Journal of Frailty, Sarcopenia and Falls

Review Article

What is the association of polypharmacy with frailty in heart failure? A systematic review and meta-analysis

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Abstract

This systematic review and meta-analysis aimed to explore the differences in the number of prescribed medications and polypharmacy risk between patients with heart failure (HF) and frailty vs. those with HF but without frailty. Eligible studies included observational or experimental studies in patients aged ≥50 years. Thirteen studies met the criteria and were included in the final analysis. Patients with frailty and HF exhibited a higher risk of polypharmacy (OR: 1.87, 95% CI 1.72 – 2.04, I^2 = 0%, P < 0.01) compared to those without frailty. Results remained significant after adjusting for comorbidity status. Additionally, patients with frailty and HF were prescribed more medications compared to those without (*k* = 6; MD: 1.43, 95% CI 0.31 – 2.55, I^2 = 94%, P = 0.01), with a high degree of heterogeneity. However, results were non-significant after adjustment for comorbidity status. Patients with HF and frailty have a higher need of polypharmacy compared to those without frailty, which may increase the risk of potentially inappropriate medications (PIM). Investigating the real-world prevalence of PIM may support clinicians in their routine assessment as part of a comprehensive management strategy in patients with HF and frailty.

Keywords: Heart failure, Frailty, Polypharmacy, Medications, PIM

Introduction

Managing drug usage patterns presents a major challenge for healthcare systems dealing with ageing populations. Concomitant with ageing comes an increased risk of developing long-term, chronic health conditions that necessitate targeted pharmacotherapy. Individuals with multiple conditions may require a combination of medications, underscoring the importance of understanding the interactions between each medicine to ensure the safety of the user[1], as certain treatments may be deemed potentially inappropriate medications (PIM) due to their interactions with others, a prevalent concern in managing ageing individuals[2].

Indeed, incidences of hospitalization have been linked to PIM, raising the importance of identifying methods to reduce the risk of indicated drug-to-drug interactions that could cause hospitilization[3], inadvertently, offering a cost-saving opportunity for healthcare systems[4]. Moreover, recent

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Edited by: *Dawn Skelton*

Accepted *22 November 2023*

studies have found a link between PIM and polypharmacy in geriatric disorders, including frailty and sarcopenia, respectively[1,2], suggesting certain conditions might be more prone to PIM.

Heart failure (HF) is defined as the presence of typical symptoms and signs due to cardiac dysfunction, associated with the renal retention of water and salt, leading to an increase in atrial and venous pressure and volume, and followed by the accumulation of water and salt in tissues[3]. HF is associated with many chronic conditions, particularly age-related morbidities like frailty, estimated to affect approximately 45% of HF patients[4]. There are multiple causes of HF, including excess adiposity, type 2 diabetes, unhealthy lifestyle choices, and smoking[5]. In fact, these same conditions are also strongly associated to musculoskeletal conditions such as sarcopenia and frailty, which may explain the high prevalence of frailty in patients with HF that could cause further adverse outcomes. Polypharmacy, often defined as the prescription of "more than 5 prescribed drugs", is becoming increasingly common in HF patients6. Although no universal definition exists for polypharmacy, and the threshold in which the number of drugs may become problematic for risk of severe drug-drug interactions may vary, many studies and clinical settings utilise 5 or more medications as the threshold, forming our criteria in the present analysis for polypharmacy.

Drug interactions, recognized as adverse drug events, have led to preventable hospitalizations, particularly among the elderly population[7,8]. In fact, according to one report by the Centers for Disease Control and Prevention, one third of adults aged 60–80 use 5 or more prescribed drugs[9]. Severe adverse outcomes may arise from PIM with polypharmacy, a risk that is higher with the increasing number of drugs prescribed, which can be both below and above the threshold of medications for polypharmacy. A cross-sectional analysis in Scotland found that among 310,000 adults, 81% of patients using more than 15 medications and 11% of patients using 2–4 was exposed to potentially serious drug-drug interactions[10]. However, it is unclear whether significant differences in polypharmacy exist between HF patients with and without frailty. Notably, frailty and HF are two conditions prone to polypharmacy and identifying any frequently prescribed PIM may lead to better health outcomes or at the least, an improved quality of life. This information would be important to ensure a considerate and robust pharmacotherapeutic approach for the management of these patients to reduce any harmful drug-drug interactions.

The aim of this systematic review and meta-analysis is to identify the difference in the number of medications and the risk of polypharmacy between patients with HF and frailty in comparison to those with HF but without frailty. We aim to provide prescribers with insights into potential additional risks or considerations in the therapeutic management of these patients, as well as guide future research in identifying PIM specific to this patient cohort, which could reduce the risk of adverse drug events. Any findings will ultimately aim to improve the overall the management of polypharmacy in these patients.

Materials and Methods

This study was conducted based on the updated 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[11]. The protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023440108).

Search strategy

Two reviewers searched PubMed, Scopus, Web of Science, and Cochrane Library from the beginning until July 2023. The literature search strategy and the search terms used are shown in Supplementary Table 1.

Inclusion and exclusion criteria

Studies were included based on: (i) data from studies including people with HF and frailty vs. without frailty, (iii) patients with mean age ≥50 years; (iv) clear diagnostic criteria for frailty and polypharmacy (i.e., ≥5 medications). Articles were excluded if they: (i) were reviews, letters, and non-human studies, and (ii) were not published in English as a full text.

Data extraction and risk of bias

Two investigators extracted data including the name of the first author, publication data, country of origin, age, body mass index (BMI) and ejection fraction rate, health status, number of participants, New York Heart Association (NYHA) functional classification, rate of participants with polypharmacy, number of medications, and definition of polypharmacy and frailty. Disagreements were resolved by a third investigator. To evaluate the quality of the included studies we used the Methodological index for non-randomized studies (MINORS) tool[12] and was performed by two reviewers (K. P. and G. D. T.). MINORS is a comprehensive tool for assessing bias in non-randomized controlled trials based on the following criteria: a clearly stated aim; consecutive patient inclusion; prospective data collection; endpoints appropriate to study aim; unbiased assessment of study endpoint; follow-up period appropriate to study aim; 5% lost to follow-up; prospective calculation of study size; adequate control group; contemporary groups; baseline equivalence of groups; and adequacy of groups. According to the scoring system, MINORS domains are rated as 0 if they are not reported, 1 if they are reported but with insufficient details, and 2 if they are reported with appropriate details. The global ideal score is 16, for scores below 8 and 10 was deemed as a high risk of bias and of some concerns, respectively.

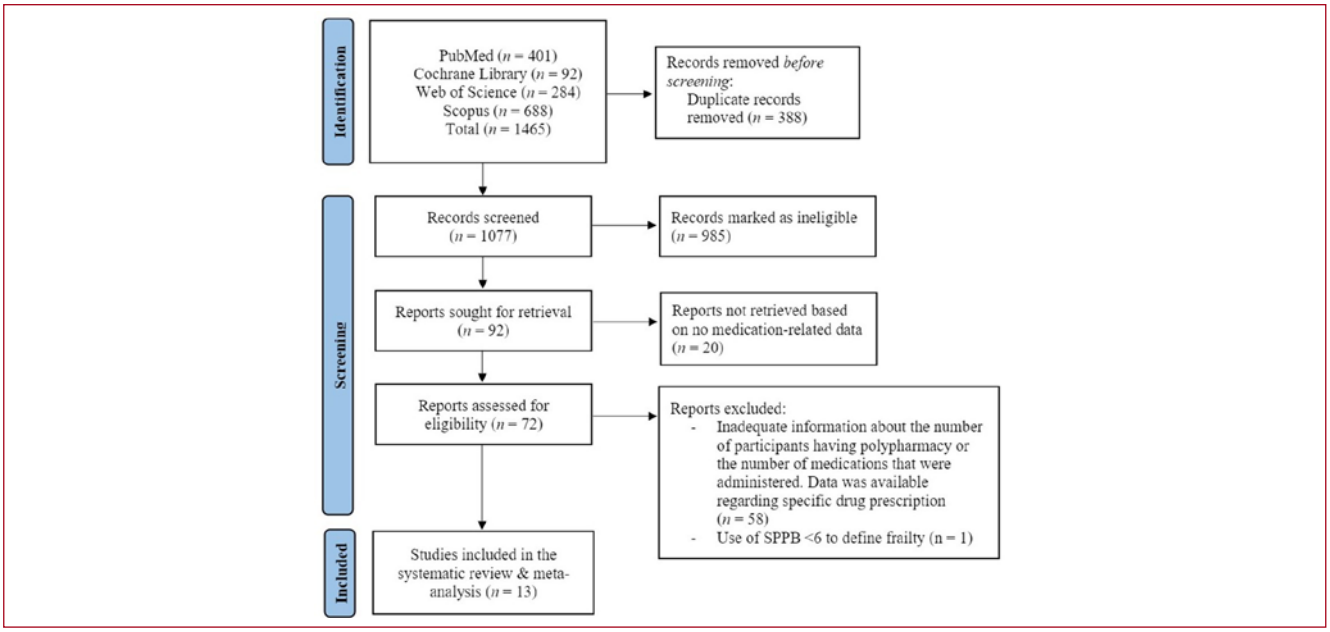

Figure 1. Flowchart of the employed literature search.

Statistical analysis

Data was treated as continuous and changes in outcomes from patients with frailty and without frailty were compared between groups to calculate mean differences (MD) in number of medications and the odds ratio (OR) in relation to the risk of polypharmacy. When studies provided interquartile ranges (IQR), we used the formula 'standard deviation (SD) = width of IQR/1.35' to calculate the missing SDs[13]. Statistical significance was assessed through the random-effects model and inverse-variance method.

Statistical heterogeneity of outcome measurements across studies was calculated using the overlap of their confidence intervals (95% CI) and expressed as Cochran's Q (Chi-square test) and I^2 measurements. I^2 was used to measure data heterogeneity (low: 30% to 49%, moderate: 50% to 74%, and high: 75% and above). Subgroup analyses were conducted based on participant age (below vs. above 70 years old), and definition of frailty. Sensitivity analyses were conducted to explore the robustness of the reported findings by discounting the effect of studies in which patients with heart failure and frailty had more comorbidities compared with patients without frailty, uncommon polypharmacy definition, and the increased risk of bias of the included studies. The Review Manager (RevMan 5.4.1) software was used to synthesise the meta-analysis, and a p value of 0.05 was considered statistically significant.

A random-effect meta-regression was employed to investigate potential confounders affecting the effect size of the reported findings, such as age, BMI, left ventricular ejection fraction rate, frailty, and polypharmacy definition.

Results

Literature search

Our literature search resulted in 1465 publications. After the exclusion of duplicates and abstracts, 92 full texts were sought for retrieval, although 20 studies did not report data in relation to medications. Of the final 72 studies identified as eligible for inclusion in our study, 58 articles included only data related to specific medications rather than polypharmacy rates and total number of medications, while one study defined frailty as short physical performance battery score below 6. Overall, 13 studies were included in this systematic review and meta-analysis (Figure 1)[14-26].

Descriptive results

Seven studies assessed the prevalence of polypharmacy[20-26] and six studies assessed the number of medications[14-19] administered by patients with HF and frailty vs. without frailty. Detailed characteristics of the included studies are presented in Tables 1 and 2.

Definition of frailty and polypharmacy

Eight studies used Fried's criteria for the definition of frailty[14-16,20-24], one study used the Rockwood score[26], one study the Korean FRAIL scale (K-FRAIL)[17], one study the FRAIL scale[19], one study the frail-VIG index[25], and one study the clinical frailty scale[18]. Polypharmacy was generally defined as the presence of 5 or more medications, although one study defined it as more than 5[24].

Table 1. Characteristics of studies measuring prevalence of polypharmacy in patients with heart failure and frailty vs. patients with heart failure and without frailty. Data are expressed as mean (standard deviation) or median (IQR).

Study, year	Country	Study design	Total *n*	Frail			Non-frail			Prevalence of Polypharmacy	Polypharmacy Definition	Frailty Definition	Higher prevalence of reported comorbidities in the frailty group	Population
				n (M/F)	Age	LVEF%	*n* (M/F)	Age	LVEF%					
Zheng et al. 2021[20]	China	Prospective study	443	129 (60/69)	79.1 (6.39)	63.1 (4.75)	334 (165/169)	75.1 (6.62)	62 (5.33)	Frail: 62.4% Non-frail: 45.5%	≥ 5 medications	Fried frailty phenotype	-	Outpatients
Valdiviesso et al. 2021[21]	Portugal	Cross-sectional study	58"	21 (8/13)	64 (49.5, 71.5)	41.2 (18.0)	37 (29/8)	55 (44.0, 64.0)	37.9 (13.2)	Frail: 81% Non-frail: 59.5%	≥ 5 medications	Fried frailty phenotype	Atrial fibrillation	Outpatients
Rech et al. 2022[22]	Brazil	Cross-sectional study	15^	6 (0/6)	67.7 (8.2)	No data	9 (7/2)	66.1 (3.9)	No data	Frail: 83.3 % Non-frail: 88.9 %	Not provided	Fried frailty phenotype	-	Community-dwelling
Meng et al. 2023[23]	China	Prospective study	520	145 (62/83)	78.5 (6.32)	63.3 (4.42)	375 (160/215)	74.3 (6.22)	63.4 (4.31)	Frail: 64.1% Non-frail: 47.2%	≥ 5 medications	Fried frailty phenotype	Stroke, Osteoporosis	Inpatients
McDonagh et al. 2023[24]	Australia	Prospective study	131	71 (48/23)	54 (13)	30 (16)	60 (51/9)	53 (16)	31 (16)	Frail: 84.5% Non-frail: 80%	>5 medications	Fried frailty phenotype	-	Inpatients
Flores-Alvarez et al. 2022[25]	Spain	Retrospective study	118*	26 (10/16)	83 (79.5-88)	No data	92 (40/52)	82 (77.2-86)	No data	Frail: 100% Non-frail: 90%	Not provided	Frail-VIG index	Depression, Delirium, Dysphagia, Chronic pain, Chronic renal disease, Neurologic diseases, Pulmonary diseases	Inpatients
Dewan et al. 2020[26]	USA	Secondary analysis of RCTs	8495**	3613 (2731/882)	67.1 (10.3)	29.8 (5.8)	4882 (3989/893)	61.0 (11.7)	28.5 (6.1)	Frail: 40.5% Non-frail: 30.1%	≥ 5 medications	Frailty Index	Renal disease, COPD, Peripheral arterial disease, Stroke, Valvular heart disease, Unstable angina, Myocardial Infraction, Atrial Fibrillation, Diabetes, Hypertension	Outpatients

Abbreviations: COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; IQR, interquartile range; M, male; F, female; RCT, randomized clinical trial.
"Total cohort: 136 patients
^ Total cohort: 55 patients
** Total cohort: 546 patients*
*** Total cohort: 13,265 patients*

Table 2. Characteristics of studies assessing the number of medications in patients with heart failure and frailty vs. patients with heart failure and without frailty. Data are expressed as mean (standard deviation) or median (IQR).

Study, year	Country	Study design	Total n	Frail			Non-frail			Number of Medications	Frailty Definition	Higher prevalence of reported comorbidities in the frailty group	Population
				n (M/F)	Age	LVEF%	n (M/F)	Age	LVEF%				
Son et al. 2022[17]	South Korea	Cross-sectional study	221"	115 (43/72)	77.63 (7.25)	58.45 (14.70)	106 (72/34)	70.30 (5.07)	57.73 (14.50)	Frail: 3.42 (1.15) Non-frail: 3.42 (1.19)	K-FRAIL scale	Hypertension, Diabetes	Outpatients
Ribeiro et al. 2021[14]	Brazil	Cross-sectional study	76^	64 (45/19)	70 (63-75)	34,47 (10,7)	12 (7/5)	66 (62,3-71,3)	32,83 (11,49)	Frail: 8 (3.03) Non-frail: 6.5 (1.68)	Fried frailty phenotype	-	Outpatients
Testa et al. 2020[15]	Italy	Prospective study	111*	31 (20/11)	81.1 (6.2)	No data	81 (40/41)	78.8 (7.3)	No data	Frail: 8.8 (3.1) Non-frail: 7.9 (2.7)	Fried frailty phenotype	-	Outpatients
Kleipool et al. 2020[16]	Netherlands	Prospective study	78**	42 (19/23)	81 (7.8)	No data	36 (25/11)	71 (7.4)	No data	Frail: 12 (4) Non-frail: 7 (2)	Fried frailty phenotype	Diabetes	Outpatients
Komici et al. 2020[18]	Italy	Prospective study	128	54 (45/9)	70.5 (5.4)	26.7 (6.1)	74 (66/8)	68.2 (4.2)	30.2 (10.2)	Frail: 4.8 (1.4) Non-frail: 4.9 (1.2)	Clinical Frailty Scale	-	Inpatients
Jimenez-Mendez et al. 2022[19]	Spain	Secondary analysis of prospective study	255°	111 (47/64)	82.9 (4.51)	46.5 (14.5)	144 (111/33)	80.2 (3.69)	40.7 (13.6)	Frail: 10.8 (3.74) Non-frail: 8.97 (2.76)	FRAIL scale	Hypertension, CKD	Outpatients

Abbreviations: CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; IQR, interquartile range; M, male; F, female.
"Total cohort: 407 patients
^ Total cohort: 106 patients
** Total cohort: 1077 patients*
*** Total cohort: 197 patients*
° Total cohort: 499 patients

Polypharmacy in heart failure and frailty vs. without frailty

Our main analysis (k = 7; n = 3991 with frailty and n = 5789 without frailty) showed that polypharmacy prevalence was higher in patients with frailty compared to patients without frailty (OR: 1.87, 95% CI 1.72 – 2.04, I^2 = 0%, P < 0.01) with low degree of heterogeneity among studies (Figure 2).

Subgroup analysis showed a significantly higher risk of polypharmacy in patients aged below 70 years (k = 3; OR: 1.86, 95% CI 1.70 – 2.03, I^2 = 0%, P < 0.01) and in patients aged above 70 (k = 4; OR: 2.02, 95% CI 1.50 – 2.71, I^2 = 0%, P < 0.01) (Supplementary Figure 1).

When we accounted for different frailty criteria, significant differences using Fried's criteria vs. patients without frailty were displayed (k = 5; OR: 1.94, 95% CI 1.48 – 2.55, I^2 = 0%, P < 0.01) (Supplementary Figure 2) as well as when patients with

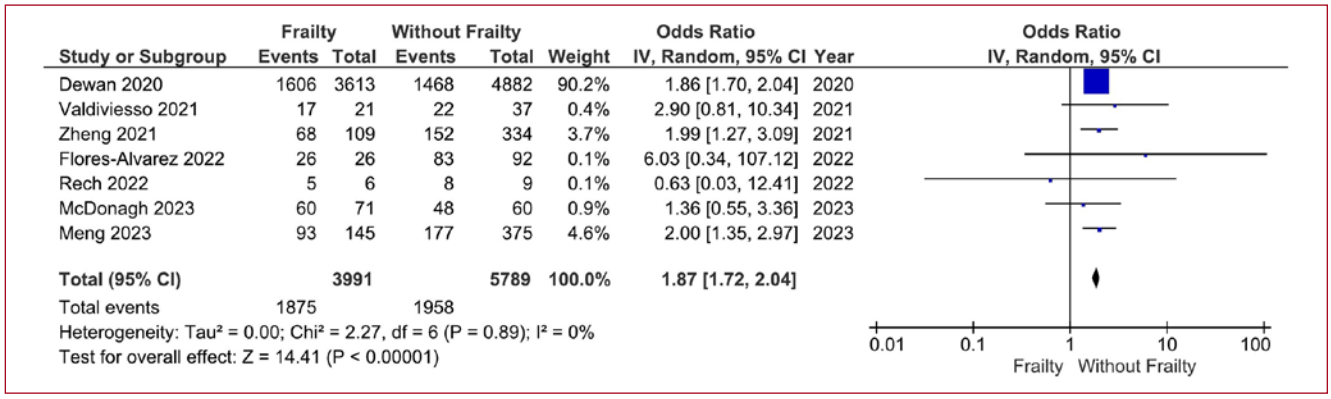

Figure 2. Polypharmacy risk of patients with heart failure and frailty vs. patients without frailty.

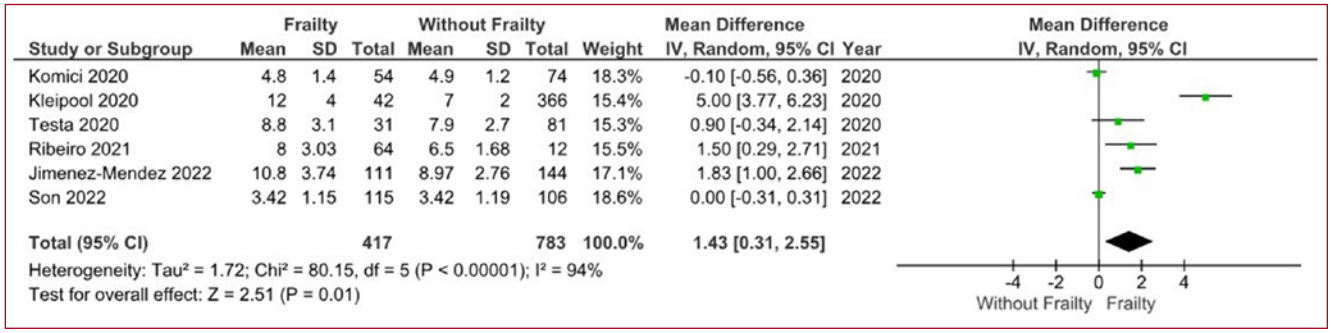

Figure 3. Differences in number of medications between patients with heart failure and frailty vs. patients without frailty.

frailty and identical reported health status (similar reported comorbidities among studies) vs. those without frailty (k = 3; OR: 1.81, 95% CI 1.22 – 2.69, I^2 = 0%, P < 0.01) (Supplementary Figure 3). In addition, our sensitivity analysis based on the combination of similar reported comorbidities and Fried's criteria also revealed a significant association of patients with frailty and polypharmacy vs. patients without frailty (k = 3; OR: 1.81, 95% CI 1.22 – 2.69, I^2 = 0%, P < 0.01) (Supplementary Figure 4) and when two studies for not providing sufficient data on polypharmacy definition were excluded (k = 5; OR: 1.87, 95% CI 1.72 – 2.04, I^2 = 0%, P < 0.01) (Supplementary Figure 5). Finally, sensitivity analysis according to one study with increased risk of bias showed identical outcomes (k = 6; OR: 1.87, 95% CI 1.71 – 2.03, I^2 = 0%, P < 0.01) (Supplementary Figure 6).

Number of medications in heart failure and frailty vs. without frailty

Our main analysis (k = 6; n = 417 with frailty and n = 783 without frailty) showed that number of medications was higher in patients with frailty (MD: 1.43, 95% CI 0.31 – 2.55, I^2 = 94%, P = 0.01) with high degree of heterogeneity (Figure 3).

Our subgroup analysis based on Fried's criteria did not reveal higher medication count in patients with frailty (k = 3; MD: 2.47, 95% CI -0.03 – 4.96, I^2 = 92%, P = 0.05) (Supplementary Figure 7). Our sensitivity analysis based on similar comorbidity status showed no significant difference between groups (k = 3; MD: 0.65, 95% CI -0.41 – 1.70, I^2 = 73%, P = 0.23) (Supplementary Figure 8). Lastly, sensitivity analysis according to one study with higher risk of bias highlighted identical statistical findings as our main analysis (k = 5; MD: 1.42, 95% CI 0.18 – 2.67, I^2 = 95%, P = 0.02) (Supplementary Figure 9).

Meta-regression analyses

Variance among studies was not detected due to differences in age, BMI, left ventricular ejection fraction rate, frailty definition, and polypharmacy definition (Supplementary Table 2).

Risk of bias

Overall, the quality of the included studies was considered moderate (Supplementary Table 3), for which three studies measuring the prevalence of polypharmacy had some concerns in relation to the risk of bias[20,21,25]. In terms of number of medications, the overall quality of the studies was evaluated as low (Supplementary Table 4), albeit one study had some concerns[14].

Discussion

In this meta-analysis of 13 studies, we systematically reviewed observational research that investigated the risk of polypharmacy in patients with HF and frailty vs. HF patients without frailty. Overall, we found that HF patients with frailty had a greater risk of polypharmacy and used a higher number of medications compared to those without frailty. Interestingly, after adjusting for comorbidity status via sensitivity analysis, patients with frailty still had a higher risk of polypharmacy compared to patients without frailty, however, the number of medications did not change significantly.

Our findings are broadly consistent with the most recent literature on the relationship between polypharmacy and frailty. Midão et al. showed that polypharmacy was 3 times more prevalent in individuals with frailty and 2 times in pre-frail individuals, when compared with those without frailty, in a community-dwelling European population[27]. It is important to emphasize that polypharmacy and frailty share a bidirectional relationship[28]. Indeed, PIM with polypharmacy, may contribute to frailty (or individual components) in older patients[29]. For instance, Veronese et al. found that polypharmacy was associated with a higher incidence of frailty over an 8-year follow-up period in a dose-response manner[30]. However, it is highly plausible that the weight of directionality for this association is caused by frailty increasing medication usage.

Typical pharmacotherapy for patients with HF and reduced ejection fraction (HFrEF) includes angiotensin receptor-neprilysin inhibitors (ARNIs),angiotensin converting enzyme inhibitors (ACEi), or angiotensin receptor blockers (ARBs), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter-2 inhibitors (SGLT2i)[31]. In addition to these, other drugs such as diuretics, calcium channel blockers, antidiabetic drugs, hypolipidemic drugs, antiplatelets, anticoagulants, vasodilators and antiarrhythmics are also commonly prescribed to patients with HF due to parallel comorbidities[32], deeming polypharmacy in certain cases essential[33]. In fact, it is essential to iterate that polypharmacy per se is not the concern, as discussed, it is critically essential for the management of disease and illness, but it is the risk of PIM that may arise with polypharmacy, that is a concern. In this case, it may be more useful to define polypharmacy as taking ≥10 medications and focus on the search for PIM and drug-drug or drug-disease interactions, especially for patients conditions like HFrEF, that require multiple medications[34-36].

A Korean study conducted on a large population of 12,759 older patients with HF showed that 46.2% of patients were administering PIM at least once and that the most frequent PIM were benzodiazepines (30.9% prevalence)[37]. Such a high proportion of PIM among older people with HF could explain the increased adverse drug risk with polypharmacy as shown by Ozasa et al. who found that the adjusted cumulative 1-year incidence of death or rehospitalization increased incrementally with an increasing number of medications[38]. However, it is important to note that the findings of this meta-analysis most likely result from the fact that patients presenting both heart failure and frailty require a higher number of prescribed medications, rather than the higher number of medications being the causative factor for these conditions.

A recent meta-analysis of 14 RCTs on deprescribing in older adults with polypharmacy showed that deprescribing is safe when PIM are present. By reducing drug number or dose, health-related quality of life (HRQOL) may improve, and cost or hospitalization may be reduced, though evidence regarding deprescribing in patients with frailty and cardiometabolic disease is inconclusive mainly due to the heterogeneity of studies, and should therefore be interpreted with caution[1,39].

According to our results, a multidisciplinary approach including experts in frailty, HF, and geriatric pharmacology may be the most effective strategy to manage patients with HF and frailty, and polypharmacy, to reduce the risk of PIM being prescribed, and as a consequence, potentially harmful drug-drug interactions taking place[40]. In fact, Essa et al. recently demonstrated that a multispecialty multidisciplinary intervention reduced hospitalizations due to adverse drug reactions by significantly reducing the anticholinergic burden in patients with HF[41]. In particular, a multidisciplinary team could be crucial for the following actions: optimize HF therapy by prescribing appropriate HF-related drugs in line with guideline recommendations, such as ARNI, BB, SGLT2i, and MRA ("good" polypharmacy); deprescribing or reconsidering the dose of HF-related drugs that may increase the risk of negative effects such as orthostatic hypotension and fall in older adults with frailty, assuming administration of diuretics and/or SGLT2i; deprescription of HF-unrelated drugs such as benzodiazepines, antihistamines, anticholinergics and antipsychotics that may increase risk of falls, cognitive dysfunction, and functional decline[42].

Future research should aim to investigate whether existing hospital registry data sets find evidence of PIM being prescribed in patients with polypharmacy, HF and frailty, and through both retrospective and prospective research, explore whether the avoidance of PIM in this patient group leads to improved health outcomes, including occurrences of drug adverse events, and quality of life. This information would be helpful to ensure the correct pharmacotherapeutic approach is implemented in future practice, and to identify commonly prescribed PIM.

Strengths and limitations

In this study, we employed multiple subgroup and sensitivity analyses to account for the high heterogeneity among studies and enhance the reliability of our results. Although this study is the first to quantitatively measure the prevalence odds of polypharmacy and number of medications in patients with HF and frailty vs. without frailty, the imputed data are cross-sectional. Therefore, causative claims cannot be established, indicating the need for longitudinal research around this area. In addition, the report of comorbidities and number of medications may be inflated given the inaccuracies that may occur by faulty coding of drug prescription and/or incorrect tabulations made electronically.

Conclusions

In conclusion, after adjusting for comorbidity status, patients with HF and frailty exhibited an increased risk of polypharmacy compared to those without frailty. Our results strongly suggest that evaluating PIM in cases of polypharmacy among patients with HF and frailty should be part of routine assessment, considering the potential interactions of PIM. These results reinforce the need for real-world evidence, observational, and controlled research to investigate the presence of PIM among patients with frailty, HF, and polypharmacy, to identify patients who can benefit from multidisciplinary treatment approaches through the inclusion of geriatrician, clinical pharmacologist, and/or pharmacist assessment to avoid PIM prescription risk.

Authors' contributions

KP, GDT, and NV wrote the manuscript. KP conducted the statistical analysis. YD, JM, LW, and RS reviewed the manuscript. All authors read and approved the final version of the article.

Disclaimer

Dr. Y. Dionyssiotis serves as Co-Editor-in-Chief in the JFSF. The manuscript underwent peer review process by independent experts.

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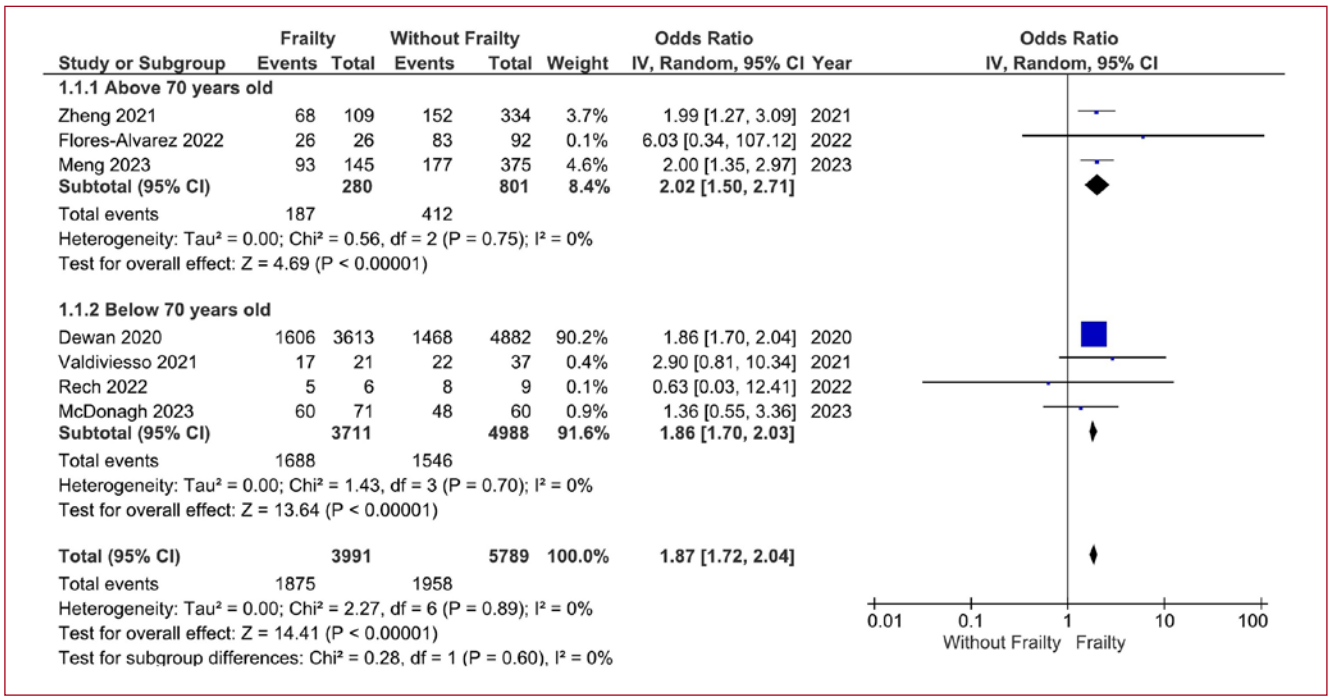
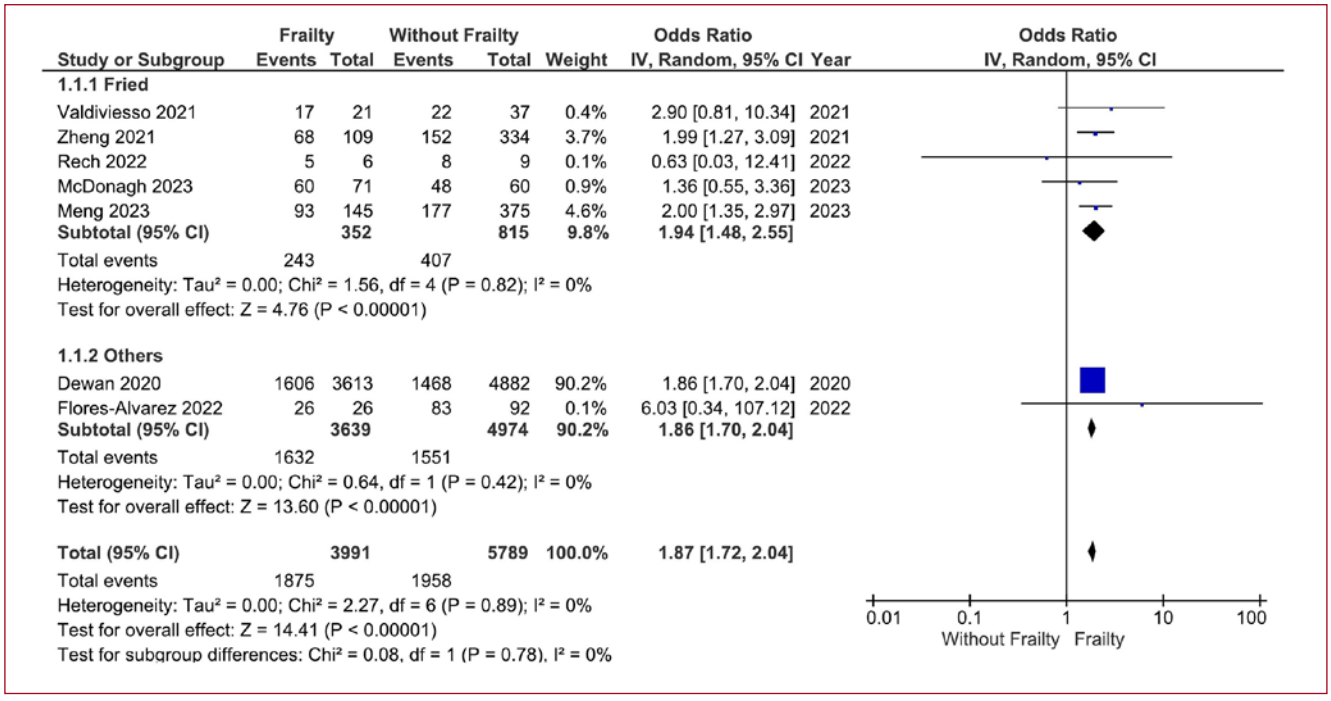
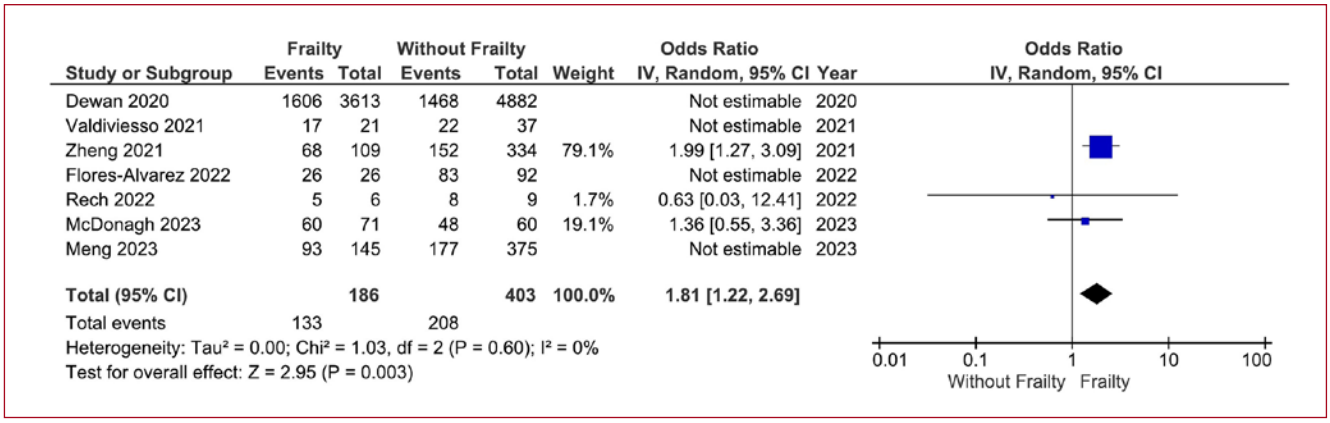
Supplementary Files



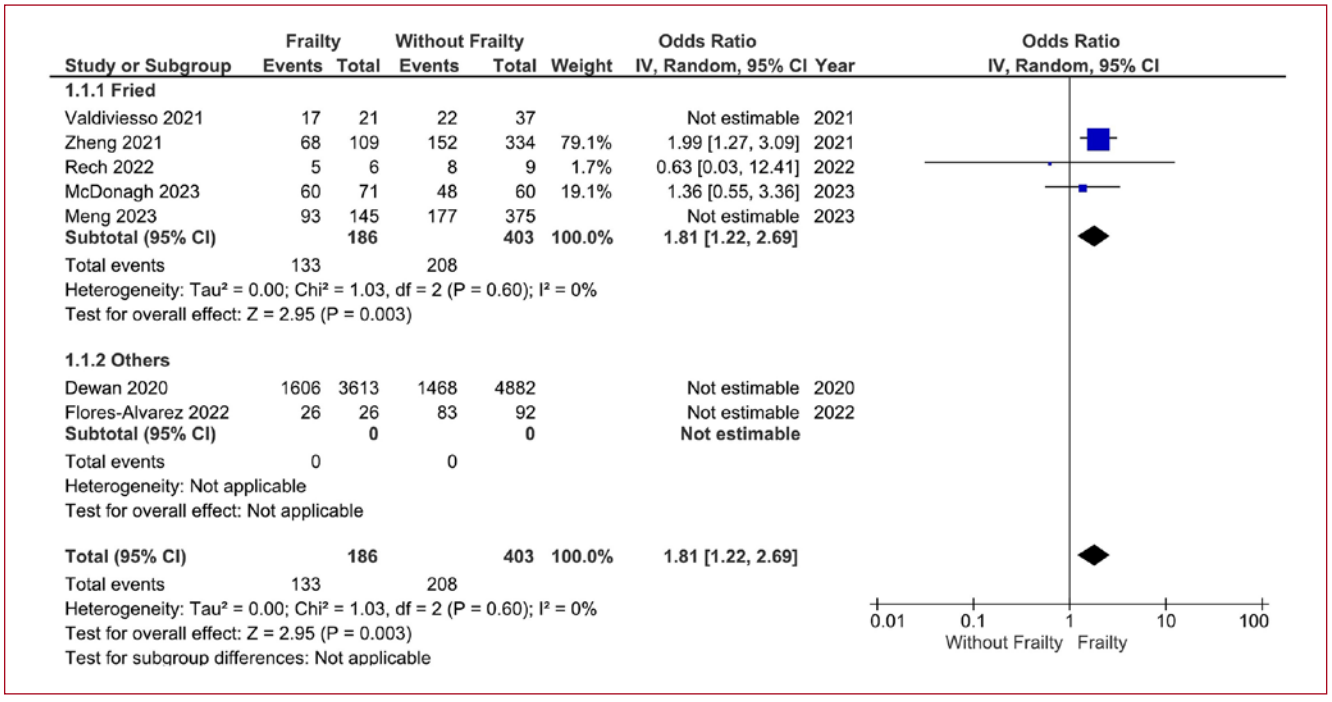
Supplementary Figure 1. Risk of polypharmacy in patients with heart failure and frailty vs. without frailty aged below 70 years and in patients aged above 70.



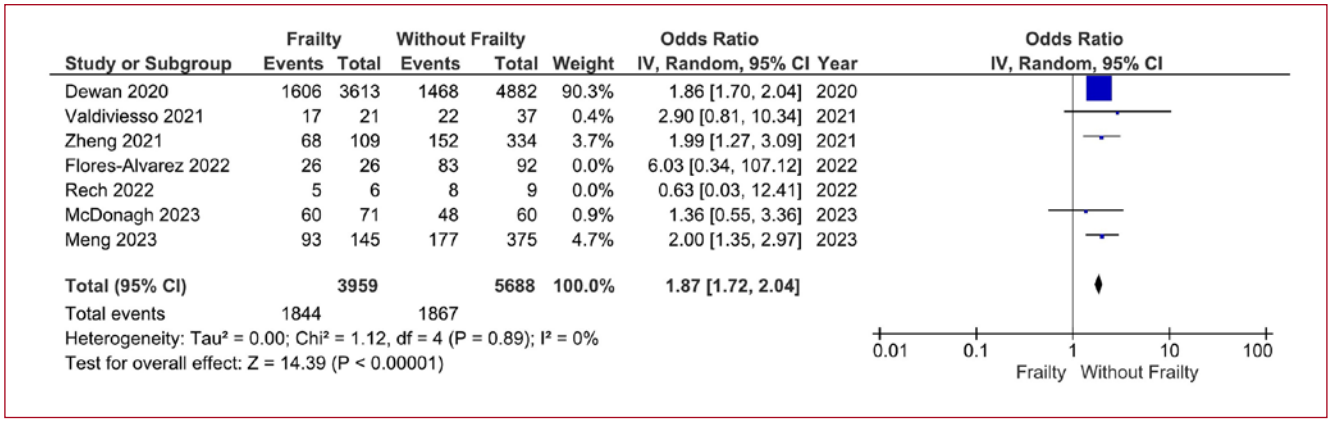
Supplementary Figure 2. Risk of polypharmacy in patients with heart failure and frailty vs. without frailty based on Fried's criteria.



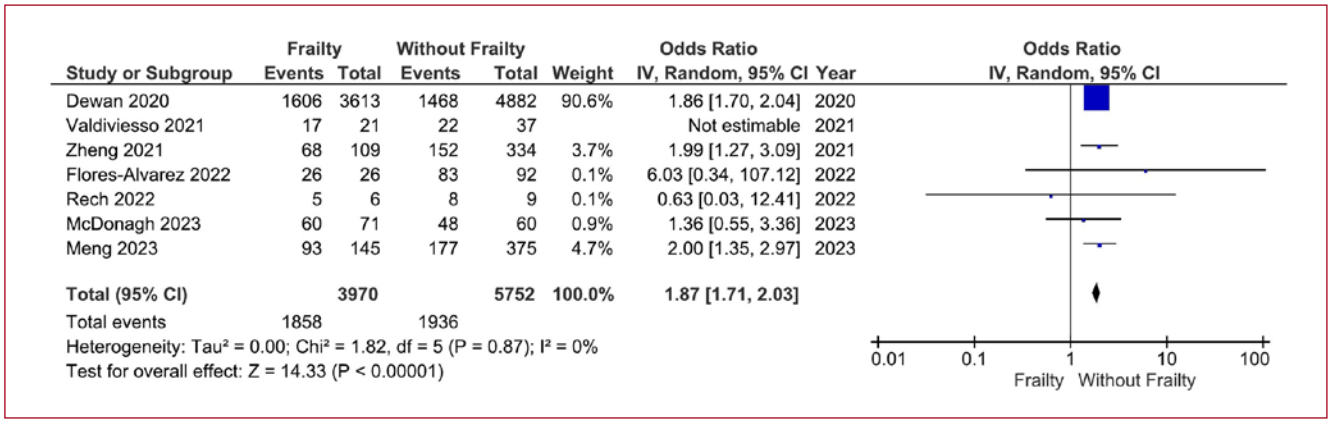
Supplementary Figure 3. Risk of polypharmacy in patients with heart failure and frailty vs. without frailty based on similar reported health status.



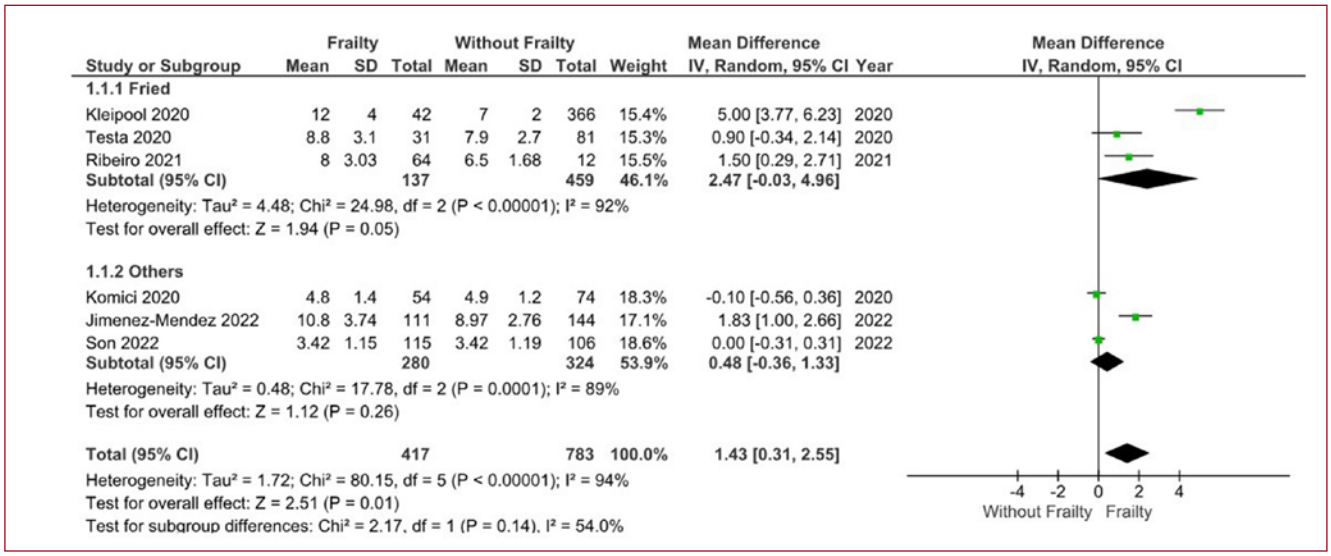
Supplementary Figure 4. Risk of polypharmacy in patients with heart failure and frailty vs. without frailty based on similar reported health status and Fried's criteria.



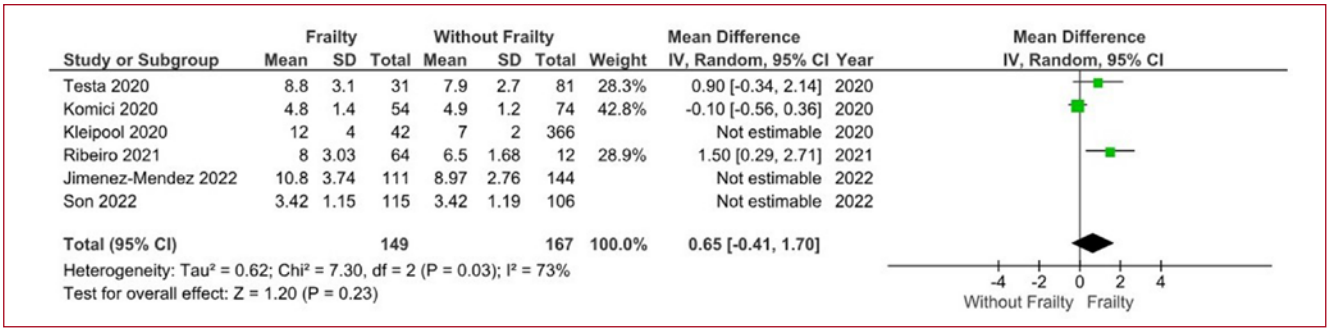
Supplementary Figure 5. Risk of polypharmacy in patients with heart failure and frailty vs. without frailty based on sufficient data regarding polypharmacy.



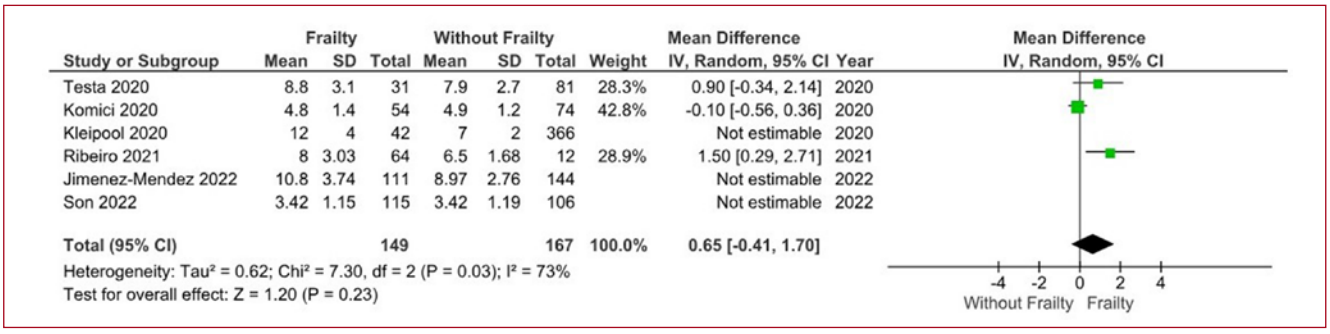
Supplementary Figure 6. Risk of polypharmacy in patients with heart failure and frailty vs. without frailty based on studies with lower risk of bias.



Supplementary Figure 7. Number of medications in patients with heart failure and frailty vs. without frailty based on Fried's criteria.



Supplementary Figure 8. Number of medications in patients with heart failure and frailty vs. without frailty based on similar reported health status.



Supplementary Figure 9. Number of medications in patients with heart failure and frailty vs. without frailty based on studies with lower risk of bias.

Database	Search terms
PubMed	("polypharmacy" OR "prescription*" OR "number of prescriptions" OR "multiple prescriptions" OR "drug*" OR "numbers of drugs" OR "multiple drugs" OR "medication*" OR "multiple medications" OR "inappropriate prescri*") AND ("heart failure" OR "ejection fraction") AND "frail*"
Cochrane Library	(polypharmacy OR number of prescriptions OR numbers of drugs OR number of medications OR no of medications OR no of drugs OR inappropriate prescription) AND (heart failure OR ejection fraction) AND frail*
Web of Science	(((polypharmacy OR (number AND of AND prescriptions) OR (number AND of AND drugs) OR (number AND of AND medications) OR prescriptions OR drugs OR medications))) AND frailty AND heart failure
Scopus	Polypharmacy OR drugs OR medications OR prescriptions AND frailty AND heart AND failure

Supplementary Table 1. Search terms employed in the screening process.

Confounder	*r*	SE	95%CI	*z*	P
Number of medications					
Age	0.060	0.0825	-0.10, -0.22	0.73	0.468
BMI	0.007	0.1233	-0.23, 0.25	0.06	0.956
LVEF%	0.025	0.0507	-0.07, 0.12	0.50	0.618
Frailty definition	-0.151	0.2065	-0.56, 0.23	-0.73	0.465
Polypharmacy					
Age	-0.035	0.0634	-0.16, 0.89	-0.55	0.581
BMI	-0.012	0.0345	-0.08, 0.06	-0.34	0.736
LVEF%	-0.040	0.0874	-0.21, 0.13	-0.46	0.649
Frailty definition	-0.025	0.0656	-0.15, -0.10	-0.38	0.703
Polypharmacy definition	0.347	0.3576	-0.35, 1.04	0.97	0.333

Supplementary Table 2. Meta-regression analyses of patients with heart failure and frailty vs. those without frailty in relation to the number of medications.

Author, Year	Aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	Total	Risk of bias
Zheng et al. 2021[20]	2	2	2	1	1	1	0	0	9/16	Some concerns
Valdiviesso et al. 2021[21]	2	1	1	1	2	1	0	0	8/16	Some concerns
Rech et al. 2022[22]	2	2	1	2	2	1	0	0	10/16	Low
Meng et al. 2023[23]	1	2	2	2	1	2	0	0	10/16	Low
Mcdonagh et al. 2023[24]	2	2	2	2	2	2	2	0	14/16	Low
Flores-Alvarez et al. 2022[25]	1	2	0	2	2	2	0	0	9/16	Some concerns
Dewan et al. 2020[26]	1	2	2	2	2	2	0	0	11/16	Low

Supplementary Table 3. Quality assessment of the included studies measuring the prevalence of polypharmacy.

Author, Year	Aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	Total	Risk of bias
Son et al. 2022[17]	2	2	2	2	2	1	1	0	12/16	Low
Ribeiro et al. 2021[14]	2	2	0	2	2	1	0	0	9/16	Some concerns
Testa et al. 2020[15]	2	2	1	2	2	2	1	0	12/16	Low
Kleipool et al. 2020[16]	2	2	1	2	2	1	1	0	11/16	Low
Komici et al. 2020[18]	2	2	1	2	2	2	0	0	11/16	Low
Jimenez-Mendez et al. 2022[19]	2	2	2	2	2	2	0	0	12/16	Low

Supplementary Table 4. Quality assessment of the included studies assessing the number of medications based on the Methodological Index for Non-Randomized Studies (MINORS) tool.