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Handle with care: A systematic review on frailty in cardiac care and its usefulness in heart transplantation

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A B S T R A C T

Background: There is growing consensus that frailty, a state of vulnerability and a decline in functioning across multiple physiological body systems, is a valuable criterion to guide clinicians' risk prediction for poor outcomes in adult transplant candidates. In its 2016 listing criteria for heart transplantation the International Society for Heart Lung Transplantation recommends frailty assessment. We aimed to summarize the usefulness of frailty assessment in heart transplant candidates or recipients reported throughout the literature.
Methods: We performed a systematic literature search in PubMed to identify papers reporting on frailty in transplantation, chronic heart failure, and ventricualr assist device implantation published over the last 10 years in English. Additionally, a hand search was conducted, including manually searching the reference lists and a citation search of relevant papers.
Results: Eleven primary research articles were included in this systematic review. Frailty is a risk factor for morbidity, hospitalization, and mortality in patients with advanced heart failure and individuals being considered for ventricualr assist device implantation. Of the patients being considered for transplantation, 33% are frail. The Frailty Phenotype by Fried is a particularly useful tool to quickly identify higher risk patients for adverse outcomes.
Conclusion: A lack of standardization and limited evidence on frailty in transplantation limit its use as a definitive listing criterion. Future research efforts should focus on systematic integration of frailty measures in transplant practice.

1. Introduction

Frailty is one of the most critical issues for healthcare due to its inherent relationship with poor clinical outcomes [1–3]. It has been defined as a cumulative decline across physiological body systems, depleting a person's ability to maintain homeostasis when faced with stressors [4–6]. Individuals undergoing organ transplantation face several major stressors, and frail transplant patients are more likely to experience sudden disproportionate deteriorations in health status compared with non-frail patients [4–6]. Following these recent insights, in their 10-year update of assessment criteria for heart transplantation the International Society for Heart Lung Transplantation (ISHLT) has recommended that patients being evaluated for heart transplantation be assessed for frailty [7]. Frailty assessment is deemed particularly relevant since respectively 20% and 17% of heart transplant candidates and recipients in the United States of America (US) are ≥65 years of age, with similar figures reported in Europe [8–10]. It is postulated that frailty can provide an important contribution to the limited evidence base to guide clinical decision-making for transplant candidacy and optimal clinical management for this older cohort [11,12]. Since frailty assessment is endorsed by ISHLT, it is timely that transplant clinicians understand the concept of frailty, its measurement in clinical practice, and outcomes. Therefore, we aimed to summarize the usefulness of frailty assessment in heart transplant candidates, recipients, and individuals being considered for destination therapy. This systematic review is expanding on a previous work on frailty in heart failure patients [13] to include specific new subgroups of populations, and to identify new evidence up to the present time.

1.1. Frailty: two distinct conceptual models that serve different purposes

Two main conceptual approaches to measuring frailty have been developed over the past 15 years. Even though there is now broad agreement on the definitions and conceptualization of the syndrome, there is no consensus on which instrument is best suited to measure frailty. [14–16] The Frailty Phenotype (FP) focuses on physical aspects of frailty

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Table 1
Fried frailty phenotype instrument [4].

Domain	Assessment and scoring
Grip Strength	**Assessment:** Grip strength as measured by the hand-held Jamar dynamometer (Sammons Preston Inc. Boiling Brook, IL), which has established test–retest, inter- and intra-rater reliability [68]. Stratified by gender and body mass index (BMI) quartiles: Men Cutoff for grip strength (kg) criterion for frailty BMI ≤ 24 ≤ 29 BMI 24.1–26 ≤ 30 BMI 26.1–29 ≤ 30 BMI > 28 ≤ 32 Women BMI ≤ 23 ≤ 17 BMI 23.1–26 ≤ 17.3 BMI 26.1–29 ≤ 18 BMI > 29 ≤ 21 **Scoring:** 1 point if weakness is present.
Walk Time	**Assessment:** stratified by gender and height (gender-specific cutoff a medium height). Men Cutoff for Time to Walk 15 f. criterion for frailty Height ≤ 173 cm ≥ 7 s Height > 173 cm ≥ 6 s Women Height ≤ 159 cm ≥ 7 s Height > 159 cm ≥6 s **Scoring:** 1 point if slowness is present.
Low level of physical activity	**Assessment:** through 1 closed-ended question: 'How often do you engage in activities that require a low or moderate level of energy, such as walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, exercise cycling, dancing, aerobics, bowling, golf, tennis, racquetball, calisthenics, swimming. Kcals per week expended are calculated using standardized algorithm, This variable is stratified by gender. **Scoring:** 1 point if: Men: Kcals of physical activity per week <383 are frail Women: Those with Kcals per week <270 are frail
Exhaustion	**Assessment:** the following two statements are read: 'I felt that everything I did was an effort?' and 'I could not get going?' "How often in the week did you feel that way?" (Answer option: 0 = rarely or none of the time (< 1 day), 1 = some or a little of the time (1–2 days), 2 = a moderate amount of the time (3–4 days), or 3 = most of the time. A response of "2" or "3" to either one or both questions is considered as exhaustion and categorized as frail. **Scoring:** 1 point if exhaustion is present.
Weight loss	**Assessment:** through 1 closed-ended question: 'In the last year, have you lost more than 10 lb unintentionally (i.e., not due to dieting or exercise)?' (If yes, then frail for weight loss criterion. **Scoring:** 1 point if weight loss is present.
Overall score	**Non-frail: 0** **Pre-frail: 1–2** **Frail: 3–5**

(Table 1). It is an internationally recognized and widely applied conceptual framework of frailty, which was first proposed and psychometrically tested in the Cardiovascular Health Study in 2001, a large cohort study in community dwelling older adults in the US [4,17–19]. This phenotype consists of five components that capture a decline in physiological reserve: (1) unintentional weight loss (10 lb in the past year); (2) self-reported exhaustion; (3) a low level of physical activity; (4) slow walk speed; and (5) reduced grip strength, and categorizes individuals as non-frail (0/5), pre-frail (1–2/5), or frail (≥3/5) [4–6]. The FP is a widely used approach for assessing frailty in a variety of chronically ill populations [20] and is endorsed for integration in the preoperative assessment for older surgical patients by the American College of Surgeons [16] and the American Geriatric Society [21].

Rockwood and colleagues used the Canadian Study of Health and Aging to develop and validate the Frailty Index (FI) in 2001 [22–25]. The FI is based on a count of up to 70 deficits, including comorbidities, physical and cognitive impairments, psychosocial factors and common geriatric syndromes (e.g. urinary incontinence, fall risk, delirium) (Table 2) [6,24–26]. The understanding here is that frailty is a condition that encompasses medical, functional and psychosocial domains, and defines an individuals' severity of frailty by the proportion of possible deficits present [27]. A total score from 0.0 (no frailty) to 1.0 (highest severity of frailty) is derived [24].

Frailty measurement is not yet routinely applied in transplantation and is frequently judged from the end of the bed, under the assumption *"I know it when I see it"*. However, this end-of-the-bed assessment is an inadequate substitution for objectively assessing frailty using standardized measurements in acute cardiology and hemodialysis [28,29]. As clinicians tend to underestimate frailty in clinical settings, the use of standardized, reliable and valid frailty screening and assessment tools is imperative [28,29]. Many different frailty measurements exist that have not been extensively validated, applied across various age- and disease groups, or compared against each other in their capacity to predict adverse outcomes. This heterogeneity in approaches provides challenges for clinicians to choose an appropriate instrument to routinely apply frailty measurement in clinical practice [16,20]. Some authors suggest that the FI is conceptually less well defined, as deficits captured include disabilities and comorbidities, concepts which co-occur with, yet are distinct from frailty [17]. The FP is reported to recognize frailty as a distinct medical condition that is separate from disability and

Table 2
Frailty Index.

Domain	Assessment
Mobility	Walking speed Number of falls in the past six months
Cognition	History of dementia Mini-Cog Test or Mini-Mental Status Exam
Function	Dependency in activities of daily living
Exhaustion	Energy level
Burden of chronic disease	Charlson Index > 5 chronic medications
Nutritional status	> 10 lb weight loss in the past 6 months low albumin, poor appetite
Mood	Depression, Sadness, Anxiety
Social vulnerability	Presence of social support Lack of interactions with other people

Scoring for frailty: classify each characteristic as present or absent based on standard cut-off points, sum the number of abnormal frail characteristics and divide by the number of total assessed characteristics.

comorbidities, which provides a major advantage for using this conceptual model.

2. Methods

2.1. Identification of relevant papers

We performed a systematic review of articles published in English over the last ten years in PubMed, followed by a citation search. A search string was built combining MeSH terms and free text words related to 'frailty' and 'transplantation' (Fig. 1). Additionally, the reference lists of studies meeting eligibility criteria were screened for relevant papers that might have been missed through the electronic search.

2.2. Selection of relevant papers

We included papers reporting on frailty in heart transplantation, chronic heart failure and ventricualr assist device (VAD) implantation. Heart failure patients requiring either bridge-to-transplant or destination VAD therapy are included in this review due to the very limited evidence pertaining to cardiac transplantation alone. Quantitative studies were included if a defined measure of frailty was assessed in a cohort of heart transplant candidates or recipients, heart failure patients, or VAD recipients. Qualitative studies, doctoral theses, books and book chapters, and case studies were excluded.

The titles and abstracts of potentially relevant papers were screened using the predefined inclusion and exclusion criteria. Then the full text articles were obtained from all abstracts meeting inclusion criteria and were further screened for eligibility. Two researchers (OM, VC) independently performed the selection and inclusion of articles, with differences being resolved through discussion with a third member (SRJ).

2.3. Data extraction and summarizing

An initial data-charting format was developed by two researchers (OM, VC). Iterative discussions within the research team guided small adjustments during the data charting process. The final version entailed information concerning prevalence, morbidity, and mortality about frailty in transplantation, chronic heart failure, and VAD implantation. Data from the included studies were extracted by one researcher (OM) and double-checked by a second reviewer (VC). The methodological quality of the studies was checked using The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) instrument of the Equator Network. The review process was reported based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

3. Results

The database search produced 1713 articles for screening (Fig. 1). After screening of titles, abstracts and full texts, 11 studies [30–40] were included and summarized in this paper (Table 3). Although over the past 10 years a rapid growing body of evidence has highlighted frailty as a highly prevalent and novel predictor for clinically relevant adverse outcomes in general [20], only one study assessing frailty in patients referred for heart transplantation could be identified [30]. Nevertheless, frailty has been examined more intensively in the related field of chronic heart failure, as well as mechanical circulatory support implant and is thus included in this review [31–40].

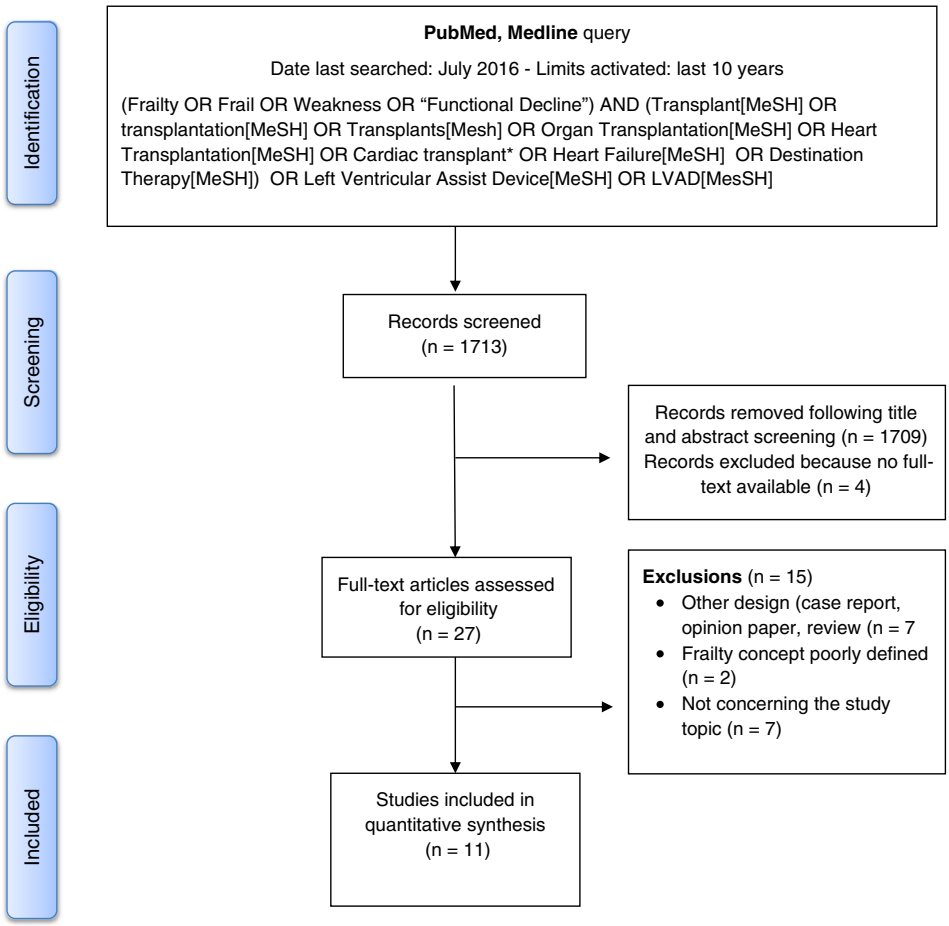

Fig. 1. Search retrieval process.

Table 3
Summary of included articles on frailty in cardiac transplantation, including frailty in heart failure, and LVAD therapy and their impact on outcomes.

References, Country	Design	Setting/Sample	*n*	Patients	Frailty Measure	Prevalence of frailty	Clinical Outcomes
Jha et al. [30] Australia	Prospective cohort	Outpatients referred for transplant assessment	120	53 ± 12 years; 83% males	Modified FP	33%	Mortality HR 2.07 (95% CI; 1.01–4.26
Madan et al. [31] USA	Single-center pilot study	Outpatients with CHF	40	74.9 ± 6.5 years; 42% males	FP	65%	All-cause hospitalization HR 1.92 (CI 95% 1.12–3.27; $P = 0.017$) Non-HF hospitalizations HR 3.31 (95% CI 1.14–9.6; $P = 0.380$) Mortality HR 1.93 (95% CI; 1.15–3.25, $P = 0.013$)
Reeves et al. [32]	Prospective 3 age-matched cohort	Patients hospitalized with acute decompensated heart failure (HF) matched with a) stable HF with preserved EF, b) stable HF with reduced EF, c) healthy older adults	27	72.9 ± 10 years; 41% males	FP	56%	Severe reduction in all domains of physical function, with ≈50% lower in acute decompensated heart failure patients than in stable heart failure or healthy older adults.
Vidan et al. [33]	Prospective cohort	Patients hospitalized for heart failure	450	80 ± 6 years; 50.5% males	FP	76%	Higher risk for functional decline [OR 2.20, 95% CI 1.19–4.08], 1-year all-cause mortality [HR 2.13, 95% CI 1.07–4.23] and 1-year hospital readmission [OR 1.96, 95% CI 1.14–3.34].
Lupon et al. [34]	Observational Study	Outpatients with CHF	622	68 (29–93) years; 72.5% males	Comprehensive geriatric assessment	40%	HR 2.09 (95% CI 1.11–3.92 q = 0.022 for 1-year mortality
Khan et al. [35] USA	Secondary analysis	Community dwelling elders	2825	74 ± 3 years; 48% males	Healthy aging and body composition & Gill index	18%	Moderate (HR 1.36 95% CI 1.08–1.710) and severe (HR 1.88, 95% CI 1.02–3.47) frailty increased the risk of HF
McNallan et al. [36] USA	Observational study	Community dwelling CHF patients	223	71 ± 14 years; 61% males	FP and deficit index	FP: 21% DI: 0.02–0.075 (± 0.25)	Mortality; FP: HR 2.04 (95% CI 0.99–4.16, q = 0) DI: HR 1.44 (95% CI 1.18–1.76; q = 0) Highly co-morbid: >60% patients had a CCI C3
Boxer et al. [37]	Prospective cohort	Outpatients with CHF	60	78 ± 12 years; 72% males	FP	27%	HR 1.64 (95% CI 1.19–2.26; q = 0.005)
Pulignano et al. [38] Italy	RCT	Outpatients with CHF	173	UC: $n = 87$; 78 ± 6 years; 53% males DMP: $n = 86$ 77 ± 6 years; 51% males	Modified frailty score		Higher 1-year mortality (16.9 vs. 4.8%; $P < 0.001$) Higher rate of hospitalization (20.5 vs. 13.3%; $P = 0.01$)
Dunlay et al. [39]	Prospective cohort study	Patients undergoing LVAD implant	99	65.1 ± 9.4 years; 72% males	Frailty deficit index	29%	Rehospitalization intermediate frail HR 1.70 (95% CI 1.23–2.34) and 1.42 (95% CI 0.98–2.06) for frail. Intermediate frail (HR 1.70 95% CI 0.71–4.31) and frail (HR 3.08, 95% CI 1.40–7.48) were at risk for death
Chung et al. [40]	Observational cohort study	Patients with advanced HF undergoing VAD implantation	72	59 ± 2 years; 64% males	Hand grip strength a component of FP		Handgrip strength of <25% of body weight showed increased postoperative complications and mortality (bleeding 54 vs 17%; and infections 85 vs 54%), and a lower 6 months survival after the device implant (75.0 vs 92.9%) that persisted up to 3 years following LVAD implant

3.1. Frailty: Its usefulness in clinical transplant practice

3.1.1. Prevalence

Jha et al. [30] assessed frailty in 120 patients (69% men; mean age 53 ± 12 years, mean left ventricular ejection fraction 27 ± 14%), with advanced heart failure referred for cardiac transplantation, using a modified version of the Fried's phenotype, and found that 33% of the patients were frail. Prevalence of frailty was independent of age, gender, heart failure duration, left ventricular ejection fraction, or renal function [30]. In the study by Madan et al. [31] 65% of patients in a heart failure clinic were found to be frail based on the Fried Frailty Phenotype. Reeves and colleagues [32] prospectively conducted a multidimensional assessment (including frailty based on Fried's phenotype) of 27 patients ≥60 years of age that had been admitted with acute decompensated heart failure. The team compared study participants' functional performance to 3 age matched cohorts: 1) stable heart failure with preserved ejection fraction, 2) stable heart failure with reduced ejection fraction, and 3) healthy older adults previously enrolled as outpatients. Frailty was common, present in >50% of participants with acute decompensated heart failure, but was rare or absent in the other cohorts (0% to 14% depending on the cohort) [32]. Vidán and colleagues [33] reported that 75% of non-dependent patients ≥70 years of age that were hospitalized for heart failure fulfilled frailty criteria. A study by Lupon et al. [38] emphasized that frailty is more prevalent in older heart failure patients, but could also be observed in younger individuals (<70 years old) with chronic heart failure.

3.1.2. Morbidity and mortality

Khan et al. [35], demonstrate that moderate and severe frailty increased the risk for heart failure incidence (HR 1.36; 95% CI 1.08–1.71 and HR 1.88; 95% CI 1.02–3.47, respectively). Another study conducted by McNallen et al. [36] included community-dwelling individuals with chronic heart failure, of which over 60% had multiple co-morbidities in the presence of frailty, which increased the disease burden. Similarly, in the study by Reeves et al. [32] patients admitted to hospital with heart failure had a severe reduction in all domains of physical function, with scores on the 3 measures of physical functioning (6-min walk distance, Short Physical Performance Battery and gait speed) being approximately 50% lower in the patients with acute decompensated heart failure than in the three age-matched outpatient cohorts (two with stable heart failures and one with health older adults).

There have been few studies investigating the impact of frailty on mortality in chronic heart failure patients, and only one within cardiac transplantation [13]. Specifically, a study by Jha et al. [30] included 120 heart failure patients on the waiting list for transplantation, and reported that frailty was an independent predictor of all-cause mortality, with a mean one year survival of 79% ± 5% in the non-frail group compared with 54% ± 9% in the frail group ($P < 0.005$). Madan et al. [31] demonstrated that the frailty status of heart failure patients was associated with mortality and all-cause hospitalization (HR 1.93; 95% CI 1.15–3.25, $P = .031$) [31]. Boxer and colleagues [37] followed sixty community dwelling patients with heart failure (EF ≤ 40%) in a heart failure center, demonstrating that frailty scores were independently predictive of mortality [HR 1.64, 95% CI 1.19–2.26]. Vidán et al. [33] reported that frail individuals ≥70 years of age who were hospitalized for heart failure showed a higher risk for functional decline [OR 2.20, 95% CI 1.19–4.08], 1-year all-cause mortality [HR 2.13, 95% CI 1.07–4.23] and 1-year hospital readmission [OR 1.96, 95% CI 1.14–3.34] than the nonfrail/normal endurance group. Similarly, a study by Pulignano et al. [38] showed a significantly higher rate of hospitalization of frail individuals than in less frail patients (frailty score < 2) (21 versus 13%; $P = 0.01$). Studies in our review highlight that frailty assessment provides valuable prognostic insights in addition to existing risk prediction models.

Concomitantly, many patients with severe heart failure have non-cardiac related comorbidities that render them ineligible for cardiac transplantation and are therefore considered for destination therapy. Dunlay et al. [39] reported that pre-operative frailty assessment, using the Frailty Index, is associated with worse outcomes following LVAD implant as destination therapy. Patients who were frail at the time of an LVAD implant had an increased risk for mortality (HR 3.08; 95% CI 1.40–7.48). Hazard ratio for re-hospitalization was 1.70 (95% CI 1.23–2.34) for intermediate frail patients, and 1.42 (95% CI 0.98–2.06) in those who were frail (based on tertiles of the deficit index >0.32 = frail, 0.23 to 0.32 = intermediate frailty, <0.23 = not frail) [39]. Findings indicate that the risk to be re-hospitalized following device implant is higher in individuals with intermediate frailty. Chung et al. [40] measured handgrip strength, a marker of frailty that is often part of the frailty scoring system, in 72 heart failure patients undergoing VAD implant. Study participants with a handgrip strength of <25% of body weight showed increased postoperative complications and mortality (bleeding 54% vs 17%; and infections 85% vs 54%), and a lower 6 months survival after the device implant (75.0% vs 92.9%) that persisted up to 3 years following VAD implant.

4. Discussion

The important clinical aspect for transplant professionals is that older individuals with multiple comorbidities require a better risk assessment when evaluating transplant candidacy. Frailty enables clinicians to focus on patients' biological age and has important implications for adverse health outcomes and is being endorsed by various organizations to improve quality of care [16,21]. Of importance, the magnitude of risks associated with frailty, increased comorbidities, and mortality is greater than from current risk predictions. Screening patients using an assessment tool based on the FP is endorsed by the ISHLT and can classify transplant candidates into new and clinically meaningful risk categories. In the management of patients with chronic conditions, disentangling frailty from comorbidities through the FP might be important when assessing chronically ill individuals for transplantation. FP as a screening tool to enhance risk stratification for adverse outcomes in clinical practice is feasible, since no prior clinical information is needed and it takes 10 to 15 min to complete [18,20]. At the same time, assessments based on the FP do not provide insights into underlying factors contributing to a patient's frailty, and thus provide limited guidance towards preventive or therapeutic interventions when frailty is identified. This is a drawback that is addressed by the FI, given its assessment of specific deficits across various domains, enabling clinicians to modify certain aspects of a patient's care to potentially improve frailty. The major disadvantage of the FI is however that it requires a comprehensive geriatric assessment for its scoring, which renders its evaluation time-consuming [41]. It is of key importance for clinicians to understand that the FP and FI cannot be considered equivalent. The optimal choice of approach depends on the purpose, e.g. whether a frailty screening for risk stratification (FP), or a more thorough frailty assessment to tailor patient care is intended (FI).

Risk stratification for frail transplant candidates and recipients, also requires evidence for feasible, effective and scalable interventions to prevent frailty, or to slow its progress. A hallmark of frailty is that the condition can deteriorate or improve over time [5,42–44]. At this point the optimal time to start an intervention to improve frailty is still not clear, especially for individuals being listed for transplantation. Given the fact that it is easier to improve small deficits, rather than larger ones it is recommended to focus on improving patient's functional status when they are pre-frail, rather than frail. Incorporating frailty screening would allow healthcare professionals to systematically identify pre-frail individuals when listing them for cardiac transplantation and initiate pre-rehabilitation. Pre-rehabilitation has shown to result in fewer complications following surgical procedures, as well as decreased hospital stay in non-transplant populations [45]. Also without intervention worsening frailty in older non-transplant populations is common. Since cardiac rehabilitation has been shown to decrease mortality and morbidity in patients with heart failure in both hospital and

community based settings, it thus might also be ideally suited to improve an individual's frailty status prior to transplantation. When patients have been enrolled in pre-rehabilitation further frailty assessments could be conducted to capture when a patient has achieved optimal benefit from the program. Although behavioral interventions focusing on physical activity and/or exercise show potential to improve clinical outcomes [5,6,18,46–50], no interventions have focused specifically on individuals with end stage organ failure and transplant recipients to mitigate effects of frailty.

In addition to building on behavior change science, such work needs to include a better understanding of underlying pathophysiological processes that impact frailty and its interrelationship with cognitive function. Current biological frameworks of frailty etiology point to the dysregulation of several key physiological systems, including the neuroendocrine, musculoskeletal, metabolic and immune/inflammatory system [51]. Recent longitudinal studies in various cohorts of older non-transplant adults suggest the latter as a key pathway [6,52–55]. Complex alterations in the innate and adaptive immune system are hypothesized to create a state of chronic low-grade systemic inflammation, which induces frailty and a higher susceptibility for chronic conditions, disability and mortality [51]. Causality of the inflammatory pathway in frailty has to date only scarcely been explored [49,56,57]. Moreover, evidence on a similar etiological pathway for mild cognitive impairment (MCI) is emerging [58] with one recent study identifying that MCI (assessed using the Montreal Cognitive Assessment Tool) was present in 64% of heart failure patients who were frail pre-transplant and in 33% of those who were not physically frail [59]. Studies in patients with end-stage heart failure that incorporated cognitive assessment in the FP improve its predictive validity for adverse outcomes [59]. Research has illuminated that MCI can accelerate the development of disability, which is predictive of hospitalization and mortality [60–63]. Thus, research exploring the interrelationships of frailty and MCI, their evolution, and joint predictive ability for negative outcomes is essential to advance frailty-screening methods [58,64]. At this point, transplant candidates with cognitive impairments are best followed up with a geriatric assessment to determine the cause of cognitive decline, followed by a personal, evidence based, multimodal intervention.

Additionally, studies show that frail patients use more healthcare resources compared to robust individuals. Frailty has therefore been recognized as a long-term condition leading to a range of adverse outcomes for individual patients and high healthcare expenses for the wider society [36,43,65–67]. Thus, research is needed to examine the impact of frailty on resource use and the cost-effectiveness of transplantation.

5. Conclusion

This systematic review demonstrates that frailty assessment in heart transplant candidates, as well as heart failure patients requiring mechanical circulatory support, is feasible and provides clinical prognostic value. Yet, its practical translation into transplant medicine is in its infancy. The evidence on poor outcomes of frail transplant candidates and a potential increased economic burden suggest an urgent need for transplant professionals to pay attention to the syndrome. Nevertheless, there is a need for more studies investigating frailty in the field of cardiac transplantation to allow any official recommendation for transplant list eligibility.

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