented regarding predictors of length-of-stay in AMI is often conflicting, with different studies/cohorts yielding different results. Predictors highlighted in the literature for length-of-stay in AMI range from laboratory values to comorbidities, biological sex, and societal/gender-related determinants.

Comorbidity burden and its impact on length-of-stay is extensively documented. One prospective cohort study conducted in patients with acute chest pain identified that comorbidity burden, as measured by the Charlson index, was independently associated with longer length-of-stay. Interestingly, however, when controlling for overall Charlson index, no individual comorbidities proved significant (25). Another similar study used comorbidity status and the Killip classification system to stratify risk of patients presenting with AMI based on the development of concomitant heart failure symptoms, with the most severe class having developed cardiogenic shock. A history of diabetes and prior AMI were both independently and additively associated

with longer lengths of hospital admission. Furthermore, Killip classes II-IV were independently associated with prolonged length of admission, Killip class IV representing the group with the most prolonged admission of 1.6 days more (26). Moreover, a large cohort of 39,000 patients with NSTEMI was researched using the ACTION registry, a merger between an American College of Cardiology and American Heart Association datasets. This group identified a subset of patients with length-of-stay greater than 4 days that possessed increased overall comorbidity burden with significant prediction in those with a history of hypertension, diabetes, or stroke (27).

An additional predictor for prolonged length-of-stay identified in the literature is timely access to PCI. In the previously mentioned ACTION registry study, the single strongest predictor of prolonged length-of-stay was a delay in use of PCI of greater than 48 hours, with a reported odds ratio of 4.87 (95% CI, 4.54-5.22) (27). Furthermore, a randomized control study conducted in Prague sought to elucidate the importance of immediate PCI on length-of-stay in patients with NSTEMI. In total, 131 patients were randomized to either first-day angiography/angioplasty or to an early conservative management group that underwent PCI only in the event of recurrent chest pain. Length-of-stay in the group that received angiography on the first day was significantly shorter to those with delayed angiography by 2.2 days (28). The relevance of immediate access to PCI is therefore important for reducing hospital admission following AMI.

Furthermore, the role of certain biomarkers in predicting length-of-stay has been addressed by one group in Portugal in 2015. In their cohort of 439 patients, independent predictors included comorbidities (mainly diabetes with complications, in addition to cerebrovascular disease), shock, respiratory infections, age of 69 years or older, cardiac dysrhythmia, and uniquely, neutrophils above level, pO2 below level, and prothrombin time above level (29).

Finally, sex differences in length-of-stay following AMI remains conflicting. While many investigators reported that females tend to have longer length-of-stays than males, others have reported no difference. In a study of patients who sustained a STEMI in the Netherlands, female sex as well as older age and previous AMI were associated with a length-of-stay of more than 6 days following PCI (30). In another study in the United States, length-of-stay was found to be only 0.3 days higher in females than males (31). Other investigators have found that despite decreases in length-of-stay following AMI in both sexes, females consistently had slightly longer length-of-stays (32). Similar sex differences have been reported in other parts of the world as well, such as in Beijing (33). Interestingly, a difference in predictors of length-of-stay may be identified when stratifying by sex, with diabetes, prior coronary bypass and prior coronary angioplasty significantly predicting longer admissions in males, and age alone in females (34)

Contrarily, however, other results have identified no significant difference in length-of-stay between sexes. In Canada, although females tended to consistently stay longer in hospital, this variation was minimal (35). Others have reported similar negative findings (36, 37). While longer length-of-stay following AMI may be explained by higher comorbidity burden and older presentation in females, consensus regarding the existence of a notable differences in length-of-stay between sexes both locally and internationally remains to be seen. Predictors of length-of-stay in AMI are complex and multifactorial, with variations depending on the country and source.

6. Sex and Gender

Sex and gender are often incorrectly used interchangeably in the medical community. While sex describes the biological aspect of males and females, gender refers to the psycho-socio-cultural characteristics attributed to males and females in society. Gender is further categorized into four distinct dimensions: institutionalized gender, gender roles, gender relations, and gender identity (38, 39). Institutionalized gender refers to the distribution of power between sexes in society such as in academia and politics, gender roles describe the behavioural norms applied to males and females in society, gender relations reflect the experience in interaction with others based on sex, and gender identity describes one's self-perception based on sex (39). **Table 1** summarizes gender-related risk factors as present in their respective subcategorizations.

Gender Roles	**Gender Relations**
Primary earner status	**Marital/Relationship Status**
Employment Status	**Family or local network (social capital)**
Occupation	**Social support**
Paid Work hours per week	Social support (any recognized social support instrument)
Unpaid work hours per week(eg care giver hours)	Availability of Caretaker (for self)
Full/part time work	**Gender Identity**
Child caregiver responsibilities The individual or others	**Stress**
Adult caregiver responsibilities	14-Item Perceived stress scale (PSS)
Number of hours per week spent on housework	Stress level at work (any measure of stress)
Status of household's primary responsibility	Stress level at home (any measure of stress)
Number of children	Stress management
Institutionalized Gender	**Personality traits**
Educational Level	Emotional intelligence Questionnaire
SES/Income	Any validated measures of personality (NEO classic 5 personality traits
Monthly finances	BEMS (instrument) measurement of gender identity
Income (personal, household)	**Depression/Anxiety**
Number of persons living in household	Patient Health Questionnaire-9
Retirement eligibilities	HAD Scale - Hospital Anxiety and Depression Scale
Perceived Social Standing Questionnaire *McArthur Scale	Anxiety/Depression any scale
GII (Gender inequality index) Questionnaire *	**Childhood trauma** (reported history)
Maternity Paternity related variables	

Table 1. Summary of multiple gender-related factors organized by overarching gender category. These factors, among others, have been identified as modifiable factors that may influence the health of an individual throughout their lifespan (40).

7. Gender as an Emerging Social Determinant of Health

Continuing advancements in areas of research pertaining to the implications of sex on clinical outcomes have led to the establishment of sex as a strong determinant of health, as recognized by the World Health Organization (WHO) (41). As such, the clinical incorporation of a patient's sex has grown pivotal in the evaluation of a patient in all domains of medicine. Recently, however, a growing body of literature has begun to demonstrate gender-specific factors that are implicated in outcomes. While the WHO recognizes gender as a determinant of health, clinical incorporation of gender-related factors in the evaluation of patients is lacking and remains in early development. An article published in Nature in 2019 highlighted the need for incorporation of gender, in addition to sex, in all biomedical research in order to increase reproducibility and generalizability of findings, as well as promote social equity (42). Gender is therefore an emerging determinant and must be evaluated in conjunction with biological sex in clinical research.

8. Gender-Related Factors and Length-of-stay in AMI

Gender-related factors have been shown to hold importance in AMI, with certain psycho-socio-cultural characteristics having led to prolonged hospital admissions. Incidence and prevalence of depression is notably higher in females, likely due to gender-related phenomena as opposed to sex-based differences (39). Furthermore, significance of depression on length-of-stay following AMI is well understood worldwide. A prospective study of 175 patients discharged from the intensive care unit following AMI in Jordan demonstrated significantly longer lengths of

admission in patients reporting depressive symptoms (43). Another study conducted in Georgia yielded similar results, with depressive symptoms independently predicting longer hospital admissions in patients with NSTEMI (44). Although North American studies looking at depression and length-of-stay are lacking, the relationship that depression exhibits with cardiac illness is well accepted.

Socioeconomic status has been observed to significantly predict length-of-stay in AMI as well. Using the Nationwide Inpatient Sample in the United states, Shen et al. found that patients with lower socioeconomic status, as measured by health insurance status and median income by zip-code, experienced a longer hospital stay than those with more favorable socioeconomic status (45). A more recent study published in 2015 examined the impact of the economic crisis in Tuscany, Italy, and observed a 13% increase in total hospital days ($p<0.001$) in areas affected most by the crisis (46). These studies highlight the impact that socioeconomic status has on outcomes related to AMI, with a direct effect on length-of-stay. Further research pertaining to the impact of additional gender-related factors on length-of-stay in AMI remains to be seen.

As such, the objectives of this project are to evaluate the impact of sex and gender-related factors on length-of-stay.

Manuscript

The Impact of Sex and Gender-Related Factors on Length-of-Stay Following NSTEMI: A Multicountry Analysis

Running Title: Sex and Gender-related factors in NSTEMI Hospitalization

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Abstract

Background: Gender-related factors refer to psycho-socio-cultural characteristics of individuals and are associated with adverse clinical outcomes in acute myocardial infarction (AMI) independent of sex. Substantial heterogeneity in hospital length-of-stay (LOS) exists among patients admitted with non-ST-segment elevation myocardial infarction (NSTEMI). Whether sex and gender-related factors predict the length-of-stay (LOS) among patients with NSTEMI remains unknown.

Methods: To examine the relationship between sex, gender-related factors and LOS in adults hospitalized for NSTEMI, data from the GENESIS-PRAXY (n=1210, Canada, U.S. and Switzerland), EVA (n=430, Italy) and VIRGO (n=3572, U.S., Spain and Australia) cohort studies of adults hospitalized for AMI were combined and analyzed. Baseline demographics and clinical characteristics including gender-related factors were assessed and descriptive analyses were conducted comparing adults with shorter (<4 days) versus longer (>/=4 days) LOS based on the median LOS in the overall cohort. To identify factors independently associated with LOS, a best-fit linear regression model was selected through incremental analysis by stepwise addition of gender-related variables.

Results: Among the overall cohort (n=5212), 2218 participants with a diagnosis of NSTEMI were analyzed (66% females, mean age = 48.5 years ± 7.9, 67.8% U.S.). Adults with a LOS longer than 4 days (n=1124) were more likely to be white and have diabetes and hypertension in comparison to those with shorter LOS. Individuals in the longer LOS group were less likely to be employed (53.6% vs 65.0%), to have completed education following high school (47.3% vs 55.4%), and were more likely to have a lower income (41.5% vs 36.0%) than the shorter LOS group. No

univariate association between sex and LOS was observed in the bivariate analysis (p=0.88). In the multivariable model adjusted for sex, age, country of hospitalization, level of education, marital status, employment status, income, and social support, age (0.62 days/10 years, p=0.0002), being unemployed (0.63 days in non-workers, p=0.01) and country relative to Canada (Italy=4.1 days; Spain=1.7 days; and the U.S.=-1.0 days, all p-value<0.001) were independently associated with a longer LOS. A history of diabetes, hypertension, depression, family history of cardiovascular disease and prior MI were found to mediate the effect of employment on LOS. No interaction between sex and employment status was observed.

Conclusion: Older age, being unemployed and the country where a patient with NSTEMI is hospitalized were independent predictors of LOS regardless of sex. Individuals who were employed at the time of hospitalization were more likely to experience a shorter LOS following a NSTEMI. Variation in LOS across different countries is likely due to institutional policy, resource allocation, and distribution of gendered factors.

Word Count: 417

Key Words: Sex, Gender, AMI, Length-of-Stay, Employment.

Introduction

Over time, the incidence of acute myocardial infarction (AMI) has considerably decreased in both Canada and the United States (U.S.) (1, 2). Nevertheless, AMI remains a leading cause of global morbidity and mortality with 8.9 million deaths worldwide in 2015 alone (3). Length of stay in hospital (LOS) has surfaced as an important cost-sensitive outcome in AMI as it relates to the severity of illness and serves as a target for resource allocation and optimization of cost-expenditure (4, 5).

The impact of LOS in AMI on healthcare system expenditure has been quantified with number of in-hospital days and related costs. For example, the mean index hospital cost for patients receiving Percutaneous Coronary Intervention (PCI) for AMI between 2010 and 2013 in the U.S. averaged $18,931, which comprised $19,327 for ST-elevation myocardial infarction (STEMI), and $18,465 for non-ST-elevation myocardial infarction (NSTEMI) with a mean LOS of 3.1 days (6). Although LOS has globally decreased following the implementation of PCI and pharmacological advances, it remains an important cost-sensitive outcome for healthcare systems and therefore identifying predictors of LOS is necessary to further increase hospital efficiency and decrease healthcare costs.

Previously identified predictors of prolonged LOS in AMI include comorbidity burden, Killip class, timely access to PCI, and hypertension, diabetes, or stroke (7-11). Whether sex differences exist in LOS remains uncertain due to varying reports but overall, longer LOS has been shown in females compared to males with differences as long as 6 days in females, who have been reported to be older and have higher severity of disease (12-14). However, previous studies have not assessed whether the psycho-socio-cultural environment of males and females, referred to as

gender, has been implicated in conjunction with biological sex (15). Indeed, both sex and gender-related factors must be explored to identify and develop interventions to reduce LOS in patients with AMI.

With the harmonization of data from three different prospective longitudinal AMI cohorts, we examined the impact of sex and gender on LOS in patients with NSTEMI. We hypothesized that females would experience longer LOS following a NSTEMI compared to males, and that this difference could be partially explained by a clustering of unfavorable gender-related factors.

Materials and Methods

Cohort Selection and Data Sources

This observational cohort study comprised three independent pre-existing prospective cohorts. In the GENdEr and Sex DetermInantS of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary Syndrome study (GENESIS-PRAXY, n=1117), young adults (18-55 years) with acute coronary syndrome (ACS) were prospectively recruited across 24 sites in Canada, 1 site in United States (US), and 1 site in Switzerland, between January 2009 and April 2013 (15). In the Endocrine Vascular disease Approach study (EVA, n=530), adults (>18 years) who were hospitalized and underwent cardiac catheterization in Italy for suspected ischemic heart disease recruited between 2016-2019 (16). In the Variation In Recovery: Role of Gender on Outcomes of Young AMI Patients study (VIRGO, n=3572), young adults (18-55 years) with AMI were prospectively recruited between 2008-2012 across 103 hospitals in the United States, 24

hospitals in Spain and 3 hospitals in Australia (17). Informed consent was acquired from each patient at the time of enrollment and ethics approval was obtained for each respective study.

For inclusion in this study, participants were aged greater than 18 years, had a recorded diagnosis of NSTEMI, were admitted to a treating hospital and had recorded LOS. In addition to clinical data, these cohorts were chosen due to their collection of gender-related variables that are hypothesized to influence cardiovascular disease outcomes including LOS. Data harmonization methodology was applied to ensure comparability of variables, achieve reliable combination of these cohorts, and reduce any potential sources for deviation in measurement across the studies (Appendix A).

Baseline Clinical and Gender-Related Characteristics

Baseline characteristics included age, sex, medical/cardiovascular comorbidities (i.e. diabetes, hypertension and dyslipidemia), prior history of AMI, family history of CVD, and smoking status. In addition to baseline clinical characteristics, socio-demographic variables included country of hospitalization and race of participants. Gender-related variables were assembled by the gender dimension categories recognized by the Institute of Gender and healthy and Canadian Institutes of Health Research and included employment status and occupation type for gender roles, education level and personal income for institutionalized gender, and marital status and social support for gender relations (18). Employment status was defined as the current state of full-time employment of the individual at the time of their NSTEMI. Occupation type was categorized into three groups: non-physical (such as entrepreneurs, shopkeepers, freelance professionals, religious workers, government employees, business and finances, administrative

work); intermediate physical (such as teachers, healthcare providers, chef/tourism, household work, sport, arts); and highly physical labor (such as construction workers, farmers, police, military, and soldiers, manufacturing workers, natural resources, agriculture, trades, transport and equipment operators).

Level of education was further categorized into 3 distinct groups: individuals that never completed high school, completed high school, or 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 Social Support Scale (ESSI). The ESSI 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 three 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 less than 3 on at least 2 items or an overall score a score of less than 18 indicate low social support (19, 20).

Outcomes

The primary outcome was the LOS defined as the number of in-hospital days from admission to discharge or occurrence of a fatal event during the in-hospital stay. Patients with missing admission or discharge dates were excluded (63 patients total).

Statistical Analysis

Descriptive statistics were calculated for the overall population using frequencies for categorical variables and means (standard deviations) 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 less than four days and greater-than or equal-to four days. A length-of-stay of 4 days in duration was chosen as the cut-off as it represented the median LOS based on the distribution of the data.

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 (AIC) using an incremental analytic approach, with forward stepwise addition of available harmonized gender variables grouped by gender dimension (employment status and occupation type for gender roles, education level and personal income for institutionalized gender, and marital status and social support for gender relations). Interaction analysis between sex and gender-related variables was performed on variables found to be significantly associated with LOS. Gender-related variables found to be significantly associated with LOS were further analyzed through mediation analysis using comorbidities. 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 a diagnosis of NSTEMI and available data on LOS were included in the present analysis (Figure 1). The median LOS in the overall cohort

was 4 days. Therefore, two groups were formed constituting LOS of less than 4 days and greater than or equal to 4 days for descriptive analysis. The mean LOS within the shorter stay group was 2.4 days, compared to 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 (78.9% vs 74.8%) and had a higher prevalence of diabetes (40.3% vs 26.0%) and hypertension (69.2% vs 62.9%) (Table 1). Individuals in the longer LOS group were less likely to be employed (53.6% vs 65.0%), less likely to have completed education following high school (47.3% vs 55.4%) and were more likely to have a lower income (41.5% vs 36.0%) (Table 2).

In the multivariable model with the best fit that included sex and gender-related factors, age (0.62 days/10 years, p=0.0002), being employed (-0.63 days in workers, p=0.01) and country (Canada reference country) (Italy=4.1 days; Spain=1.7 days; and the U.S.=-1.0 days, all p-value<0.001) were significant independent predictors of LOS (Table 3).

Further explorative analyses revealed that unemployed individuals were more likely to be female (74.1% vs 42.0%), diabetic (42.4% vs 27.0%), hypertensive (75.4% vs 59.6%), have a prior history of MI (29.7% vs 16.5%) and family history of CVD (58.8% vs 44.9%), and have a history of depression/anxiety (58.8% vs 44.9%). Adjustment for these comorbidities and prior history of events in the best model decreased the estimate and association for employment status from -0.63 days to -0.38 days (p=0.13).

To further explore if employment had a different effect on LOS in males and females, we added an interaction term to the multivariate analysis. No interaction between sex and employment was observed (p=0.74).

Discussion

The main finding of this project is that older age, being unemployed and the country where a patient with NSTEMI is treated are major contributors to the LOS regardless of sex. In terms of gender-related factors, unemployment was the only factor associated with a longer LOS in patients hospitalized for NSTEMI. Of note, female sex, diabetes, hypertension, a prior history of MI, a family history of CVD and a history of depression/anxiety appear to partially mediate the effect of unemployment. Furthermore, this relationship was independent of sex and country where the patient was treated for AMI.

A reduction in LOS following NSTEMI remains a focus for healthcare cost optimization. Overtime, LOS has shortened mostly as a result of novel procedural and pharmacological treatment and care-driven algorithm design (21, 22), however NSTEMI remains responsible for up to 1.2 million hospitalizations and $75.2 billion per year in the United States (23). Several studies have identified female sex as a predictor of longer LOS, reporting up-to 6-day longer LOS following AMI in females compared to males (24-27). 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. Furthermore, the burden of CVD in females is high and continues to be the leading cause of death resulting in an increased mortality rate compared to their male counterparts (28-30). This observation is postulated to result from inherent pathophysiological differences in coronary obstruction, as well as lower revascularization rates and higher comorbidity burden and presenting age in females (25, 26, 31-33). Nevertheless, others studies (12-14) have reported no sex differences in LOS. Such

conflicting results suggest that other patient-level or structural-level features of individuals beyond biological sex contribute to the duration of in-hospital stay among individuals with NSTEMI

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

A novel finding of the study was that although sex was not a predictor of LOS in our analysis and the analyses of prior authors, we found that among the gender-related variables included (i.e. gender roles, institutionalized gender, and gender relations), only gender roles, represented by employment status, was associated with LOS duration independent of biological sex. More specifically, in the final multivariate model, being unemployed was independently associated with 0.63-day longer LOS compared to their employed counterparts; this difference is not negligible and represents a 15% longer LOS based on employment status alone. While unemployment status is known to adversely impact the risk for cardiovascular disease, 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).

In order to explore the 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 female, diabetic, hypertensive,

and possess a prior history of MI, a family history of CVD, and/or a history of depression/anxiety, which have themselves been identified as predictors of prolonged LOS and were found to mediate the effect of employment on LOS in our cohort (8, 9, 35, 37). One suggested explanation for this relationship is that the prolonged LOS observed in unemployed individuals, mostly females, 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 risk factors. Another postulated mechanism may be that unemployment delays disposition due to a lack of social support leading to difficult discharge planning. It is interesting to note that although no sex difference in LOS was observed, unemployed individuals were far more likely to be female. Since the social environment of the individual is known to impact CVD and AMI outcomes, our analysis highlights that in addition to biological 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 (11). Postulated mechanisms for shorter hospitalizations in the U.S. in contrast with longer hospitalizations in Spain and Italy relative to Canada include differences in institutional level policy, healthcare 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. Additionally, 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 multicountry 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. Furthermore, although appropriate data harmonization methodology was employed 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 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 due to 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. 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.

Conclusions

Employment status, 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 MI, depression/anxiety, and a family history of CVD mediated the effect of unemployment on LOS. Variation in LOS exists across different countries likely due to institutional policy, resource allocation, and distribution of gendered factors. Employment status represents a 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 gender may have on LOS, as well as highlight a significant target for improvement in healthcare expenditure and resource allocation.

Figure 1. Flowchart of Cohort Selection for Patients With NSTEMI and Recorded LOS.

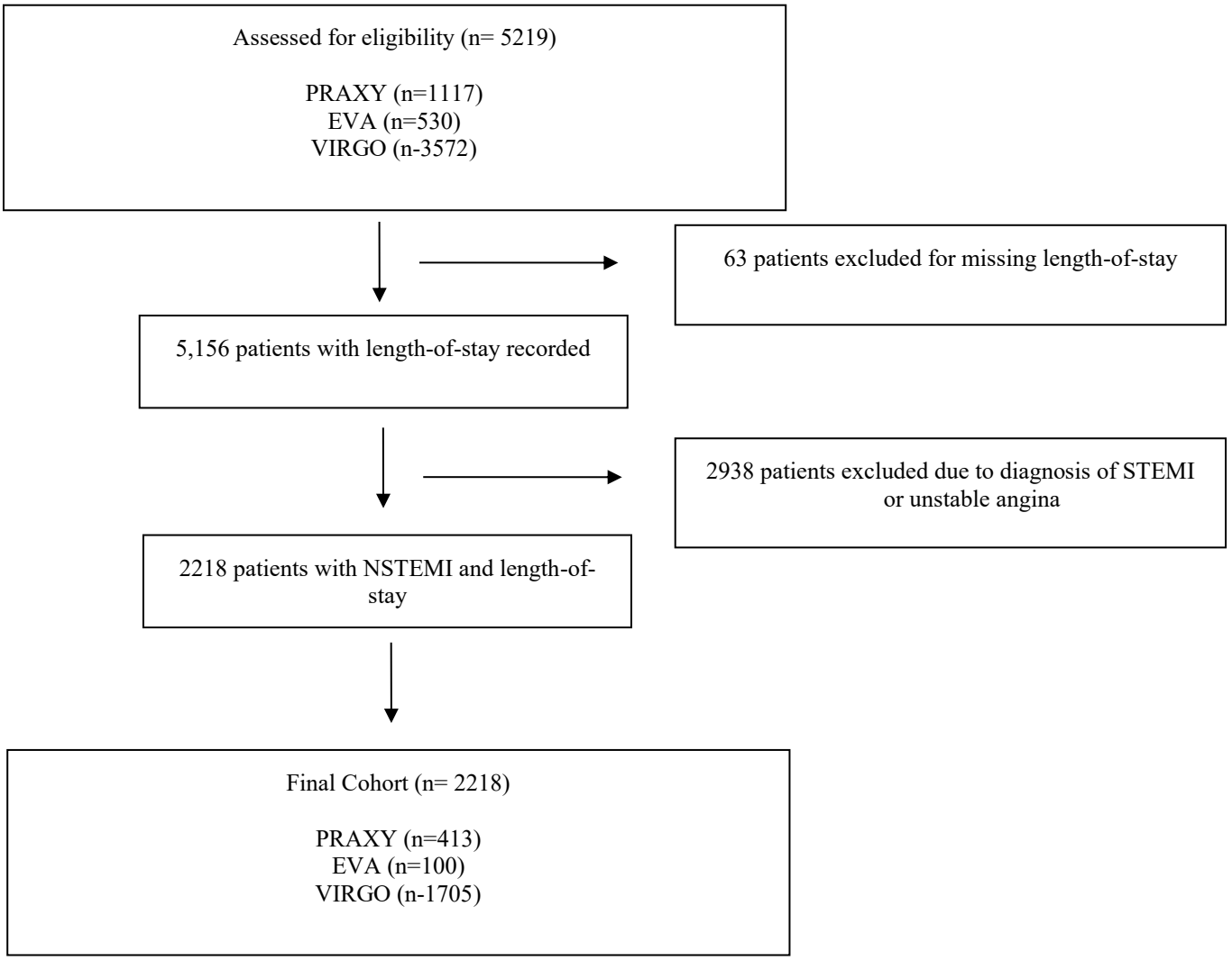


Figure 2. Distribution of LOS Overall and by Sex in Patients With NSTEMI.

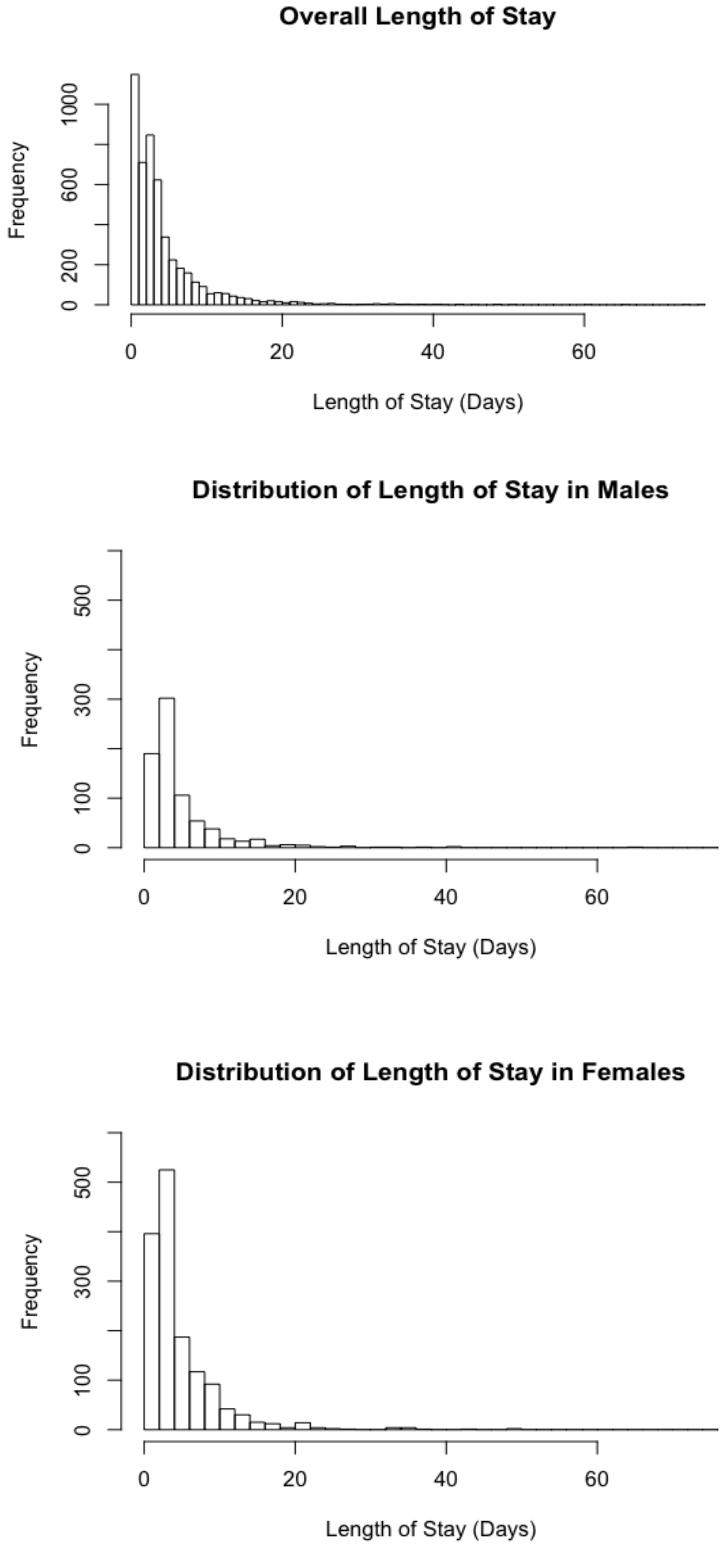


Table 1. Baseline characteristics of patients with NSTEMI according to LOS.

Variables (%)	LOS<4 Days (N=1094)	LOS>/=4 Days (N=1124)
Age in Years (±SD)	47.3 (±6.5)	49.8 (±8.9)
Female (n)	64.9 (710)	66.1 (743)
White Race (n)	74.8 (818)	78.9 (887)
Canada (n)	15.4 (168)	18.5 (208)
Diabetes (n)	**26.0 (284)***	**40.3 (453)***
Hypertension (n)	**62.9 (688)***	**69.2 (778)***
Dyslipidemia (n)	80.2 (877)	77.8 (875)
Prior Myocardial Infarction (n)	20.4 (223)	23.5 (264)
Family History of Cardiovascular Disease (n)	54.8 (600)	55.3 (622)
Depression/Anxiety (n)	**48.4 (529)***	**52.4 (589)***
Currently Smoking (n)	32.0 (350)	31.9 (358)

SD: Standard Deviation. ***p<0.05.**

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

Variables (%)	LOS<4 Days (N=1094)	LOS>/=4 Days (N=1124)
Employed (n)	**65.0 (711)***	**53.6 (602)***
More Than High School Education (n)	**55.4 (606)***	**47.3 (532)***
Low Income (n)	**36.0 (394)***	**41.5 (466)***
Married (n)	58.0%(635)	57.7 (649)
Highly Physical Work (n)	17.8 (195)	16.9 (190)
Low Social Support (n)	19.6 (214)	21.3 (239)

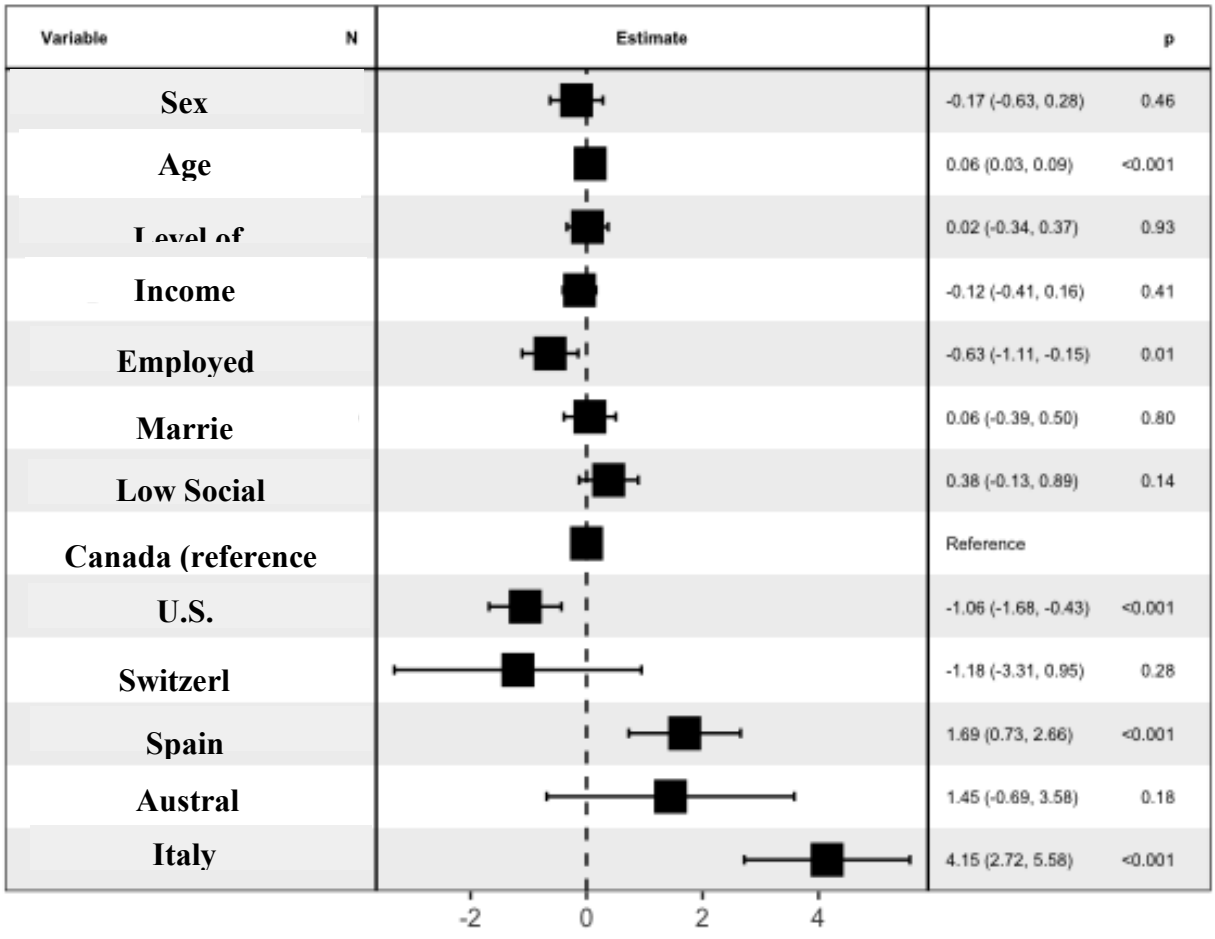
- **Employed**: Employment status; **More than high school education**: Individuals having completed high-school and pursued either trade school or further academia; **Married**: Marital status; **Low Income**: Household income of less than 30,000$/year if living in the U.S., Canada, Australia, less than 500 euro/month if Italian or from Spain, or less than 2300 franks/month if Swiss; **Highly physical work**: defined as working in trades, transport and equipment operators, manufacturing and utilities, natural resources, agriculture, labor, farming, construction, and military/soldier/police; **Low Social Support**: As defined by a score of less than 3 on at least 2 items or an overall score a score of less than 18 on the ESSI. ***p<0.05.**

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

Variables	Sex	Sex +Age +Country	Sex +Age +Country +Institutionalized Gender	Sex +Age +Country +Institutionalized Gender +Gender Roles	Sex +Age +Country +Institutionalized Gender +Gender Roles +Gender Relations
Intercept	5.23***	1.69*	3.00**	3.21***	3.14***
	(0.14)	(0.82)	(0.93)	(0.93)	(0.95)
Sex	0.036	-0.14	-0.19	-0.13	-0.17
	(0.23)	(0.22)	(0.23)	(0.23)	(0.23)
Age		0.077***	0.068***	0.065***	0.062***
		(0.016)	(0.016)	(0.016)	(0.017)
Country Relative to Canada: 1)U.S. 2)Switzerland 3)Spain 4)Australia 5)Italy		1) -0.78** (0.29) 2) -0.58 (0.96) 3) 1.82*** (0.44) 4) 1.07 (1.06) 5) 5.84*** (0.64)	1) -1.11*** (0.31) 2) -1.27 (1.09) 3) 1.53** (0.48) 4) 1.32 (1.09) 5) 4.09*** (0.70)	1) -1.15** (0.31) 2) -1.36 (1.09) 3) 1.61*** (0.48) 4) 1.32 (1.09) 5) 3.87*** (0.70)	1) -1.06*** (0.32) 2) -1.18 (1.09) 3) 1.69*** (0.49) 4) 1.45 (1.09) 5) 4.14*** (0.73)
Education level			-0.037 (0.18)	0.010 (0.18)	0.016 (0.18)
Income			-0.26* (0.13)	-0.092 (0.14)	-0.12 (0.15)
Employment status				-0.74** (0.24)	-0.63* (0.25)
Low social support					0.38 (0.26)
Marital Status					0.057 (0.23)
AIC	13571	13256	11553	11546	11290

*p<0.05, **p<0.01, ***p<0.001. All statistically significant results are reported in bold. Coefficient estimates are reported as the first number, followed by standard error in parentheses. The final model was chosen for its lowest AIC of 11290.

Figure 3. Forest Plot of the Multivariate Linear Regression Model Including Sex and Gender-Related Factors



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 (38). Data harmonization for the present study consisted of the following four steps and is summarized in **Figure 5**: ***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 biological sex 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 (39, 40). 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.

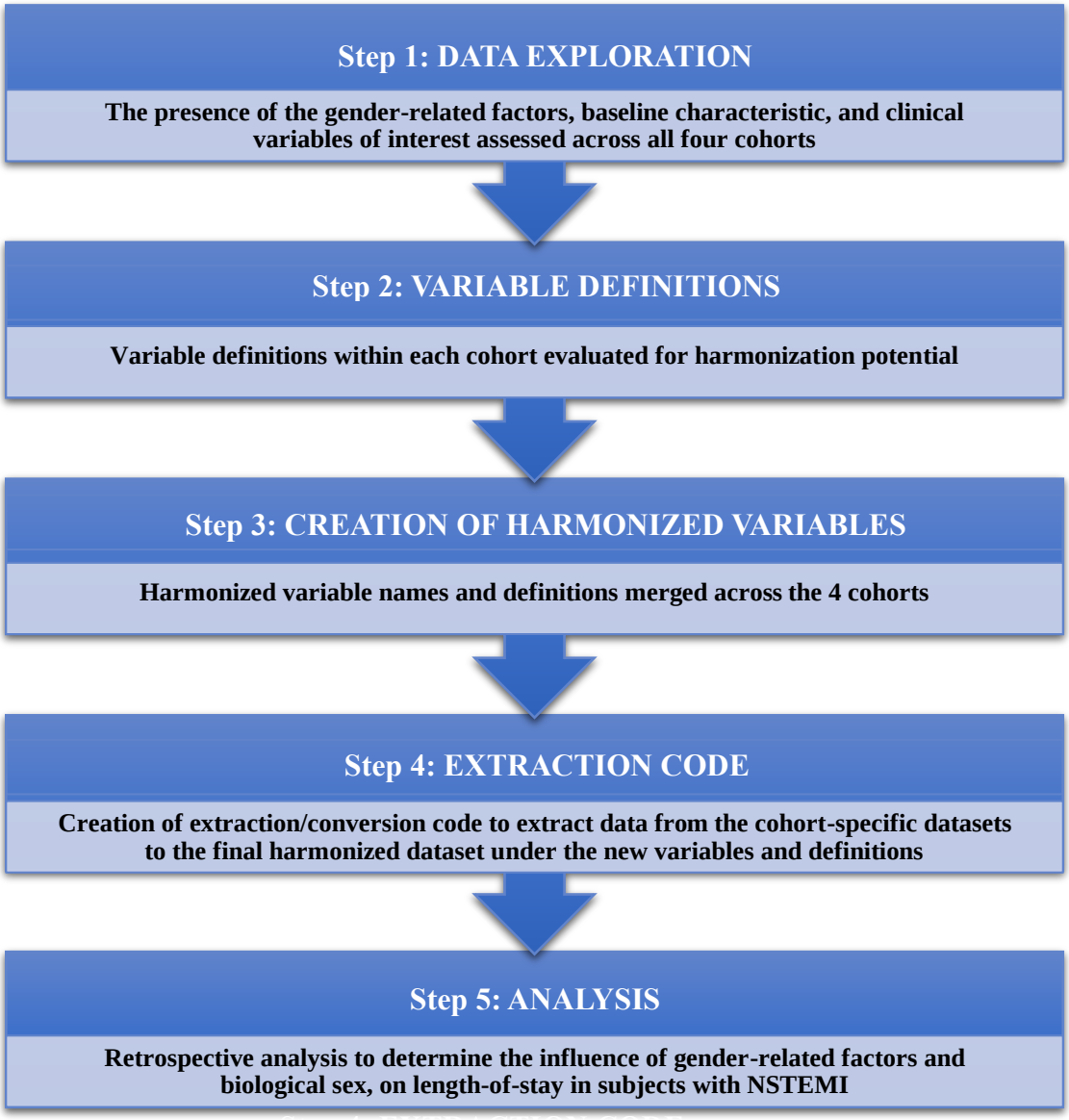


Figure 4. Overview of data harmonization methodology employed in the construction of the present cohort.

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General Discussion

1. Statistical Application of Mediational Modelling

During the conceptualization phase of statistical modelling, a directed acyclic graph was constructed in order to elucidate the relationships between gender and LOS as shown in **Figure 4.** As represented in the figure, we hypothesized that if an effect of biological sex were uncovered it would possibly be mediated by gender. Additionally, we also hypothesized that the effect of gender on LOS would be at least partially mediated by comorbidities and associated severity of NSTEMI. As such, inclusion of comorbidities in the regression models would likely lessen the association between gender-related variables and LOS. Although we could not determine which gender-related factors mediated the effect of sex on LOS as no effect of sex was uncovered, we sought to explore which clinical factors mediated the effect of employment on LOS. In order to do so, we used the traditional approach to mediational analysis (47). This approach consisted of comparing two multivariate regression models: the final selected model including the gender dimensions, sex, age, and country, was compared to the same model with the addition of depression/anxiety, diabetes, hypertension, prior history of myocardial infarction and family history of CVD. These clinical variables were selected for inclusion due to their asymmetrical distribution by employment status. The exposure term of interest in this analysis was employment status, and the coefficient estimate of employment status in the original model was compared to that of the model adjusted for clinical variables. The result was a drop in the estimate for employment status, as well as its loss of association with LOS seen prior. This finding implies that the clinical variables mediated the effect of employment status on LOS, suggesting that these characteristics are involved in the

causal pathway delineating the effect of employment of LOS. Thus, it appears that the longer LOS experienced by unemployed individuals following NSTEMI is at least in part due to their acquisition of these cardiovascular risk factors.

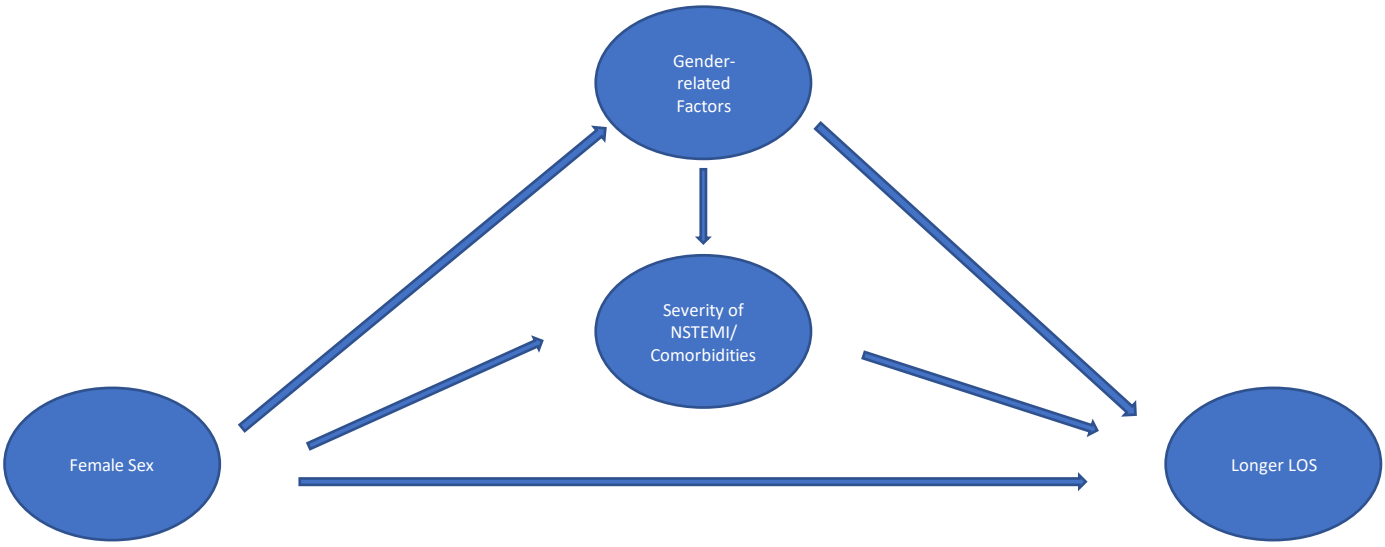

Figure 4. Directed acyclic graph depicting the relationship between sex and gender and their impact on LOS.

2. Future Directions

Our findings that employment status is associated with LOS following NSTEMI offer insight into the association between gender-related factors and health-related outcomes.

In our study, unemployment was statistically significantly associated with a longer LOS in patients with NSTEMI. Although we have uncovered a potential causal pathway for this relationship through the acquisition of cardiovascular risk factors, the impact of social organizational factors, such as help at home and living situation, may also contribute to the observed effect of employment on LOS. Given the complexity of the multifactorial nature through which unemployment influences an individual's social environment, further research into the various social impacts of unemployment and their translational significance on healthcare is warranted.

Furthermore, the mechanism through which employment status results in prolonged LOS following NSTEMI requires further exploration. Future research incorporating the severity of NSTEMI, as well as disease-specific measures such as presentation, coronary anatomy, type of management, and adherence to medication, would provide useful insight into this relationship and permit for targeted patient therapy in conjunction with further social support.

Another significant aspect of our study included the significant variation in LOS by country-of-hospitalization. While country-of-hospitalization was included in order to control for differences across these countries, this uncovered relationship must be further explored in order to discover its causes. Future research comparing differences in healthcare, institutional policy, and lifestyle/cultural habits would provide a clearer understanding of these differences and potential

explanations for the observed country-specific variation in LOS as well as country-specific avenues for interventions.

Current risk stratification tools utilized across a variety of clinical diseases often incorporate measures of biological sex, however they lack incorporation of gender; this is often a result of the lack of gender-related measures in the cohorts from which these tools have been derived. In light of our findings and the growing body of literature suggesting that gender plays a role in the development, severity of illness and outcome independent of sex, re-evaluation of the risk stratification tools must be conducted with incorporation of gender-related factors in order to better predict outcomes.

Better outcome prediction will help elaborate more targeted interventions. Our cohort was limited in its availability of gender-related variables due to inconsistent surveying across the individual constituent cohorts. Future incorporation of additional gender-related variables would permit for a more comprehensive evaluation of the entirety of the gendered environment surrounding the individual and implicated in the development, process of care and outcomes.

Conclusion

In summary, our analysis demonstrated the impact of employment status on LOS following NSTEMI, with longer LOS in unemployed individuals independent of biological sex. This effect was mediated by a history of diabetes, hypertension, prior MI, depression/anxiety, and a family history of CVD. Both age and country of hospitalization were also found to significantly impact LOS. The gender of an individual plays an important role in LOS following NSTEMI. Further

analysis must be conducted to determine the mechanism through which employment status exerts its effect on LOS.

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