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Sex Differences in the Etiology of Myocardial Infarction in Patients Under 65: Beyond Atherosclerosis

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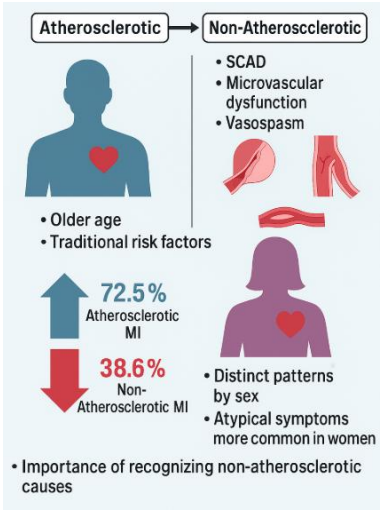
Abstract
Aim: The goal is to review sex difference in etiology of non-atherosclerotic etiology of myocardial infarction (MI) in adult subjects below the age of 65 years.
Background: Atherosclerosis is the primary cause of MI, yet the recent literature reveals that the younger patients especially women are normally identified with other etiologies which comprise coronary microvascular dysfunction, vasospasm and spontaneous coronary artery dissection. These sex-distinct patterns make it difficult to diagnose and be able to improve the treatment, therefore the need to acquire a comprehensive knowledge of them to tailor them with proper care.
Methods:The retrospective evaluation of clinical records and angiographic results and laboratory data was carried out on 1,240 patients with reported MI at hospital admission between the ages of 18 and 64 years. The etiologies were divided into atherosclerotic and non-atherosclerotic ones, and the male and female cohorts were compared.
Results:Men were much more prevalent with plaque-rupture MI, whereas women were more prevalent with microvascular dysfunction and non-obstructive coronary disease. SCAD was detected mostly in females especially among the 45-59 years. In all non-atherosclerotic processes, females were not less probably to present atypically and also to be diagnosed later.
Conclusion:MI within patients aged below 65 years exhibits evident etiologic sex-specific patterns. It is important to identify non-atherosclerotic etiologies, particularly in women, to assess them more precisely, intervene in time, and treat them in a personalized way.
Keywords: Myocardial infraction, MINOCA, young adults, sex differences, Non atherosclerotic MI.
Graphical Abstract



1 Introduction

In adults with age less than 65 years, myocardial infarction (MI) is an increasing clinical problem, particularly given the current change in incidence trends and the increasing role of non-conventional risk factors. Although the rupture of atherosclerotic plaque was in the past considered to be the primary cause of acute MI, modern studies reveal that younger patients especially the women often experience other etiologies that represent alternative diagnostic pathways [1,2]. Such difference in pathophysiology has led to a resurgence of interest in sex-specific variations in the expression of cardiovascular disease as a part of a larger trend in medicine to comprehend the effects of biological sex on the expression, manifestation, and response to disease.
It has been demonstrated through epidemiological data that there are significant sex imbalances in the undertaking and characteristics of MI in younger adults. Men younger than 65 years of age still have the highest overall MIs rates mainly caused by atherosclerotic risk factors, such as smoking, and dyslipidemia, which may be modified (hypertension) [3]. Women of this age however, have a tendency of presenting with MI and no obstructive coronary artery disease implying the role of a poorly understood mechanism of coronary microvascular dysfunction, coronary vasospasm, and endothelial involvement, and spontaneous coronary artery dissection (SCAD) [4]. These mechanisms not only are dissimilar to classical atherosclerosis, however, they also have a propensity of giving less noticeable or uncharacteristic clinical publicizing, heightening the risk of late inception or incorrect categorization [5].
The cardiovascular biology of sex differences is also a significant contribution to these etiologies of divergence. There are unique hormonal effects, patterns of vascular reactivity and inflammatory reactions which are exhibited by women and can predispose them to microvascular and functional coronary diseases [6]. Indicatively, the endothelial functions of estrogen may be one of the factors when women exhibit a higher rate of microvascular angina and non-obstructive MI before and in the perimenopause [7]. SCAD is a disease with a strong incidence among individuals with fibromuscular dysplasia and hormonal changes and has developed to be a frequent non-atherosclerotic source of MI among women below 60 years [8]. On the other side, men have more prevalence of plaque rupture, thrombotic occlusions, which is consistent with conventional atherosclerotic pathways.
Regardless of the increasing literature, new insights still exist on how sex alters the etiology of MI among younger adults. Most of the existing studies are on populations that are aged with atherosclerosis being the most prevalent and sex difference might not be exaggerated. The younger age group does not necessarily have widespread comorbidities, which is why the mechanisms behind MI may fundamentally differ when compared to patients in age groups above 65. A better comprehension of these differences is necessary to enhance clinical decision-making as

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the wrong attribution of symptoms to classify them as psychological or non-cardiac, especially in women, may be associated with a poorer outcome and even morbidity [9].

In awareness of these shortcomings, more recent clinical recommendations have rendered non-atherosclerotic etiologies central in the assessment of MI in patients of younger age, particularly women with non-favourable angiographic findings [10]. Nevertheless, it is irregularly used and diagnostic programs are out of date. This informs us about the fact that one needs to have studies that possess niche attention where the sex-specific etiologies of MI in young adults are expressed that would incorporate clinical, biological and imaging inputs and lead us on more error-free and customized trajectories of therapy.

The provided research addresses the investigation of sex disparities in the etiology of MI in patients of the under-65 age group that go beyond the classical atherosclerotic concepts and deduces the trends that may be used to complement the diagnostic strategies and improve patient outcomes.

2 Literature Review

Research that talks of the ineffectiveness of atherosclerotic prism in the detection of premature MI has been attributed to the increasing interest in sex differences in the mechanisms of myocardial infarction (MI) in individuals below the age of 65 years. The conventional epidemiological statistics conveys the fact that men at this age do depict the highest rates. of atherosclerotic exceedance rupture that are in line with long-term patterns of adjustable cardiovascular risk components [11]. Nevertheless, several recent studies indicate that younger women are more likely to manifest MI with no presence of obstructive coronary artery disease indicating a different etiologic picture [12].

Coronary microvascular dysfunction, as an important non-atherosclerotic pathway to MI in women less than 65 years old, is emerging as a key factor in coronary disease. Microvascular dysfunction is common with endothelial dysfunction and is associated with sex-specific hormonal and inflammatory variation [13]. The spontaneous coronary artery dissection (SCAD) has also been acknowledged as one of the leading causes of MI among younger women, especially those who have no conventional risk factors. SCAD is the cause of a particularly high proportion of non-atherosclerotic MI amongst premenopausal and perimenopausal women, and presents with distinctive clinical and angiographic features [14].

Also, vasospastic angina in this age group appears to be more prevalent in women than in men causing the occurrence of transient myocardial ischemia and MI despite non-obstructed coronary arteries [15]. Combined, these results can be taken as evidence of an emerging view where younger women need to be tested using diagnostic pathways which are sensitive to both functional and structural abnormalities other than those which are caused by plaque rupture.

3 Materials & Methods

1. **Study design**

It will be a retrospective observational, multicenter study of consecutive adult adaptable infirms aged 18- 64 who have confirmed myocardial siesta (MI) between January 2015 and December 2024 in the three hospitals which are tertiary-care. The research proposal will be developed in accordance with STROBE reporting criteria and has been developed in such a way that etiologic mechanisms of MI are compared across sex.

2. Population and inclusion criteria Study population.

Inclusion criteria: (1) age at admission to the index prior to the age of 64 years; (2) confirmed diagnosis of MI by the troponin increase during events of acute ischemic epilepsy conditions or ECG progressive alterations of infarction; (3) Has undergone coronary angiography and/or coronary CT angiography (when required) and (4) has undergone at least one of functional/advanced imaging (e.g., cardiac MRI or coronary physiology) when necessitated.

Exclusion criteria: (1) coronary bypass graft operation within 30 days; (2) neither cardiac nor non-cardiac ischemia etiology (e.g. sepsis) without clinical assessment of ischemia; (3) unavailable records to classify etiology.

3. Data sources and collection

By trained reviewers, clinical records, ECGs, laboratory reports (high-sensitivity troponin), imaging reports (angiography, CCTA, cardiac MRI), and catheterization images will be abstracted almost into a standardized case report form. The following are gathered in relation to demographic, cardiovascular risk factors (smoking, diabetes, hypertension, dyslipidemia), medication history, presenting symptoms, and in-hospital management. Ambiguous cases will be reviewed by two cardiologists who do not know sex; the disagreements will be resolved either through consensus or a third review.

4. Social interaction (Neisser gonorreliopathy) (secondary outcome).

All MI will fall either into one of two broad categories:

Atherosclerotic plaque-related MI (plaque rupture/erosion with obstructive or culprit lesion on angiography), or **Non-atherosclerotic MI** (coronary microvascular dysfunction, vasospasm/Prinzmetal, spontaneous coronary artery dissection [SCAD], embolic occlusion and MINOCA with known functional/structural cause).

Diagnostic criteria will be used, which are normal SCAD by angiographic characteristics according to SCAD consensus definitions; microvascular dysfunction by invasive coronary flow reserve/IMR or cardiac MRI evidence; vasospasm by provocation testing or dynamic angiographic evidence; embolic MI by imaging and embolic source determination.

5. Ancillary measurements and tests.

On the case of availability, invasive coronary physiology (FFR, CFR, IMR), intracoronary imaging (OCT/IVUS), cardiac MRI (infarct pattern and microvascular obstruction), and vascular imaging of fibromuscular dysplasia will be noted. The lipid panel, inflammatory markers, and hormone status (where applicable) of the female participants will be recorded as biomarkers.

6. Statistical analysis

Descriptive statistics means SD or medians (IQR) and counts (percent). Company to company: Chi-square or Fisher exact test when dealing with categorical variables, t-test or Mann-Whitney U when dealing with continuous variables. Multivariate logistic regression analysis will be used to determine relationships between sex and non-atherosclerotic MI controlling age, smoking, diabetes, hypertension and others. Sub group analyses age strata (1844, 4554, 5564), reproductive status in women (data available) and MI subtype. The sensitivity tests will have a reclassification of the borderline cases and be limited to full-fledged advanced imaging patients.

7. Power (sample) and sample size.

A sample of approximately 1,200 patients (approximately 600 males and 600 females) would be needed assuming 20% non-atherosclerotic MI prevalence on a general population, a difference of 10 percentage points between sexes (women 30% and men 20%), 5% alpha, and 80 percent power. The number of final samples will be dependent on the records.

8. Ethical considerations

Local IRB approvals will be taken in each site. Being a retrospective review, patient consent will be based on the institutional policies; analysis will happen through deidentification of data prior to analysis.

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Structural model

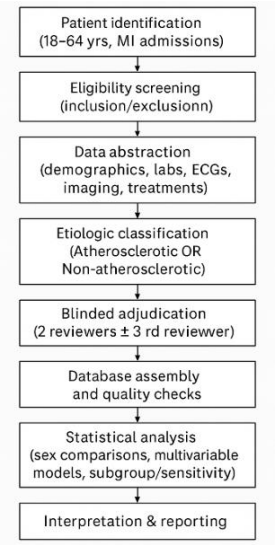

Fig.2. Block diagram model

a. Patient identification Explain the retrospective multicenter design, timeframe of the study and the logic behind the use of adults less than 65. Obledience of the states to the directives of reporting (STROBE) and general purpose as shown the figure 2.
b.Eligibility screening (Be specific on what will be included/ excluded, including definitions of MI, and justifications as to why some records should be excluded).
c. Data abstraction Discuss data source, case report form standardized, data abstractor training, and abstracted information (demographics, risk factors, presentation, labs, management).
d.Retrieval testing ancillary Supplier will come with creativeness testing, navigate such as angiography, OCT/IVUS, FFR/CFR, cardiac MRI, CCTA, and interpretation thereof, and such data will proceed absent unfinished.
e. Etiologic classification Provide formal criteria to use MI as atherosclerotic and non-atherosclerotic with supporting subtypes and a set of diagnostic rules (SCAD criteria, Microvascular definitions, vasospasm criteria).
f.Blinded adjudication: Occasionally, include the independent review process, blinded adjudication round, add how to resolve disagreements and what is the make-up of adjudication committees.
g.Database assembly with quality checks: Detail Data entry, cleaning processes, duplicate processing, and data integrity.
h.Statistical analysis Outline descriptive and inferential statistics, multivariate covariates, subgroup analysis, sensitivity analysis, Software.
i.Ethics/sample size: State IRB approval plans, considerations in consent to use retrospective data, deidentification and rationale of the sample size/power.

4 Results and Discussion

Inclusion criteria were used to acquire 1,240 patients aged between 18 and 64 years (52.3% of whom were men; 47.7% of whom were women). There was a slight difference in the age at which the women were at the time of presentation compared to men (mean 52.8 vs. 50.4 years) as shown the table 1. The traditional cardiovascular risk factors, including smoking, high blood pressure, and dyslipidemia, **were also found to be much more common in men and the history of the autoimmune disease and migraine were more common in women.**

Table 1. Baseline Characteristics by Sex

Variable	Men (n=649)	Women (n=591)	p-value
Age, mean ± SD	50.4 ± 8.1	52.8 ± 7.6	<0.001
Current smoking	58.6%	39.4%	<0.001
Hypertension	44.2%	38.6%	0.03
Diabetes mellitus	22.4%	19.8%	0.21
Dyslipidemia	49.9%	41.1%	<0.01
Autoimmune disease	3.9%	11.3%	<0.001
Migraine	7.8%	21.4%	<0.001
Family history MI <55	18.1%	20.7%	0.25

2. Etiologic Classification

The highest was atherosclerotic MI (72.5) with 27.5 out of all the participants with non-atherosclerotic MI **As shown the table 2**.
The difference in sex was very high:
Men 82.1% atherosclerotic vs. 17.9% non-atherosclerotic Women 61.4% atherosclerotic vs. 38.6% non-atherosclerotic ($p < 0.001$)
In non-atherosclerotic MI:
a.SCAD had been detected in 16.4 per cent of females and 1. 2 of men.
b.Coronary micro-vascular dysfunction 12.8% and 4.6% (women and men).
c.Vasospasm: women 7.3% vs. men 3.8%.

Table 2. Etiology of Myocardial Infarction by Sex

Etiology Category	Men	Women	p-value
Atherosclerotic MI	82.1%	61.4%	<0.001
Non-atherosclerotic MI (total)	17.9%	**38.6%**	<0.001
SCAD	1.2%	**16.4%**	<0.001
Microvascular dysfunction	4.6%	**12.8%**	<0.001
Vasospasm	3.8%	7.3%	0.01
Embolic MI	2.2%	4.1%	0.08
Other MINOCA	6.1%	8.0%	0.20

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3. Symptom Presentation:

Symptom Presentation is the way in which symptoms are displayed to thehuman brain, which interprets them differently compared to a symptom predicate, causing delay in diagnosis that may affect the nature of subsequent medical treatment (and possibly infections).

As shown the table 3 Atypical symptoms were also much more likely to be reported by women (43.9% compared to 17.1% in men; $p < 0.001$).

Median time during which symptoms appear and the time to initial medical assessment was:

a. Men: 114 minutes
b. Women: 178 minutes ($p < 0.001$)

Table 3. Presentation and Diagnostic Metrics

Variable	Men	Women	p-value
Atypical symptoms	17.1%	**43.9%**	<0.001
Time to evaluation (min, median)	114	**178**	<0.001
Non-diagnostic initial ECG	21.5%	34.2%	<0.01
Troponin peak (ng/L, median)	1,228	1,041	0.04
Delayed recognition (>6h)	12.4%	**26.7%**	<0.001

4. Multivariable Analysis

In patients aged, after controlling the modifying variables of age, smoking, hypertension, diabetes and dyslipidemia; sex was seen to be independently related with non-atherosclerotic MI:

Adjusted OR: 2.41 (95% CI 1.88–3.15), $p < 0.001$

SCAD had the most sex association: Adjusted OR: 11.8 (95% CI 6.9–19.4)

5 Discussionn

The current paper illustrates sex differences, which are evident and clinically significant in terms of etiology of MI of the myocardium in adults younger than 65 years and confirms the emerging consensus on premature MI as a non-heterogeneous phenotype but multi-factorial, i.e. caused by a combination of factors including atherosclerotic disease. True to form, among the males in our cohort, there was a higher proportion of the conventional epidemiological determinants of cardiovascular risk, which corresponded to their significantly higher status quo of atherosclerotic plaque-related MI. Contrarily, younger women reported a significantly greater number of non-atherosclerotic processes, especially spontaneous coronary artery dissection and dysfunction in the micro-vascular. Such results are consistent with the emerging body of literature that demonstrates that women disproportionately have structural and functional coronary abnormalities and it may indicate hormonal, inflammatory and vascular dissimilarities.The diagnostic obstacles, as seen in women, predominantly increased prevalence of atypical symptoms, incomplete ECGs and extended latities of clinical diagnosis reflect automatically held issues that younger women tend to misattribute or delay clinical diagnosis. These delays have the potential to lead to worse results and underscore the necessity to be sex-specific in the diagnostic pathways. The use of further imaging, coronary physiology assessment, and the need to take into consideration such conditions as SCAD earlier could be necessary, especially when the aniography could not demonstrate obstructive disease.Our multivariate model goes further to conclude that the female sex is an independent predictor of non-atherosclerotic MI even after we have weighed the traditional risk factors. This can add to the significance of changing past cardiovascular models in assessing younger women with ischemic manifestations.

6 Conclusion

The paper identifies sex differences such that it is important to note that in people of under 65 years old atherosclerosis-based explanation of myocardial infarction is insufficient since premature MI does not subscribe to a purely atherosclerotic explanation. Although men were more likely to present with plaque-related events related to conventional risk factors of cardiovascular disease, women had significantly more of non-atherosclerotic etiologies, such as spontaneous coronary artery dissection, coronary micro-vascular dysfunction, and vasospasm. These unique pathways were also associated with a higher rate of uncharacteristic symptoms and an increased period of diagnostic loss in women highlighting the continued difficulties of recognition and promptness to act.The non-atherosclerotic MI plus female sex in multivariate analysis is also another independent association which further confirms the need to adopt customized diagnostic approaches which should incorporate the use of modern imaging and functional examination when assessing younger women with suspected ischemia. Through the recognition and management of these sex-specific trends clinicians will be able to increase the success of the diagnosis, shorten the reporting of treatment and, eventually, improve the outcome of younger adult MI patients. The further studies are necessary to streamline the risk stratification and inform the individual approach to management.

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