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Original Study

Frailty and Clinical Outcomes in Advanced Heart Failure Patients Undergoing Left Ventricular Assist Device Implantation: A Systematic Review and Meta-analysis

Gary Tse MPH, PhD, FESC, FACC, FRCP [a,b,*], Mengqi Gong BS [c], Sunny Hei Wong DPhil, MRCP, FHKAM, FHKCP [a,b], William K.K. Wu PhD, FRCPath [b,d], George Bazoukis MD [e], Konstantinos Lampropoulos MD, PhD, FESC [e], Wing Tak Wong PhD [f], Yunlong Xia MD, PhD [g], Martin C.S. Wong MPH, MBA, MD, FRACGP, FHKAM [h,i], Tong Liu MD, PhD [c], Jean Woo MA, MD, FRCP [a], International Health Informatics Study (IHIS) Network

[a] *Department of Medicine and Therapeutics, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, SAR, People's Republic of China*
[b] *Li Ka Shing Institute of Health Sciences, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, SAR, People's Republic of China*
[c] *Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, People's Republic of China*
[d] *Department of Anaesthesia and Intensive Care, State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, People's Republic of China*
[e] *Second Department of Cardiology, Laboratory of Cardiac Electrophysiology, Evangelismos General Hospital of Athens, Athens, Greece*
[f] *School of Life Sciences, The Chinese University of Hong Kong, Hong Kong, People's Republic of China*
[g] *Department of Cardiology, First Affiliated Hospital of Dalian Medical University, Dalian, People's Republic of China*
[h] *JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong, People's Republic of China*
[i] *State Key Laboratory of Digestive Disease, Chinese University of Hong Kong*

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A B S T R A C T

Background: Frailty has been identified as a risk factor for adverse clinical outcomes after cardiac intervention or surgery. However, whether it increases the risk of adverse outcomes in patients undergoing left ventricular assist device (LVAD) therapy has been controversial. Therefore, we conducted a systematic review and meta-analysis of the frailty measures and clinical outcomes of length of stay and mortality in this setting.

Methods: PubMed and Embase were searched until September 11, 2017, for studies evaluating the association between frailty and clinical outcomes in advanced heart failure patients undergoing LVAD implantation.

Results: A total of 46 and 79 entries were retrieved from our search strategy. A total of 13 studies involving 3435 patients were included in the final meta-analysis (mean age: 57.7 ± 15.3 years; 79% male, follow-up duration was 13 ± 14 months). Compared to nonfrail patients (n = 2721), frail patients (n = 579) had significantly longer time-to-extubation (n = 3; mean difference: 45 ± 6 hours; I^2: 0%) and hospital length of stay (n = 4; mean difference: 2.9 ± 1.2 days; $P = .001$; I^2: 21%). Frailty was not a predictor of inpatient or short-term mortality [n = 3; hazard ratio (HR): 1.22, 95% confidence interval (CI): 0.66-2.26; $P > .05$; I^2: 0%] but predicted long-term mortality (n = 7; HR: 1.44, 95% CI: 1.15-1.80; $P = .001$; I^2: 0%).

Conclusions: Frailty leads to significantly longer time to extubation, hospital length of stay, and long-term mortality in advanced heart failure patients who have undergone LVAD implantation. Older patients being considered for LVAD implantation should therefore be assessed for frailty status. The risk and benefit of the procedure should be explained to the patient, emphasizing that frailty increases the likelihood of adverse clinical outcomes.

The authors declare no conflicts of interest.

* Address correspondence to Gary Tse, MPH, PhD, FESC, FACC, FRCP, Department of Medicine and Therapeutics, Li Ka Shing Institute of Health Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, SAR, People's Republic of China.
E-mail address: tseg@cuhk.edu.hk (G. Tse).

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Over the past years, there has been an increasing number of patients who have received a left ventricular assist device (LVAD), many of them for destination therapy. For advanced heart failure patients who do not meet the criteria for heart transplantation, LVAD destination therapy significantly improves survival rates. However, not all patients are the same, and risk stratification for the advanced heart failure cohort is needed to identify those who are most likely to benefit from it with favorable outcomes. Frailty is a complex clinical entity characterized by increased physiological vulnerability, reduced resilience to stressors and a progressive loss of physiological functions.[1] Recent meta-analytical studies have confirmed that frailty increases mortality in cardiac patients undergoing percutaneous coronary intervention,[2] and those undergoing transcatheter aortic valve implantation.[3] However, it is unclear the extent to which frailty increases the likelihood of adverse clinical outcomes in advanced heart failure patients undergoing LVAD implantation. Therefore, we conducted this systematic review and meta-analysis is to examine the effects of frailty on time-to-extubation, hospital length of stay, and short-term as well as long-term mortality for patients who have undergone LVAD implantation.

Methods

Search Strategy, Inclusion and Exclusion Criteria

The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. PubMed and Embase were searched for studies that investigated the relationship between frailty and clinical outcomes in patients receiving left ventricular assist device (LVAD) using the following terms: [Frailty AND (((assist device) OR circulatory support OR heart transplantation))]. The search period was from the beginning of the databases through to September 11, 2017, with no language restrictions. The following inclusion criteria were applied: (1) the design was a case-control, prospective, or retrospective cohort study in humans, (2) patients underwent LVAD implantation, and (3) frailty was quantified and subsequently related to any of the following clinical outcomes of time to extubation, length of stay, hospitalizations, and mortality. Two reviewers (G.T. and M.G.) independently reviewed each included study, and disagreements were resolved by adjudication with input from a third reviewer (T.L.).

Quality Assessment

The quality assessment of these studies included in our meta-analysis was performed using the Newcastle-Ottawa Quality Assessment Scale (NOS). The point score system evaluated the categories of study participant selection, comparability of the results, and quality of the outcomes. The following characteristics were assessed: (1) representativeness of the exposed cohort; (2) selection of the nonexposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at the start of study; (5) comparability of cohorts on the basis of the design or analysis; (6) assessment of outcomes; (7) follow-up period sufficiently long for outcomes to occur; and (8) adequacy of follow-up of cohorts. This scale varied from 0 to 9 stars, which indicated that studies were graded as poor quality if they met <5 criteria, fair if they met 5 to 7 criteria, and good if they met >8 criteria. The details of the NOS quality assessment are shown in Supplementary Table 1.

Data Extraction and Statistical Analysis

Data from the different studies were entered in a prespecified spreadsheet in Microsoft Excel. All publications identified were assessed for compliance with the inclusion criteria. In this meta-analysis, the extracted data elements consisted of (1) publication details, that is, surname of first author, publication year; (2) study design; (3) follow-up duration; (4) definition of frailty, (5) the quality score; and (6) the characteristics of the population, including sample size, gender, and age.

For time-to-extubation and hospital length of stay, mean and interquartile range (IQR) values were extracted. For the meta-analysis, IQR was converted to standard deviation (SD) using the formula IQR/1.35. For mortality risk, multivariate hazard ratios (HRs) with 95% confidence interval (CI) were extracted. Where these were not available, univariate HRs were extracted or calculated from the published data. Mortality was classified as short-term for deaths that occurred during inpatient stay or within 30 days of discharge, and as long-term for durations beyond the 30 days from discharge.

Heterogeneity across studies was determined using Cochran's Q value, which is the weighted sum of squared differences between individual study effects and the pooled effect across studies, and the I^2 statistic from the standard chi-square test, which describes the percentage of the variability in the effect estimates resulting from heterogeneity. I^2 >50% was considered to reflect significant statistical heterogeneity. The random-effects model using the inverse variance heterogeneity method was used if $I^2 > 50\%$. To locate the origin of the heterogeneity, sensitivity analysis excluding 1 study at a time and subgroup analyses based on different frailty measures were performed. Funnel plots showing standard errors or precision against the logarithms of the odds ratio were constructed. Begg and Mazumdar rank correlation and Egger tests were used to detect publication bias.

Results

A flow diagram detailing the above search terms with inclusion and exclusion criteria is depicted in Figure 1. A total of 46 and 79 entries were retrieved from PubMed and Embase, respectively. Of the 125 articles, 32 were removed as they were duplicates. For the remaining 93 articles, 80 were excluded for the following reasons: basic science paper (n = 1), study protocol, guidelines, or letters to editor (n = 7), review articles (n = 20), irrelevant to heart failure (n = 16), frailty not measured (n = 6), did not study outcomes after LVAD implantation (n = 7), did not report outcomes as a function of frailty (n = 11), or described duplicate or overlapping populations (n = 12). After exclusion, a total of 13 publications were included in this meta-analysis.[4–16]

The following frailty measures were used: Fried score meeting 3 or more of the 5 criteria (n = 6 studies),[7,9–12,16] Deficit Index more than 25% (n = 1)[6] and provider-assisted frailty defined as clinician assessment before LVAD implantation, and objective measures of functional capacity, specifically the gait speed test with <0.8 m/s as the cut-off (n = 1).[5] For the remaining 5 studies, the following surrogates were used: (1) sarcopenia, defined as psoas area in the lowest, gender-based tertile,[8] or psoas area below the median value,[14] on computed tomography imaging (n = 2); (2) handgrip strength (n = 2; using handgrip strength—body weight ratio <25%[4] or 28.5%[15]); and (3) cachexia with >10-kg weight loss over 6 to 12 months, or absolute body mass index (BMI) <20 (n = 1).[13] The baseline characteristics of these studies are listed in Table 1. Nine were prospective studies[4,6,7,9–12,15,16] and 4 were retrospective studies.[5,8,13,14] A total of 3435 patients were analyzed. They had a mean age of 57.7 ± 15.3 years, of whom 79% were male, with a mean follow-up duration of 13 ± 14 months. Eleven of the 3 studies reported the numbers in frail and nonfrail groups: frailty was diagnosed in 579 of 2721 patients (21%) undergoing LVAD implantation.[4–6,8–13,15,16]

Frailty Is Associated With Longer Time-to-Extubation and Hospital Length of Stay in Patients Who Have Undergone LVAD Implantation

Three studies investigated the time-to-extubation in frail versus nonfrail patients. Of these, one study reported significantly longer