Frailty Assessment Tools in Chronic Kidney Disease: A Systematic Review and Meta-analysis

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Rationale & Objective: Frailty represents a loss of physiologic reserve across multiple biological systems, confers a higher risk of adverse health outcomes, and is highly prevalent among people with chronic kidney disease (CKD). We evaluated the measurement properties of frailty tools used in CKD and summarized the association of frailty with death and hospitalization.

Study Design: Systematic review and meta-analysis.

Setting & Study Populations: Studies assessing multidimensional frailty tools in adults at any stage of CKD and evaluating a measurement property of interest as per the Consensus-based Standards for the Selection of Health Measurement Instruments taxonomy.

Selection Criteria for Studies: Observational studies and randomized trials.

Data Extraction: Risk and precision measurements; measurement properties.

Analytical Approach: The Comprehensive Geriatric Assessment was the clinical standard for frailty identification. We pooled data using random effects models or summarized with narrative synthesis when data were too heterogenous to pool.

Results: We included 105 studies with data for at least one of the following: discriminative (n = 84; 80%), convergent (n = 20; 19%), and criterion validity (n = 2; 2%); responsiveness (n = 9; 9%) and reliability (n = 1; 0.1%). For the Fried Frailty Phenotype (FFP), the pooled adjusted HR (aHR) for mortality was 2.01 (95% confidence intervals [CI], 1.35-2.98; $P = 0.001$; $I^2 = 58\%$) and 1.89 (95% CI, 1.25-2.85; $P = 0.002$; $I^2 = 0\%$) for hospitalization in kidney failure (KF) populations. The pooled aHR for the Clinical Frailty Scale for mortality in pre-frail versus non-frail was 1.75 (95% CI, 1.17-2.60; $I^2 = 26\%$) and 2.20 (95% CI, 1.00-4.80; $I^2 = 66\%$) in frail versus non-frail. The Fatigue, Resistance, Ambulation, Illness, and Loss of weight scale showed consistent discriminative validity for higher mortality in non-dialysis CKD. The modified FFP (self-reported) showed acceptable discriminative validity and agreement with the FFP in patients with KF. In CKD and KF populations, agreement between clinicians' subjective impression of frailty and frailty tools was low.

Limitations: Few studies compared the accuracy of frailty tools to the Comprehensive Geriatric Assessment. Only 1 study reported reliability. Studies were of overall low-moderate quality.

Conclusions: The FFP and Clinical Frailty Scale showed acceptable discriminant validity for clinical outcomes, and the modified FFP is an alternative tool to use if direct measurements are not feasible. The evidence does not support the use of clinicians' subjective impression to identify frailty.

Complete author and article information provided before references.

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Frailty is defined as a loss of physiologic reserve across multiple biological systems or a state of heightened vulnerability to stress.[1] Among people with chronic kidney disease (CKD), the prevalence of frailty is inversely related to kidney function, with as many as 71% of people with dialysis-dependent kidney failure assessed as frail.[2-5] Frail dialysis patients have a lower quality of life, a higher risk of hospitalization and mortality, are less likely to receive a kidney transplant, and have more postoperative complications than their non-frail counterparts.[4,6,7]

The Comprehensive Geriatric Assessment (CGA) or Geriatric Assessment (GA) is used by trained clinicians to quantify frailty and identify which domains are affected (eg, cognition, mood, physical health) and is considered the clinical standard.[8] However, the CGA has practical limitations, such as the time required for the assessment and lack of access to or funding for its multidisciplinary assessments, and is generally not used for case identification. In both CKD and non-CKD populations, it is unclear which of the over 90 unique tools are best suited for frailty identification, prognostication, or measuring changes in response to frailty interventions.[9-11]

Frailty measures are commonly operationalized as a physical phenotype using the 5 physical components developed by Fried et al[12] or as age-related cumulative deficits in multiple systems as measured by the Frailty Index (FI).[4,5] To build on these models and to address some of their limitations, numerous frailty assessment tools have been developed to include geriatric syndromes and multidimensional concepts (eg, psychological, social). These tools also differ in terms of whether they are self-reported and/or require performance-based measures and expertise to complete. For example, the Fried Frailty Phenotype (FFP) includes self-report and performance-based measures (a walking test and grip strength), whereas a modified version of the FFP is entirely self-reported.[4] The FI generally includes 30-70 items from multiple domains, which, although lengthy, can be collected from health data.[13] The Clinical Frailty Scale

PLAIN-LANGUAGE SUMMARY

Frailty is a medical condition characterized by the loss of physiological reserve across multiple domains or an increased vulnerability to stress. Frailty is common among people with chronic kidney disease and is associated with poor health outcomes. There are numerous tools to assess frailty but the measurement properties of these tools, either for frailty identification, prognostication, or measuring changes in response to frailty interventions have not been identified in people with CKD. This information is important as frailty in CKD may be confounded by factors, such as those associated with uremia. By conducting this systematic review and meta-analysis, we found that frailty status, as measured by the Fried Frailty Phenotype and the Clinical Frailty Scale provided important prognostic information beyond age and clinical factors on the risk of mortality and hospitalization, with an approximate doubling in the hazard for these events among people with kidney failure. We also found that in both the kidney failure and non-dialysis CKD populations, the agreement between clinicians' subjective impression of frailty and the FFP was low. There were limitations across studies, including heterogeneous follow-up period and covariate adjustment that may have influenced the results. In order to make recommendations for frailty tools across measurement domains, future studies should compare the diagnostic accuracy to the clinical standard, geriatric assessment, and examine responsiveness to change.

(CFS) uses the clinical assessment and judgment to classify the patient into 1 of 8 frailty risk scores.[14] Importantly, the clinician's subjective "yes/no" impression or "gut instinct" is a commonly used approach with unclear accuracy.[15,16]

Frailty identification in people with CKD may be confounded by several factors. For example, a high degree of physical impairment, such as that associated with uremic symptoms and low nutritional intake, may limit the predictive accuracy of the phenotypic approach.[17] Weight changes due to fluid loss or gain may influence reliability. Therefore, we aimed to systematically review the validity and reliability of multidimensional frailty tools in people across the spectrum of CKD. We also aimed to summarize the association between frailty and all-cause death and hospitalizations.

METHODS

Overview

We followed the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) initiative and Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[18-20] The protocol was registered in PROSPERO as CRD42021234558.

Data Sources and Search Strategy

A health sciences librarian (S.M.C.) designed a search of the following databases: PROSPERO, OVID Medline, OVID EMBASE, OVID Health and Psychosocial Instruments, Cochrane Library (CDSR and Central), EBSCO CINAHL, Web of Science Proquest Dissertations and Theses Citation Index, and SCOPUS. We used controlled terms (eg, MeSH, Emtree, etc) and key words representing the concepts "chronic kidney disease," "frailty," and "measures or instruments" (Table S1). No limits were applied. We searched databases from inception to April 1, 2024. We exported search results to the Covidence systematic review software (Veritas Health Innovation) for screening (www.covidence.org).

Eligibility Criteria

Two reviewers (A.P., A.M.L., or S.T.) independently screened titles and abstracts using predetermined eligibility criteria, and the third reviewer resolved disagreements. We retrieved full-text articles of studies published in English considered potentially relevant by one or both reviewers and assessed them for inclusion using the following eligibility criteria: randomized clinical trials or observational studies involving adult participants (aged greater than or equal to 18 years) with CKD (dialysis-dependent and non-dialysis) or kidney transplant recipient and (a) frailty assessment using at least one established multidimensional tool, defined as a tool assessing 2 or more domains of frailty[21] and (b) at least one measurement property of the tool(s) was evaluated using the COSMIN taxonomy for items of relevance: construct validity, criterion validity, reliability, or responsiveness.[20] For construct validity, we decided a priori to only include articles with mortality and hospitalizations as outcomes. Consistent with clinical practice, we used the CGA/GA as the clinical standard or "criterion" for the diagnosis of frailty.[8] We used the measurement property definitions as per COSMIN[20] (Box 1).

Data Extraction

Two reviewers (A.M.L., A.P.) independently extracted data using a standardized database. We recorded the following items in the database: study characteristics (year, country, design, population type, sample size), participant information (demographics, comorbid conditions, dialysis modality/duration, time since transplant, CKD severity, estimated glomerular filtration rate), and information on the frailty assessment tool(s) administered. To evaluate the diagnostic properties of each tool, we extracted data on diagnostic/screening performance measures (eg, sensitivity), summary statistics measuring strength of relationships (eg, correlation), summary statistics comparing frail versus non-frail groups and discrimination and calibration

Box 1. Measurement Properties With Corresponding Definitions

Measurement Property[a]	Definition
Construct validity (hypothesis testing)	
Discriminative	The degree to which frailty scores are consistent with the hypothesis that the tool can detect differences between subgroups
Convergent	The degree to which the scores agree with the hypothesis tested
Criterion validity	Correlation with the clinical standard
Reliability	The degree to which frailty tool scores remain unchanged for repeated measurements under different conditions (includes measurement error)
Responsiveness	The ability of the tool to detect change over time

[a]Mokkink et al.[20]

measures of model prediction for the a priori outcomes of all-cause mortality and hospitalizations (eg, hazard ratios, area under the receiver operating characteristic curve), and frailty scores measured at multiple time points. To estimate responsiveness, we extracted data to calculate the standardized response mean (mean difference between measurements divided by the standard deviation of the change).[22]

Data Synthesis

We performed the analyses using Stata/MP, version 17 (StataCorp, LLC). Because of the expected diversity between studies, we decided a priori to combine results (eg, hazard ratios, odds ratios, c-statistics, κ coefficients) using random effects models.[23-25] We pooled outcomes by population, frailty assessment tool, measurement property, and summary statistic, given sufficient data. We categorized study populations by CKD severity and modality as follows: (a) kidney failure: dialysis and non-dialysis stage 5 CKD, and "preemptive" kidney transplant recipient; (b) mixed: dialysis combined with non-dialysis CKD; (c) non-dialysis CKD; and (d) post kidney transplant. We prioritized adjusted results over unadjusted if both were presented; we calculated unadjusted odds ratios for studies in which only counts of outcomes of interest were presented (and no other usable results were available). We pooled adjusted results separately from unadjusted results and quantified statistical heterogeneity using the I^2 statistic.[26] For studies with overlapping populations that presented the same type of result, we pooled outcomes from the larger cohort. For outcomes that could not be pooled, we narratively summarized the findings.

Methodological Risk of Bias

Two reviewers (A.P., S.T., or A.M.L.) individually assessed methodological quality using the COSMIN Risk of Bias Checklist for measurement properties.[27] We assigned the overall quality rating for each measurement property within a study as "very good," "adequate," "doubtful," or "inadequate" using the lowest score of any of the criteria within each measurement property domain.[27] For studies that assessed multiple properties, we assigned the "lowest scores" rating for the overall risk of bias for the study.

Quality Assessment of the Accuracy of Measurement Properties

We rated the accuracy of the measurement properties within each study as per the COSMIN recommendations[18]: "sufficient (+)," "insufficient (−)," or "indeterminate (?)." To receive a "sufficient (+)" rating, we required the following: for results measuring strength of relationships (eg, correlation), a value ≥0.5; for diagnostic/screening performance measures, we considered sensitivity and specificity together where sensitivity ≥0.8 and specificity ≥0.6 were acceptable; for percentage agreement, ≥70% was required; for area under the curve, ≥0.7 was required; and for summary statistics comparing frail versus non-frail groups, results that rejected the applicable null value were acceptable. Standardized response mean values of 0.2, 0.5, and 0.8 represented small, moderate, and large responsiveness, respectively.[28] For all results (except those measuring strength of relationships), we also considered the width of the confidence intervals (CIs) in determining the rating.

Overall Quality, GRADE Determination

We evaluated the overall quality of the evidence for each measurement property per tool using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) rating, and based on the methodological risk of bias, COSMIN's accuracy of measurement properties (ie, inconsistency), imprecision, and indirectness. Each measurement property per tool started with high quality of evidence, which we downgraded (moderate, low, very low) as each of the 4 factors were evaluated. For methodological risk of bias, we downgraded the evidence if <50% of ratings were "very good" or "adequate." For inconsistency, we downgraded the evidence if <75% of results were either "+" (sufficient) or "−"(insufficient), which generally reflected summary statistics being in the same direction, and examined for overlap in CIs (for both pooled and unpooled results). For imprecision, we downgraded 1 level if the total study population was between 50-100 and 2 levels if <50. For indirectness, we considered several elements depending on the type of measurement property, including important adjustment variables, type of follow-up (eg, "post kidney transplant"), and length of follow-up and downgraded 1 level for heterogeneity. For measurement properties with only a single study contributing results, we assessed both inconsistency and indirectness as "unknown." If overlapping studies existed, we first chose the study contributing to pooled results; otherwise, we chose the largest study when assessing GRADE.

RESULTS

Study Characteristics

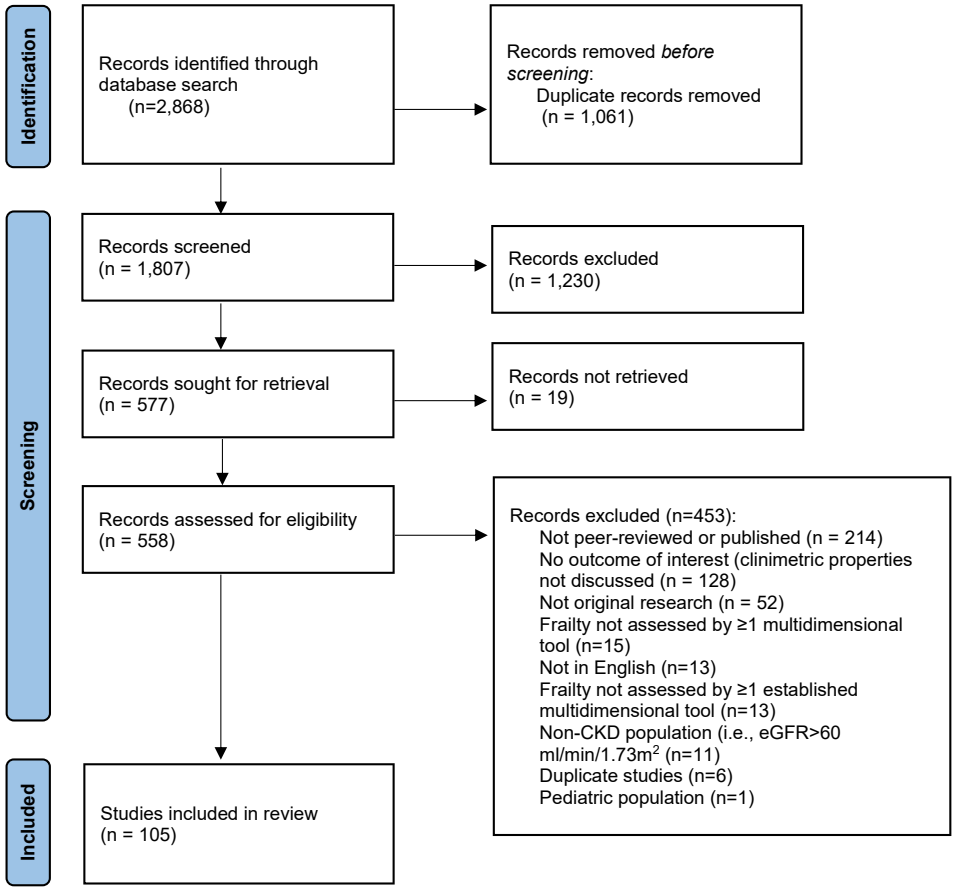
Of the 1,807 unique records identified, 105 studies were included (Fig 1). Of the 105 studies, 95 were cohort studies (70 prospective, 25 retrospective), 8 cross-sectional studies, 1 secondary analysis of a randomized clinical trial, and 1 randomized clinical trial (Table 1[3,29-131]). The subpopulation with the highest number of studies was kidney failure (n = 81) followed by non-dialysis CKD (n=18) and mixed (n = 6). Forty-three of the kidney failure and 8 of the non-dialysis CKD studies contained overlapping populations. Among the studies with kidney failure populations, 55 studies were in dialysis (including 27 overlapping studies), 20 had a mix of dialysis and stage 5 non-dialysis CKD (including 12 overlapping studies), 2 studies were in stage 5 non-dialysis, and for 4 studies, the population features were unclear (Table 1).[3,29-131] Twenty-eight studies (27%) were conducted in the United States, followed by the United Kingdom (10%), China (10%), and Canada (9%). Across the 105 included studies, 7 frailty assessment tools were most commonly evaluated: FFP (n = 48; 46%); CFS (n = 28; 27%); FI (n = 15; 14%); modified (self-reported) FFP (n = 8; 8%); Fatigue, Resistance, Ambulation, Illness, and Loss of weight (FRAIL) scale (n = 13; 12%), Groningen Frailty Index (n = 8; 8%); and GA or CGA (n = 7; 7%) (Table 1).[3,29-131]

Measurement Properties

Among the included studies, 4 measurement properties could be evaluated: construct validity (discriminative [n = 84; 80%]; convergent [n = 20; 19%]), criterion validity (n = 2; 2%), responsiveness (n = 9; 9%) and reliability (n = 1; 0.1%). Studies evaluating more than one measurement property were reported separately (Tables 2 and 3; Tables S2-S4).[3,29,30,36,38,51-53,57-59,63,64,67,70,73,74,76,78,83,85-88,91,96,98,103,105,107,121,128] Unpooled results are shown in Table S2-S4.

Construct Validity—Discriminative

In the included studies with kidney failure populations (Table 2, Table S2),[3,29,30,36,38,51-53,57-59,63,64,67,70,73,74,76,78,83,85-88,91,96,98,103,105,107] n = 64 (79%) evaluated discriminative validity, most frequently using the FFP (n = 29; 45%) followed by the CFS (n = 16; 25%), FI (n = 5; 8%), FRAIL scale (n = 5; 8%), modified FFP (n = 4;



CKD chronic kidney disease; eGFR estimate glomerular filtration rate

Figure 1. Flow diagram. Abbreviations: CKD, chronic kidney disease; eGFR, estimate glomerular filtration rate.

Table 1. Study Characteristics

Study	Country	Study Design	Number of Participants, n	Mean Age, y	Male, %	Modality or CKD Stage, %	Frailty Tool
Kidney failure							
Alfaadhel et al[3] (2015)[a]	Canada	Prospective cohort	390	63	67%	HD (77%), PD (23%)	CFS
Anderson et al[29] (2023)[b]	United Kingdom	Prospective cohort	453	63[r]	59%	HD	CFS, CFS-MDT
Anderson et al[30] (2023)[b]	United Kingdom	Prospective cohort	448	63[r]	57%	HD	CFS, EFS, FI, Fried
Anderson et al[31] (2023)[b]	United Kingdom	Prospective cohort	485	63[r]	59%	HD	CFS, EFS, FI, Fried
Anderson et al[32] (2022)[b]	United Kingdom	Prospective cohort	485	63[r]	59%	HD	CFS, EFS, FI, Fried
Aroca-Martinez et al[33] (2023)	Columbia	Prospective cohort	57	42	63%	HD	CFS
Bancu et al[34] (2017)	Spain	Retrospective cohort	320	70	59%	HD	Fried (adapted)
Barbosa et al[35] (2023)	Brazil	Prospective cohort	137	60[r]	60%	HD	CFS, FRAIL
Bloomfield et al[36] (2021)	New Zealand	Prospective cohort	138	62	49%	HD	EFS, Fried
Bouwmans et al[37] (2022)	Multiple countries	Prospective cohort	1,501	68	63%	HD (94%), PD (6%)	CFS
Brar et al[38] (2019)[c]	Canada	Prospective cohort	109	55[r]	67%	HHD (30%), PD (70%)	Fried, nurse impression, physician impression
Campbell et al[39] (2022)	United States	Prospective cohort	171	69	58%	HD (71%), PD (8%), stage 5 ND (22%)	GA
Chan et al[40] (2022)[d]	China	Prospective cohort	573	60	55%	PD	FQ
Chan et al[41] (2022)[d]	China	Prospective cohort	148	58	75%	PD	CFS
Chan et al[42] (2021)[d]	China	Retrospective cohort	432	59	54%	PD	CFS, FQ
Chan et al[43] (2022)[d]	China	Prospective cohort	167	58	77%	PD	CFS
Chao et al[44] (2020)[e]	Taiwan	Prospective cohort	33	70	45%	HD	Fried (modified)
Chao et al[45] (2015)[e]	Taiwan	Cross-sectional	46	67	43%	HD	EFS, FRAIL, GFI, G8, SF, TFI (all Chinese versions)
Chen et al[46] (2024)	United States	Prospective cohort	3,220	55	60%	HD (56%), PD (13%), stage 5 ND (31%)	Fried (original, adapted)
Chen et al[47] (2022)[f]	United States	Prospective cohort	1,113	53	61%	HD (66%), PD (15%), stage 5 ND (19%)	Fried (original, adapted)
Chu et al[48] (2019)[f]	United States	Prospective cohort	569	52	61%	HD (58%), PD (14%), stage 5 ND (27%)	Fried
Clark et al[49](2021)[a,g]	Canada	Retrospective cohort	564	62	63%	HD (79%), PD (21%)	CFS
Clark et al[50] (2017)[g]	Canada	Prospective cohort	98	61	58%	HHD (3%), HD (82%), PD (15%)	CFS, FACT-CFS, FI, Fried (modified)
Drost et al[51] (2016)[h]	Netherlands	Cross-sectional	95	65	57%	HD (44%), PD (15%), stage 5 ND (41%)	Fried, FI
Fitzpatrick et al[52] (2019)[i]	United States	Prospective cohort	370	55	58%	HD	Fried (original, adapted)
Fu et al[53] (2021)	China	Prospective cohort	208	60	54%	HD	Fried
Garcia-Canton et al[54] (2019)	Spain	Prospective cohort	277	65[r]	66%	HD	EFS
Gopinathan et al[55] (2020)	India	Cross-sectional	39	78	80%	HD	Fried (original, modified)

(Continued)

Table 1 (Cont'd). Study Characteristics

Study	Country	Study Design	Number of Participants, n	Mean Age, y	Male, %	Modality or CKD Stage, %	Frailty Tool
Goto et al[56] (2019)[j]	Netherlands	Prospective cohort	187	75	67%	HD (77%), PD (23%)	Fried, GA, GFI
Guo et al[57] (2022)	China	Prospective cohort	204	72	55%	HD	Fried
Hall et al[58] (2022)	United States	Retrospective cohort	Derivation: 20,974 Validation: 21,355	Derivation: 75 Validation: 75	Derivation: 57% Validation: 58%	Derivation: HD (87%), other modality (13%) Validation: HD (85%), other modality (15%)	FI
Hamiduzzaman et al[59] (2023)[k]	United States	Retrospective cohort	764	57	59%	HD	Fried, VAFI
Haugen et al[60] (2021)[f]	United States	Prospective cohort	378	56	70%	Dialysis	Fried
Haugen et al[61] (2020)[f]	United States	Prospective cohort	3,255	54	60%	HD (55%), stage 5 ND (34%), NR (11%)	Fried
Haugen et al[6] (2019)[f]	United States	Prospective cohort	5,423	54	60%	Dialysis	Fried
Hwang et al[62] (2019)	Korea	Retrospective cohort	219	80	48%	HD	CFS
Imamura et al[63] (2023)	Japan	Prospective cohort	315	68	61%	HD	CFS, FRAIL, Fried, FSI
Jafari et al[64] (2020)	Canada	Prospective cohort	100	63	58%	HD	Fried
Jegatheswaran et al[65] (2020)	Canada	Prospective cohort	261	63	63%	HHD (10%), HD (51%), PD (39%)	FRAIL
Johansen et al[66] (2014)[k]	United States	Cross-sectional	731	57	59%	HD	Fried (original, modified)
Kamijo et al[67] (2018)	Japan	Prospective cohort	119	67	71%	PD	CFS
Kang et al[68] (2017)[i]	Korea	Prospective cohort	1,616	56	56%	HD (77%), PD (23%)	Fried (modified)
Kim et al[69] (2023)	Korea	RCT	Treatment: 18 Control: 21	Treatment: 58 Control: 57	Treatment: 56% Control: 48%	HD	Fried
Konel et al[70] (2018)[f]	United States	Prospective cohort	773	54	62%	Dialysis (74%), stage 5 ND (26%)	Fried
Lee et al[71] (2017)[l]	South Korea	Prospective cohort	1,658	56	56%	HD (76%), PD (24%)	Fried (modified)
Lee et al[72] (2017)	Korea	Prospective cohort	46	72[r]	63%	HD	CGA
Li et al[73] (2021)	China	Prospective cohort	150	69[r]	49%	HD	Fried
López-Montes et al[74] (2020)	Spain	Prospective cohort	117	78	63%	Stage 5 ND	Fried
Lorenz et al[75] (2019)	United States	Retrospective cohort	272	62	62%	Dialysis (57%), stage 5 ND (43%)	Fried
McAdams-DeMarco et al[76] (2018)[f]	United States	Prospective cohort	1,975	54	60%	HD (67%), PD (15%), stage 5 ND (18%)	Fried
McAdams-DeMarco et al[77] (2015)[f]	United States	Prospective cohort	537	53	60%	NR	Fried
McAdams-DeMarco et al[78] (2015)[i]	United States	Prospective cohort	324	55	57%	HD	Fried
McAdams-DeMarco et al[79] (2013)[f]	United States	Prospective cohort	383	53	60%	NR	Fried
McDonnell et al[80] (2024)	United States	Prospective cohort	40	59	56%	Dialysis or stage 5 ND	PRISMA-7
Moreno et al[81] (2023)	Columbia	Prospective cohort	93	64[r]	59%	HD (88%), PD (12%)	FRAIL

(Continued)

Table 1 (Cont'd). Study Characteristics

Study	Country	Study Design	Number of Participants, n	Mean Age, y	Male, %	Modality or CKD Stage, %	Frailty Tool
Nguyen et al[82] (2023)	Vietnam	Prospective cohort	175	72	41%	HD	CFS
Oki et al[83] (2022)	Japan	Retrospective cohort	155	67	71%	HD (89%), PD (11%)	CFS
Parajuli et al[84] (2022)	United States	Prospective cohort	825	55	60%	Dialysis (81%), stage 5 ND (19%)	Fried (modified)
Pérez-Saéz et al[85] (2022)[m]	Spain	Prospective cohort	451	61	68%	HD (56%), NR (44%)	FRAIL, Fried
Pérez-Saéz et al[86] (2022)[m]	Spain	Retrospective cohort	296	63	71%	HD (55%), PD (22%), stage 5 ND (12%), previous KTR (7%), other (3%)	Fried
Pérez-Saéz et al[87] (2022)[m]	Spain	Prospective cohort	153	61.5	67%	HD (70%), PD (14%), stage 5 ND (16%)	FRAIL, Fried
Pyart et al[88] (2020)[n]	United Kingdom	Retrospective cohort	1,216	78[r]	62%	Stage 5 ND	CFS
Salter et al[89] (2015)	United States	Cross-sectional	146	61[r]	53%	HD	Fried, nephrologist-perceived, NP-perceived, patient-perceived
dos Santos Mantovani et al[90](2022)[o]	Brazil	Prospective cohort	87	45	59%	HD (82%), PD (15%), stage 5 ND (3%)	Fried
dos Santos Mantovani et al[91] (2020)[o]	Brazil	Prospective cohort	87	45	59%	HD (82%), PD (15%), stage 5 ND (3%)	Fried
Schaenman et al[92] (2019)	United States	Retrospective cohort	60	52[r]	65%	Dialysis (80%), stage 5 ND (20%)	FRS
Schopmeyer et al[93] (2019)	Netherlands	Prospective cohort	139	52	63%	Dialysis (58%), stage 5 ND (42%)	GFI
Schweitzer et al[94] (2022)	United States	Retrospective cohort	1,718	NR	NR	Dialysis	sFI
Soldati et al[95] (2022)	Italy	Retrospective cohort	105	79	65%	HD	FI
Sy et al[96] (2019)[k]	United States	Retrospective cohort	425	57	58%	HD	Fried
van Loon et al[97] (2017)[j]	Netherlands	Prospective cohort	123	76	64%	HD (76%), PD (24%)	Fried, GA, GFI, G8, VMS
van Loon et al[98] (2019)[j]	Netherlands	Prospective cohort	192	75	67%	HD (77%), PD (23%)	Fried, GA, GFI
van Munster et al[99] (2016)[h]	Netherlands	Cross-sectional	95	65	57%	HD (44%), PD (15%), stage 5 ND (41%)	FI, GFI, VMS
Vázquez-Sánchez et al[100] (2023)	Spain	Prospective cohort	65	57	71%	Unclear	FRAIL
Vinson et al[101] (2020)[a]	Canada	Retrospective cohort	455	62	66%	HD (75%), PD (25%)	CFS
Wang et al[102] (2022)	China	Retrospective cohort	185	56	48%	HD	Chinese TFI
Worthen et al[103] (2021)	Canada	Prospective cohort	542	54	64%	HD (46%), PD (20%), HHD (6%), stage 5 ND (24%), NR (3%)	CFS, FI, Fried
Xu et al[104] (2024)	United States	Prospective cohort	40 (moderate-high and high risk subset)	56	65%	HD (48%), PD (10%), stage 5 ND (33%), NR (10%)	GFI
Yadla et al[105] (2017)	India	Prospective cohort	205	45	69%	HD	Fried

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Table 1 (Cont'd). Study Characteristics

Study	Country	Study Design	Number of Participants, n	Mean Age, y	Male, %	Modality or CKD Stage, %	Frailty Tool
Yang et al[106] (2023)	China	Retrospective cohort	157	67[r]	51%	HD (38%), HD + HDF (47%), HDF (6%), other (10%)	Fried
Yoshida et al[107] (2020)	Japan	Prospective cohort	310	83[r]	54%	HD	CFS
Mixed							
Lorenz et al[108] (2020)	United States	Prospective cohort	21	62[r]	57%	Stage 4 ND (29%), stage 5 ND (5%), dialysis (67%)	Fried
Meyer et al[109] (2022)	Germany	Prospective cohort	190	78	64%	HD (67%), PD (6%), stage 4-5 ND (27%)	MPI
Neradova et al[110] (2021)	United Kingdom	Prospective cohort	174	65	58%	Dialysis (89%), KTR (4%), ND (8%)	CFS
Nixon et al[111] (2021)	United Kingdom	Prospective cohort	450	76[r]	55%	HD (19%), ND (81%)	CFS
Nixon et al[112] (2019)	United Kingdom	Cross-sectional	90	69	50%	Stage 4-5 ND (67%), HD (33%)	CFS, CKD FI, Fried, PRISMA
Ongzalima et al[113] (2022)	Australia	Retrospective cohort	74	85	35%	Dialysis (9%), stage 4-5 ND (91%)	CFS
CKD not treated with dialysis							
Ali et al[114] (2018)	United Kingdom	Prospective cohort	104	77[r]	51%	Stage 4	PRISMA + TUG
Brar et al[115] (2021)[c]	Canada	Prospective cohort	603	68[r]	59%	Stage 5 ND (30%), <stage 5 ND (70%)	Fried, nurse impression, physician impression
Chao et al[116] (2021)[p]	Taiwan	Retrospective cohort	79,887	60	70%	Stage 5 ND (2%), <stage 5 ND (98%)	Modified FRAIL scale
Chao et al[117] (2019)[p]	Taiwan	Retrospective cohort	165,461	62	55%	Stage 5 ND (0.2%), <stage 5 ND (99%)	FRAIL
Chiu et al[118] (2022)[q]	United States	Prospective cohort	864	67[r]	53%	Stage 2 (15%), stage 3 (67%), stage 4 (15%), stage 5 ND (2%)	CKD-CGA
Delgado et al[119] (2015)	United States	Secondary analysis of RCT	812	52[r]	61%	Stage 3 to 5	Fried (modified)
Hannan et al[120] (2024)[q]	United States	Prospective cohort	2,539	62	54%	Stage 2 to 4	Fried
King et al[121] (2023)	Australia	Prospective cohort	98	76	55%	Stage 4, stage 5 ND	FI
Lee et al[122] (2020)[p]	Taiwan	Retrospective cohort	52,058	63	52%	Stage 5 ND (6%), <stage 5 ND (94%)	FRAIL
Lee et al[123] (2021)[p]	Taiwan	Retrospective cohort	149,145	61	56%	Stage 5 ND (2%), <Stage 5 ND (98%)	Modified FRAIL scale
Meulendijks et al[124] (2015)	Netherlands	Prospective cohort	63	75[r]	65%	Stage 4	GFI
Pugh et al[125] (2016)[n]	United Kingdom	Prospective cohort	283	74[r]	56%	Stage 4	CFS
Rodrigues et al[126] (2024)	Brazil	Prospective cohort	153	65[r]	49%	Stage 3b (41%), stage 4 (48%), stage 5 ND (11%)	FRAIL, Fried
Vettoretti et al[127] (2020)	Italy	Cross-sectional	112	80	70%	Stage 4	CGA, Fried

(Continued)

Table 1 (Cont'd). Study Characteristics

Study	Country	Study Design	Number of Participants, n	Mean Age, y	Male, %	Modality or CKD Stage, %	Frailty Tool
Wang et al[128] (2023)	China	Prospective cohort	774	67[r]	66%	Stage 1 (17%), stage 2 (24%), stage 3 (37%), stage 4 (22%)	FI
Weng et al[129] (2021)	Taiwan	Retrospective cohort	331	81	70%	Stage 3a (44%), stage 3b (31%), stage 4 (16%), stage 5 ND (9%)	Modified FI
Wilkinson et al[130] (2022)	United Kingdom	Retrospective cohort	140,674	78	38%	Stage 3a (61%), stage 3b (31%), stage 4 (7%), stage 5 (1%)	eFI
Post kidney transplant							
Malinowska et al[131] (2022)	Poland	Retrospective cohort	COVID-19: 77 Control: 71	COVID-19: 51 Control: 51	COVID-19: 58% Control: 52%	KTR	CFS

Abbreviations: CFS, Clinical Frailty Scale; CFS-MDT, Clinical Frailty Scale derived from multidisciplinary team discussion; CGA, Comprehensive Geriatric Assessment; CKD, chronic kidney disease; CKD-CGA, chronic kidney disease-specific Comprehensive Geriatric Assessment; COVID-19, coronavirus 2019; eFI, electronic frailty index; EFS, Edmonton Frailty Scale; FACT-CFS, Frailty Assessment for Care Planning Tool–Clinical Frailty Scale; FI, Frailty Index; FRAIL, Fatigue, Resistance, Ambulation, Illness, and Loss of weight; FQ, Frailty Questionnaire; FRS, Frailty Risk Score; FSI, Frail Screening Index; G8, Geriatric-8; GA, Geriatric Assessment; GFI, Groningen Frailty Indicator; HD, hemodialysis; HDF, hemodiafiltration; HHD, home hemodialysis; KTR, kidney transplant recipient; MPI, Multidimensional Prognostic Index; ND, non-dialysis; NP, nurse practitioner; NR, not reported; PD, peritoneal dialysis; PRISMA, Program of Research to Integrate Services for the Maintenance of Autonomy; RCT, randomized controlled trial; SF, Short Form Survey; sFI, Simplified Frailty Index; TFI, Tilburg Frailty Indicator; TUG, timed up-and-go; VAFI, Veterans Affairs Frailty Index; VMS, Veiligheids Management System.

[a-q]: Studies in which all (or a portion of) included participants are overlapping:

[a]Alfaadhel et al[3] (2015), Clark et al[49] (2021), Vinson et al[101] (2020).

[b]Anderson et al[29] (2023), Anderson et al[30] (2023), Anderson et al[31] (2023), Anderson et al[32] (2022).

[c]Brar et al[38] (2019), Brar et al[115] (2021).

[d]Chan et al[40] (2022), Chan et al[41] (2022), Chan et al[42] (2021), Chan et al[43] (2021).

[e]Chao et al[45] (2015), Chao et al[44] (2020).

[f]Chen et al[46] (2024), Chen et al[47] (2022), Konel et al[70] (2018), Haugen et al[60] (2021), McAdams-DeMarco et al[79] (2013), McAdams-DeMarco et al[78] (2015), Chu et al[48] (2019), McAdams-DeMarco et al[76] (2018), Haugen et al[61] (2020), Haugen et al[6] (2019).

[g]Clark et al[49] (2021), Clark et al[50] (2017).

[h]Drost et al[51] (2016), van Munster et al[99] (2016).

[i]Fitzpatrick et al[52] (2019), McAdams-DeMarco et al[77] (2015).

[j]Goto et al[56] (2019), van Loon et al[97] (2017), van Loon et al[98] (2019).

[k]Sy et al[96] (2020), Johansen et al[66] (2014), Hamiduzzaman et al[59] (2023).

[l]Lee et al[71] (2017), Kang et al[68] (2017).

[m]Pérez-Saéz et al[86] (2022), Pérez-Saéz et al[85] (2022), Pérez-Saéz et al[87] (2022).

[n]Pyart et al[88] (2020), Pugh et al[125] (2016).

[o]dos Santos Mantovani et al[90] (2022), dos Santos Mantovani et al[91] (2020).

[p]Chao et al[117] (2019), Chao et al[116] (2021), Lee et al[122] (2020), Lee et al[123] (2021).

[q]Chiu et al[118] (2022), Hannan et al[120] (2024).

[r]Median age was extracted.

Table 2. Summary of Pooled Findings (Kidney Failure)

Study	Pooled Result	Follow-up	Adjustment Variables
Fried frailty assessment tool (original) *Construct validity—discriminative*			
Brar et al[38] (2019) Fitzpatrick et al[52] (2019) Guo et al[57] (2022) Hamiduzzaman et al[59] (2023) Li et al[73] (2021) López-Montes et al[74] (2020) van Loon et al[98] (2019) Yadla et al[105] (2017)	*pooled* aHR death, n = 8 studies frail (≥3) vs pre-frail/non-frail (0-2): 2.01; 95% CI, 1.35-2.98; $P = 0.001$, $I^2 = 58\%$	Brar: 1 y Fitzpatrick: median, 2.48 y; IQR, 1.37-3.51 y Guo: mean, 46.5 ± 12.5 w Hamiduzzaman: 2 y Li: mean, 1 y López-Montes: 1 y van Loon: 1 y Yadla: median, 3.3 y; IQR, 2.5-4.1 y	Brar: age, sex, albumin, hemoglobin, and comorbid condition count Fitzpatrick: age, sex, race, BMI, waist-to-hip ratio, CCI and serum albumin, dialysis vintage Guo: all covariate associated at the $P < 0.10$ level with death in unadjusted analyses (including age, history of diabetes, MoCA <26, single-pool Kt/V, and levels of albumin, iPTH) Hamiduzzaman: age, sex, race, BMI, diabetes, heart failure, coronary artery disease, inflammatory markers (CRP and interleukin-6) Li: age, sex, albumin, mini-nutritional assessment short form, medical history of CHD and T2DM, urea reduction rate López-Montes: frailty, age, sex, CCI, BMI van Loon: age, sex, CIRS-G comorbid condition burden, smoking, residual kidney function, and dialysis modality Yadla: unclear
Jafari et al[64] (2020) McAdams-DeMarco et al[78] (2015) Sy et al[96] (2020)	*pooled* uOR death, n = 3 studies frail (≥3) vs pre-frail/non-frail (0-2): 2.01; 95% CI, 0.97-4.17; $P = 0.06$; $I^2 = 57\%$	Jafari: 1 y McAdams-DeMarco: 1 y Sy: up to 3 y	Not applicable
Anderson et al[30] (2023) Guo et al[57] (2022)	*pooled* aHR death, n = 2 studies frailty (continuous): 1.29; 95% CI, 1.08-1.56; $P = 0.006$; $I^2 = 10\%$	Anderson: median, 685 d; IQR, 543-812 d; min 1 y Guo: mean, 46.5 ± 12.5 w	Anderson: age, sex, MoCA, ethnicity, BMI, index of multiple deprivation, CCI (chronic kidney disease omitted), number of hospitalization episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, KT wait-listing status Guo: covariates associated at the $P < 0.10$ level with death in unadjusted analyses (including age, history of diabetes, MoCA <26, single-pool Kt/V, albumin, iPTH)
McAdams-DeMarco et al[76] (2018) Pérez-Saéz et al[87] (2022)	*pooled* aHR "KT waitlist" death, n = 2 studies pre-frail (1-2) vs non-frail (0): 1.85; 95% CI, 1.14-3.03; $P = 0.01$; $I^2 = 0\%$ frail (≥3) vs non-frail (0): 2.30; 95% CI, 1.35-3.91; $P = 0.002$; $I^2 = 0\%$	McAdams-DeMarco: mean, 1.6 ± 1.3 y Pérez-Saéz: median, 26 mo; IQR, 16-39 mo	McAdams-DeMarco: age, race, sex, blood type, cause of kidney failure, smoking Pérez-Saéz: all covariates associated at the $P < 0.10$ level with death in unadjusted analyses (including age, sex, comorbid condition, dialysis vintage)

(Continued)

Table 2 (Cont'd). Summary of Pooled Findings (Kidney Failure)

Study	Pooled Result	Follow-up	Adjustment Variables
dos Santos Mantovani et al[91] (2020) Konel et al[70] (2018)	*pooled* uOR "post KT" death, n = 2 studies frail (≥3) vs pre-frail/non-frail (0-2): 1.15; 95% CI, 0.50-2.66); $P = 0.74$; $I^2 = 0\%$ dos Santos Mantovani[a] Konel[a]	dos Santos Mantovani: 3 mo post KT Konel: 1 y post KT	Not applicable
Bloomfield et al[36] (2021) Fu et al[53] (2021)	*pooled* c-statistic prediction of death, n = 2 studies 0.74; 95% CI, 0.57-0.86; $P = 0.007$; $I^2 = 74\%$	Bloomfield: 2 y Fu: 2 y	Bloomfield: unclear Fu: unclear
Li et al[73] (2021) Yadla et al[105] (2017)	*pooled* aHR hospitalization, n = 2 studies frail (≥3) vs pre-frail/non-frail (0-2): 1.89; 95% CI, 1.25-2.85; $P = 0.002$, $I^2 = 0\%$	Li: 1 y Yadla: 1 y	Li: age, sex, albumin, mini-nutritional assessment short form, medical history of CHD and T2DM, urea reduction rate Yadla: unclear
Frailty Index vs Fried (original) *Construct validity—convergent*			
Anderson et al[30] (2022) Drost et al[51] (2016) Worthen et al[103] (2021)	FI (≥0.25) vs Fried (≥3) *pooled* κ, n = 3 studies 0.48; 95% CI, 0.43-0.54; $P < 0.001$; $I^2 = 0\%$ Drost[b]	Not applicable	Not applicable
Clinical Frailty Scale vs Fried (original) *Construct validity—convergent*			
Anderson et al[30] (2022) Imamura et al[63] (2023)	CFS (≥5, 4, <4) vs Fried (≥3, 1-2, 0) *pooled* κ, n = 2 studies 0.45; 95% CI, 0.19-0.71; $P = 0.001$; $I^2 = 97\%$	Not applicable	Not applicable
FRAIL vs Fried (original) *Construct validity—convergent*			
Imamura et al[63] (2023) Pérez-Saéz et al[85] (2022)	FRAIL (≥3, 1-2, 0) vs Fried (≥3, 1-2, 0) *pooled* κ, n = 2 studies 0.36; 95% CI, 0.28-0.44; $P < 0.001$; $I^2 = 56\%$	Not applicable	Not applicable
Clinical Frailty Scale *Construct validity—discriminative*			
Alfaadhel et al[3] (2015) Anderson et al[29] (2023) Yoshida et al[107] (2020)	*pooled* aHR death, n = 3 studies pre-frail (4) vs robust (1-3): 1.75; 95% CI, 1.17-2.60; $P = 0.007$; $I^2 = 26\%$	Alfaadhel: median, 1.7 y; IQR, 0.9-2.8 y Anderson: median, 685 d; IQR, 544-812 d; min 1 y Yoshida: median, 27.3 mo; IQR 8.0-46.2 mo	Alfaadhel: age, race, sex, CCI ≥5, diabetic kidney failure, GFR, albumin, dialysis modality, location of dialysis start Anderson: age, sex, ethnicity, BMI, English Indices of Multiple Deprivation quintile, CCI, previous admission, number of medications, smoking Yoshida: Controlling Nutritional Status score, CCI, and SPICES score

(Continued)

Table 2 (Cont'd). Summary of Pooled Findings (Kidney Failure)

Study	Pooled Result	Follow-up	Adjustment Variables
Anderson et al[29] (2023) Yoshida et al[107] (2020)	*pooled* aHR death, n = 2 studies frail (≥5) vs robust (1-3): 2.20; 95% CI, 1.00-4.80; $P = 0.049$, $I^2 = 66\%$	Anderson: median 685 d; IQR, 544-812 d; min 1 y Yoshida: median, 27.3 mo; IQR, 8.0-46.2 mo	Anderson: age, sex, ethnicity, BMI, English Indices of Multiple Deprivation quintile, CCI, previous admission, number of medications, smoking Yoshida: Controlling Nutritional Status score, CCI, and SPICES score
Alfaadhel et al[3] (2015) Anderson et al[29] (2023) Kamijo et al[67] (2018) Oki et al[83] (2022) Pyart et al[88] (2020)	*pooled* aHR death, n = 5 studies frailty (continuous): 1.37; 95% CI, 1.18-1.59; $P < 0.001$; $I^2 = 58\%$	Alfaadhel: median, 1.7 y; IQR, 0.9-2.8 y Anderson: median, 685 d; IQR, 544-812 d ; min 1 y Kamijo: mean, 589 d Oki: 2 y Pyart: 5 y	Alfaadhel: age, race, sex, CCI ≥5, diabetic kidney failure, GFR, albumin, dialysis modality, location of dialysis start Anderson: age, sex, ethnicity, BMI, English Indices of Multiple Deprivation quintile, CCI, previous admission, number of medications, smoking status, albumin, walk aid use, HD vintage, transplant listing status Kamijo: age, sex, walking speed, skeletal muscle mass index, grip strength Oki: age, CRP Pyart: age, CCI, choice in KRT
Anderson et al[29] (2023) Oki et al[83] (2022)	*pooled* aHR death or hospitalization, n = 2 studies frailty (continuous): 1.17; 95% CI, 1.05-1.29; $P = 0.003$; $I^2 = 4\%$	Anderson: median, 685 d; IQR, 544-812 d; min 1 y Oki: 2 y	Anderson: age, sex, ethnicity, BMI, English Indices of Multiple Deprivation quintile, CCI, previous admission, number of medications, smoking status, albumin, walk aid use, HD vintage, transplant listing status Oki: age, planned initiation of dialysis, systolic blood pressure, total cholesterol, brain natriuretic peptide
Frailty Index *Construct validity—discriminative*			
Anderson et al[30] (2023) Hall et al[58] (2022)	*pooled* aHR death, n = 2 studies frailty (continuous per 0.1 unit): 1.21; 95% CI, 1.17-1.25; $P < 0.001$; $I^2 = 0\%$	Anderson: median, 685 d; IQR, 543-812 d; min 1y Hall: 1 y	Anderson: age, sex, MoCA, ethnicity, BMI, index of multiple deprivation, CCI (chronic kidney disease omitted), number of hospitalization episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, KT wait-listing status Hall: age, sex, Liu comorbidity index

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CCI, Charlson comorbidity index; CFS, Clinical Frailty Scale; CHD, coronary heart disease; CI, confidence interval; CIRS-G, Cumulative Illness Rating Scale Geriatrics; CRP, C-reactive protein; FI, Frailty Index; FRAIL, Fatigue, Resistance, Ambulation, Illness, and Loss of weight; GFR, glomerular filtration rate; HD, hemodialysis; I^2, heterogeneity index; iPTH, intact parathyroid hormone; IQR, interquartile range; KT, kidney transplant; Kt/V, dialyzer clearance (mL/min) × time (min)/ distribution volume of urea (mL); MoCA, Montreal Cognitive Assessment; KRT, kidney replacement therapy; SPICES, Skin integrity, Problems eating, Incontinence, Confusion, Evidence of falls, and Sleep disturbance; T2DM, type 2 diabetes mellitus; our, unadjusted odds ratio.

[a]uOR was calculated based on the number of events reported by frailty group.

[b]κ was calculated due to no referent tool specified.

Table 3. Summary of Pooled Findings (CKD Not Treated with Dialysis)

Study	Pooled Result	Follow-up	Adjustment Variables
Frailty Index			
Construct validity—discriminative			
King et al[121] (2023) Wang et al[128] (2023)	*pooled* aHR death, n = 2 studies frailty (continuous per 0.1 unit): 1.27; 95% CI, 0.85-1.88; $P = 0.24$, $I^2 = 87\%$	King: median, 3.4 y; 95% CI, 2.85-4.65 y Wang: median, 36.5 mo	King: age, sex, eGFR Wang: age, sex, CKD stage

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; I^2, heterogeneity index.

6%), GA (n = 4; 6%), and Groningen Frailty Index (n = 3; 5%). Pooled adjusted estimates are shown in Figure 1. From 8 studies (Fig. 2), the pooled adjusted hazard ratio (aHR) for the discriminative validity of the FFP to identify mortality risk according to frail versus pre-frail/non-frail was 2.01 (95% CI, 1.35-2.98; $I^2 = 58\%$), and from 2 studies, the pooled c-statistic was 0.74 (95% CI, 0.57-0.86; $I^2 = 74\%$). Among those with kidney failure evaluated for kidney transplant, the risk of death for pre-frail versus non-frail was an aHR of 1.85 (95% CI, 1.14-3.03; $I^2 = 0\%$) and 2.30 (95% CI, 1.35-3.91; $I^2 = 0\%$) for frail versus non-frail. The pooled aHR for hospitalization for frail versus pre-frail/non-frail was 1.89 (95% CI, 1.25-2.85; $I^2 = 0\%$). For the CFS (Fig 3), the pooled aHR for death in pre-frail versus non-frail was 1.75 (95% CI, 1.17-2.60; $I^2 = 26\%$) and 2.20 (95% CI, 1.00-4.80; $I^2 = 66\%$) in frail versus non-frail and an aHR of 1.37 (95% CI, 1.18-1.59; $I^2 = 58\%$) when frailty was applied as a continuous measure. For the FI (Fig 4), the pooled aHR for death when frailty was applied as a continuous measure was 1.21 (95% CI, 1.17-1.25; $I^2 = 0\%$). The modified FFP was assessed in 4 studies (Table S2), with 2 studies reporting aHRs for death of 2.35 (95% CI, 1.36-4.06; P = 0.002 [hemodialysis]); 1.75 (95% CI, 0.68-4.50; P = 0.243 [peritoneal dialysis])[44] in the first study; 2.08 (95% CI, 1.04-4.16; P = 0.039 for frail versus

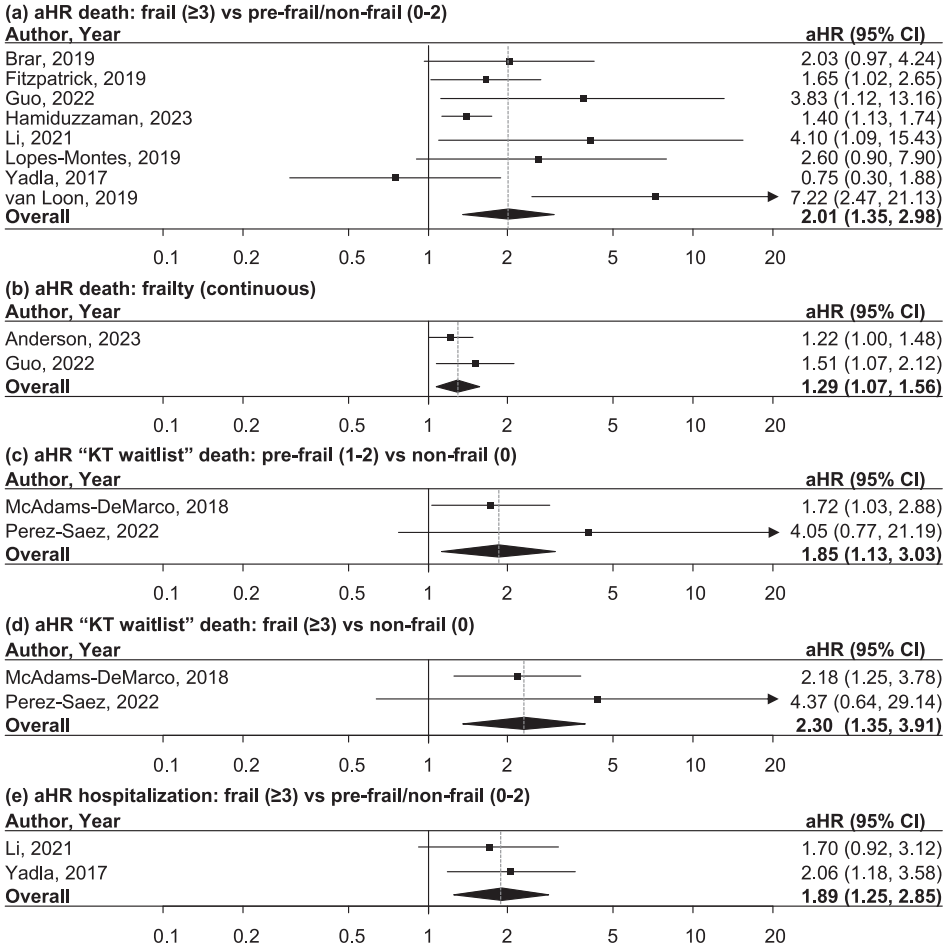

Figure 2. Forest plot of the discriminative validity of the Fried Frailty Phenotype in kidney failure studies. Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; KT, kidney transfer.

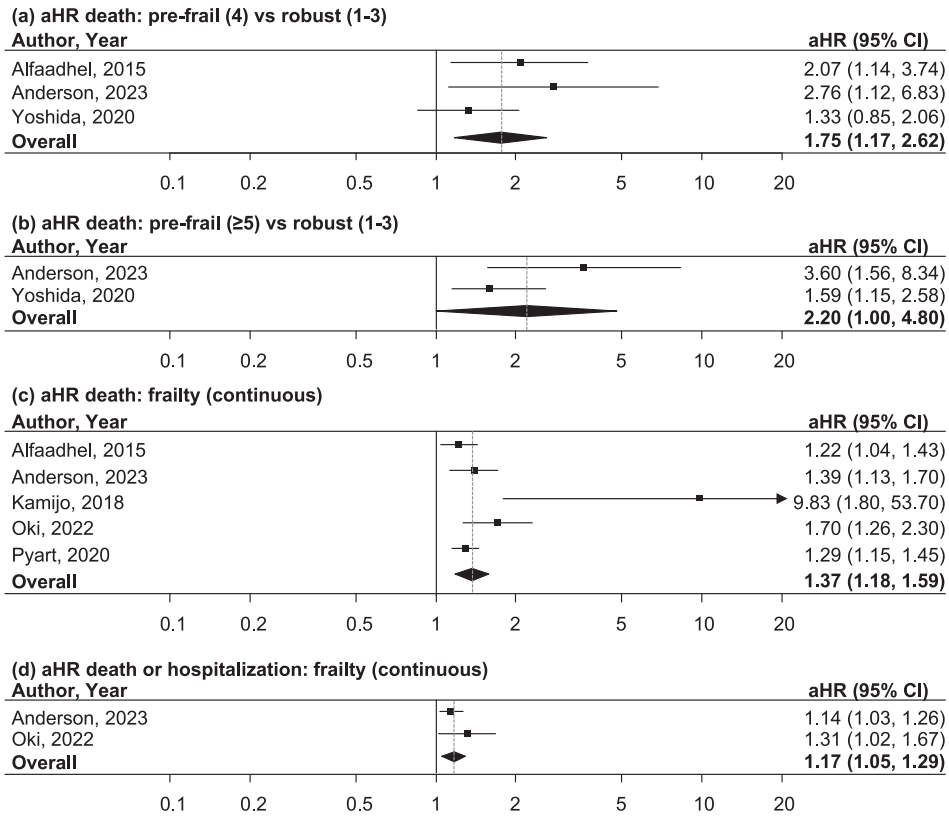

Figure 3. Forest plot of the discriminative validity of the Clinical Frailty Scale in kidney failure studies. Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

non-frail and no association with pre-frail versus non-frail status in the second study.[71]

In non-dialysis CKD studies (Table 3, Table S3),[121,128] the majority (n = 16; 89%) evaluated the discriminative validity of the following frailty tools: FRAIL scale (n = 5;31%), FI (n = 4; 25%), FFP (n = 3; 19%) followed by single studies evaluating the modified FFP, CFS, GA, Groningen Frailty Index, and "Program of Research to Integrate Services for the Maintenance of Autonomy and timed up-and-go" (Table S3). From 2 studies (Fig 5), the pooled aHR for the discriminative validity of the FI to identify mortality risk when frailty was applied as a continuous measure was 1.27 (95% CI, 0.85-1.88; $I^2 = 87\%$). The FRAIL scale showed consistent discriminative validity for mortality.

In studies including mixed populations, discriminative validity (n = 4; 67%) was evaluated by the CFS (n = 3) and Multidimensional Prognostic Index (n = 1) (Table S4).

Construct Validity—Convergent

The FI, CFS, and FRAIL scale were commonly compared against the FFP in kidney failure populations (Table 2, Table S2)[3,29,30,36,38,51-53,57-59,63,64,67,70,73,74,76,78,83,85-88,91,96,98,103,105,107] with inconsistent results. In 3 kidney failure studies comparing the FI versus the FFP, the pooled κ coefficient was 0.48 (95% CI, 0.43-0.54; $I^2 = 0\%$. The pooled κ coefficient was 0.45 (95% CI, 0.19-0.71; $I^2 = 97\%$) comparing the CFS versus the FFP and 0.36 (95% CI, 0.28-0.44; $I^2 = 56\%$) comparing the FRAIL scale versus the FFP. In 1 study, the correlation was 0.790

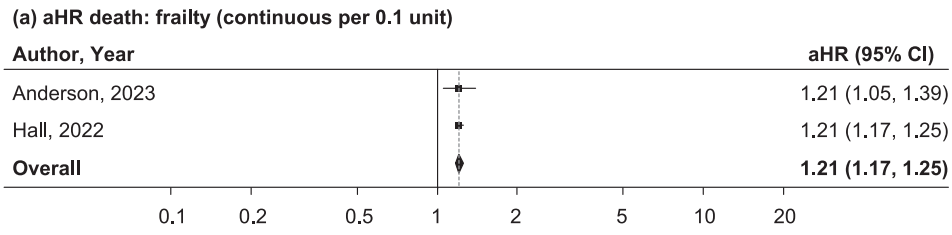

Figure 4. Forest plot of the discriminative validity of the Frailty Index in kidney failure studies. Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

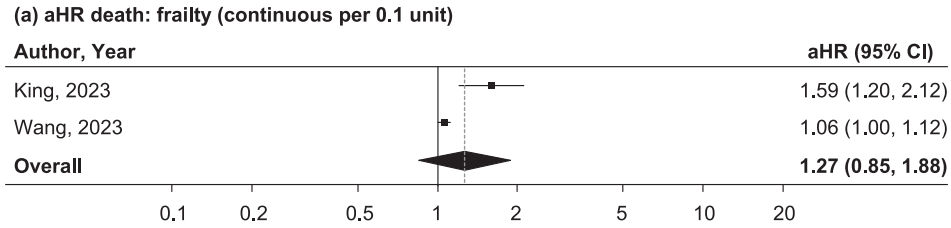

Figure 5. Forest plot of the discriminative validity of the Frailty Index in non-dialysis chronic kidney disease studies. Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

(Spearman's ρ) between the FI and the FFP.[32] Using the FFP as the referent, 1 study reported an area under the curve of 0.86 for the FI and 0.69 for the CFS.[103] Two studies evaluated the agreement between the FFP and the modified FFP (κ = 0.84; 95% CI, 0.66-1.00)[55] and sensitivity of 90%[66] (Table S2). Agreement between clinicians' subjective impression (no tool) and the FFP was low (κ of 0.46 for physician impression and 0.38 for nurse impression),[38] with lower agreement in a second study.[89] Two studies examined convergent validity in non-dialysis CKD comparing the FFP with physician and nurse impression of frailty (κ of 0.33 and 0.31, respectively)[115] and comparing the FFP with the FRAIL scale (κ of 0.28)[126] (Table S3). One study in a mixed population (Table S4) reported the correlations between the CFS and FI versus the FFP as 0.77 and 0.75, respectively.[112]

Criterion Validity

In kidney failure populations, only the Geriatric-8 and Veiligheids Management System had >80% sensitivity for detecting frailty compared with ≥2 impairments on the CGA, while the FFP versus GA (≥2 impairments) yielded a sensitivity and specificity of 59% (95% CI, 48%-70%) and 85% (95% CI, 66%-96%), respectively[97] (Table S2). In a study in individuals with non-dialysis CKD, the sensitivity of the FFP compared to the GA was 83% (95% CI, 71%-95%), and the specificity was 76% (95% CI, 66%-86%)[127] (Table S3).

Responsiveness

Frailty scores were measured pre- and post-initiation of dialysis, kidney transplant, exercise, and COVID-19 infection, primarily using the CFS and Fried (Table S2). In the majority of studies, the tools did not detect a change in frailty status[72,90,104,108,131]; however, with the exception of 1 study,[41] data to calculate the standardized response mean were not available. Chan et al[41] reported no difference in the mean CFS change score of 0.05 ± 1.5 (P = 0.686) from dialysis start to 1 year post-initiation (standardized response mean = 0.03).

Reliability

A single study among kidney failure studies reported on reliability for the CFS tool.[83] Inter-rater reliability reported by a weighted Cohen's κ was 0.64; intraclass correlation was 0.80.

Study Quality

Among the 105 studies, 48 (46%) were rated as having inadequate, 29 (28%) doubtful, 26 (25%) adequate, and 2 (2%) very good methodological quality (Tables S5-S7). The accuracy of measurement properties ratings was mixed between sufficient (+) and insufficient (−) (Tables S5-S7). In kidney failure studies, the discriminative validity of the FFP and GA for death or hospitalization was downgraded due to inconsistency and indirectness; the modified FFP, FI, and Groningen Frailty Index were downgraded due to methodological bias and indirectness, resulting in GRADE ratings of "low." Methodological bias, inconsistency, and indirectness were the factors downgrading the quality of the discriminative validity of the FRAIL scale and Edmonton Frailty Scale in kidney failure studies with "very low" GRADE. The CFS received a "moderate" GRADE rating due to indirectness. The GRADE rating for convergent validity among kidney failure studies was commonly "unknown" or downgraded 1 level for methodological bias (inconsistency and indirectness could not be assessed). In kidney failure studies, the FI, CFS, health care provider impressions, and modified FFP compared to the FFP were rated as "low," "moderate," "moderate," and "moderate," respectively. For discriminative validity in non-dialysis CKD studies, the FFP, FRAIL scale, and FI received "low," "low," and "very low" GRADE ratings, respectively. For discriminative validity among the remaining tools, methodological bias was downgraded for half; however, the corresponding GRADE ratings were "unknown" because there was only a single study per measurement property and tool. In mixed studies, most GRADE ratings were "unknown" due to singular studies, with only CFS receiving a "very low" rating for discriminative validity (Tables 4-6).[34,46,47,52]

DISCUSSION

In this systematic review, we evaluated the measurement properties of established multidimensional frailty tools according to CKD stage. We report the following key

Table 4. Overall GRADE Determination in Kidney Failure Studies

Measurement Property	Tool	GRADE
Construct validity—discriminative	Fried	Low
Construct validity—discriminative	Fried (modified)	Low
Construct validity—discriminative	Fried (adapted[a]) from Bancu et al[34] (2017)	Unknown
Construct validity—discriminative	Fried (adapted[a]) from Chen et al[47] (2022)	Unknown
Construct validity—discriminative	Fried (adapted[a]) from Fitzpatrick et al[52] (2019)	Unknown
Construct validity—discriminative	Fried (adapted) from Chen et al[46] (2024)	Unknown
Construct validity—convergent	FI vs Fried	Low
Construct validity—convergent	CFS vs Fried	Moderate
Construct validity—convergent	Fried (modified) vs Fried	Moderate
Construct validity—convergent	Impressions vs Fried	Moderate
Construct validity—convergent	EFS vs Fried	Unknown
Construct validity—convergent	Fried (adapted[a]) from Chen et al[47] (2022) vs Fried	Unknown
Construct validity—convergent	Fried (adapted) from Chen et al[46] (2024) vs Fried	Unknown
Construct validity—convergent	FRAIL vs Fried	Moderate
Construct validity—convergent	Frail Screening Index vs Fried	Unknown
Construct validity—convergent	VAFI vs Fried	Unknown
Construct validity—convergent	FI vs Fried (modified)	Unknown
Construct validity—convergent	CFS vs Fried (modified)	Unknown
Construct validity—convergent	FACT-CFS vs Fried (modified)	Unknown
Responsiveness	Fried	Very low
Reliability	CFS	Unknown
Construct validity—discriminative	CFS	Moderate
Construct validity—discriminative	CFS-MDT	Unknown
Construct validity—convergent	CFS-MDT vs CFS	Unknown
Construct validity—convergent	FQ vs CFS	Unknown
Construct validity—convergent	FI vs CFS	Unknown
Construct validity—convergent	FACT-CFS vs CFS	Unknown
Responsiveness	CFS	Very low
Construct validity—discriminative	sFI	Unknown
Construct validity—discriminative	FI	Low
Construct validity—convergent	FACT-CFS vs FI	Unknown
Construct validity—convergent	GFI vs FI	Unknown
Construct validity—convergent	VMS vs FI	Unknown
Construct validity—discriminative	GA	Low
Criterion validity	Fried vs GA	Unknown
Criterion validity	GFI vs GA	Unknown
Criterion validity	G8 vs GA	Unknown
Criterion validity	VMS vs GA	Unknown
Responsiveness	GA	Unknown
Construct validity—discriminative	GFI	Low
Construct validity—convergent	SF vs GFI	Unknown
Construct validity—convergent	EFS vs GFI	Unknown
Construct validity—convergent	TFI vs GFI	Unknown
Construct validity—convergent	G8 vs GFI	Unknown
Responsiveness	GFI	Unknown
Construct validity—discriminative	FRAIL	Very low
Construct validity—convergent	SF vs FRAIL	Unknown
Construct validity—convergent	EFS vs FRAIL	Unknown
Construct validity—convergent	GFI vs FRAIL	Unknown
Construct validity—convergent	G8 vs FRAIL	Unknown
Construct validity—convergent	TFI vs FRAIL	Unknown
Construct validity—discriminative	Fried & physician impression	Unknown
Construct validity—discriminative	EFS	Very low
Construct validity—discriminative	FRS	Unknown
Construct validity—discriminative	FQ	Unknown

(Continued)

Table 4 (Cont'd). Overall GRADE Determination in Kidney Failure Studies

Measurement Property	Tool	GRADE
Construct validity—discriminative	VAFI	Unknown
Construct validity—discriminative	PRISMA-7	Unknown
Construct validity—discriminative	Chinese TFI	Unknown
Construct validity—convergent	EFS vs SF	Unknown
Construct validity—convergent	SF vs TFI	Unknown
Construct validity—convergent	G8 vs SF	Unknown
Construct validity—convergent	EFS vs G8	Unknown
Construct validity—convergent	EFS vs TFI	Unknown
Construct validity—convergent	G8 vs TFI	Unknown

Abbreviations: CFS, Clinical Frailty Scale; CFS-MDT, Clinical Frailty Scale derived from multidisciplinary team discussion; EFS, Edmonton Frailty Scale; FACT-CFS, Frailty Assessment for Care Planning Tool–Clinical Frailty Scale; FI, Frailty Index; FQ, Frailty Questionnaire; FRAIL, Fatigue, Resistance, Ambulation, Illness, and Loss of weight; FRS, Frailty Risk Score; G8, Geriatric-8; GA, Geriatric Assessment; GFI, Groningen Frailty Indicator; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PRISMA, Program of Research to Integrate Services for the Maintenance of Autonomy; SF, Short Form Survey; sFI, Simplified Frailty Index; TFI, Tilburg Frailty Indicator; VAFI, Veterans Affairs Frailty Index; VMS, Veiligheids Management System.
[a]Because of differences in adapted Fried between studies, each adapted version is treated as a unique tool.

findings. First, the majority of studies were conducted in the kidney failure population and evaluated the discriminative validity of the FFP followed by the CFS. From our pooled results, the FFP and CFS showed acceptable discriminant validity in identifying those at higher risk of mortality based on frailty status among individuals with kidney failure. Fewer studies examined the association between frailty and hospitalization, though the FFP and CFS were generally able to detect a higher risk of hospitalization in kidney failure based on frailty status. Second, the modified FFP (self-report) showed adequate discriminative validity for mortality based on frailty status and high agreement with the original FFP in kidney failure. Third, in both the kidney failure and non-dialysis CKD populations, the agreement between clinicians' subjective impression of frailty and the FFP was low. Fourth, when adjusted for a range of clinical characteristics, frailty status as measured by the FFP or the CFS was associated with an approximate doubling in the hazard for death among people with kidney failure.

Though the optimal frailty tool will vary according to its intended purpose and practical considerations, frailty assessment is commonly used to accurately identify frailty (versus comorbid condition or disability), discriminate those at higher risk for adverse health outcomes, and/or to measure changes in frailty in response to an intervention. We found that few studies compared the diagnostic accuracy of frailty tools to the clinical standard, the CGA/GA. In one study in people with kidney failure, the Geriatric-8 and the Veiligheids Management System showed good sensitivity (≥80%) compared with ≥2 impairments in the CGA, whereas the sensitivity of the FFP was low in kidney failure and good in CKD. Though conclusions on the diagnostic accuracy of the Fried is limited by the data, its physical conceptualization of frailty is less likely to identify those with cognitive or social frailty. There was limited data to adequately evaluate responsiveness, which is an important metric for selecting frailty tools as outcomes in clinical trials. In the general population, the FI, which is a continuous measure, was more responsive to change than other frailty measures.[132] Although limited to 2 studies, the FI had adequate discriminative validity in kidney failure populations and should be examined further in this population.

Given the overlapping pathophysiology between frailty and kidney failure, a higher risk of death and hospitalization due to this syndrome is not surprising. Uremic toxins, oxidative stress and insulin resistance contribute to the persistent inflammatory state of CKD.[133] The overproduction of proinflammatory cytokines has also been proposed as a biological basis for frailty, and inflammation directly contributes to the development of frailty through its catabolic effects on muscle.[134] Similarly, generalized endocrine dysfunction, such as imbalances in vitamin D,

Table 5. Overall GRADE Determination in CKD Non-dialysis Studies

Measurement Property	Tool	GRADE
Construct validity—discriminative	Fried (original)	Low
Construct validity—discriminative	Fried (modified)	Unknown
Construct validity—convergent	FRAIL vs Fried	Unknown
Construct validity—convergent	Impressions vs Fried	Unknown
Construct validity—discriminative	CFS	Unknown
Construct validity—discriminative	FI	Very low
Responsiveness	FI	Unknown
Construct validity—discriminative	GA	Unknown
Criterion validity	Fried vs GA >1 impairment Fried vs GA >2 impairments	Unknown
Construct validity—discriminative	GFI	Unknown
Construct validity—discriminative	FRAIL	Low
Construct validity—discriminative	PRISMA + TUG	Unknown
Construct validity—discriminative	Impressions	Unknown
Post kidney transplant		
Responsiveness	CFS	Unknown

Abbreviations: CFS, Clinical Frailty Scale; FI, Frailty Index; FRAIL, Fatigue, Resistance, Ambulation, Illness, and Loss of weight; GA, Geriatric Assessment; GRADE, Grading of Recommendations Assessment, Development and Evaluation; GFI, Groningen Frailty Indicator; PRISMA, Program of Research to Integrate Services for the Maintenance of Autonomy; TUG, timed up-and-go.

Table 6. Overall GRADE Determination in Mixed Population Studies

Measurement Property	Tool	GRADE
Construct validity—convergent	CFS vs Fried	Unknown
Construct validity—convergent	FI vs Fried	Unknown
Construct validity—convergent	PRISMA vs Fried	Unknown
Responsiveness	Fried	Unknown
Construct validity—discriminative	CFS	Very low
Construct validity—discriminative	MPI	Unknown

Abbreviations: CFS, Clinical Frailty Scale; FI, Frailty Index; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MPI, Multidimensional Prognostic Index; PRISMA, Program of Research to Integrate Services for the Maintenance of Autonomy.

androgens, and growth hormones described in CKD, are also implicated in the pathogenesis of frailty.[135] Consistent with our findings, a doubling in mortality risk based on the FFP in people with dialysis-dependent and non-dependent CKD[10,136] and dialysis dependence alone[137] has been reported in other meta-analyses. However, less is known about the discriminative abilities of specific frailty tools in CKD populations. In a systematic review on frailty outcomes in CKD, Mei et al[10] reported that only the FFP and the modified FFP showed a significant association with mortality; however, the majority of studies used the FFP, with only single studies of other tools available for inclusion (CFS, Edmonton Frailty Scale, and the Frailty Score). Our finding that the CFS score was independently associated with mortality is potentially relevant for frailty tool selection in the clinical context because the CFS is favored for its simplicity in frailty screening.

Consistent with a review examining frailty score agreement in the general population,[138] we found that frailty scores across tools were generally not interchangeable. This finding was not unexpected given the comparisons often represented different frailty constructs, eg, the FI (cumulative deficits) and the CFS (clinical judgment) were commonly compared against the FFP (physical frailty). Our finding that the FFP (performance-based measure) and the modified Fried (self-reported performance) showed high agreement is of relevance for settings with more limited resources or for virtual frailty assessment. We also found that clinicians' subjective "yes/no" impression of frailty had low agreement with frailty as assessed by the FFP, although physician impression of frailty was associated with a higher risk of death. This raises the possibility that subjective assessment may be identifying conditions other than frailty, such as a comorbid condition, which could have significant management implications if used in lieu of a frailty tool, eg, a de-escalation of treatment or change in goals of care in those with severe irreversible frailty or the implementation of frailty-specific interventions to address reversible components[139-141] versus an escalation in treatment to optimize comorbid conditions.

To our knowledge, this is the first systematic review to examine the measurement properties of frailty tools in CKD populations. Our findings describe important considerations when selecting a frailty tool in a number of different settings according to CKD stage, modality, and intended purpose. We used an established framework (COSMIN methodology) to evaluate measurement properties and their quality. Consistent with the concept of frailty as a distinct multidimensional biological syndrome, we only included studies that evaluated tools with more than one frailty domain, and consistent with clinical practice, we considered the CGA/GA as the "clinical standard" for detecting frailty. Because there are differences in age, comorbid condition, and the risk of poor health outcomes in those with kidney failure versus milder stages of CKD, we analyzed these populations separately. However, there are limitations to our review that prevented us from reaching a definitive recommendation on the ideal tool for research and clinical practice. Despite analyzing the studies according to severity of CKD, differences in study populations across studies persisted, including sample size, follow-up period, and covariate adjustment, which could influence the accuracy of our results. Our ability to pool estimates was also limited by the range of effect measures and the infrequent use of some tools. Finally, study quality was low-moderate overall. However, it is important to note that the methodological quality rating that contributed to the GRADE is obtained using the worst counts score; therefore, low scores may not reflect the entirety of the evidence.

In summary, frailty status as measured by the FFP and CFS provides important prognostic information beyond age and clinical factors on the risk of mortality and hospitalization and are both relatively feasible to use in the clinical context. With respect to accurately identifying those who may benefit from CGA/GA and/or frailty interventions, additional studies are needed to better understand the diagnostic accuracy of these tools compared with the clinical standard, the CGA/GA. In addition, because identification of frailty earlier in its trajectory may make it more amenable to modification,[142] future research should also focus on establishing the accuracy of tools to identify the pre-frail or vulnerable state. We also did not find evidence to support the use of a clinician's impression in detecting frailty without a tool because of its uncertain accuracy in identifying those with frailty versus other associated conditions. Importantly, data to show that frailty as measured by any tool improved the accuracy of prediction models for hospitalization were limited to single studies and showed only modest improvements. We recommend that future studies aiming to evaluate the predictive accuracy of frailty tools should report discrimination and calibration. Models intended for clinical decision making should also report decision analytic measures (including calculating the net benefit across varying thresholds).[143] In support of the utility of frailty screening in this population, there is evidence from trials to show that first-line approaches from the general population, such as exercise,[8,144-146] can improve frailty surrogates (ie,

performance-based physical function) and the physical domain of health-related quality of life, as well as domains of frailty, such as depression and fatigue in dialysis-dependent populations.[147,148] Randomized studies are needed to determine effective interventions for reducing frailty, as are longitudinal studies designed to determine which frailty tools are responsive to changes in overall health status.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Table S1: Search Strategy.

Table S2: Summary of Findings (Kidney Failure).

Table S3: Summary of Findings (CKD Not on Dialysis).

Table S4: Summary of Findings (Mixed).

Table S5: Methodological Risk of Bias and Accuracy Assessment in Kidney Failure Studies.

Table S6: Methodological Risk of Bias and Accuracy Assessment in CKD Not on Dialysis Studies.

Table S7: Methodological Risk of Bias and Accuracy Assessment in Mixed Studies.

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