A simple effective method for frailty in Heart Failure with impact on clinical outcomes in north Indian population

A Simple Effective Method for Frailty in Heart Failure with Impact on Clinical Outcomes in North Indian Population

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Abstract

Introduction and objectives: Frailty has been studied extensively in elderly population as a predictor and prognostic marker for morbidity and mortality. Frailty is being increasingly recognized as a distinct pathophysiological condition which plays a major role in outcomes of various disease states including heart failure. Our aim was to study the prevalence of frailty in heart failure and see its prognostic significance in such patients.

Methods: This was a prospective study conducted in an out-patient HF clinic. All consecutive patients with HF, ≥ 25 years age, with LVEF<40% were included. All patients were asked a simple frailty questionnaire. Hand-dynamometer was used to assess handgrip strength in kilograms and were classified as frail, pre-frail or non-frail. The primary end point was cardiovascular mortality and hospitalization, and secondary end-point was composite of all cause mortality, hospitalization, device implantation and documented arrythmia.

Results: 210 patients were studied for clinical outcomes.Mean age was 60.59 ± 11.55 years with 15% patients aged less than 50 years. Mean LVEF was $30.24 \pm 6.8\%$. Handgrip strength was poor in the frail vs non/pre-frail patients (p = 0.001) with a strength >16.95 kg having sensitivity of 72% and specificity of 63% for the prediction of survival. Frailty was an independent predictor of mortality with higher mortality and re-hospitalization in frail population (p = 0.001). Hazard for mortality or hospitalization was 4.7 fold in frail population.

Conclusion: Frailty is associated with a significant morbidity and mortality in heart failure. A simple bedside hand-dynamometer may aid as a frailty screening tool in these patients and help in planning treatment strategies.

Keywords: Heart failure, Frailty, Handgrip measurement

1. Background

Presence of frailty in chronic heart failure is an important prognostic marker in addition to the cardiac hemodynamic status per se. Fried et al. [1] defined frailty when three out of following criteria were met- 1) Unintentional weight loss, 2) self-reported exhaustion, 3) weakness (grip strength), 4) slow walking speed, and 5) low physical activity. All these criteria were phenotypic components of the syndrome of frailty. Further, the search for a conceptual definition of frailty has seen various parameters being included [2]. Frailty is a pathologic state characterized by multiorgan involvement resulting in poor quality of life and morbidity. Frailty in heart failure has been reported to be present in 36.2—52.8% patients owing to disturbances in

neurohormonal, musculoskeletal, metabolic and immunological systems in the body [3,4]. It has been widely noted that frailty is associated with higher mortality rates, cognitive decline, disability, falls, social detachment and behavioral changes [5]. Frail individuals are also at higher risk of development of heart failure [2]. Aili SR et al. studied the frailty and cognition together as predictors of mortality in patients with heart failure referred to their transplant unit. They found that physical frailty predicted early mortality and addition of cognitive assessment further identified patients who had a poor prognosis [6]. As the heart failure advances, it causes a decline in oxidative capacity of skeletal muscle along with reduced capillary density and cross sectional area of myocardial fibre [7,8].

The early identification of Frailty in heart failure provides an opportunity for correction of reversible factors like nutrition, physical strengthening, neuromuscular coordination, mobility, endurance and balance [9]. As compared to the western population there are considerable differences in the body habitus, muscle mass, endurance, dietary patterns and nutritional status in Indian population. There is no frailty measurement score or calculator which is validated for heart failure patients. Measurement of frailty in heart failure may help identify and correct reversible factors thus improving quality of life and clinical outcomes especially in a developing country like India. These observational studies have mostly been carried out in elderly population with CHF, however, it is noted to be prevalent in the younger age groups also [10—12]. The data regarding the morbidity and mortality in the real world outpatient setting in heart failure population has been lacking. We aim to study the prevalence of frailty in heart failure and see its prognostic significance in such patients.

2. Material and methods

This study design is prospective and non-randomized, done at the Department of cardiology outpatient clinic with enrolment of patients from Jan 2019—Dec 2019. All consecutive patients undergoing management of chronic heart failure were enrolled. We hypothesized that presence of frailty is an independent marker of morbidity and mortality in chronic heart failure patients. Our aim was to study the prevalence of frailty in chronic heart failure patients and to assess the prognostic relevance of frailty in relation to one-year outcomes. The study

Abbrevations	
ACE-I	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
BNP	Brain natriuretic peptide
BMI	Body mass index
HFrEF	Heart failure with reduced ejection fraction
HF	Heart failure
IHD	Ischemic heart disease
LVEF	Left ventricular ejection fraction
TSH	Thyroid stimulating hormone

design was approved by the institute ethics clearance board. Informed consent was taken from all patients before enrollment. All consecutive patients with age >25 years, and left ventricular ejection fraction <40% with a diagnosis of chronic heart failure on medical therapy for at least 6 months were included. The exclusion criteria were: 1) patients who have a received a cardiac resynchronization therapy device, 2) patients on maintenance hemodialysis, 3) non-ambulatory patients due to other causes like neurological/orthopaedic diseases, 4) life expectancy less than one year due to comorbid conditions. The flow chart of the study is given in Fig. 1.

2.1. Procedure

All patients enrolled were asked a questionnaire as given by Fried phenotypic definition of Frailty [1]. The patients were classified as per the phenotypes. The handgrip was measured with a digital hand dynamometer and a minimum of two attempts were taken. The best attempt out of two will be counted for score calculation. A patient is labelled as frail if ≥ 3/5 criteria are met, 1—2 are classified as pre frail and score 0 were non-frail.

This frailty calculator was used in our population as the study population included patients from different age groups and educational backgrounds. Additionally, we wanted to test a method which is easy to use and understand for the patient, nursing and paramedical staff. This method offers a wider application to patients who are residents of peripheral locations where availability of advanced health services might not be possible. Further, frailty measurement may act as a screening tool to identify patients who might benefit from certain interventions and if needed referral to higher centers for management. One of the drawbacks of using this method is that heart failure patients may have different clinical condition during different times in a year. For example, during winter heart failure may
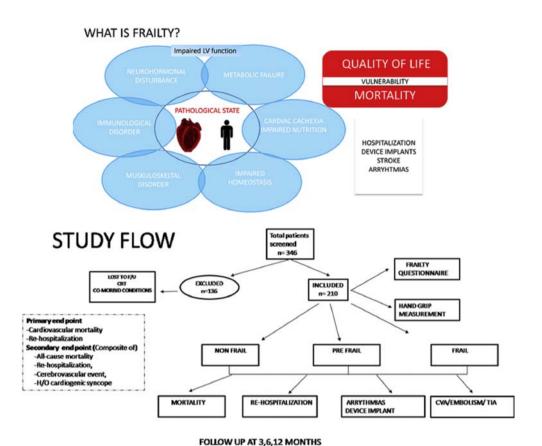
Fig. 1. Impact of frailty on patients with heart failure. Flow-chart of the study.

worsen, during summer renal parameters may change due to change in fluid intake. Therefore this may make changes to the frailty measurement and assessment. However, still the identification of parameters early may allow intervention at an appropriate time.

2.2. Nutritional assessment

The nutritional assessment was done at baseline at the time of enrolment by the mini nutritional assessment score.A) Anthropometric: calculation of body mass index B)biochemical evaluation, C) dietary history: simple questionnaire-a)frequency of meals in last 2 days out of 3 meals, b) snacks in between, c) appetite, d) approximate fluid intake per day.

2.3. Followup

All the patients were assessed and examined during the followup visits in out-patient clinics or during the hospital admissions. Various events were recorded from the outpatient visit records, electronic records, investigations and assessment sheets. If some patient was admitted that record file was analysed. Further, on follow-up visits all the patients were asked for admissions at other hospitals or need for medication from other clinics.

Mortality was confirmed from hospital records or telephonic calls if the patient did not report till 4 weeks after the appointment date. In case we were unable to connect to the family, we contacted the family through mail or physical visit to the house of the patient by one of hospital staff/through some other patient/relative/village head/head of the locality for all patients from the state of Punjab. Patients from other states whom we were unable to reach by all the above measures were excluded from the analysis.

During the followup visits the aim of heart failure clinic was to titrate the guideline directed medical therapy to maximally tolerated doses and all patients were educated for drug compliance.

2.4. Study-endpoints

The primary end-points were all-cause mortality and heart failure-related hospitalization. The secondary end-points were composite of 1) All-cause mortality and HF related hospitalization, 2) Device implantation (pacemaker/intra-cardiac defibrillator

or cardiac re-synchronization),3) Documented arrhythmia, 4) CVA (cerebrovascular accident). All patients were followed till one year for clinical endpoints.

2.5. Statistics

All data was handled with care to maintain patient confidentiality. Records are maintained in both computer and paper formats. Descriptive summaries are presented as frequencies and percentages for categorical data, and as means and standard deviations for continuous variables. Survival analysis was done with Kaplan Meir curves and log rank test was used to calculate p value. All statistical analyses were performed using the SPSS statistical software package (release 20.0, SPSS Inc.; Chicago, Ill).

3. Results

This study included all patients with a diagnosis of heart failure at a tertiary care center in North India (Fig. 1). We screened 346 patients for inclusion in the study. 19 patients were lost to follow up and data was not available for analysis. 117 patients were excluded from the study analysis (27 patients refused to participate, 23 had other co-morbid conditions like advanced neurological diseases who were not ambulatory, 22 had malignancies with poor prognosis, 19 were on hemodialysis, 19 underwent cardiac resynchronization device, 6 had unnatural cause of death (road side accidents, anake bite, and gunshot injury), 2 patients shifted to non-allopathic medications and refused followup). A total of 210 patients were studied for the clinical end-points. The baseline characteristics are given in (Table 1a). The mean age of the study population

Table 1. a) Baseline characteristics of patients (ACE-I/ARB-Angiotensin converting enzyme inhibitor, Angiotensin receptor blocker, BNP-Brain natriuretic peptide,BMI-Body mass index, IHD-Ischemic heart disease, TSH-Thyroid stimulating hormone). b) Baseline characteristics according to presence of frailty.

a)

	N = 210
Age(years)Mean + SD	60.59 ± 11.55
Sex(M/F)	1.61:1
BMI(Kg/m2)	24.1 ± 1.83
Diabetes(n,%)	72 (31.4)
Hypertension (n,%)	96 (41.9)
IHD(n,%)	102 (44.5)
Smoker	54 (23.6)
LVEF(%)Mean ± SD	30.24 ± 6.8
Creatinine(mg/dl)Mean ± SD	1.30 ± 1.14
Beta blockers(n, %)	88(41.9)
Diuretics(n, %)	196 (93.3)
ACE I/ARB(n, %)	157 (74.8)
Hemoglobin(gm/dl) Mean + SD	12.22 ± 1.88
TSH Mean + SD	4.35 ± 3.08
BNP Mean + SD	915.43 ± 889.19

b)

	Frailty type			p-value
	Non-Frail (n = 6)	Pre-Frail(n = 111)	Frail(n = 93)	
Age group				
<50 (years(%))	2 (6.3)	21 (65.6)	9 (28.1)	0.001
50-75 (years(%))	4 (2.5)	87 (55.4)	66 (42)	
>75 (years(%))	0 (0)	3 (14.3)	18 (85.7)	
LVEF(%)	33.7 ± 7.4	30.10 ± 7.6	30.19 ± 5.7	0.444
SEX				
Female(n,%)	0 (0)	37 (54.4)	31 (45.6)	
Male(n,%)	6 (4.2)	74 (52.1)	62 (43.7)	0.228
DRUGS-				
Beta blockers(n,%)	4 (4.5)	52 (59.1)	32 (36.4)	0.092
ACE I/ARB (n,%)	6 (3.8)	93 (59.2)	58 (36.9)	0.001
Diuretics(n,%)	6 (3.1)	102 (52)	88 (44.9)	0.592
BMI(Kg/m)	24.8 ± 0.85	24.02 ± 1.7	24.2 ± 1.99	0.413
Creatinine(mg/dl)	1.01 ± 0.17	1.07 ± 0.61	1.59 ± 1.52	0.005
Hemoglobin(gm/dl)	13.05 ± 1.40	12.5 ± 1.6	11.81 ± 2.1	0.017

Table 2. *Study endpoints according to the frailty. (*p value < 0.05). (CVA- Cerebrovascular accident).*

Endpoint	Non-frail(n = 6)	Pre-frail(n = 111)	Frail(n = 93)	P value (non/pre frail vs frail)
Re-Hospitalization(n,%)	0 (0)	7 (26.9)	19 (73.1)	0.006
Mortality(n,%)	1 (3.7)	3 (11.1)	23 (85.2)	0.001
Device Implant(n,%)	1 (5)	11 (55)	9 (45)	0.857
CVA(n,%)	0 (0)	2 (20)	8 (80)	0.061
Arrythmias(n,%)	1 (3.6)	13 (46.4)	14 (50)	0.760

was 60.59 ± 11.55 years with 15% patients aged less than 50 years. Majority of patient populations consisted of farmers (34.1%) followed by retired/unemployed (26.2%). The male female ratio was 1.6:1. Although most of the patients were in age group 50−75 years, there were 30 patients less than 50 years age who were either frail or pre-frail. Of all the patients with heart failure enrolled in the study, 44.5% patients had coronary artery disease. The mean left ventricular ejection fraction (LVEF) was 30.24 ± 6.8%. Majority of the patients were on diuretics (93.3%), however, only 42% patients were on beta blockers and around three-fourth population was on ACE-I/ARB.

The study population was further classified into non-frail (2.8%), pre-frail (52.8%) and frail (44.2%) according to the Fried frailty index (Table 1b).When comparing the drug usage beta blocker and ACE I usage was less in the frail population as compared to the non-frail and pre-frail patients.

3.1. Study end-points

This study showed a significant mortality in the frail patient population as compared to the pre-frail/non frail population (Table 2). Further, the rehospitalization rates till 12 months were higher in the frail patients. The device implant rate for both the populations was similar. Cerebrovascular events

were also higher in frail patients as compared to the non-frail/pre-frail population. Documented arrhythmias were similar in both the groups. The composite of heart failure related hospitalization and mortality was significantly higher in the frail populations as compared to the other group. Kaplan meir analysis showed a higher event free survival in the non-frail or pre-frail population as compared to the frail population at the end of one year (Fig. 2). On univariate analysis, older age, frail patient, poor hand grip, raised BNP were predictors for mortality. It was also seen that the use of beta blockers and ACE inhibitors prevented mortality. On multivariate analysis, frailty and poor hand grip could identify the patients at increased risk of clinical events (Table 3). On Cox regression analysis ACE I and handgrip were inversely related to mortality. Frailty was an independent predictor of mortality (Hazard ratio 4.75, 95% CI 1.58 to 14.27, p Value - 0.006). Handgrip strength was significantly different in the survivors and non-survivor group. The mean handgrip strength in the survivors was 21.7 ± 7.6 kg and 15.8 ± 5.5 kg in non-survivor group (p value < 0.001). Predictive accuracy of handgrip strength for prognosis is shown in the receiver-operating characteristic curve of hangrip strength to predict survival in patients with CHF (Area under the curve = 0.75 with a p value=<0.001) (Fig. 3). Handgrip strength >16.95 kg had a sensitivity of
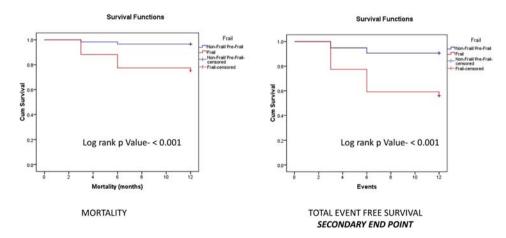

Fig. 2. *Survival analysis for the a) Mortality, b) Event free survival.*

Table 3. a) Univariate analysis. Older age/poor handgrip/frailty and raised BNP were predictors of mortality and ACE inhibitors and beta-blockers prevented mortality. (*p value < 0.05). b) Multivariate analysis: Frailty and handgrip strength can identify heart failure patients at increased risk.

	Survival	Died	Chi-square value/Z	p-value
Age				
<50	27 (14.8)	5 (18.5)	9.606	0.008
50—75	142 (77.6)	15 (55.6)		
>75	14 (7.7)	7 (25.9)		
Sex				
F	60 (32.8)	8 (29.6)	0.107	0.743
M	123 (67.2)	19 (70.4)		
DRUGS-				
Beta blockers	83 (45.4)	5 (18.5)	6.961	0.008
ACE I	146 (79.8)	11 (40.7)	19.006	0.001
Diuretics	170 (92.9)	26 (96.3)	0.437	0.508
Frailty type				
Non-frail/Pre-Frail	113 (61.7)	4 (14.8)	21.006	0.001
Frail	70 (38.3)	23 (85.2)		
Re-hospitalization	25 (13.7)	1 (3.7)	2.151	0.143
BMI(Kg/m) (Mean ± SD)	24.22 ± 1.81	23.58 ± 1.84	1.712	0.088
LVEF(%) (Mean ± SD)	29.94 ± 5.82	32.30 ± 11.37	−1.687	0.093
Hemoglobin(gm/dl)(Mean ± SD)	12.41 ± 1.81	11.07 ± 1.97	3.508	0.001
BNP (Mean ± SD)	792.12 ± 801.3	1575.47 ± 1061.2	−3.506	0.001
HAND GRIP(Mean ± SD)	21.38 ± 6.61	16.41 ± 5.48	3.725	0.001

MULTIVARIATE ANALYSIS

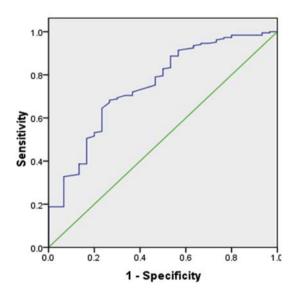|	p-value	Exp(B)	95% C.I. for EXP(B)	
			Lower	Upper
AGE	0.780	0.994	0.953	1.037
ACE I	0.004	0.252	0.100	0.637
HANDGRIP	0.016	0.889	0.807	0.978
Frail	0.003	5.835	1.799	18.928

ROC Curve

Fig. 3. Predictive accuracy of handgrip strength for prognosis is shown in the receiver-operating characteristic curve of handgrip strength to predict survival in patients with CHF (Area under the curve = 0.75 with a p value=<0.001).

72% and specificity of 63% for the prediction of survival in the patients with heart failure.

4. Discussion

Frailty has been recognized as a potential target in management of cardiovascular diseases and is seen to be a dynamic condition which may be reversible with appropriate interventions. To the best of our knowledge this is the first study in India evaluating the outcome of frail population in heart failure patients with a simple bed-side/out-patient method. This method of determination of frailty which may be done by paramedical staff at rural areas and out-patient departments may be useful to identify the high risk subset of patients which may improve significantly with measures aimed at frailty. Frailty is a complex syndrome characterised by poor body reserve with multiple organ systems involved and is seen to occur increasingly with advancing age, however, should not be considered synonymous with ageing. We could see a striking presence of frailty in younger age group patients with heart failure. In our prospective study the left ventricular ejection fraction did not differ in both the groups (non frail/pre-frail versus frail). Similar to the heart failure data from southern part of India from Trivandrum heart failure registry (THFR) [13], the mean age of our population was 60.52 years.

However, ischemic heart disease as a cause of heart failure in our population was seen in 44.5% as compared to 72% population in the THFR. Our data differs from the south Indian data as we included patients with LVEF<40%. From previous studies mortality at 5 years is seen to be around 50% from the time of initial diagnosis [14]. Out of 93 frail patients in our study 23 (24.7%) died within one year, which is higher mortality for patients on medical therapy and constant supervision of physicians. One of the important factor, is frailty which we found to be associated with increased mortality rates in patients with heart failure. In our study 42% patients were on beta blockers and 75% patients were on ACE I/ARB. Thus guideline directed medical therapy could not be achieved in significant number of patients. This may be due to intolerance to beta blockers or ACE I/ARB in our population. It has been seen that elderly frail patients are less likely to receive standard HF regimens [15] and frail HF patients benefit more from an interdisciplinary approach than non-frail HF patients [16]. In our study the use of beta-blockers and ACEI/ARB was associated with less mortality, and diuretics did not prevent mortality. Raised BNP levels and anemia in out-patients was also seen to associate with higher mortality. Vidan et al. in the FRAIL HF study [17], evaluated the relationships between the frailty phenotype and associated issues (i.e. comorbidities, coexistent geriatric syndromes, self-care and social support) with clinical, functional and quality-of-life outcomes in patients after heart failure hospitalization. The study found that even in non-dependent patients, frailty was a risk factor for early disability, long-term mortality and hospital readmission. As compared to the data from western world, 40.6% of the patients with heart failure we studied were frail. The presence of frailty was associated with higher mortality and hospitalization rates. In a recently published meta-analysis by Yang et al. [18] frailty had 1.5 fold hazard for death or hospitalization. In our study the hazard for mortality or hospitalization for frail patients with heart failure was 4.7 fold. This may be in part due to lesser use of guideline recommended drugs, lower BMI of patients, compliance issues with drugs besides other factors like anemia, dietery differences, monitoring and supervision of the patients. We could demonstrate that poor handgrip and presence of frailty had a higher risk of mortality and cardiovascular events in patients with heart failure. Handgrip strength measurement is a easy to use method which may be used in peripheral centers and also in bed-ridden patients. Although there are many frailty scales available, but in a developing country like India with limited resources it is important to have simple and practical method to apply on a large scale. This method used in our study employs a hand held dynamometer and a simple questionnaire which is easy to use and may be used in other diseases also. The pre-frail category of patients in this study had lesser events as compared to the frail population, which gives us an opportunity to intervene in this group of patients to improve outcomes. Currently frailty assessment is not done in all patients with heart failure. This study highlights the impact of frailty on clinical outcomes in heart failure patients and encourages including frailty as a routine assessment tool in all patients of heart failure.

5. Limitations

There are certain limitations to our study. It is a single center non-randomized study. This is initial study aimed to assess the utility of frailty measurement and effect of frailty on the outcomes. There could have been a selections bias in our study as we included the patients who came for hospital visits. There are more number of patients who are unable to visit hospitals due to various reasons; however, this method may help identify the patients at primary health care level due to its ease of use. The effect of intervention aimed at frailty needs to be studied in a larger randomized multicenter trial.

6. Conclusion

Prevalence of frailty in heart failure is seen commonly and may be present in younger age group in Indian population. Presence of frailty increases the risk of mortality and rehospitalization. Identification of frailty may help to guide management (reduce mortality/improve quality of life) which may be feasible at primary health care level in a developing country with limited resources.This study encourages to design a multinational study to compare prevalence in different populations and see effect of interventions.

Financial interests

Author contribution

Conception and design of Study: Gurbhej Singh, Rohit Tandon, Gurpreet Singh Wander, Bishav Mohan. Literature review: Gurbhej Singh, Bishav

Acknowledgement

Conflict of interest

None.

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