NARRATIVE REVIEW

Predictive role of frailty and malnutrition in rehospitalisation of cardiac failure patients: A literature review

Farhan Muhammad Qureshi[1], Ayyaz Ali Khan[2]

Abstract

Frailty and malnutrition are two conditions that are frequently present in cardiac failure patients that eventually contribute to hospitalisation and recurrent admissions. Malnutrition and frailty are interrelated and a predictive indicator of hospitalisations and subsequent readmissions that worsen the prognosis of cardiac failure patients. Research does not typically measure both nutritional status and frailty together in cardiac failure patients, and they are not even considered when planning and implementing the interventions. The life quality can be improved by early identification of frailty secondary to malnutrition and timely nutritional interventions. Rehospitalisations after discharge due to these conditions significantly increase the risk of death which can be avoided. The current narrative review was planned to highlight frailty and malnutrition as predictive indicators of hospitalisations and subsequent readmissions. Attempts to reduce the social and economic burden owing to these conditions in cardiac failure patients have emerged as a major public health priority worldwide, particularly in the developing countries.

Keywords: Frailty, Heart failure, Malnutrition, Patient readmission, Rehospitalisation.

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Introduction

Cardiac failure (CF) is becoming a multifaceted and life-threatening syndrome, which is now considered a global pandemic significantly associated with morbidity and mortality.[1] The global burden of CF is high with an estimated prevalence of 64.3 million people worldwide.[2] The highest prevalence rates were observed in the Middle East, Central Europe and North Africa regions, whereas rates were low in Southeast Asia and eastern parts of Europe.[2] Unlike developed countries with established healthcare system, studies on CF prevalence in Pakistan and other South Asian countries are very limited. However, some South Asian countries, such as China and India, have reported the CF burden ranging 1.3-6.7%.[1,2] Hospital admissions for CF and subsequent rehospitalisation are very common, adding to the financial burden and worsening the symptoms, leading to poor prognosis.[1,2] The two most common worse outcomes in CF patients are rehospitalisation and death. Rehospitalisation following discharge significantly raises the risk of death that can be avoided in 25% of patients by early identification, appropriate care and prompt intervention.[2,3] Patients of CF suffer at least one comorbidity, and it is even common to have multiple comorbidities at the same time.[2] Out of these, malnutrition[3] and frailty are the two most common conditions associated with CF patients that are usually overlooked.[4]

[1]Department of Community Health Sciences, Karachi Institute of Medical Sciences, National University of Medical Sciences, Karachi, Pakistan; [2]Baqai Institute of Health Sciences, Baqai Medical University, Karachi, Pakistan.

Correspondence: Farhan Muhammad Qureshi.
e-mail: drfarhanqureshi@hotmail.com
ORCID ID: 0000-0001-7044-6751

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Frailty and malnutrition

Frailty is a multidimensional syndrome with several causes and contributors that is characterised by reduced strength, deteriorating physical and impaired physiological functions.[5] Frailty is critical in triggering severe complications leading to adverse effects on health outcomes, such as regression in mobility and independence, fall, hospitalisation, disability and death.[5] Frailty is also a significant predictor of utilisation of most medical and social healthcare services.[4] Several definitions of malnutrition with some similar concepts have been documented, but there is no single definition or set of diagnostic criteria for malnutrition accepted worldwide. Nevertheless, malnutrition is generally described as an insufficient intake of nutrients, which eventually results in impaired body function, changes in body composition, and deteriorating clinical outcomes.[2] Malnourished patients have significantly higher rehospitalisation rates and experience worse outcomes in comparison to well-nourished patients in terms of length of hospital stay (LOS) and mortality.[4] Malnourished patients incur greater expenditure during hospitalisation due to longer stay and extraordinary utilisation of hospital resources.[4] The extent to which frailty and malnutrition are related remains debatable due to divergence and similarities.

Prevalence of frailty in CF

Patients' frailty is an independent predictor of poor clinical outcomes and mortality among CF patients, with the

estimated prevalence rate ranging 27-80% among hospitalised patients in various cultures and geographies.[6] Frailty has now been recognised as a common coexistent condition and highly prevalent among adults with CF. A study indicated that the likelihood of frailty and pre-frailty was high among the Asians, and was linked to advanced age, female gender, numerous comorbidities, use of multiple medications, mental and functional incapacity, weak hand grip, and low nutritional status.[7] Evidence suggested that frail patients are more vulnerable compared to non-frail patients to developing CF, and have shown significant associations between frailty and heart failure (HF). The association between frailty and cardiovascular diseases (CVDs) has been highlighted in studies.[8] CF patients with frailty became physically inactive and lose endurance with the passage of time to deal with the consequences of the condition. Hence, the risk of rehospitalisation and death is high. In a cohort in Italy, the risk of death was found high in CF patients with the increasing frailty scores using Lach's Frailty Score.[8]

Gender-wise variations in the prevalence of frailty in CF

Although it is well established that frailty is linked to adverse outcomes with poor prognosis, gender-specific variations in frailty in CF have not been fully investigated. A recent meta-analysis of 29 studies analysed that nearly half of the patients with CF were frail and, among them, females had substantially higher risk of being frail than males.[9,10] Male-female health survival paradox reported higher rates of frailty with poor health and quality of life of women compared to men.[10] Davis et al. concluded in their meta-analysis that in older adults, females scored more frailty scores than men of all ages.[9] In addition, results of a review revealed that women had greater rates of frailty than men (9% vs 5%) but concurrently had a higher longevity than men at any given frailty score.[11] The overall proportion of frail females across studies in a meta-analysis was 57%9 that was significantly higher than other documented evidence.[12] However, female predominance of having frailty might be the results of participant characteristics or study design. Also, gender variations in frailty are influenced by a range of biological (sex hormones, genetics, epigenetics and immune function), psychosocial (attitudes, emotions, social engagements, socioeconomic status) and environmental factors.[11] Moreover, higher frailty rates in women are not surprising as women tend to have lower average levels of lean body mass and muscle strength compared to men. Nonetheless, women are prone to developing osteoporosis and experiencing decline in bone density with advancing age.[11]

Predictive role of frailty in rehospitalisation and poor outcome among CF patients

Frailty has proven to be an independent and strong predictor of hospitalisations, rehospitalisations and emergency room (ER) visits for CF patients.[9] Although the pathogenesis of frailty is still unclear, the coexistence of frailty and CF worsen each other due to complex and multiple pathological mechanisms, such as dysregulations and disorders of muscular, immune, metabolic and endocrine systems etc.[13] This aggravates the deterioration of muscle mass and strength due to imbalance between the anabolic and catabolic states in CF patients, leading to sarcopenia, or lean muscle mass, and cachexia, which is generalised wasting.[13] CF patients had a high rate of rehospitalisations within 30 days of initial discharge with a risk of post-discharge rehospitalisations reaching up to 20-30%.[4] ER visits, rehospitalisations and frailty are strongly associated with each other, which translates into 65% risk for rehospitalisations and 92% chances for ER visits.[11] Research in Poland revealed frailty to be a major cause of frequent rehospitalisations, and it was more prevalent in CF patients.[14] Similarly, CF patients with frailty had significantly higher rate of rehospitalisation and one-year mortality than those who were non-frail.[14]

Prevalence of malnutrition in CF

Malnutrition is a substantial predictor of poor prognosis and outcomes for CVDs.[15] Malnutrition is one of the modifiable risk factors that medical practitioners can work on, and has an advantage over other clinical variables.[15] CF is associated with multiple factors that can lead to malnutrition, such as decreased appetite, chronic inflammation, protein malabsorption secondary to gastrointestinal oedema, and loss of skeletal muscle mass.[16] For myocardial contractility and to maintain cardiac efficiency, the prime source of energy production is nutrition. The imbalance between anabolic and catabolic conditions due to malnutrition fosters illnesses, such as frailty and cardiac cachexia; the most severe form of malnutrition.[17] Prevalence of malnutrition among CF patients is not only present in under-developed countries, but also in developed countries. Lin H et al. linked malnutrition with severe disability, morbidity and mortality in CF patients, and revealed the prevalence of malnutrition in 16% to 90% patients.[18] Variation in prevalence depends on the screening tools used. Research conducted in United Kingdom and China among hospitalised CF patients showed 6% to 60% and 5.7% to 78.1% prevalence, respectively, using several screening tools.[19,20] However, the frequency of malnutrition in CF patients also depends on other factors, such as patient's outpatient or inpatient status, type of assistance (public or private sector) as well as the severity of the disease.[21] Malnutrition can be

evaluated using several screening tools that are classified as simple or multidimensional.[19] Anthropometric measurements and laboratory test have been considered simple tools for malnutrition screening. Alternatively, multidimensional tools are recommended for extensive assessment of nutritional status by evaluating a range of factors, including mobility and flexibility, acute ailments, comorbidities and dietary consumption. Multidimensional tools are barely used in routine clinical practice because of their complexity and because they require much time, effort and attention.[19] The Geriatric Nutritional Risk Index (GNRI) has been reported as a quick and simple tool having prognostic value as an alternative to multidimensional instruments, such as Subjective Global Assessment (SGA), which predicts mortality in CF patients. However, GNRI is also unlikely to be employed in practice if it does not provide the same information as does the SGA.[19] Therefore, to ascertain whether the ideal solution of a useful and quick tool is realistic, it is crucial to compare the two tools.

Pathophysiology of malnutrition in CF

Epidemiological evidence suggests that malnutrition usually occurs in chronic CF (CCF) patients. The pathophysiological process and mechanism in CF patients are unclear. The reason might be that CF patients have decreased heart function, raised pulmonary circulatory pressure, raised peripheral circulatory resistance, and insufficient organ perfusion, causing gastrointestinal stasis. Consequently, altered systematic basal metabolism due to low nutritional intake leading to increased consumption and reduced absorption, results in a high prevalence of malnutrition.[20] Patients with CF who are malnourished experience increased fluid retention and decreased molecular synthesis, which results in an irreversible cachectic state.[15,20] A considerable number of CF patients tend to suffer from cardiac cachexia. Cardiac cachexia is an involuntary loss of weight due to progressive skeletal muscle mass reduction with or without the loss of adipose tissue.[22] It is caused by hormonal and immunological irregularities that switch the body from anabolic to catabolic state by decreasing the levels and activities of anabolic mediators, such as growth hormone and insulin, and raising the levels and activities of catabolic mediators, such as pro-inflammatory cytokines and glucocorticoids.[22] Static blood in pulmonary and systematic circulation due to progressive decline of ejection fraction (EF) causes sluggish gastrointestinal peristalsis, altered digestive enzymes secretion and cytokines-induced high metabolism, further leading to dystrophic absorption.[20] CF patients lose weight and show symptoms, like dyspnoea, fatigue, decreased muscle volume, dysphagia and cognitive impairment, which consecutively lead to either limit or completely halt routine life activities.[20,23] As the prognosis gradually worsens with the progression of disease's course, CF patients usually are also affected by psychological problems, such as depression and anxiety, and, hence, the body attains a condition of prolonged vigorous catabolism.[22]

Relationship of blood markers with malnutrition in CF

Pre-albumin (PA) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels are effective and significant predictive indicators for the occurrence of cardiac events as well as the disease progression and its prognosis in CF patients. The levels of PA and NT-proBNP levels are significantly associated with the severity of CF in patients of congestive heart failure (CHF). When assessing the prognosis of elderly patients with CCF, the measurement of PA and NT-pro-BNP provides significant predictive value.[24] Albumin is the frequently used indicator for monitoring general nutritional status, and low levels of albumin serves as a risk factor for poor prognosis in CF patients.[25] However, for short-term acute malnutrition, albumin is not a sensitive indicator. Serum PA is a more sensitive indicator than albumin, which is widely used for the early identification of malnutrition, determining that the plasma PA concentration has a specific diagnostic value for detecting malnutrition and severity of disease.[24] Cabassi et al. demonstrated that plasma PA was more precise predictor for the risk of death in CF patients with high levels of pro-BNP, and, therefore, it could be used to identify the need of nutritional support in CF patients.[26] NT-proBNP is mostly produced from atrial tissues mainly under normal conditions with a lower concentration level. NT-proBNP is secreted by cardiomyocytes and through cell stretching it enters the blood circulation. The levels of NT-proBNP are noticeably raised in pathophysiological conditions of heart, such as increased ventricular wall tension, myocardial ischemia, altered ventricular volume and hypoxia.[24] Research revealed that CF patients with varying degrees of cardiac function exhibited a clear intergroup difference in NT-proBNP level, but variations in levels of NT-proBNP levels and its measurements can be influenced by a number of factors, such as age, gender and body mass.[24-27] NT-proBNP can be raised in malnutrition due to the loss of cell mass. It has been suggested that patients with elevated levels of NT-proBNP should be assessed for malnutrition, as it is not only raised in patients with volume overload. Over 9-fold higher risk of malnutrition was found with higher concentration of NT-proBNP compared to subjects with lower concentration. Among CF patients, the relationship between NT-proBNP and nutritional status was even stronger.[28]

Role of nutrition in frailty

Frailty is now becoming a distinctly attractive concept

because of its place in the continuum from robustness to disease-related impairment, morbidity and disability.[29] Frailty is a part of dynamic multifactorial process in which the nutrition level appears as the main component in the assessment of frailty. Nutrition is believed to be a modifiable factor that potentially could be associated with the prevention of the frailty status. Research confirmed that an altered nutrition status, either undernutrition or overnutrition or both, must be considered crucial and useful factor for the identification of frail individuals.[29,30] Even though frailty has proven to be a contributory factor to unfavourable outcomes and poor prognosis, this condition is particularly interesting from public health perspective since it is potentially reversible through accessible preventive strategies.[30]

Relationship between macro/micronutrients, energy and frailty

Much of the literature concerns the contributions of macronutrients, particularly total energy from calories and proteins, and micronutrients, such as vitamin D, towards frailty. Studies have documented that frail patients have remarkably low energy intakes, and malnutrition has been found to be significantly associated with higher prevalence of frailty.[15,17,21,29] However, protein and vitamin D play a crucial role in preventing frailty. A dietary survey reported that 1g/kg/day protein intake was associated with a low prevalence of frailty, independent of total calorie intake i.e., 30kcal/kg/day.[31] Many longitudinal studies have also reported findings in line with this survey, showing that participants with satisfactory intake of protein could avoid frailty.[21,25] Among the micronutrients, vitamin D is of particular interest in relation to frailty.[28] Vitamin D follows phosphocalcic metabolism pathway where vitamin D acts as a cardinal element for mineralisation of bone and strength of the muscles by bindings its receptor in skeletal muscle cells to induce protein synthesis.[31] Also, micronutrients, such as vitamins A, E, C, B6, and circulating biomarkers of carotenoids, such as beta (β) carotene, zeaxanthin and lutein, were found significantly associated with a higher prevalence and increasing risk of frailty.[28]

Assessment tools of prognostic value for frailty and malnutrition in CF

Various tools have been proposed and used to measure frailty. Most of them were developed from Fried criteria and the Deficit Index (DI). Fried criteria tools, such as the Short Physical Performance Battery (SPPB), assess physical frailty, while DI tools focus on multidimensional assessment of frailty. Examples of DI tools are the Edmonton Frailty Scale, the Groningen Frailty Index and the Tilburg Frailty Indicator.[32] The Fried frailty phenotype group uses a 5-point criterion to define frailty as a physical syndrome, which are weakness, reduced physical activity, slow walking speed, unplanned weight-loss, and self-reported exhaustion. It is a precise, clear, easy-to-measure and the most frequently used tool for frailty. An individual is classified frail if at least 3 or more of points of the criterion are met. The criterion has been extensively validated to predict adverse health outcomes.[32] However, the Fried frailty concept lacks sensitivity and specificity in distinguishing frailty in patients with malignancies and neurological disorders, such as dementia and Parkinson's disease. Also, it does not grade the severity of frailty.[32,33] The DI was developed by Mitnitski et al. and defined frailty as a condition of susceptibility due to accumulation of health deficits. DI quantifies frailty using 92 variables related to signs and symptoms, disability, and laboratory investigations. The DI tool is a widely studied mechanism using combinations of health deficits, and has been proven to have substantial prognostic value as it takes into account multiple dimensions of frailty, and generates a degree of flexibility for frailty evaluation.[33] But requirement of a vast amount of health information and plenty of time to execute limits its use, especially in certain clinical settings. Recently, some rapid and simple-to-use frailty screening tools have been suggested, such as the Acute Frailty Network (AFN) frailty criteria, the Clinical Frailty Scale (CFS), and the Derby Frailty Index (DFI).[33] Among them, CFS is simple to apply and has been shown to predict hospitalisation and mortality risks of the affected individuals. Also, to increase the objectivity of frailty evaluation, the single physical test has been introduced, which includes walk tests, gait speed and grip strength. Furthermore, a meta-analysis of CVDs revealed that decreased grip strength predicted hospitalisation and mortality in CF patients.[34]

Malnutrition identification tools

Several tools have been proposed to detect malnutrition, but there is no standard method for assessing malnutrition. Nutritional assessment tools can generally be categorised as simple and multidimensional tools.[1,19] Simple malnutrition scoring tools, such as Controlling Nutritional Status (COUNT) score, GNRI, the Prognostic Nutritional Index (PNI), the Nutritional Risk Index and the Instant Nutritional Assessment, need to be combined with individual biochemical tests and anthropometric measurements to improve diagnostic accuracy.[18,19] These scoring tools are easy to use and simple, identify malnutrition and predict morbidity and mortality.[19,21] Anthropometric measurements include weight and height ratio, skinfold thickness, arm circumference and bioelectrical impedance analysis that are used to estimate body composition in medical practice. Low body mass index (BMI), low-fat mass and smaller waist circumference

on bioelectrical impedance investigation have been shown to be independent predictors of death in CF patients.[35] BMI and weight do not discriminate between fat mass and lean, and are influenced by fluctuations in volume status. Hence, they may not produce a correct reflection of the nutritional status in CF patients. Also, they are likely to be related to the underlying disorder itself, or secondary to medicinal therapies rather than malnutrition. Serum albumin has shown to be a marker of malnutrition, but its level fluctuates in acute illness, inflammation, hepatic dysfunction and haemodilution. Hence, it has a limited role in isolation as a nutritional assessment tool. Other biomarkers, including highly sensitive C-reactive protein (hsCRP), transferrin, and insulin-like growth factor-1, are not used commonly because they lack in sensitivity and specificity.[24,26] Multidimensional nutritional assessment tools are considered more comprehensive for the evaluation of nutritional status compared to quick and easy-to–use malnutrition assessment scoring tools. The former includes findings related to laboratory investigations, dietary assessments, comorbid diseases, functional status, anthropometric measurements and general physical examination.[18] Some most commonly used multidimensional instruments are Mini Nutritional Assessment (MNA), Malnutritional Universal Screening Tool (MUST) and SGA.[19]

The current review has a few limitations. Due to unsatisfactory reporting and surveillance system in developing countries, the review relied heavily on available data from existing literature from the developed world. Also, limited data of developing countries may lead to potential gaps in understanding. There is a need to fill the research gap, especially in the developing world, to assess and elaborate the association between frailty and malnutrition, and its impact on rehospitalisation among CF patients. Better understanding of conceptual overlap of malnutrition and its associated frailty will help cardiac physicians consider these two conditions together for diagnosis and management. Hence, screening is necessary where the population is vulnerable and the risk of malnutrition is high. Further, nutritional interventions, such as dietary counselling and targetted nutritional interventions, are required to address frailty and its associated malnutrition. However, the effectiveness and feasibility of the recommendations provided in the review may vary depending the local context and specific implementation strategies.

Conclusion

Malnutrition, frailty and physical disability are interrelated and increase the risk of adverse health outcomes in CF patients. There is a strong evidence regarding the predictive and clinical role of frailty and malnutrition in CF patients. Physical frailty and malnutrition are common among individuals affected by cardiac failure. Gender wise variations in frailty with higher incidence of frailty in women. Understanding of the predictive role of frailty and malnutrition in rehospitalisation of cardiac failure patients is important. Pathophysiology of malnutrition in cardiac failure should be well understood along with recognizing the relationship between macro/micronutrients, energy and frailty. Studies investigating longitudinal association between malnutrition induced frailty in rehospitalisation of cardiac failure patients should be undertaken. Future research is recommended on nutrition-induced frailty in CF patients, especially in the developing countries, to improve the prognosis of diseased individuals.

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Author Contribution:

FMQ: Conceived idea, drafting and responsible and accountable for the accuracy or integrity of work.
AAK: Reviewing and final approval.