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Metabolic Syndrome and Risk of Early Heart Failure Rehospitalization in Older Adults: A Sex-Specific Analysis and Update

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Highlights

- A high rate of early heart failure (HF) rehospitalization persists after index HF hospitalization among older adults
- Risk predictors such as the metabolic syndrome or its components make vital contributions to early HF rehospitalization after discharge but show substantial inconsistencies.
- Important sex-specific differences exist in HF rehospitalization, yet significant gaps in knowledge to accurately predict early HF rehospitalization remain
- A machine-learning approach can be developed to guide research examining MetS, early HF hospitalization, and sex-specific differences in older women.

Abstract

Metabolic syndrome (MetS) and heart failure (HF) remain important global health issues affecting young and older adults, independently contributing to HF hospitalizations and early rehospitalizations. Understanding sex-specific differences in HF research and accurately identifying risk of rehospitalization in patients with HF remains important for clinical decision making and management. We recently conducted a literature review and retrospective analysis of data specifically focusing on predictors of the 31 to 60-day HF rehospitalization timeframe among older women, as well as derivation of a conceptual model. Our review confirmed that the influence of risk predictors such as sex-based disparities, risk factor profiles, and therapeutic interventions on early (≤ 60-day) HF rehospitalization remain inconsistent and challenging. The presence of risk predictors predates the clinical event and further understanding is warranted given the prevalence and potentially serious consequences of the MetS and recurrent HF rehospitalizations. In this mini-review, we examined recent published data that address MetS and sex-specific differences within the context of HF rehospitalization, and determined contributions from machine-learning approaches.

Keywords: Heart failure, Metabolic syndrome, Rehospitalization

Introduction

Metabolic syndrome (MetS), viewed as a collection of interrelated risk factors that includes hypertension, central obesity, insulin resistance, and atherogenic dyslipidemia, causes structural changes of the left or right ventricles, which often lead to increased cardiovascular events, incident heart failure (HF), and HF hospitalization [1-8]. The combination of obesity and other components of the metabolic syndrome creates unique physiologic challenges that affect myocardial structure and function. The population-attributable risk of obesity affects both subtypes of HF: heart failure preserved ejection fraction (HFpEF; LVEF ≥ 50%), and heart failure reduced ejection fraction (HFrEF; LVEF ≤ 40%), but appears more

prevalent in HFpEF [9]. Obesity affects more women than men globally, and visceral adiposity contributes to cardiometabolic HFpEF through various mechanisms. Thus, HFpEF has emerged as the more dominant subtype globally in women [9,10]. In contrast, diabetes mellitus affects approximately 40-45% of patients with HFpEF or HFrEF [11-14].

The clustering of metabolic risk factors, obesity, diabetes, and hypertension in the context of their association with older women and subtypes of heart failure has essential implications for the therapeutic and preventive approach toward primary prevention of HF in this cohort, as well as early HF rehospitalization [15-18]. Both Faulkner [17] and Kim *et al.* [18] strongly agreed that MetS or its components are independent risk factors for HFpEF and in older women. Even though this association was addressed since 2006 [16], a limited amount of research has been published addressing MetS and incident HF hospitalization or early HF rehospitalization among older women (**Table 1**). Sue-ling & Jairath [19,20] recently published two papers addressing predictors of early HF rehospitalization and older women after an index HF hospitalization. A unique timeframe, 31 to 60 days post-discharge, was selected since previous research addressed early (≤ 30 days) or beyond 60 days.

The literature review identified only two studies (**Table 1**) that addressed components of the MetS and early HF rehospitalization [21,22]. Neither study specifically addressed women nor represented >50% of the study population [20]. One of the two studies evaluated type II diabetes as one of the predictors. This risk factor was associated with an increased 30-day HF rehospitalization after an index HF hospitalization and affected 47.1% of patients who were rehospitalized for HF [21]. The second study showed a reduction in body mass index (BMI) after an index HF hospitalization, which correlated with HF rehospitalization in patients with HFpEF and HFrEF [22]. These findings demonstrated that further research is necessary to understand the relationships between MetS and its components with HF. We, therefore, designed this mini-review to address recent publications investigating the MetS or early HF rehospitalizations, with emphasis on sex differences, HF subtypes, and machine learning methods or artificial intelligence (AI) that can be developed to stratify and predict risk in HF patients.

Biomarker Profiles and the Metabolic Syndrome

Several interconnected risk factors characterize the MetS and are common in patients with HF. These risk factors include: 1. Central obesity, defined as body mass index (BMI) ≥ 28.1 kg/m^2 in men and ≥ 27.5 kg/m^2 in women; 2. Elevated serum triglyceride; 3. Reduced high-density lipoprotein cholesterol (HDLc); 4. Diabetes or insulin resistance; 5. Hypertension (systolic blood pressure ≥ 130 mmHg and diastolic blood pressure ≥ 85 mmHg [23]. The criteria for MetS is having any three of the five risk factors [23]. Based on this criterion for MetS, van der Hoef [23] conducted a retrospective post-hoc analysis of 1,103 patients with HF and metabolic syndrome (n = 468 [42%]) to determine biomarker expression among a panel of 363 biomarkers. In patients with MetS, the most significantly elevated biomarkers were leptin, fatty acid-binding protein 4, interleukin-1 receptor antagonist, tumor necrosis factor receptor superfamily member, and proto-oncogene tyrosine-protein kinase receptor. Since these biomarkers relate to

Table 1. Summary of Studies Examining Features of Metabolic Syndrome and Early HF Rehospitalization.

Authors/ Year	Sample Size/ Characteristics	Study Design/Purpose	Key Findings
Arora et al. (2017) [21]	n = 301,892 73.5% age ≥ 65 years women = 49.2%	The study cohort was derived from the Healthcare Cost and Utilization Project's National Readmission Data (2013) Features of the metabolic syndrome as predictors of HF rehospitalization 30-day HF rehospitalization after index HF hospitalization	30-day HF rehospitalization = 35.3% Diabetes a significant predictor for 30-day rehospitalization after index HF hospitalization 18.8% of rehospitalized patients with HF met criteria for obesity 71.2 % of patients rehospitalized with HF suffered with hypertension
Nishikido et al. (2019) [22]	n = 971 mean age = 73.2 ± 11.2 years women = 30.9% Patients hospitalized with either HFpEF or HFrEF	Retrospective analysis (2009-2013) Non-obese patients Patients are classified into four categories based on frequency of early rehospitalizations: twice, three times, four times, and > 5 times Correlate reduction in body mass index (BMI) with frequency of rehospitalizations	Reductions in BMI after index HF hospitalization signified repeat early HF rehospitalizations and poor outcomes in HF patients Greater reductions in BMI correlated with higher recurrences of HF rehospitalizations BMI reduction after discharge had a more profound effect on patients with HFpEF

Source: Sue-Ling et al. (2023) [22].

obesity, lipid metabolism, and chronic inflammation, the authors concluded that MetS is highly prevalent in HF patients [23]. A prospective study analyzing HF patients also confirmed that abnormal lipid metabolism (elevated triglyceride index ≥ 9.47) was associated with HFpEF and rehospitalization [24].

Predictors of Early Heart Failure Rehospitalization

Heart failure is prevalent among older adults with either (HFpEF) or (HFrEF) and has a high rate of early HF rehospitalization [19,20]. Preventing early rehospitalization is complex because of significant differences between the two subtypes of HF, as well as inadequate predictive models to identify key contributing factors [19,20]. A recent retrospective study evaluating risk factors and early (31 to 60-day) HF rehospitalizations in older women could not determine which predictors made significant contributions [19]. Neither subtype of HF (reduced or preserved) nor race predicted the likelihood of rehospitalization [19]. This study was conducted using a unique timeframe (31 to 60-day) post-discharge rather than the traditional ≤ 30 days or ≥ 60-day timeframes while also evaluating common social, hemodynamic, and comorbid risk factors. Six recent studies evaluated predictors of HF rehospitalizations during different timeframes post-discharge [25-30]. Three studies retrospectively collected data on older adults with multiple comorbidities and evaluated 30-day unplanned rehospitalizations [25-27]. One study evaluated hospitalized patients with HF as a primary versus secondary diagnosis [26]. Predictors that were associated with increased risk for rehospitalization varied and included age, substance use, comorbidities, length of stay, and triglycerides. None of the studies evaluated a specific cohort of older women or men. Another study retrospectively collected data in patients with acute myocardial infarction (AMI) and type 2 diabetes mellitus over four years, with HF hospitalizations occurring during a median follow-up of 540 days [30]. The study attempted to determine the effect of dapagliflozin (DAPA) on the rate of HF rehospitalizations [30]. Data showed that DAPA usage in patients with diabetic AMI resulted in a significantly lower risk of HF rehospitalization (HR=0.417, 95%CI=0.417-0.838, p=0.001) [30].

Sex Differences in Heart Failure

Women in certain racial groups represent over 50% of patients with HF, and older women suffer predominantly from HFpEF, which accounts for approximately 50% of all HF-related hospitalizations and HF rehospitalizations [31-36]. Patients with HFpEF also appear more likely to have traditional risk factors such as hypertension, diabetes, higher body mass indexes, less coronary heart disease, and other components of metabolic syndrome (MetS) [20,35,36]. Further, sex-based differences include risk factors unique to women, such as breast cancer-related therapy, pregnancy, autoimmune disease, and stress-induced cardiomyopathy [35]. Obesity predisposes women to heart failure to a greater extent than men. Pathophysiology and response to treatment are different, and initiatives are essential to understand the sex disparities that exist in HF management, device-based therapies, and sex-specific medical therapy [35,36].

Two studies that examined sex differences across different HF subtypes evaluated symptom characteristics and clinical outcomes in older adults to initiate a sex-specific approach to treatment [37,38]. In a prospective, multicenter, observational study, women had diastolic dysfunction more frequently than men (52.8% versus 32.0%, p<0.001), which translated into worse outcomes, possibly related to anemia, sex hormone deficiency, and obesity [37]. The second study examined sex differences, HF subtypes, and characteristics of self-reported change in symptoms. Women with HFpEF developed worsening symptoms compared to women with other subtypes of HF [38].

Machine Learning Methods (Artificial Intelligence) and Heart Failure Rehospitalization

Developing models of risk predictors to reduce HF rehospitalization in older adults remains challenging. Sex and racial disparities exist, with African-American (AA) individuals showing the highest HF risk and a 48% higher risk of hospitalization compared to Caucasians and Asians [20]. Six studies evaluated machine learning approaches or AI to predict the risk of hospitalization or rehospitalization in HF patients as well as clinical decision-making, characteristics of symptoms, classification, and developing integrated frameworks for HF research [39-44]. In three studies, a machine learning approach accurately assessed rehospitalization risk in patients with both subtypes of HF compared to clinical domain knowledge [39-41]. Existing data suggest that future roles for machine-learning protocols would include symptom assessment, clinical decision-making, and creation of a GENERATOR HF DataMart as AI tools in healthcare adoption become more widespread and human cognitive biases diminish [42-44].

Conclusion

The association between MetS and early HF rehospitalization in older adults after an index HF hospitalization involves an elusive understanding of relationships between sex-specific differences in the context of HF, subtypes of HF, comorbid risk factors, and older adults. Overall, recent available data suggest that women are more susceptible to developing HFpEF, and traditional risk factors associated with MetS predispose women to developing HF to a greater extent than men. Understanding sex-based risk factors unique to women will play a vital role in guideline-directed and device-based medical therapy. However, a concerted effort is necessary to bridge existing gaps in HF research in order to understand what risk predictors or their combinations influence early (≤ 60-day) HF rehospitalization after an index HF hospitalization, possibly guided by a machine-learning approach.

Declaration of Conflicting Interests

The authors declare that there are no conflicts of interests.

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