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Measuring Frailty in Heart Failure: A Community Perspective

Sheila M. McNallan, MPH^a, Alanna M. Chamberlain, PhD^a, Yariv Gerber, PhD^{a,c}, Mandeep Singh, MD^b, Robert L. Kane, MD^d, Susan A. Weston, MS^a, Shannon M. Dunlay, MD, MSc^b, Ruoxiang Jiang, BS^a, and Véronique L. Roger, MD, MPH^{a,b}

^aDepartment of Health Sciences Research, Mayo Clinic, Rochester Minnesota, USA

^bDivision of Cardiovascular Diseases in the Department of Internal Medicine, Mayo Clinic, Rochester Minnesota, USA

^cDepartment of Epidemiology and Preventative Medicine, School of Public Health, Tel Aviv University, Tel Aviv, Israel

^dDivision of Health Policy and Management, University of Minnesota School of Public Health, Minneapolis, MN

Abstract

Background—Frailty, an important prognostic indicator in heart failure (HF), may be defined as a biological phenotype or an accumulation of deficits. Each method has strengths and limitations, but their utility has never been evaluated in the same community HF cohort.

Methods—Southeastern Minnesota residents with HF were recruited from 2007–2011. Frailty according to the biological phenotype was defined as 3 or more of: weak grip strength, physical exhaustion, slowness, low activity and unintentional weight loss >10 lbs. in 1 year. Intermediate frailty was defined as 1–2. The deficit index was defined as the proportion of deficits present out of 32 deficits.

Results—Among 223 patients (mean age 71±14, 61% male), 21% were frail and 48% intermediate frail according to the biological phenotype. The deficit index ranged from 0.02–0.75, with a mean (SD) of 0.25 (0.13). Over a mean follow-up of 2.4 years, 63 patients died. After adjustment for age, sex and ejection fraction, patients categorized as frail by the biological phenotype had a 2-fold increased risk of death compared to those with no frailty, whereas a 0.1 unit increase in the deficit index was associated with a 44% increased risk of death. Both measures predicted death equally (C-statistics: 0.687 for biological phenotype and 0.700 for deficit index).

Conclusion—The deficit index and the biological phenotype equally predict mortality. As the biological phenotype is not routinely assessed clinically, the deficit index, which can be ascertained from medical records, is a feasible alternative to ascertain frailty.

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Corresponding author: Véronique L. Roger, MD, MPH, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, Fax: (507) 284-1516; Telephone: (507) 538-6916; roger.veronique@mayo.edu.

Disclosures

None.

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Introduction

Frailty is increasingly recognized as an important prognostic indicator in heart failure (HF).^{1–3} Frailty is more prevalent in HF than the general population^{1, 4, 5} and increases the risk of death and hospitalizations.^{1–3} However, methods to measure frailty vary widely throughout the literature.^{6–14} Some have conceptualized frailty as a biologic syndrome, characterized by a decline in overall function and loss of resistance to stressors.⁷ This biological frailty phenotype, referred to herein as the biological phenotype, is comprised of five physical indicators including low physical activity, weak grip strength, slow walking speed, exhaustion and unintentional weight loss. Alternatively, Rockwood and colleagues have defined frailty as the accumulation of deficits (impairments, disabilities and diseases).^{8, 15} Under this definition, frailty is measured by an index, termed the deficit index, which quantifies the cumulative burden of deficits.⁸

The biological phenotype has been shown to adversely impact outcomes.^{7, 16–19} However, despite its recognized prognostic value, it is not routinely assessed in clinical practice and cannot be obtained by review of the medical records. Conversely, the deficit index, which is also associated with adverse outcomes,^{15, 20} can be abstracted from the medical record and may be more feasible to ascertain frailty in large cohorts.

While each approach has conceptual strengths and limitations, few studies have evaluated them in the same cohort^{11, 15, 20–22} and to the best of our knowledge, these two methods have never been evaluated in the same community-based HF cohort. Thus, we aimed to evaluate how the biological phenotype and the deficit index predict mortality in a community cohort of HF patients.

Methods

Study Setting

This study was conducted in southeastern Minnesota, an area relatively isolated from other urban centers. Thus, as previously described, only a few providers deliver nearly all health care to the local residents.²³ The medical records from each provider are indexed via the Rochester Epidemiology Project, resulting in the linkage of records from nearly all sources of care.²³

Identification of Patients

Our HF case identification methods have been previously described.^{24–26} In brief, patients residing in Olmsted, Dodge and Fillmore County, MN with potential HF were identified by natural language processing of the electronic health record. The complete records of potential cases were reviewed to verify the HF diagnosis using the Framingham criteria.²⁷ We enrolled incident and prevalent HF cases, systolic and diastolic HF as well as inpatients and outpatients, capturing the complete spectrum of HF. Patients with HF were contacted about study participation. After consent, patients completed questionnaires and a hand grip test administered by a registered nurse at a median (25th–75th percentile) of 41(26–58) days post the index HF date. All aspects of the study were approved by the appropriate Institutional Review Boards.

Biological Phenotype

As described previously,²⁸ the biological frailty phenotype was ascertained using a modified version of the definition used in the Cardiovascular Health Study.⁷ Patients were classified as frail if they met three or more of the following criteria: weak grip strength,

physical exhaustion, slowness, low physical activity and unintentional weight loss. Intermediate frailty was defined as meeting one or two criteria.

Grip strength was measured using a Jamar dynamometer (kg) and was considered weak if the average of three tests was in the lowest 20% of the sex and BMI-adjusted community dwelling older adults.⁷ Physical exhaustion was assessed with a question from the Patient Health Questionnaire (PHQ-9)²⁹: “Over the past 2 weeks have you been bothered by feeling tired or having little energy?” Patients who answered ‘more than half the days’ or ‘nearly every day’ were classified as experiencing physical exhaustion.

The physical component score of the Short Form 12 (SF-12)³⁰ was used as an indicator of slowness and low physical activity, as was done in previous studies.^{18, 31} All study participants completed the SF-12, which includes a validated physical component scale.³⁰ The SF-12 physical component score ranges from 0 to 100 and higher scores indicate better physical health. A physical component score of 25 or less was used as an indicator of both low physical activity and slow walking speed. Unintentional weight loss was assessed with the following question: “In the past year, have you lost any weight unintentionally (without trying)?” A response of ‘10 pounds or more’ was classified as unintentional weight loss.

Deficit Index

The deficit index was based on 32 deficits obtained from the medical record and defined as the proportion of deficits present for each patient (Table 1). For example, if a patient exhibited 5 out of the 32 possible deficits, the frailty index for that patient would be 5/32 or 0.16. If a patient was missing less than 3 items, the patient was retained in the study and their denominator was adjusted accordingly. For example, the denominator for a patient that was missing 2 deficits would be 30. If that patient had 5 deficits, their index would be calculated as 5/30 or 0.17.

The first 14 items (activity of daily living questions) on the deficit index were collected from a patient-provided questionnaire completed 30 days before to 60 days after the HF date. The remaining items were manually collected by nurse abstractors at the time of HF diagnosis. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or a clinician diagnosis.³² Diabetes mellitus was defined according to the criteria of the American Diabetes Association.³³ Body mass index (BMI) (kg/m^2) was calculated using height at the time of HF diagnosis and weight from the last outpatient visit prior to HF diagnosis. The hemoglobin value closest to HF diagnosis (± 1 year) was used to define anemia (hemoglobin concentration <13.0 g/dL in men and <12.0 g/dL in women).³⁴ Clinicians’ diagnoses documented in the medical record were used to define depression, hyperlipidemia, myocardial infarction, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, cerebrovascular disease, dementia, peptic ulcer, hemiplegia/paraplegia, moderate/severe liver disease, renal disease, any malignancy, metastatic solid tumor, and rheumatologic disease.

The deficits selected for the deficit index were based on previously published criteria.⁸ The variables were associated with health status, the prevalence of the deficits generally increased with age and did not saturate too early (i.e. presbyopia), the deficits covered a range of systems, and we selected variables that could be measured serially on the same people. Furthermore, it is suggested that the index include at least 30–40 total deficits in order to obtain precise estimates,⁸ accordingly we included 32 deficits in our index.

Other patient characteristics

Clinician diagnosis was used to define atrial fibrillation. Smoking status was also obtained from the medical record. Estimated glomerular filtration rate (eGFR) was calculated with the

last serum creatinine value prior to the diagnosis of HF or the first value post HF diagnosis (± 1 year), using the Modification of Diet in Renal Disease Study (MDRD) equation.³⁵ Comorbidity was measured by the Charlson comorbidity index.³⁶

Left ventricular ejection fraction (EF) (%) was obtained using the closest value from an echocardiogram within 6 months prior to 2 months after HF date. Reduced EF was defined as $<50\%$ and preserved as EF $\geq 50\%$.³⁷

Mortality

Participants were followed through July 31, 2012 for death from any cause. Deaths were obtained from inpatient and outpatient medical records, as well as death certificates received from Olmsted County and the state of Minnesota. Cause of death was classified into cardiovascular or non-cardiovascular using the American Heart Association categories for cardiovascular death (International Classification of Diseases, Tenth Revision, codes I00-I99).³⁸

Statistical analysis

Baseline characteristics are presented as frequencies (percent) for categorical variables and mean (SD) for normally-distributed continuous variables and median (first quartile, third quartile) for continuous variables with a skewed distribution. Chi-square tests and linear regression were used to test differences between tertile of deficit index. The mean, standard deviation, median, 25th and 75th quartile and range of the deficit index was calculated overall and for each biological phenotype group. Linear regression was used to test the relationship between the deficit index and the biological phenotype groups.

Survival was analyzed with the Kaplan-Meier method according to frailty status and was compared by the log-rank test. The deficit index was categorized into tertiles (0.02–0.17, 0.18–0.30, 0.31–0.75), while the biological phenotype was categorized as frail, intermediate frail and not frail. Cox proportional hazards regression was used to examine the association between each measure of frailty and death, univariately and while controlling for age, sex and EF. The deficit index was analyzed as a continuous variable. As the deficit index could range from 0–1, we reported the hazard ratio per a 0.1 unit increase. The biological phenotype was analyzed as a 3-level variable (frail, intermediate frail and not frail). The proportional hazard assumption was tested using the scaled Schoenfeld residuals and was found to be valid.

The concordance (C-statistic), a measure of discrimination, was calculated for the unadjusted and fully-adjusted Cox regression models for each frailty measure, and 95% confidence intervals for the C-statistics were estimated using approximate jackknife methods.³⁹

Analyses were performed using SAS[®] statistical software, version 9.2 (SAS Institute Inc., Cary, NC).

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Results

Patient Characteristics and Frailty Status

A total of 223 HF patients completed the frailty assessments. The mean (SD) age was 71(14) years and 60% were men (Table 2). Fifty-four percent of patients had prevalent HF, with a median (first quartile, third quartile) duration of 1583 (734–3001) days, which did not differ across tertiles of deficit index ($p=0.187$). Furthermore, 51% of patients were hospitalized at index and this did not differ according to the deficit index ($p=0.321$). The burden of comorbidity was high with over 60% of patients having a Charlson comorbidity index of 3 or more.

Patients in the highest tertile of deficit index were more likely to be older, have hypertension, hyperlipidemia, prior MI, diabetes, COPD, depression, prevalent HF, anemia, Charlson Index ≥ 3 , higher EF, and were more likely to be prescribed a statin. Sex, smoking status, BMI, eGFR, history of atrial fibrillation, the proportion of patients with reduced EF (EF<50%), and the proportion of patients prescribed beta-blockers and angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ACE/ARBs) at index did not differ according to the deficit index.

Based on the biological phenotype, 46 (21%) patients were frail and 108 (48%) patients were intermediate frail. The deficit index ranged from 0.02–0.75 with a mean (SD) of 0.25 (0.13). The deficit index increased across the biological phenotype groups (Figure 1, $p<0.001$). The mean (SD) of the deficit index was 0.17 (0.08), 0.25 (0.11) and 0.37 (0.13) among the not frail, intermediate frail and frail biological phenotypes, respectively.

Frailty and Mortality

Over a mean (SD) follow-up of 2.4(1.2) years, 63 patients died. Frailty, according to the biological phenotype definition, was associated with an increased risk of death (Figure 2, $p=0.009$). The one-year mortality estimate was 17% for frail patients, 8% for intermediate frail and 6% for not frail patients. After adjustment for age, sex and ejection fraction, frail patients had a 2-fold increased risk of death (HR 2.04, 95% CI 0.99–4.18) compared to those who were not frail (Table 3), while intermediate frail patients did not have an increased risk of death (HR 1.04, 95% CI 0.53–2.03).

Frailty, according to the deficit index, was also associated with mortality (Figure 2, $p<0.001$). The one-year mortality estimate was 14% for patients in the highest tertile of the deficit index, 12% for those in the middle tertile and 2% for those in the lowest tertile. After adjustment, a 0.1 unit increase in the deficit index was associated with a 1.44-fold increased risk of death (HR 1.44, 95% CI 1.18–1.76). Furthermore, approximately 47% of the total deaths were related to cardiovascular causes and this did not differ according to tertile of the deficit index ($p=0.319$).

Each measure of frailty, when individually added to a model with age, sex, and ejection fraction, had good discrimination for predicting death (Table 3). The C-statistic was 0.687 for the model with the biological phenotype and 0.700 for the model with the deficit index. The models were not significantly different from each other when we calculated 95% confidence intervals for the difference between 2 models using bootstrapping methods (95% CI for difference: -0.08 – 0.08), thus indicating that both measures of frailty performed equally well in discriminating between those who would die and those who would survive.

Discussion

Among a community cohort of HF patients, two commonly used measures of frailty, the deficit index and biological phenotype, were significantly associated with one another. Frailty assessed by either method strongly predicted mortality. A distinct feature of the deficit index is the ability to use data extracted from medical records.

Frailty in HF

Among the community HF patients herein, 21% met the biological phenotype criteria for frailty and 48% met criteria for intermediate frailty. The mean (SD) of the deficit index was 0.25 (0.13). Collectively, our results support previous findings that indicate frailty is prevalent among HF patients.¹⁻⁴

Evaluation of Frailty Measurements

Few studies have evaluated the biological phenotype and the deficit index in the same cohort.^{11, 15, 20-22} Rockwood, et al, compared these two measures of frailty in the Canadian Study of Health and Aging. They found that the measures correlated moderately well with each other and that the deficit index predicted death more precisely than the biological phenotype.¹⁵ The Cardiovascular Health Study also found that the deficit index was associated with the biological phenotype and predicted death more precisely than the biological phenotype.²⁰ Finally, in Hong Kong, a cohort study of 4000 men and women aged 65 and older found that the deficit index was comparable with the biological phenotype in predicting mortality and physical limitations.²²

Our results, in conjunction with the previously mentioned studies, provide evidence that the biological phenotype and deficit index are correlated and equally predict mortality. Although the biological phenotype is widely used and validated,⁷ the components are not routinely assessed clinically and it is not feasible to measure all the components in a large cohort of patients. Therefore, since the deficits can be extracted from the medical records and the index can be easily constructed,⁸ we propose using the deficit index to measure frailty. In fact, a distinct advantage of the deficit index is that it can be modified based on the data available as long as a minimum number (30-40) of deficits are included.⁸ Therefore, other studies can create their own deficit index if not all the variables that we used are available to them. This unique feature makes the deficit index easy to implement.

Limitations and Strengths

Some limitations should be acknowledged. First, based on available data in our cohort, we modified the biological phenotype definition of frailty from the Cardiovascular Health Study,⁷ as walking speed was not uniformly available. However, physical health scores such as the SF-12 have been shown to be associated with walking speed and physical activity and have been used as surrogates in previous studies.^{18, 31} Second, we had a relatively small sample size. Finally, while southeastern Minnesota is becoming increasingly diverse, our results need replication in communities of different racial and ethnic composition.

Our study also has notable strengths. This was a community-based study including inpatients and outpatients, systolic and diastolic HF as well as incident and prevalent cases, capturing the complete spectrum of HF, which optimizes clinical relevance. Each HF diagnosis was validated using rigorous methods. Furthermore, our study is the first to evaluate the utility of the biological phenotype and the deficit index in the same cohort of HF patients.

Clinical Implications, Future Directions and Conclusions

Our data indicate that frailty, measured by either the deficit index or the biological phenotype, is associated with an increased risk of mortality among community HF patients. Frailty is potentially modifiable, thus if these patients who are at highest risk for death could be identified, they could be targeted for interventions and their outcomes could be improved. As the components of the biological phenotype are not routinely measured in the clinical setting, we suggest the deficit index as a viable method to measure frailty clinically because it can be easily calculated and is comprised of information already in the medical record. Evidence suggests that exercise-based interventions may be effective among frail patients^{40, 41} and have also been shown to be efficacious and safe in HF patients.⁴² Thus, incorporating the assessment of frailty into the clinical evaluation of HF patients could lead to improved outcomes; however this requires confirmation in future studies. Furthermore, future studies should evaluate other outcomes of frailty, such as healthcare utilization.

In conclusion, frailty is prevalent among community HF patients and is recognized as an important prognostic indicator. Our results indicate that the deficit index may be used as an alternative approach to measure frailty rather than the biological phenotype. The deficit index is straightforward to implement because it can be created from data obtained from the medical records. Further, studies can adapt their own deficit index if not all the variables that we included are available to them. Thus, the deficit index offers a convenient option for measuring frailty, especially in large cohorts.

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Figure 1.
Boxplot of the Deficit Index by the Biological Phenotype

Figure 2.

Figure 2a. Survival after heart failure by biological frailty phenotype group

Figure 2b. Survival after heart failure by deficit index tertile

Table I

Frailty Definitions

Biological Frailty Phenotype	
Unintentional weight loss >10 lbs in 1 year	Self-reported
Physical exhaustion	Self-reported from Patient Health Questionnaire (PHQ-9)
Weak grip strength	Predefined cut-points
Slowness	Short Form 12 physical function score 25
Weakness	Short Form 12 physical function score 25
Deficit Index	
1. Need help preparing meals	Yes=1, No=0
2. Need help feeding yourself	Yes=1, No=0
3. Need help dressing yourself	Yes=1, No=0
4. Need help using the toilet	Yes=1, No=0
5. Need help with housekeeping	Yes=1, No=0
6. Need help climbing stairs	Yes=1, No=0
7. Need help bathing	Yes=1, No=0
8. Need help walking	Yes=1, No=0
9. Need help using transportation	Yes=1, No=0
10. Need help getting in and out of bed	Yes=1, No=0
11. Need help managing medications	Yes=1, No=0
12. Depend on assistive devices (walker, cane, etc) or other people to perform activities of daily life	Yes=1, No=0
13. Dependent on a device for normal breathing	Yes=1, No=0
14. Climb 2 flights of stairs without rest	No, can't do at all=1 Yes, with difficulty=0.5 Yes with no difficulty=0
15. Myocardial infarction	Yes=1, No=0
16. Diabetes	Yes=1, No=0
17. Peripheral Vascular Disease	Yes=1, No=0
18. Cerebrovascular Disease	Yes=1, No=0
19. Dementia	Yes=1, No=0
20. Chronic obstructive pulmonary disease	Yes=1, No=0
21. Peptic ulcer	Yes=1, No=0
22. Hemiplegia/Paraplegia	Yes=1, No=0
23. Renal disease	Yes=1, No=0
24. Moderate/severe liver disease	Yes=1, No=0
25. Any malignancy	Yes=1, No=0
26. Metastatic solid tumor	Yes=1, No=0
27. Rheumatologic disease	Yes=1, No=0
28. Hypertension	Yes=1, No=0
29. Hyperlipidemia	Yes=1, No=0
30. Body mass index	Underweight or obese=1, overweight=0.5

	normal=0
31. Depression	Yes=1, No=0
32. Anemia	Yes=1, No=0

Table II

Baseline characteristics overall and by tertile of Deficit Index*

	N Missing	Total (N=223)	Tertile 1	Tertile 2	Tertile 3	P for trend
Age, mean $\pm$ SD, y	-	71.1 $\pm$ 13.9	66.9 $\pm$ 13.5	71.7 $\pm$ 13.5	74.8 $\pm$ 13.7	0.001
Men	-	135 (60.5)	48 (64.9)	46 (59.7)	41 (56.9)	0.328
Cardiovascular risk factors						
Hypertension	-	200 (89.7)	56 (75.7)	73 (94.8)	71 (98.6)	<.001
Current or former smoker	-	128 (57.4)	41 (55.4)	41 (53.2)	46 (63.9)	0.305
Diabetes mellitus	-	91 (40.8)	10 (13.5)	38 (49.4)	43 (59.7)	<.001
Hyperlipidemia	1	180 (81.1)	44 (59.5)	67 (87.0)	69 (97.2)	<.001
BMI, median (Q1–Q3)		30.5 (26–37)	29.7(26–35)	31.3(27–37)	30.9 (26–40)	0.165
Comorbidities						
Prior MI	1	60 (27.0)	6 (8.1)	24 (31.2)	30 (42.3)	<.001
Chronic obstructive pulmonary disease	-	49 (22.0)	1 (1.4)	17 (22.1)	31 (43.1)	<.001
Atrial fibrillation/flutter	-	135 (60.5)	43 (58.1)	50 (64.9)	42 (58.3)	0.972
Depression	1	88 (39.6)	15 (20.3)	27 (35.5)	46 (63.9)	<.001
Estimated glomerular filtration rate, median (Q1–Q3), mL/min per 1.73 m ²	40	58.3 (44–72)	66.2(49–72)	58.3(47–72)	51.7(40–72)	0.175
Anemia	2	94 (42.5)	19 (25.7)	33 (43.4)	42 (59.2)	<.001
Comorbidity index	3	137 (61.7)	14 (18.9)	58 (75.3)	65 (91.5)	<.001
HF characteristics and severity indices						
Prevalent HF		121 (54.3)	23 (31.1)	44 (57.1)	54 (75.0)	<.001
EF, mean $\pm$ SD	5	44.1 $\pm$ 16.6	41.2 (17.2)	43.9 (15.7)	47.4 (16.6)	0.027
Reduced EF (EF<50)	5	124(56.9)	46 (62.2)	45 (59.2)	33 (48.5)	0.105
Medications						
ACE/ARBs		148 (66.4)	52 (70.3)	52 (67.5)	44 (61.1)	0.244
Beta Blockers		183 (82.1)	56 (75.7)	65 (84.4)	62 (86.1)	0.100
Statins		131 (58.7)	30 (40.5)	48 (62.3)	53 (73.6)	<.0001

* All values are N (%) unless otherwise noted.

SD=standard deviation; Q1=first quartile; Q3=third quartile; EF=ejection fraction; ACE=angiotensin converting enzyme inhibitors; ARB=angiotensin II receptor blockers

Table III

Hazard ratios (95 CI) and C-statistics (95 CI) for death and hospitalizations

	Unadjusted Model	Adjusted Model*
<i>Death</i>		
Frailty Phenotype		
Not frail	1 (reference)	1 (reference)
Intermediate frail	1.41 (0.74–2.71)	1.04 (0.53–2.03)
Frail	2.48 (1.22–5.07), p=0.01 [†]	2.04 (0.99–4.18), p=0.05 [†]
C-statistic	0.599 (0.524–0.668)	0.687 (0.624–0.774)
Deficit Index		
0.1 unit increase	1.50 (1.25–1.80), p<0.001	1.44 (1.18–1.76), p<0.001
C-statistic	0.670 (0.607–0.728)	0.700 (0.642–0.782)

* Adjusted for age, sex and ejection fraction

[†] p for trend