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Review article

# Prevalence of frailty in cardiac transthyretin amyloidosis: A systematic review and meta-analysis

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ABSTRACT

*Background:* Cardiac amyloidosis (CA) is an increasingly recognized cause of heart failure. Frailty is common among older adults and strongly associated with adverse outcomes. However, its prevalence and clinical relevance in the context of CA have not been systematically examined. This review aimed to assess the prevalence of frailty in CA and qualitatively synthesize the evidence on its association with clinical outcomes.
*Methods:* A systematic review and meta-analysis of observational studies was conducted to assess frailty prevalence in CA. Databases searched included Embase, PubMed, CINAHL, Cochrane Library, and Google Scholar up to April 15, 2025. Studies reporting frailty prevalence in CA patients were included. Six assessors independently screened the articles, extracted data, and resolved conflicts by consensus. The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale.
*Results:* Out of 565 articles identified, six studies met inclusion criteria, including a total of 1422 participants with cardiac transthyretin amyloidosis (ATTR-CA). Reported frailty prevalence ranged from 14.5 % to 75 %, depending on the assessment method. A meta-analysis restricted to studies using the Clinical Frailty Scale (N = 1164) yielded a pooled frailty prevalence of 66 % (95 % CI, 57–74 %), with substantial heterogeneity ($I^2$ = 89.1 %). Frailty was consistently associated with higher mortality and poorer quality of life.
*Conclusions:* Frailty is highly prevalent in individuals with ATTR-CA and is independently associated with adverse clinical outcomes. These findings support the routine evaluation of frailty in the management of individuals with CA. PROSPERO registration (CRD42024607807).

## 1. Introduction

Cardiac amyloidosis (CA), resulting from extracellular deposition of misfolded proteins in the heart, is an increasingly recognized cause of heart failure (HF)(Ruberg et al., 2019). In over 98 % of cases, this deposition involves fibrils composed of either monoclonal immunoglobulin light chains (AL) or transthyretin (ATTR), either in its hereditary (ATTRv) or acquired (ATTRwt) form (Garcia-Pavia et al., 2021). Although historically considered a rare disease, the actual prevalence of CA, especially in older patients, is debated. ATTRwt CA has been identified in 13–20 % of older patients with HFpEF or severe aortic stenosis (Castaño et al., 2017; González-López et al., 2015), and

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amyloid deposits were presented in up to 25 % of autopsies of older patients with HFpEF (Tanskanen et al., 2008), although its clinical relevance in incidental necropsy finding is still debated.

Frailty is an age-related condition with multifactorial causes, characterized by reduced strength, endurance, and physiologic function, leading to increased vulnerability towards external and internal stressors(Clegg et al., 2013; Morley et al., 2013). The two most commonly used methods for frailty assessment are the Frailty Index (Rockwood et al., 2005) and the Frailty Phenotype(Fried et al., 2001). The Frailty Index, developed by Rockwood et al., is based on the cumulative deficit model, which conceptualizes frailty as an aggregate burden of symptoms, signs, diseases, and disabilities (Rockwood et al., 2005). The Fried Phenotype, by comparison, defines frailty by the presence of at least three of five criteria – unintentional weight loss, self-reported exhaustion, weakness, slow gait speed, and low energy expenditure– while one or two criteria indicate pre-frailty (Fried et al., 2001).

In recent years, several frailty screening tools reflecting both conceptual models have been developed (Buta et al., 2016). While agreement among these tools is generally modest (Theou et al., 2013), there is consistent evidence that, irrespective of the instrument employed, frailty significantly increases the risk of adverse outcomes – including falls, disability, and death – in patients with cardiovascular diseases (Afilalo, 2011; Finn and Green, 2015). Assessing frailty in individuals with CA may be particularly relevant for risk stratification, as it may help identify patients at increased risk of suboptimal therapeutic response or adverse events, independent of CA severity. However, no systematic review and meta-analysis has specifically examined the prevalence and clinical impact of frailty in this population. This study aims to bridge this gap by synthesizing existing evidence on frailty prevalence in CA and its association with clinical outcomes.

## 2. Methods

This systematic review and meta-analysis of published observational and interventional studies provides information on the prevalence of frailty in CA. The authors conducted it in accordance with the PRISMA standards of quality for reporting meta-analysis and the guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (Moher et al., 2009). The protocol was registered in the international prospective register of systematic reviews PROSPERO (registration number CRD42024607807).

### 2.1. Search strategy and eligibility criteria

The research question was created using the Population, Intervention, Comparison and Outcomes (PICO) format: What is the prevalence of frailty among older patients affected by cardiac amyloidosis? (supplementary Table 1).

We searched Embase, Google Scholar, Pubmed, CINAHL and the Cochrane Library up to April 15th, 2025. The search used for Embase was the following ('card* amyloid*' OR 'amyloid* card*' OR 'heart* amyloid*') AND ('frailty'/exp OR 'fragility' OR 'frail*' OR 'fragil*' OR 'geriatric assessment'/exp). The term "geriatric assessment" was used to include studies in which frailty assessment is categorized as geriatric assessment. A similar search (fulfilling the requirements of each database) was run in the other databases (supplementary Table 2). All results were exported to EndNote (Claryvate, Philadelphia, PA, USA) for duplicate removal. Studies were considered eligible for inclusion if they met the following criteria: (1) the study sample or subsample included individuals affected by CA; (2) frailty prevalence in CA individuals was reported, regardless of the assessment method used to evaluate frailty; (3) the study had an observational or interventional design; (4) full text was available; and (5) the article was published in English or another European language.

### 2.2. Study selection and data extraction

Six reviewers, divided in two groups (A.F., E.E., and L.L.; A.A.B., E. M., and C.R.) independently performed study selection and data extraction. Disagreements were resolved through consultation with a seventh reviewer (C.O.). Articles were excluded if they (1) did not address the aims of the review; (2) did not report original data (e.g., editorial); (3) did not provide an explicit definition of frailty; or (4) were duplicates.

The full texts of the articles selected by one or more reviewers were retrieved for evaluation. The two groups independently read the full texts and extracted data for the following variables: (1) first author and year of publication; (2) country, study design, and inclusion criteria; (3) exclusion criteria; (4) number of individuals with CA in the sample or subsample, categorized by subtype of amyloid deposit (ATTRw, ATTRv, AL); (5) mean (±SD) or median age (IQR); (6) sex (percentage of women); (7) description of the frailty assessment tool; and (8) prevalence of frailty within the sample. Data extraction was independently reviewed by a third assessor and any discrepancies were resolved by consensus. The number of abstracts screened, and studies assessed for eligibility, together with reasons for exclusion at each stage, are presented in Fig. 1 (PRISMA flow-chart).

### 2.3. Assessment of risk of bias

The methodological quality of the studies included in the systematic review was evaluated with the Newcastle Ottawa Scale (NOS) (Stang, 2010). Two assessors independently rated each study and consensus discussion was used to resolve any disagreement. A score $> 7$ was considered high quality, 5–7 a moderate quality, and $< 5$ a low quality.

### 2.4. Statistical analysis

Heterogeneity was quantified using $I^2$ statistics, with values $> 75$ % indicating substantial heterogeneity. The Cochran's Q test was used to assess the statistical significance of heterogeneity.

Subgroup analyses were conducted according to the frailty assessment tool used. In studies using multiple tools, the most widely used and validated tool, as determined by prior literature, was selected. For instance, in Broussier's study (Broussier et al., 2025), the Fried phenotype was chosen over the SEGA scale (Kim and Rockwood, 2024). Regarding the Clinical Frailty Scale (CFS), we used a threshold of $\geq 4$ to define frailty, consistent with the latest guidance from its developers (Rockwood and Theou, 2020), and expert consensus on when to initiate frailty-specific interventions (Kim and Rockwood, 2024).

The meta-analysis was conducted using a random-effects model to account for variability across studies. Prevalence estimates were pooled using a logit transformation. Pooled estimates were reported with relative 95 % confidence intervals (CIs).

All statistical analyses were conducted using SAS and R (metafor package), with statistical significance determined using the $\chi 2$ test ($P < 0.05$).

## 3. Results

Fig. 1 shows the PRISMA flow chart. A total of 565 articles were retrieved from six databases. Of these, 156 duplicates were identified and removed. After screening titles and abstracts, 390 articles were excluded and 6 could not be retrieved, leaving 13 articles for full-text assessment. Among these, 3 were excluded in favor of updated versions, and 4 were excluded for not reporting frailty prevalence. In total, 6 studies met the inclusion criteria and were included in the review.

### 3.1. Risk of bias assessment

The quality of the included studies was heterogeneous. Based on the

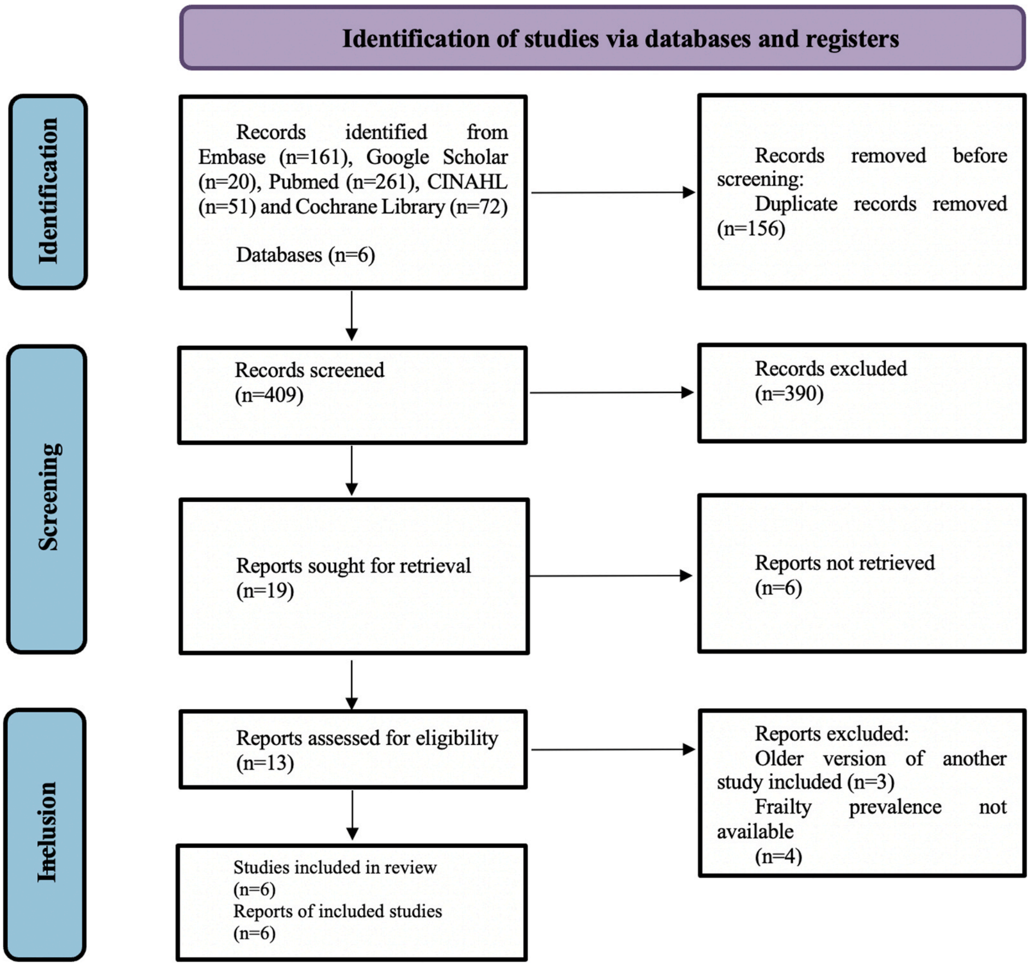


**Fig. 1.** PRISMA flow-chart.

risk of bias evaluation, two studies were classified as high quality, three as moderate quality, and one having an elevated risk of bias.

### 3.2. Study description

The main characteristics of the 6 studies eligible for this systematic review are summarized in Table 1. The overall number of participants was 1422, the mean/median age ranged from 78 to 84, and 9–19 % were female. Three studies were prospective, two were retrospective, and one cross-sectional. Four studies were carried out in Europe/United Kingdom and two in Canada.

### 3.3. Frailty assessment

As shown in Fig. 2, a variety of frailty assessment tools were employed across the six studies included in this review.

Fumagalli et al. (2024b) used a modified Frailty Index (mFI), derived from 11 variables selected from the 70-item Canadian Study of Health and Aging Frailty Index (Rockwood and Mitnitski, 2007). These variables encompassed non-independent functional status, diabetes mellitus, chronic obstructive pulmonary disease or pneumonia, heart failure, myocardial infarction, angina or coronary revascularization, hypertension, peripheral vascular disease, impaired sensorium, and a history of transient ischemic attack (TIA) or cerebrovascular events (with or without deficits). Frailty was defined by a mFI ratio $\geq$ 0.36; however, the authors did not specify the criteria used to determine this cutoff.

Broussier's study (Broussier et al., 2025) employed both the Fried's Frailty Phenotype (Fried et al., 2001) and the modified Short Emergency Geriatric Assessment (m-SEGA) (Oubaya et al., 2014). The operational criteria to define the five items to assess frailty according to the Fried's Phenotype were unintentional weight loss (>4.5 kg in the past 12 months), muscle weakness, fatigue (defined by a "yes" response to the question, 'Have you experienced significant or unusual tiredness in the past year?'), reduced walking speed, and low physical activity. The m-SEGA, in contrast, evaluates 13 graded items including age, living arrangements (home, home with professional assistance, or nursing home), medication count, mood, self-perceived health, falls in the past six months, nutrition, comorbidities, IADL, mobility, meal management, and cognitive function. Each item is scored from 0 to 2, and the total score categorizes individuals as 'not very frail' (score $\leq$8), 'frail' (score 8–11), or 'very frail' (score >11).

Cazalbou's study (Cazalbou et al., 2023) used the Geriatric 8 (G8) score, a screening tool comprising eight questions evaluating food intake over the past three months, weight loss during the last three months, mobility, neuropsychological issues, body mass index, daily use of more than three prescription medications, self-rated health status, and age (Bellera et al., 2012). Individuals with a G8 score > 14 were classified as frail.

Fumagalli et al. (2025a), Shahi et al. (2024), and Fine and McMillan (2021) employed the CFS, a validated, judgment-based tool that assigns scores from 1 (very fit) to 9 (terminally ill) and is extensively used in geriatric and cardiovascular populations to predict adverse outcomes (Church et al., 2020). However, the studies used different cutoffs for defining frailty: Fumagalli 2025 and Shahi adopted a threshold of CFS $\geq$ 4, while Fine and McMillan (2021) used CFS $\geq$ 5, reflecting variability in the operationalization of the scale.

**Table 1**
Characteristics of the studies included.

| Author (year) | Country, definition of study population (inclusion criteria) | Exclusion Criteria | No., subtype of amyloid diagnosed (ATTRwt, ATTRv, AL) | Enrollment period | Age Mean (SD) or median (IQR) | Women (%) | Frailty definition and measure | Frailty prevalence | NOS |
|---|---|---|---|---|---|---|---|---|---|
| Broussier et al. (2025) | France, cross-sectional comparative, outpatient clinic, HF patients with or without ATTR-CA | Age under 60, acute HF, systemic disease with cardiac involvement, treatment with tafamidis > 3 months, ATTRv, others* | n = 68, ATTRwt | April 2018 – April 2021 | 81.8 (6.3) | 13 % | SEGA, Fried | 48.5 % SEGA 57.4 % Fried | 7 |
| Fumagalli et al., 2025a | United Kingdom and Italy, retrospective study, CGA at baseline | - | n = 880, ATTR | September 2019 – March 2023 | 80 (75–84) | 13.3 % | CFS ≥ 4 | 57.1 % | 7 |
| Fumagalli et al., 2024b | Italy, prospective study, > 75yo, outpatient clinic | Cognitive impairment Language (only italian) Refusal | n = 138, ATTR (81.9 % wt, 18.1 % v) | September 2021 – September 2023 | 79 (75–84) | 16.7 % | Modified Frailty Index (mFI) | 14.5 % | 6 |
| Shahi K. et al. (2024) | Canada, retrospective study, outpatient clinic | - | n = 139, ATTR (94.2 % wt, 5.8 % v) | May 2011 – November 2022 | 80.9 (74.3–86.6) | 12.9 % | CFS ≥ 4 | 74.1 % | 9 |
| Cazalbou et al. (2023) | France, prospective study, > 75 yo, outpatient clinic | AL-Amyloidosis, refusal | n = 52, ATTR (92 % wt, 8 % v) | January 2020 – April 2021 | 84 (4) | 19 % | G8 | 75 % | 3 |
| Fine and McMillan (2021) | Canada, prospective study, ≥ 65 yo | AL-Amyloidosis, patients with hereditary transthyretin amyloidosis with non-pV142I mutation | n = 145, ATTR (93.8 % wt, 6.2 % v) | January 2014 – December 2019 | 78 (73–84) | 9 % | CFS ≥ 5 | 39 % *68.3 % *CFS ≥ 4 | 8 |

* Others: previous heart transplantation, uncontrolled solid tumor, language barrier, and refusal.
Abbreviations: ATTR-CA, transthyretin cardiac amyloidosis; HF, heart failure; wt, wild-type; v, variant; AL, light-chain amyloidosis; CFS, clinical frailty scale; CGA, Comprehensive Geriatric Assessment; SEGA, Short Emergency Geriatric Assessment; G8, geriatric 8 questionnaire.

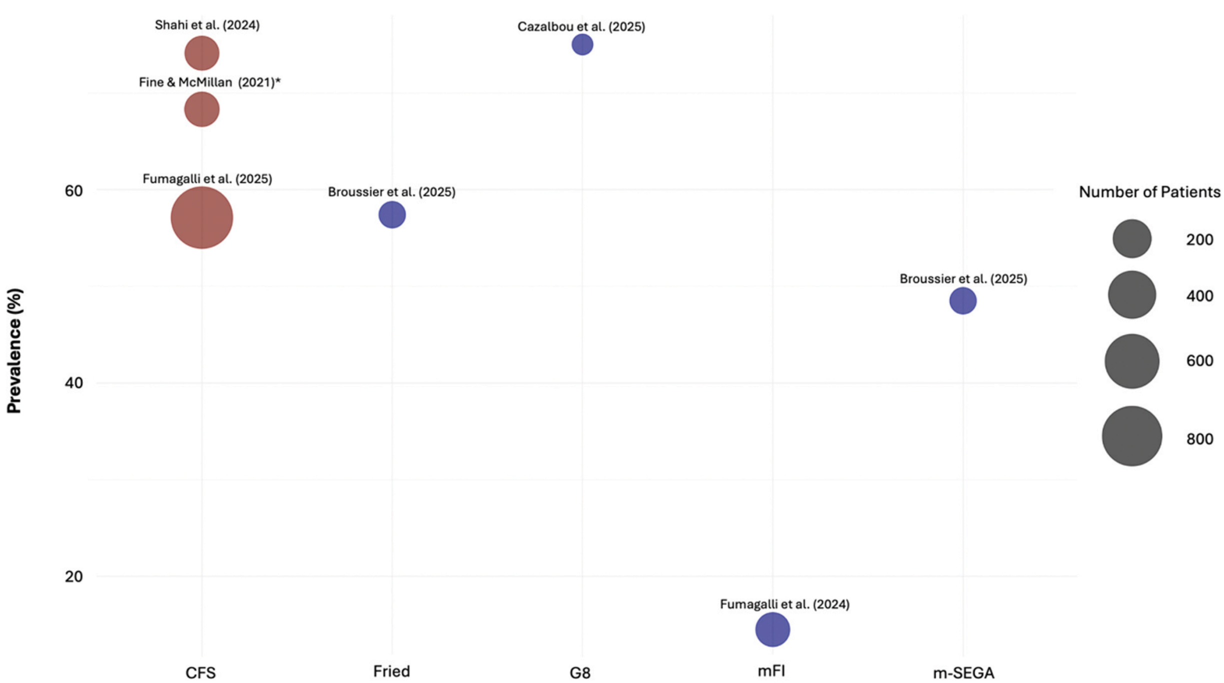


**Fig. 2.** Bubble Chart representing frailty prevalence and assessment tools across included studies. **Footnotes.** * Frailty prevalence reported here is based on the criterion chosen in the other two studies using the Clinical Frailty Scale (CFS ≥ 4). Abbreviations: CFS, Clinical Frailty Scale; Fried, Fried Phenotype; G8, geriatric 8 questionnaire; mFI, modified Frailty Index; m-SEGA, modified Short Emergency Geriatric Assessment.

*3.4. Amyloidosis diagnosis and assessment*

All studies included in this review focused on patients with ATTR-CA. Diagnosis was established based on the following criteria: a strong uptake on bone scintigraphy (Perugini score ≥2) in the absence of monoclonal gammopathy enabled a non-invasive diagnosis. In cases of low-grade scintigraphy uptake or evidence monoclonal gammopathy, confirmation of ATTR-CA was obtained through tissue biopsy, either from cardiac or extracardiac sites. Following diagnostic confirmation, genetic testing was offered to differentiate between the hereditary and wild-type forms of ATTR-CA. Broussier's study (Broussier et al., 2025) included only patients with wild-type ATTR-CA, while Fine and McMillan's study (Fine and McMillan, 2021) excluded those with hereditary transthyretin amyloidosis carrying non-p.V142I mutations. The remaining four articles included patients with both wild-type and hereditary forms of ATTR-CA. Patients with light-chain amyloidosis were excluded from all studies.

The clinical severity of the disease was assessed in four studies using the National Amyloid Center (NAC) staging system, as proposed by Gillmore in 2018 (Gillmore et al., 2018). The NAC staging system is based on renal function (estimated glomerular filtration rate <45 mL/min/1.73 m$^2$) and NT-proBNP levels (>3000 pg/mL), categorizing patients into stages I, II, and III depending on the number of the abnormal parameters involved.

### 3.5. Prevalence and clinical significance of frailty in amyloidosis

The prevalence of frailty varied widely among the included studies, ranging from 14.5 % to 75 %. Fumagalli et al., 2024 reported a frailty prevalence of 14.5 % using the m-FI tool. Notably, frailty was independently associated with poorer perceived quality of life (QoL), according to Kansas City Cardiomyopathy Questionnaire (KCCQ), even after adjusting for age, disease duration, New York Heart Association (NYHA) class, and ATTR-CA severity (Fumagalli et al., 2024b).

Broussier et al. reported a frailty prevalence of 57.4 % using the Fried's phenotype and 48.5 % using the SEGA tool (Broussier et al., 2021), while Cazalbou reported a frailty prevalence of 75 % using the G8 tool (Cazalbou et al., 2023). Cazalbou et al. found that frailty was more common in individuals with severe ATTR-CA (NAC stage II and III), suggesting a potential link between disease severity and frailty status.

Using a CFS ≥ 4 cut-off, Shahi found a frailty prevalence of 74.1 %, further showing that frailty independently predicted all-cause and cardiovascular mortality, even after adjustments for age, systolic blood pressure, laboratory and imaging parameters (Shahi et al., 2024). In the study by Fine and McMillan, frailty – defined as a CFS score ≥ 5– was identified in 39 % of participants (Fine and McMillan, 2021), but prevalence increased to 68.3 %, when a CFS ≥ 4 cutoff was applied, aligning with Shahi's results (Shahi et al., 2024). Importantly, frailty remains independently associated with mortality, after adjustments for NAC stage, NYHA class, and treatment with tafamidis. Fumagalli et al. (2025a) reported on the largest cohort (n = 880 individuals), finding a frailty prevalence of 57.1 % and demonstrating a graded increase in mortality risk across CFS categories (HR 2.9 for CFS 4–5, HR 4.1 for CFS 6–7, and HR 9.7 for CFS 8–9), independent of established predictors such as NAC stage.

### 3.6. Evidence from meta-analysis

Three studies Broussier et al. (2025); Cazalbou et al. (2023); Fumagalli et al. (2024b) employed different frailty assessment tools, raising concerns about the comparability of reported prevalence rates. Assuming similar underlying populations, we performed a chi-square test (p-value <0.001), to assess whether the observed variability could be attributed to chance. The result (p-value <0.001) suggests that the differences between studies are systematic, likely reflecting heterogeneity in frailty measurement methods (m-FI, Fried, and G8, respectively). Accordingly, we restricted the meta-analysis to studies that used CFS as the frailty assessment tool (Fine and McMillan, 2021; Fumagalli et al., 2025a; Shahi et al., 2024). In this subset (N = 1164), the pooled estimate of prevalence was 66 % (95 % CI, 57–74 %). As reported in Fig. 3, heterogeneity was substantial ($I^2 = 89.1$ %, $p < 0.001$).

## 4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to assess the prevalence of frailty and its clinical implications in patients with ATTR-CA. The findings reveal a substantial variability in reported frailty prevalence, ranging from 14.5 % to 75 % across studies; however, when the same frailty assessment was employed, namely CFS, the pooled prevalence was 66 % (95 % CI, 57–74 %). Moreover, several studies found a significant association between frailty and adverse clinical outcomes, including increased mortality and reduced QoL.

Since the conceptualization of frailty in 2001(Fried et al., 2001; Rockwood et al., 2005), over 60 assessment tools have been developed (Buta et al., 2016), none of which has proven unequivocally superior, leading to the proliferation of further tools. Comparative studies also reveal differences in the conceptual construction of the tools' items, measured domains, and clinometric properties (Buta et al., 2016; Dent et al., 2016; Kim and Rockwood, 2024; Theou et al., 2013). The high heterogeneity in frailty prevalence observed across studies in our systematic review likely reflects the differences in the assessment tools employed and the cut-off values applied. Certain tools exhibit methodological limitations, either due to questionable development methodologies or inappropriate use for diagnostic purposes, despite being originally designed for screening. For instance, the m-FI incorporated only 11 health deficit variables(Fumagalli et al., 2024b), whereas a robust frailty index should ideally assess at least 30 variables (e.g. symptoms, signs, diseases and functional limitations), covering multiple physiological systems and domains(Searle et al., 2008; Theou et al., 2023). Additionally, the m-FI used a cut-off to define the presence of frailty (i.e., ≥0.36) that is markedly higher than the standard used by most Frailty Indices (≥0.25). Similarly, the m-SEGA scale evaluates frailty through a 13-item assessment (Zulfiqar et al., 2023), but given its alignment with Rockwood et al.'s health deficit accumulation concept, it might be possible that the limited number of variables assessed is insufficient to fully capture the overall complexity of frailty (Searle et al., 2008). The G8 tool also raises concerns, particularly due to the inclusion of age as one of its assessment items. Since the concept of frailty was originally proposed to differentiate chronological from biological aging, including age may undermine this distinction, as individuals of the same chronological age can respond differently to the same stressor (Bellelli et al., 2024). Moreover, the G8 was specifically

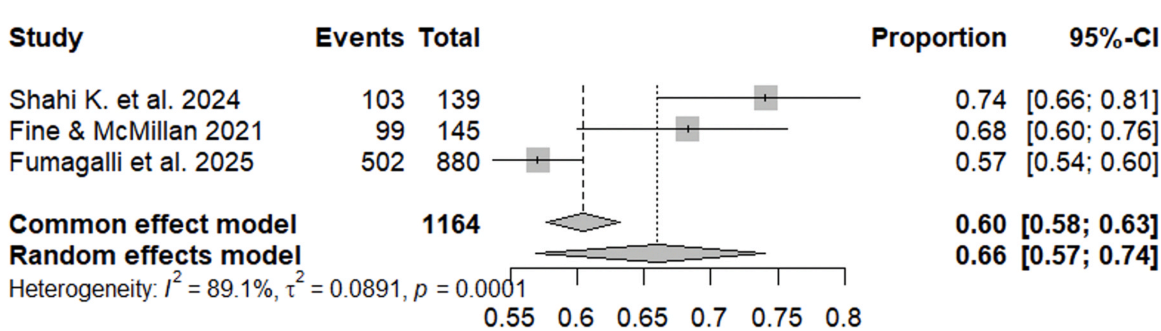


**Fig. 3.** The pooled prevalence of frailty estimated using a random-effects model with logit transformation.

developed as a screening tool to identify patients requiring a more comprehensive assessment, which may subsequently lead to a frailty diagnosis (Bellera et al., 2012).

Among studies using the CFS, the meta-analysis yielded a pooled frailty prevalence of 66 % (95 % CI, 57–74 %). However, the substantial heterogeneity observed ($I^2 = 89.1$ %, $p < 0.001$) warrants further consideration. Being inherently subjective, the CFS heavily relies on assessor's clinical judgment; nonetheless formal training in its administration is uncommon outside geriatric practice (Theou et al., 2021), potentially introducing rater bias, especially among less experienced assessors. Notably, only one study (Fumagalli et al., 2025a) reported that CFS assessments were performed by geriatricians or nurses with specialized training in frailty. Thus, variability in assessor expertise may have contributed to the observed heterogeneity. Additionally, differences in patient populations may have also influenced prevalence estimates.

A high prevalence of frailty is, however, not entirely unexpected. Given that ATTR-CA primarily affects older adults, frailty prevalence aligns with rates reported in the general geriatric population and in patients with other cardiovascular diseases (Denfeld et al., 2017; Liperoti et al., 2021; Proietti et al., 2022). Specifically, a recent meta-analysis of 26 studies involving a total of 6896 patients reported a frailty prevalence of nearly 50 % in heart failure, with five studies reporting rates exceeding 70 % (Denfeld et al., 2017).

Beyond its prevalence, frailty holds significant prognostic value, further supporting the rationale for its systematic screening in ATTR-CA (Denfeld et al., 2017). Most studies included in this review reported an association between frailty and adverse outcomes, particularly increased mortality. Shahi et al. identified frailty as an independent predictor of all-cause and cardiovascular mortality, while Fine and McMillan found that frailty remained a significant mortality predictor after adjusting for disease severity, NYHA class, and tafamidis use. Fumagalli et al. (2025a) demonstrated the prognostic impact of frailty, independent of other recognized strong prognostic factors, such as NT-proBNP, NYHA functional class and multiple chronic conditions. Notably, higher CFS categories were associated with incrementally greater risk of mortality. These findings align with prior evidence that frailty is a key prognostic determinant in cardiovascular disease, independent of age and multimorbidity (James et al., 2024). Although preliminary, the observation that frailty predicts mortality even in tafamidis-treated patients suggests its potential relevance in therapeutic decision-making. In older adults, where frailty is associated with short-term mortality risk and diminished treatment efficacy, incorporating frailty assessment into routine evaluation could facilitate risk stratification and inform individualized management strategies.

Frailty is also strongly associated to QoL in ATTR-CA. Fumagalli et al., 2024 demonstrated that frailty independently correlates with lower scores on the KCCQ, a well-established disease-specific QoL measure, adjusting for disease severity and other clinical variables. Given the demonstrated impact of tafamidis treatment on QoL in terms of KCCQ scores (Maurer et al., 2018), it could therefore be hypothesized that disease-modifying treatments may have a role even in frail older patients with ATTR-CA. However, as discussed before, frailty remains an independent predictor of poor survival, raising critical considerations regarding the appropriate use of disease-modifying drugs, particularly in the context of cost-effectiveness constraints that may limit access to such treatments (Kazi et al., 2020). In frail older adults, the potential futility of pharmacological therapies should be carefully weighed against the expected benefits, as has already been proposed for several other cardiologic procedures (Baldasseroni et al., 2020; Ferry et al., 2025). In this regard, frailty assessment may be instrumental in informing treatment decisions, by integrating considerations of clinical benefit, anticipated outcomes, costs and overall risk/benefit profiles. Although frailty itself was not explicitly measured, recent findings from a cohort of patients with ATTR-CA support this notion, showing that functional status, as measured by ECOG-PS, was independently associated with mortality (Milani et al., 2025). This underscores the prognostic relevance of functional status and highlights the limitations of solely relying on cardiac parameters and comorbidities in clinical decision-making.

Overall, the findings of our review — particularly the high prevalence of frailty among individuals with ATTR-CA — underscore the importance of integrating Comprehensive Geriatric Assessment (CGA) into routine clinical practice. This approach would support more personalized, needs-based care, in line with recent expert recommendations (Fumagalli et al., 2024a; Kittleson et al., 2023). Given its multidimensional, multidisciplinary, and multicomponent structure, CGA remains the most effective strategy for identifying older patient needs and developing individualized care plans (Pilotto et al., 2017). Preliminary evidence in the context of ATTR-CA suggests that CGA may enhance risk stratification, reduce age-related bias, and, by addressing potentially reversible geriatric syndromes, improve clinical outcomes (Fumagalli et al., 2025b). Further studies are needed to expand the evidence of CGA implementation in the setting of specific amyloidosis subtypes for which data are more limited (e.g. variant ATTR-CA and AL).

A critical next step will be to optimize interdisciplinary collaboration between cardiologists and geriatricians. Drawing on experiences from cardiogeriatric care models in heart failure (Okoye et al., 2025), the use of brief frailty screening tools may help identify patients most likely to benefit from CGA. This is particularly relevant in resource-limited settings, where it may not be feasible to offer a full geriatric assessment to all patients with ATTR-CA. Further efforts—both in research and clinical practice—are needed to develop a more comprehensive model of care in ATTR-CA, addressing not only disease-specific factors but also broader patient needs.

### 4.1. *Strengths and limitations*

Key strengths of this systematic review and metanalysis lie in its rigorous methodology, including a comprehensive literature search, systematic study selection, and thorough quality assessment. Additionally, the diagnostic criteria for CA were largely consistent across studies. However, several limitations warrant consideration. The limited availability of relevant literature constrained the number of included studies, though no apparent publication bias was identified. Potential overlap of patients across studies was carefully assessed during study selection and appears unlikely, although it cannot be entirely excluded in the absence of individual-level data. Furthermore, the heterogeneity in frailty assessment tools and proportions limited the results of the meta-analysis. Moreover, in patients with variant ATTR-CA forms, frailty assessment might be influenced by a higher prevalence of neuropathy due to nerve involvement.

Lastly, the very low number of variant ATTR-CA and the absence of AL amyloidosis may limit the generalizability of these findings to wild-type ATTR-CA.

## 5. Conclusion

This is the first systematic review and meta-analysis to examine frailty in ATTR-CA, revealing a significant prevalence, particularly when assessed with CFS. Frailty was associated with adverse outcomes, including increased mortality and reduced QoL. Therefore, standardized frailty assessment should be considered in routine clinical practice for patients with ATTR-CA.

## CRediT authorship contribution statement

Alberto Finazzi: Conceptualization, Methodology, Investigation, Writing – original draft, Visualization. **Emma Esposito**: Data curation, Investigation, Writing – review & editing, Visualization. **Chiara Riva, Elisabetta Mangili, Lorenzo Lodovici, Adriana Antonella Bruni**: Investigation, Writing - Review & Editing. **Stefano Perlini, Francesco Musca, Daniela Pini, Elena Pinardi, Maria Cristina Ferrara**: Writing

– review & editing. **Antonella Zambon**: Formal analysis, Writing – review & editing. **Chukwuma Okoye**: Conceptualization, Supervision, Investigation, Writing – review & editing. **Giuseppe Bellelli**: Conceptualization, Supervision, Project administration, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2025.102903.

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