ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 3427–3437
Published online 21 September 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12827

REVIEW

Frailty and the risk of all-cause mortality and hospitalization in chronic heart failure: a meta-analysis

Izabella Uchmanowicz[1]*, Christopher S. Lee[2], Cristiana Vitale[3], Stanisław Manulik[1], Quin E. Denfeld[4], Bartosz Uchmanowicz[1], Joanna Rosińczuk[1], Marcin Drozd[1,5], Joanna Jaroch[1] and Ewa A. Jankowska[1,5]

[1]*Department of Clinical Nursing, Faculty of Health Sciences, Wroclaw Medical University, Bartla 5, Wroclaw, 51-618, Poland;* [2]*William F. Connell School of Nursing, Boston College, Boston, MA, USA;* [3]*Centre for Clinical and Basic Research, IRCCS San Raffaele Pisana, Rome, Italy;* [4]*Oregon Health and Science University School of Nursing, Portland, OR, USA;* [5]*Centre for Heart Diseases, Wroclaw Medical University, Wroclaw, Poland*

Abstract

To estimate the risk of all-cause mortality and hospitalization in frail patients with chronic heart failure (HF), a systematic search and meta-analysis was carried out to identify all prospective cohort studies conducted among adults with HF where frailty was quantified and related to the primary endpoints of all-cause mortality and/or hospitalization. Twenty-nine studies reporting the link between frailty and all-cause mortality in 18 757 patients were available for the meta-analysis, along with 11 studies, with 13 525 patients, reporting the association between frailty and hospitalization. Frailty was a predictor of all-cause mortality and hospitalization with summary hazard ratios (HRs) of 1.48 [95% confidence interval (CI): 1.31–1.65, $P < 0.001$] and 1.40 (95% CI: 1.27–1.54, $P < 0.001$), respectively. Summary HRs for all-cause mortality among frail inpatients undergoing ventricular assist device implantation, inpatients hospitalized for HF, and outpatients were 1.46 (95% CI: 1.18–1.73, $P < 0.001$), 1.58 (95% CI: 0.94–2.22, P = not significant), and 1.53 (95% CI: 1.28–1.78, $P < 0.001$), respectively. Summary HRs for all-cause mortality and frailty based on Fried's phenotype were 1.48 (95% CI: 1.03–1.93, $P < 0.001$) and 1.42 (95% CI: 1.05–1.79, $P < 0.001$) for inpatients and outpatients, respectively, and based on other frailty measures were 1.42 (95% CI: 1.12–1.72, $P < 0.001$) and 1.60 (95% CI: 1.43–1.77, $P < 0.001$) for inpatients and outpatients, respectively. Across clinical contexts, frailty in chronic HF is associated with an average of 48% and 40% increase in the hazard of all-cause mortality and hospitalization, respectively. The relationship between frailty and all-cause mortality is similar across clinical settings and comparing measurement using Fried's phenotype or other measures.

Keywords Heart failure; Frailty; Fried's phenotype; Mortality; Hospitalization; Meta-analysis

Received: 3 January 2020; Revised: 10 May 2020; Accepted: 21 May 2020
**Correspondence to: Izabella Uchmanowicz, Department of Clinical Nursing, Faculty of Health Sciences, Wrocław Medical University, Bartla 5, Wroclaw 51-618, Poland. Tel: +48 71 348 42 10; Fax: +48 71 345 93 24.*
Email: izabella.uchmanowicz@umed.wroc.pl

Introduction

Chronic heart failure (HF), a leading cause of morbidity and mortality worldwide, contributes to a substantial deterioration of quality of life for individual patients and constitutes a huge economic burden for healthcare systems.[1] High treatment costs justify optimization of risk assessments and therapeutic decisions made for patients with chronic HF.[2] Hence, inquiry into novel prognostic factors in HF beyond classic diagnostic tests, such as frailty, has become more common. Although it does not have a uniform and widely recognized definition, frailty is generally considered an increased vulnerability to external stressors, which results from multi-organ dysfunction.[3–7] Current evidence suggests that the pathophysiological hallmarks of frailty are oxidative stress and chronic inflammation, both of which are also common in chronic HF[8,9]; however, the pathophysiological pathways of frailty in HF have yet to be elucidated. Moreover, the relationship between frailty and HF is complex, in part due to the overlap between frailty, ageing, and co-morbidity with HF.[10–13] Given that frailty is strongly linked to adverse outcomes, such as mortality, hospitalization, and institutionalization,[14–17] among older adults in general, it is worthwhile to examine how frailty impacts outcomes in HF.

Up to 76% of patients with chronic HF may be frail, depending on the setting.[18] Frailty was also shown to be associated with an increased risk of all-cause mortality and hospitalization in chronic HF.[19–22] However, published data on the relationship between frailty and clinical outcomes are inconsistent and frequently inconclusive.[23–33] Moreover, the effect sizes reported in relation to frailty and clinical outcomes are highly variable with hazard ratios (HRs) for all-cause mortality ranging between 1.11[34] and 17.41.[35] Heterogeneity across studies of frailty and clinical outcomes is undoubtedly multifactorial but at least in part constitutes a function of different clinical settings and the lack of an operational definition and measure of frailty.[36] The lack of the standardization was also reflected in a few recently published meta-analyses examining the effects of frailty on all-cause mortality and hospitalization risk; depending on the authors' approach to source study selection, the results differed, especially in terms of the magnitude of the effect of frailty on outcomes.[19–22] Given significant variation in both setting and the conceptualization and measurement of frailty in HF, and a constant influx of new evidence, the purpose of this meta-analysis was to quantify the relationship between frailty and clinical outcomes (all-cause mortality and hospitalization) among adults with HF. In addition, we examined the effect of clinical setting (inpatient for HF exacerbation, inpatient for left ventricular assist device implantation, and outpatient) and selection of frailty measure (physical and multidimensional) on the relationship between frailty and clinical outcomes.

Methods

This study was carried out in strict accordance with the recommendations in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Search strategy

A systematic search of the PubMed, Scopus, and Google Scholar using the Cochrane guidelines to conduct the meta-analysis following PRISMA statement was used (Appendix 1). All published studies that investigated the relationship between frailty and outcomes in patients with HF and used the terms 'frailty' AND 'heart failure' were identified. The search limits were defined as 'English' (language) and 'the beginning of a given database through to 31 May 2019' (publication date).

Eligibility criteria

We included case–control, prospective, or retrospective studies conducted in humans with a definite diagnosis of HF and frailty quantified and related to the primary endpoints of all-cause mortality and/or hospitalization. If multiple papers came out of the same cohort, those that reported on the largest sample size were chosen. We excluded studies on patients with acute HF, without well-specified frailty definition/measure, with composite primary endpoints, and without HR values for frailty effect or numbers of frail and non-frail patients who achieved/not achieved the primary endpoint, as well as reviews, case reports, and the studies we were unable to extract for full-text review.

Review process

During the first stage, all records were identified from searches of the electronic databases, and duplicates were removed. During the second stage, four researchers (IU SM, BU, JJ) independently screened the titles and abstracts to identify the potentially eligible studies. During the third stage, potentially eligible studies were selected for full-text review (*Figure 1*). The disagreement was resolved by mutual consent after discussion.

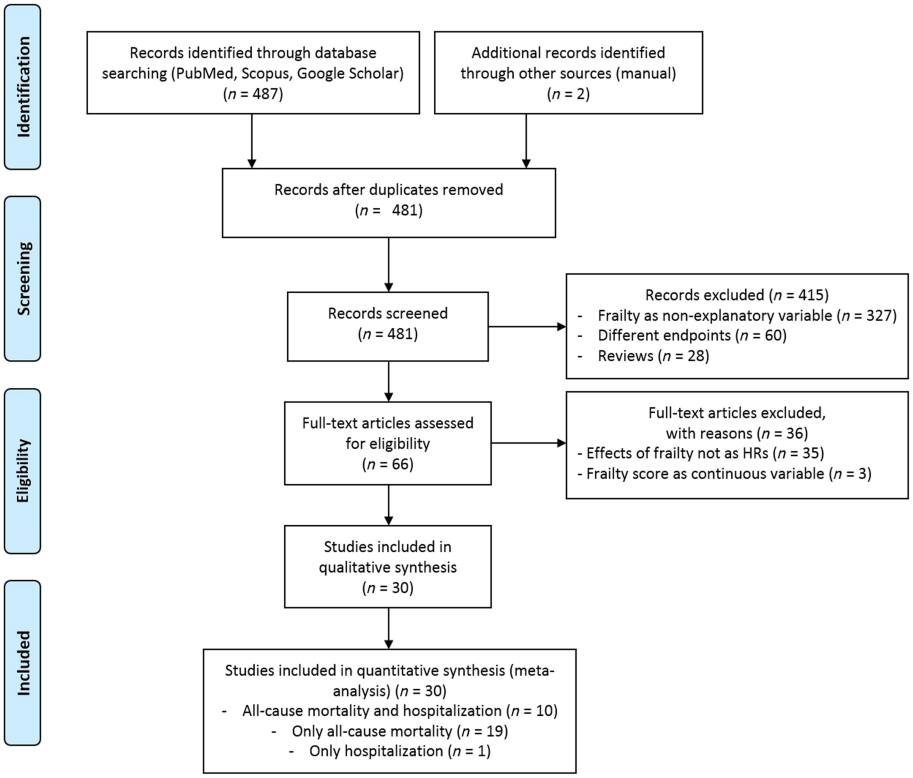
Data extraction

The characteristics recorded for each study included authors' names, publication year, country of origin, study design, setting (outpatients, inpatients hospitalized due to exacerbation of chronic HF, and inpatients undergoing ventricular assist device implantation), sample size, numbers of frail and non-frail patients, age of the patients, proportions of women and men, instrument used to diagnose frailty, duration of follow-up, primary endpoint (all-cause mortality and/or HR-related hospitalization), and HR for the frailty effect or numbers of frail and non-frail patients who achieved/not achieved the primary endpoint.

Data analysis

All meta-analytic procedures were conducted with StataMP v. 15 (College Station, Texas, USA). Random-effects meta-analyses were used to quantify pooled HRs and 95% confidence intervals (CIs) because this approach takes into account both within-study and between-study variance. Studies were weighted using the DerSimonian and Laird method. Variation in HRs across studies attributed to heterogeneity was quantified using Q and I^2. Predictive intervals were calculated to present the expected range of HRs related

Figure 1 Flow diagram of the study (PRISMA).



to frailty that may be observed in similar studies in the future. Summary HRs were compared by clinical setting (i.e. outpatients vs. inpatients hospitalized due to exacerbation of chronic HF vs. inpatients undergoing ventricular assist device implantation) and frailty measurement (i.e. Fried's phenotype-based scales vs. other instruments) using a random-effects test for heterogeneity between subgroups. Finally, risk of publication and small sample bias were evaluated using funnel plots and Egger's tests, respectively.

Results

Study characteristics

The flow chart of the literature search is presented in *Figure 1*. Out of 66 full-text articles reviewed, 36 were excluded as they did not report the effects of frailty as HRs (n = 35) and/or analysed the effect of frailty as a continuous rather than a dichotomous measure (n = 3). Eventually, 29 studies analysing the link between frailty and all-cause mortality, including a total of 18 757 patients with chronic HF, were available for the meta-analysis, along with 11 studies, with a total of 13 525 patients, analysing the association between frailty and hospitalization risk. All but three studies[24,28,33] analysing the link between frailty and all-cause mortality and all studies on the association between frailty and hospitalization risk were prospective cohort studies (*Table 1*). Based on the percentages of satisfied STROBE criteria,[53] the quality of all studies was assessed as high or borderline high (Appendix 2).

Influence of frailty on all-cause mortality

The studies analysing the link between frailty and all-cause mortality were published between 2005 and 2018. The vast majority of those studies were conducted in Europe (n = 10) or the USA (n = 11). Among the 29 studies, 11 involved outpatients,[30,35,37–40,42–45,47–49] 5 involved patients hospitalized due to exacerbation of chronic HF,[27,32,34,45,49] and 13 involved patients who underwent scheduled implantation of a ventricular assist device.[23–26,28,29,33,41,46,51,52] The sample sizes in the included studies ranged between 40[30] and 9964.[43] The mean age of the study patients varied between 48.4[26] and 85.2 years[48] and the proportions of women between 11.1%[23] and 62%.[44] In 13 studies, frailty was determined based on Fried's criteria[26,29–32,34,40,43,45–48,51] and in 16 with other frailty scales or indices.[23–25,27,28,33,35,37–39,41,42,44,49,50,52] The duration of follow-up in prospective cohort studies ranged between 30 days[47,50,52] and 12 years.[37] The proportions of included frail patients varied from

Table 1 Characteristics of studies included in the meta-analysis

Authors (year)	Country	Design	Setting	Patients (*n*)	Age (years)	Women (%)	Frail (%)	Frailty measure(s)	Follow-up time	HR (95% CI)
All-cause mortality										

AFN, Acute Frailty Network; BI, Barthel Index; CFS, Clinical Frailty Scale; CI, confidence interval; CSHA, Canadian Study of Health and Aging; DI, Deficit Index; DFI, Derby Frailty Index; FFI, Fried Frailty Index; FFP, Fried frailty phenotype; FSS, frailty staging system; GDS, Geriatric Depression Scale; HF, heart failure; HR, hazard ratio; I, patients hospitalized due to exacerbation of chronic HF; n/a, not applicable; O, outpatients; OARSS, Older Americans Resources and Services Scale; P, prospective study; PT, Pfeiffer Test; R, retrospective study; SD, standard deviation; SHARE-FI, Survey of Health, Aging and Retirement in Europe–Frailty Instrument; V, patients hospitalized for implantation of a ventricular assist device; VMS, Veiligheids Management System frailty score.

9.2%[24] to 76.0%,[45] with the overall percentage of frail persons equals 45.1% (*Table 1*).

The HRs for all-cause mortality in frail patients are shown in *Figure 2*. Across studies, the summary HR for all-cause mortality was 1.48 (95% CI: 1.31–1.65), $P < 0.001$. There was significant [Q = 61.4 (d.f. = 28), $P < 0.001$] and considerable heterogeneity (I^2 = 54.4%) in HRs across studies. The expected range of HRs that may be observed in similar studies in the future was approximately 1–2. The funnel plot was symmetric around the summary HR at all levels of variance indicating limited publication bias. Egger's test was positive for bias from small sample studies favouring higher HRs (bias = 1.02 ± 0.29, t = 3.54, P = 0.002).

The HRs for all-cause mortality in frail patients by clinical setting are shown in *Figure 3*. The summary HR for all-cause mortality in 13 studies conducted in 3817 patients hospitalized for implantation of a ventricular assist device was 1.46 (95% CI: 1.18–1.73, $P < 0.001$). The summary HR for all-cause mortality determined for five studies including 1318 patients hospitalized due to the exacerbation of chronic HF, 59.0% of whom were frail, was 1.58 (95% CI: 0.94–2.22, P = not significant). The summary HR for all-cause mortality in 11 studies conducted in 13 622 outpatients, 32.3% of whom were frail, was 1.53 (95% CI: 1.28–1.78, $P < 0.001$). There was significant [Q = 29.2 (d.f. = 10), P = 0.001] and considerable heterogeneity (I^2 = 64.8%) among HRs of outpatient studies; there was no significant heterogeneity in HRs in other settings. There was no statistical difference in summary HRs across clinical settings (P = 0.790).

The HRs for all-cause mortality in frail patients by frailty measurement and setting are shown in *Figure 4*. The summary HRs for all-cause mortality determined in 13 studies

Figure 2 Forest plot presenting risk of all-cause mortality in frail chronic heart failure patients as compared with non-frail chronic heart failure patients. CI, confidence interval; HR, hazard ratio.

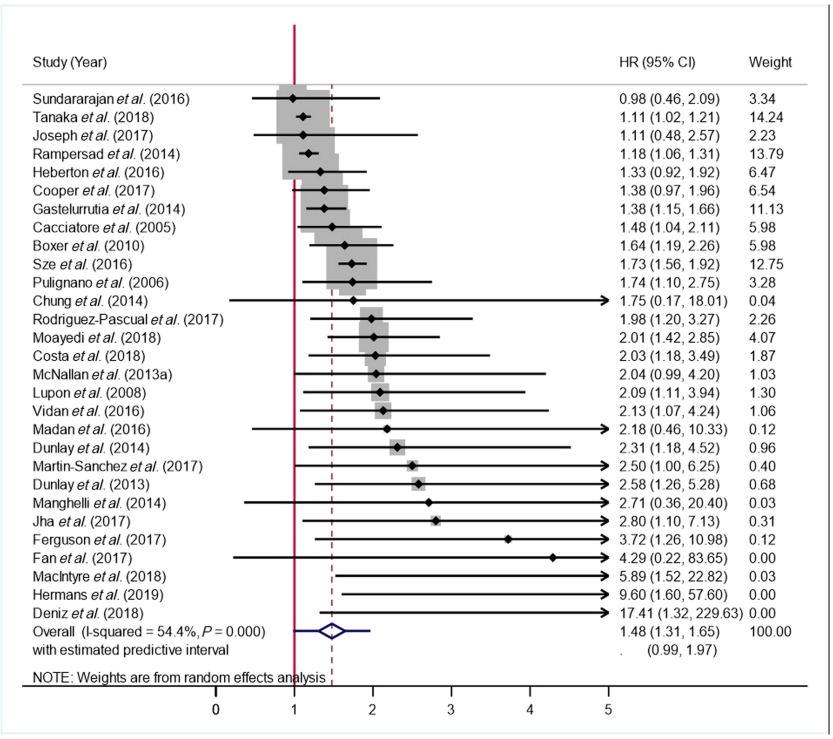
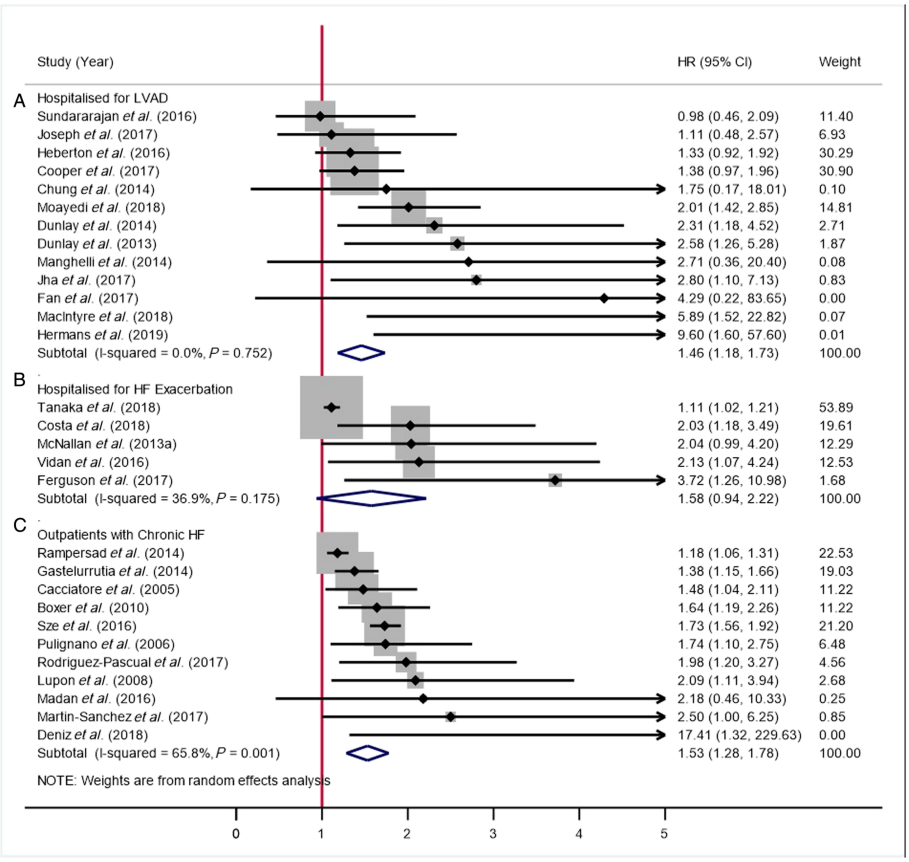


Figure 3 Forest plots comparing risk of all-cause mortality in chronic heart failure (HF) between frail and non-frail patients: (A) in inpatients with chronic HF hospitalized for implantation of a ventricular assist device, (B) in inpatients hospitalized due to exacerbation of chronic HF, and (C) in outpatients with chronic HF. CI, confidence interval; HR, hazard ratio; LVAD, left ventricular assist device.



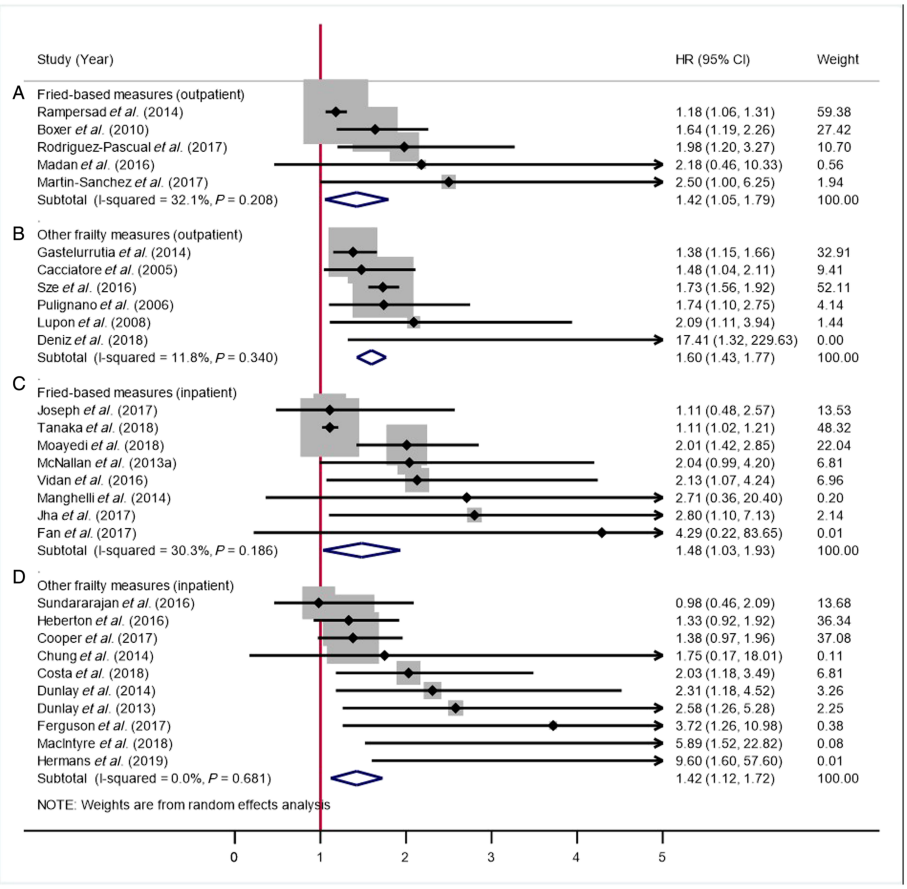
using Fried's criteria-based measures to identify frailty (12 630 patients) varied from 1.42 (95% CI: 1.05–1.97, $P < 0.001$) in outpatient settings to 1.48 (95% CI: 1.03–1.93, $P < 0.001$) in inpatient settings. The summary HR for all-cause mortality in 16 studies that used other frailty measures (6127 patients) varied from 1.60 (95% CI: 1.43–1.77, $P < 0.001$) in outpatient settings to 1.42 (95% CI: 1.12–1.72, $P < 0.001$) in inpatient settings. There was no significant heterogeneity in HRs within each group of studies based on frailty measure and setting. There also was no statistical difference in summary HRs by the type of frailty measure ($P = 0.902$).

Influence of frailty on heart failure-related hospitalization risk

The studies analysing the association between frailty and HF-related hospitalization risk were published between 2006 and 2017. Only two of those studies[27,43] were conducted outside Europe or the USA. Among the 11 studies, six involved outpatients,[30,38,39,42,43,48] two involved patients hospitalized due to exacerbation of chronic HF,[27,43] one involved both inpatients and outpatients,[54] and two involved patients who underwent scheduled implantation of a ventricular assist device.[25,41] The sample sizes in the included studies ranged between 40[30] and 9964.[43] Mean age of the study patients varied between 65[25,41] and 85.2 years[48] and the proportions of women between 18%[25,41] and 58%.[30] In five studies, frailty was identified based on Fried's phenotype[30,43,45,48,54] and in another six using other frailty measures.[27,38,39,41,42] The duration of follow-up ranged between 12 months[27,38,39,43,45,48] and 3.6 years.[42] The percentages of participating patients diagnosed with frailty ranged from 27.8%[43] to 76.0%,[45] with the overall proportion of frail patients amounting to 52.5% (*Table 1*).

The HRs for HF-related hospitalization in frail patients are shown in *Figure 5*. The summary HR for frailty and HF-related hospitalization was 1.40 (95% CI: 1.27–1.54, $P < 0.001$). HRs reported across studies were homogeneous [$Q = 11.3$ (d.f. = 10), $P = 0.339$; $I^2 = 11.1\%$]. The funnel plot was symmetric around the summary HR at all levels of

Figure 4 Forest plots comparing risk of all-cause mortality in chronic heart failure between frail and non-frail patients: (A) in outpatients in whom frailty was diagnosed based on Fried-based measures, (B) in outpatients in whom frailty was diagnosed using other measures, (C) in inpatients in whom frailty was diagnosed based on Fried-based measures, and (D) in inpatients in whom frailty was diagnosed using other measures. CI, confidence interval; HR, hazard ratio.



variance, indicating limited publication bias. Egger's test was positive for bias from small sample studies favouring higher HRs (bias = 1.16 ± 0.30, t = 3.84, P = 0.004).

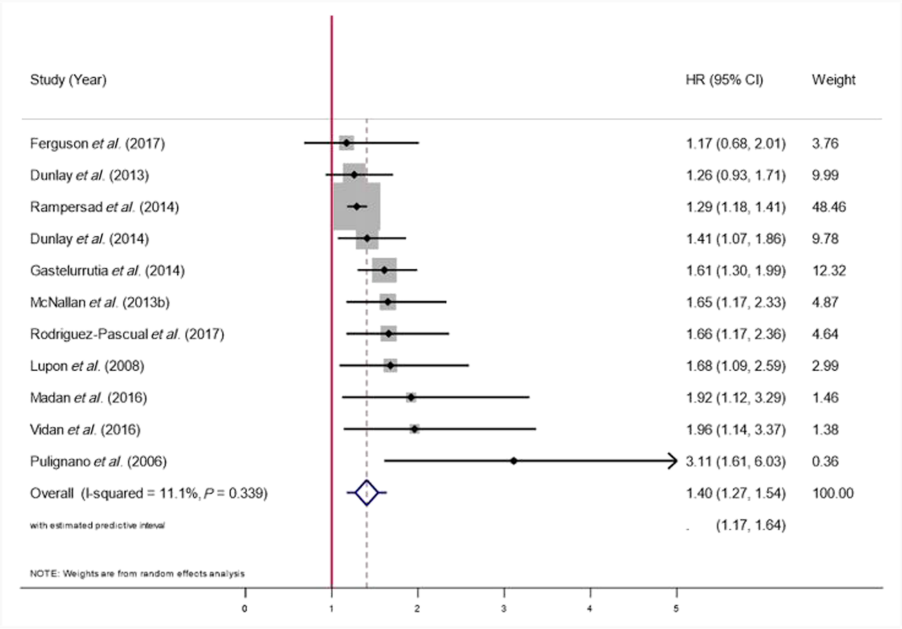
Discussion

This meta-analysis demonstrated that frailty was a significant predictor of all-cause mortality (29 studies with 18 757 patients, among them 45.1% frail) and HF-related hospitalization (11 studies with 13 525 patients, among them 52.5% frail). These findings are consistent with both the evidence from most source studies (20/29 studies on all-cause mortality and 9/11 studies on HR-related hospitalization) and the results of recently published meta-analyses.[19–21]

The above-mentioned observations are not surprising, as HF and frailty share some underlying mechanisms, symptoms, and manifestations, among them are chronic inflammation and oxidative stress,[8,9] sarcopenia and skeletal muscle weakness, and impaired cardiorespiratory and physical performance,[55] and it has been even postulated that both HF increases the likelihood of becoming frail and frailty increases the risk of HF.[20] The high prevalence of frailty in HF documented in our present meta-analysis demonstrates that there is commonality in the mechanisms and manifestations of both conditions. Further, the fact that frail HF patients had worse outcomes across settings and measures strengthens this commonality and shows that regardless of setting or measure, there is something going on physiologically between the two conditions.

Noticeably, the size of frailty effect on either all-cause mortality or hospitalization hazard varied considerably, whether in the source studies or previously published systematic reviews and meta-analyses. The HRs for all-cause mortality in the source studies included in our meta-analysis ranged between 0.98[33] and 17.41,[35] and those for HF-related hospitalization varied between 1.17[27] and 3.11,[38] with the overall HRs for all-cause mortality and hospitalization equal 1.66 (95% CI: 1.45–1.90) and 1.51 (95% CI: 1.34–

Figure 5 Forest plot presenting the risk of heart failure-related hospitalization in chronic heart failure between frail and non-frail patients. CI, confidence interval; HR, hazard ratio.



1.70), respectively. Also, previous meta-analyses quantifying the link between frailty and outcomes in HF produced variable results, with overall HRs of 1.44–1.70 and 1.31–1.56 for all-cause mortality and hospitalization, respectively.[19–21] These results are somehow different from those documented in our present meta-analysis, despite the substantial overlap in the included source studies. Our findings suggest that this variance might originate from two sources: (i) characteristics of the study patients/setting and (ii) considered frailty measure.

Our present meta-analysis included three groups of patients: outpatients, inpatients hospitalized due to exacerbation of chronic HF, and patients hospitalized for implantation of a ventricular assist device. The HRs for all-cause mortality in these three groups were similar, 1.53 (95% CI: 1.28–1.78), 1.58 (95% CI: 0.94–2.22), and 1.46 (95% CI: 1.18–1.73), respectively. Exacerbation of HF or deterioration of heart function requiring implantation of a ventricular assist device is with no doubt associated with increased mortality risk, in whether frail or non-frail patients. However, our study demonstrated that frailty may be associated with a similar mortality risk also in an outpatient setting. The results of previous meta-analyses quantifying the hazard of all-cause mortality in frail patients with HF are not so straightforward, as only two of them included homogenous groups of patients. Tse *et al*.[19] analysed short-term and long-term mortality rates solely in frail patients hospitalized for ventricular assist device implantation; frailty was not associated with short-term mortality in three eligible studies (HR = 1.22, 95% CI: 0.66–2.26) but turned out to be a significant predictor of long-term mortality in another seven studies (HR = 1.44, 95% CI: 1.15–1.80). The set of 20 studies analysed by Zhang *et al*.[22] included 11 that examined frail patients undergoing ventricular assist device implantation; HR for all-cause mortality (during short, long, or unspecified follow-up) was estimated at 1.62 (95% CI: 1.36–1.93). This value did not differ substantially from all-cause mortality hazard in all 20 source studies, some of them including outpatients (HR = 1.59, 95% CI: 1.39–1.82).

In one of recently published meta-analyses, Wang *et al*.[20] demonstrated high prevalence of frailty among older (≥65 years) patients with HF and showed that elderly persons with HF and frailty had poorer prognosis than non-frail HF patients. Our present meta-analysis, including the results for persons with mean ages from 48.4 to 85.2 years, adds to this evidence, demonstrating that frailty can affect HF patients across the lifespan.

The most important source of discrepancies between the results of studies quantifying the risk of all-cause mortality in frail patients might be the instrument used to detect frailty. However, in our present study, the overall HRs for all-cause mortality in studies that used Fried's criteria to identify frailty were statistically similar to the HRs from 16 studies that employed other frailty measures or indices, whether in outpatients or inpatients. Previously, Yang *et al*.[21] demonstrated substantial differences between the HRs for all-cause mortality in HF documented in five studies that used Fried's phenotype to identify frailty and all eight studies

included in their meta-analysis (1.80 vs. 1.54), with the use of Fried's criteria seemingly associated with an overestimation of all-cause mortality hazard. Yang *et al.*[21] explained this phenomenon as a consequence of overlapping clinical and pathophysiological characteristics of Fried's phenotype (such as unintentional weight loss and weakness) and cardiac cachexia in advanced chronic HF, both associated with a poor prognosis. However, another reason behind the discrepancy between the results published by Yang *et al.*[21] and our findings might be low power of the meta-analysis conducted by those authors, who considered only eight studies, among them only three in which frailty was diagnosed using a non-Fried's measure.

Nevertheless, the results mentioned previously highlight an important problem of frailty research, namely, the lack of an operational definition of frailty. According to literature, the most commonly used frailty measures, such as Frailty Index, FRAIL scale, Tilburg Frailty Index, and Clinical Frailty Scale, provide similar sensitivity in the identification of frail persons in geriatric population,[56] and the Frailty Index, Fried's phenotype, FRAIL scale, and the Hubbard modified frailty score were demonstrated to perform similarly in the prediction of death and physical limitations in the elderly.[57] Nevertheless, frailty assessment in the group of patients with HF, which according to literature may include even 76% of frail persons,[21] requires standardization and unification to ensure that all subjects are screened for the same condition and to facilitate comparisons between studies and big data research. Currently, the most commonly used frailty measure is Fried's phenotypic model with five domains: grip strength, exhaustion, unintended weight loss, slow gait speed, and low physical activity[3]; also, in the present meta-analysis, nearly half of the source studies used Fried's phenotype-derived instruments to detect frailty. However, we cannot state whether Fried's model may become a universal frailty measure in HF unless its predictive value in terms of all-cause mortality, hospitalization, and perhaps also other outcome measures (e.g. institutionalization) is verified in large studies conducted in various settings and involving HF patients with different risk factor profiles. Furthermore, it needs to be stressed that based on these published studies, both approaches to measure frailty (based solely on physical components or physical, psychological, and social components) seem to be equally valid as they demonstrate worse clinical outcomes in frail persons. Very recently, a multidimensional frailty assessment was shown to be superior to Fried's Index in predicting mortality, disability, and hospitalizations among older adults with HF (mean age: 81.5 years) in an observational study.[58] Hence, the debate about which method of measuring frailty in HF is the best, particularly in subgroups of patients, will continue. Where frailty measurement methods clearly differ is in terms of what mechanisms of frailty they are tapping into, which will in turn drive different interventions.

Although to the best of our knowledge, this study was the largest meta-analysis of outcomes in frail patients with chronic HF, it also had some limitations. They were primarily related to the fact that the source studies included various populations of patients followed up for variably long periods and diagnosed with frailty with the aid of different instruments. We attempted to overcome these limitations by stratifying the results according to the study setting and frailty instrument used. Furthermore, the sample bias was relatively small; after removing the smallest (most variable) studies on sensitivity analyses, the results were neither significantly nor substantially different. Additionally, we verified all-cause mortality heterogeneity using subgroups for refined estimates and found no significant heterogeneity in all but one case. Finally, there was no significant heterogeneity for hospitalization risk, and therefore, we did not need to examine subgroups of any kind.

Conclusions

This meta-analysis demonstrated that frailty in chronic HF is associated with an average of 48% and 40% increase in the hazard of all-cause mortality and hospitalization, respectively. The relationship between frailty and all-cause mortality is similar across clinical settings and comparing measurement using Fried's phenotype or other measures. Nevertheless, future work should focus on harmonizing frailty measurement to increase its reliability and to facilitate study-to-study comparisons and big data research. Furthermore, considering high related risks of all-cause mortality and hospitalization documented in this meta-analysis, aside from monitoring for frailty, we also need to develop and implement adequate interventions for frail patients with HF.

Conflict of interest

None declared.

Funding

This review paper was conducted as a theoretical part of a research project funded by the Ministry of Science and Higher Education in Poland as a part of a statutory grant of the Wroclaw Medical University for maintaining research potential (no. SUB.E020.19.003).

Author contributions

There were no other contributors to the article other than the authors as well as there was no writing assistance required.

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Appendix 1

PRISMA checklist

Section/topic	Number	Checklist item	Reported on page number
Title			

n/a, not applicable.
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. PLoS Med 6 (7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit: www.prisma-statement.org.

Appendix 2

Quality of the source studies rated according to the STROBE checklist

	STROBE checklist item																						Satisfied criteria	
Authors (year)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	*n*	%
Cacciatore *et al*. (2005)[37]	1	1	1	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	19	86.4