Canadian Society of Nephrology/
Société canadienne de néphrologie
CSN/SCN
CANADIAN JOURNAL OF
KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Original Clinical Research Quantitative

Canadian Journal of Kidney Health and Disease
Volume 11: 1–16
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DOI: 10.1177/20543581241300777
journals.sagepub.com/home/cjk
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Physical Frailty and Functional Status in Kidney Transplantation: A Systematic Review

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Abstract

Background: Frailty and functional decline are being recognized as important conditions in kidney transplant candidates. However, the ideal measures of functional status and frailty remain unknown as there is not a complete understanding of the relationship between these conditions and important post-transplant outcomes.
Objective: The objective was to examine the association between different measures of frailty and functional status evaluated before or at the time of transplant with adverse clinical outcomes post-transplantation.
Design: This study is a systematic review.
Setting: Observational studies including cohort, case-control, or cross-sectional studies examining the effect of frailty and functional status on clinical outcomes. There were no restrictions on type of setting or country of origin.
Patients: Adults who were waitlisted for kidney transplant or had received a kidney transplant.
Measurements: Data including demographic information (eg, sample size, age, country), assessments of frailty or functional status and their domains, and outcomes including mortality, transplantation, graft loss, delayed graft function and hospital readmission were extracted.
Methods: A search was performed in Medline, Embase, and Cochrane Central Register for Controlled Trials. Studies were included from inception to February 7, 2023. The eligibility of studies was screened by 2 independent reviewers. Data were presented by frailty/functional status instrument and clinical outcome. Point estimates and 95% confidence intervals from fully adjusted statistical models were reported or calculated from the raw data.
Results: A total of 50 studies were identified, among which 36 unique instruments were found. Measurements of these instruments occurred mostly at time of kidney transplant, transplant evaluation, and waitlisting. The median sample size of studies was 457 patients (interquartile range = 183-1760). Frailty and lower functional status were associated with an increased risk for mortality. Similar trends were observed among other clinical outcomes such as graft loss and rehospitalization.
Limitations: The heterogeneity in measurement instruments, study designs, and outcome definitions prevents pooling of the data. Selection bias and the validity of data collection could not be ascertained for some studies.
Conclusion: Frailty and functional status measures are important predictors of post-kidney transplant outcomes. Further studies are needed to evaluate the best instruments to assess frailty and functional status, and importantly, interventional studies are needed to determine whether prehabilitation strategies can improve post-transplant outcomes.
Registration (PROSPERO): CRD42016045251.

Abrégé

Contexte: La fragilité et le déclin de l'état fonctionnel sont connus comme problèmes importants chez les candidats à la transplantation rénale. On ignore toutefois quelles mesures sont idéales pour évaluer la fragilité et l'état fonctionnel, car on comprend encore mal la relation entre ces derniers et les principaux résultats post-transplantation.
Objectif: Examiner l'association entre les différentes mesures de la fragilité et de l'état fonctionnel, évaluées avant ou au moment de la transplantation, et les résultats cliniques indésirables après la transplantation.
Conception: Revue systématique.
Cadre: Les études observationnelles, incluant les études de cohorte, les études cas-témoins ou les études transversales, examinant l'incidence de la fragilité et de l'état fonctionnel sur les résultats cliniques; sans restriction quant au cadre ou au pays de l'étude.
Sujets: Des adultes sur liste d'attente pour une transplantation rénale ou ayant reçu une greffe de rein.

Mesures: Les données suivantes ont été extraites: les données démographiques (p. ex., taille de l'échantillon, âge des patients, pays), les évaluations de la fragilité ou de l'état fonctionnel et leurs domaines, ainsi que les résultats cliniques (mortalité, greffe, perte du greffon, fonction retardée du greffon et réadmission à l'hôpital).
Méthodologie: Recherche effectuée dans Medline, Embase et Cochrane Central Register for Controlled Trials pour les études pertinentes depuis leur création jusqu'au 7 février 2023. L'admissibilité des études a été déterminée par deux examinateurs indépendants. Les données ont été présentées selon l'instrument de mesure de la fragilité ou de l'état fonctionnel et selon le résultat clinique. Des estimations ponctuelles et des intervalles de confiance à 95 % du modèle statistique ajusté ont été rapportés ou calculés à partir des données brutes.
Résultats: 50 études ont été répertoriées, desquelles 36 instruments uniques ont été notés. Les mesures avaient été effectuées principalement au moment de la greffe de rein, de l'évaluation de la greffe ou de l'ajout sur la liste d'attente. La taille médiane de l'échantillon des études incluses était de 457 patients (ÉIQ: 183 à 1760). La fragilité et un faible état fonctionnel ont été associés à un risque accru de décès. Des tendances similaires ont été observées pour d'autres résultats cliniques comme la perte du greffon et la réadmission à l'hôpital.
Limites: L'hétérogénéité dans les instruments de mesure, les conceptions des études et les définitions des résultats cliniques a empêché le regroupement des données. Pour certaines études, il n'a pas été possible de vérifier la présence d'un biais de sélection ni la validité de la collecte des données.
Conclusion: La mesure de la fragilité et de l'état fonctionnel est un important prédicteur des résultats post-transplantation rénale. D'autres études sont nécessaires pour identifier les meilleurs instruments à utiliser pour évaluer la fragilité et l'état fonctionnel. Plus important encore, des études interventionnelles sont nécessaires pour vérifier si les stratégies de préréadaptation améliorent les résultats post-transplantation.

Keywords
frailty, functional status, kidney transplantation, outcomes, transplant patients

Received July 16, 2024. Accepted for publication October 9, 2024.

Introduction

Kidney transplantation is the treatment of choice for most patients suffering from end-stage kidney disease, offering improvements in survival and quality of life compared with dialysis.[1,2] Over the last decade, there has been an increase in the number of individuals added to the waitlist for kidney transplants in Canada.[3] Although the number of kidney transplant procedures has also increased concurrently, it has not kept pace with the rate of waitlisting.[3] Consequently, the demand for kidney transplants has surpassed the available supply, making it challenging to provide life-prolonging procedures to everyone in need.[4,5] In addition, candidates for kidney transplants tend to have health challenges such as older age, health comorbidities, frailty, and reduced functional capacity, making the evaluation assessment process more challenging.[6-11]

Frailty is an important determinant in health outcomes and is defined as a heightened state of vulnerability due to declines in strength, endurance, and physiologic function.[12,13] Among waitlisted kidney transplant candidates, frailty has been associated with adverse outcomes following transplantation including delayed graft function (DGF), longer hospitalizations, and mortality.[6,14] Similarly, a patient's functional status is an indicator of their overall health and preparedness for transplantation.[15,16] Functional status is distinct from frailty in that it measures the ability to complete tasks. Although decreased function is highly associated with frailty, where decreased strength and physiologic function can directly impact one's abilities,[17,18] persons with significant functional limitations due to conditions such as stroke or arthritis may not be frail. Conversely, persons with frailty may not demonstrate functional loss. An enhanced understanding of these risk factors is essential for identifying and mitigating adverse outcomes among at-risk transplant candidates. In addition, research has shown a potential improvement in physical function and frailty following transplantation.[7,14,19-21] This potential reversibility with improved kidney function highlights the importance of understanding the impact of frailty and functional status on outcomes in the field of transplantation.

The objective of this systematic review was to examine the association between different measures of frailty and functional status evaluated before or at the time of transplantation with adverse clinical outcomes following kidney transplantation.

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Methodology

The methodology used in this study expands upon a previously published systematic review examining frailty in advanced chronic kidney disease (CKD)[22] but with a specific focus on the kidney transplant recipient population. This review was written according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines[23] and has been registered in the PROSPERO database (CRD42016045251).

Literature Search

A tailored literature search was performed in Medline, Embase, and the Cochrane Central Register of Controlled Trials. We searched for studies from inception to February 7, 2023. Search terms relating to frailty and functional status were used and included the following: kidney transplantation, frailty, muscle weakness, sarcopenia, and functional status (Item S1 in Supplementary Material). Eligibility was restricted to studies in the English language.

Primary research studies including cohort, case-control, and cross-sectional studies were eligible for review. No limitations were set on the duration of follow-up, study setting, or country of origin. Other inclusion criteria were as follows: (a) *Population:* Adults (≥18 years of age) who were waitlisted for kidney transplant or had received a kidney transplant. (b) *Instrument:* An assessment of overall frailty or functional status, or their individual domains, provided they measured impairment prior to or at time of transplantation. Both performance-based and self-reported measures were accepted. Frailty was defined as a syndrome resulting from various factors and characterized by reduced strength, endurance, and physiological function. Functional status was defined as an individual's ability to carry out the normal activities of daily living required to meet basic needs, fulfill usual roles, and maintain health and well-being. (c) *Outcome:* The primary outcome of interest was mortality post-transplant or while on the kidney transplant waitlist. The following post-transplant outcomes were also collected: graft loss, DGF, hospital readmission, hospital length of stay, and transplantation. The following waitlist outcomes were collected: hospitalization and waitlist inclusion/removal. Composite outcomes such as death or delisting, post-transplant severe adverse events, and hospitalization or death were also captured.

Article Selection and Data Extraction

Studies were examined for eligibility by 2 independent reviewers. Articles that were deemed potentially relevant based on title and abstract were subsequently screened in greater detail, in which the full text was retrieved. When an article was not available in academic databases nor through our academic library, we contacted the corresponding authors in attempt to gain access to the article. The reference lists of included studies were scanned for validation and additional titles. When disagreements arose and consensus could not be reached between 2 reviewers, a third reviewer was consulted for final input.

An abstraction form was utilized to extract data points from the included studies. Items of interest were study design, subject characteristics, details on frailty and functional status instruments, and outcomes. Data were extracted by 2 independent reviewers and verified by both to minimize discrepancies.

Quality Assessment

Each of the included studies was assessed for risk of bias using a modified version of the Quality in Prognosis Studies tool.[24-26] This tool provides 6 domains in which several prompting questions are asked about study participation and attrition, instrument and outcome measurements, study confounding, and statistical analysis and reporting. Each of the domains is given a rating of high, moderate, or low risk of bias by a reviewer and verified by another.

Data Analysis and Presentation

Study characteristics were compiled for each study. Sample size and population age were presented as means and standard deviations, unless otherwise indicated. Frailty and functional status instruments were categorized based on the domain they assessed and examined as separate exposures for each outcome (Box 1). Frailty was classified into 5

Box 1. Definition of Frailty and Functional Status and Their Groupings.

Frailty: a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiological function that increases an individual's vulnerability for developing increased dependency and/or death.[32]

- Sarcopenia/weight loss[27]
- Slowness[27]
- Weakness[27]
- Poor endurance/exhaustion[27]
- Low physical activity[27]

Functional status: an individual's ability to carry out the normal activities of daily living required to meet basic needs, fulfill usual roles, and maintain health and well-being.

- Activities of daily living impairments[28,29]
- Performance scale[30]
- Physical performance[31]

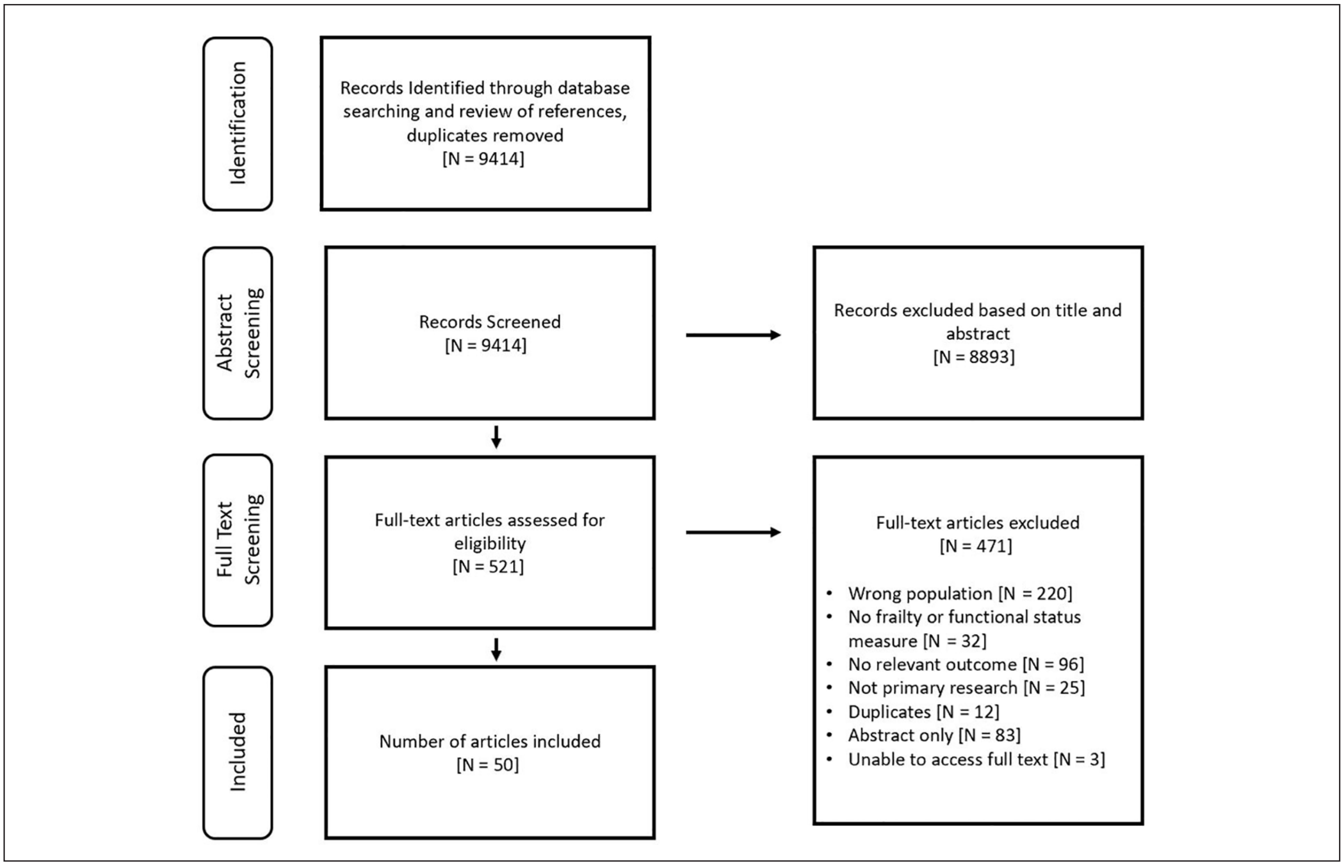

Figure 1. Search results and study selection.

domains: overall frailty, sarcopenia, slow gait, strength measurement, and physical activity and fatigue.[27] Functional status measures were grouped into 3 categories: Activities of Daily Living (ADL),[28,29] performance scale,[30] and physical performance.[31]

Key outcomes were reported as point estimates and 95% confidence intervals of fully adjusted statistical models. These analyses reported hazard ratios (HRs), odds ratios (ORs), and relative risks (RRs) and were adjusted for a minimum of sex and age, unless indicated differently. In the absence of such data points, unadjusted estimates were reported or calculated using frequencies of healthy vs impaired subject groups. When the same measurements were reported in different units, they were converted to the same units mathematically (eg, studies reporting on the 6-minute walk test were all presented as 100 m unit measures). The heterogeneity in study designs and instruments precluded the pooling of results; therefore, no specific heterogeneity testing was done, and a meta-analysis could not be performed. Finally, main study findings were reported as assessments, with the potential for multiple instruments and/or outcome assessments within a single article. For example, a study measuring the 5 independent frailty domains resulted in 5 distinct outcomes in the systematic review.

Results

Overview

The literature search identified 9414 unique citations (Figure 1). After the initial screening of titles and abstracts, 521 articles were further assessed for eligibility at the full-text level. After this stage, an additional 471 studies were excluded because they focused on a different population, did not report a relevant outcome, or did not measure frailty or functional status. The remaining 50 studies were included in this review.

Supplementary Table S1 provides an overview of the demographic characteristics of the included studies (references available in Item S2). Overall, there were 21 studies (42%) that used a prospective cohort design, 15 studies (30%) used hospital records for data sources and 11 studies (22%) used registry data. The remaining 3 studies performed secondary analysis of established cohorts. Publication dates ranged from 2006 to 2022, with a median publication year of 2019. Most studies (n = 38; 76%) originated from the United States. The median sample size of included studies was 457 patients (interquartile range = 183-1760), and the total sum of sample size for all studies was 668 103 patients.

Instruments

The characteristics of the instruments used to examine frailty and functional status are reported in Supplementary Table S2. Among 50 studies, there were 36 unique instruments used to measure frailty (29 instruments) and functional status (7 instruments). In total, these instruments accounted for 86 assessments, including 63 assessments of frailty. Overall frailty was the primary domain of focus of these studies, noted in 26 assessments, followed by sarcopenia (n = 13 assessments), gait (n = 10 assessments), strength measurements (n = 9 assessments), and physical activity and fatigue (n = 5 assessments). The Fried Frailty Index, including variations of it, was the most frequently used instrument for frailty (n = 13). Functional status instruments accounted for 23 assessments, with the Karnofsky Performance Scale (Karnofsky) and 36-item short-form health survey (SF-36) physical functioning scales being the most used instruments (n = 6 each).

Measurements using these instruments occurred at various clinical milestones, notably at time of kidney transplantation (n = 13), transplant evaluation (n = 13), or waitlisting (n = 7). Some studies reported multiple time points including at waitlisting and before transplantation (n = 3). The remaining 14 studies reported varying time points' pre-kidney transplant.

There were 15 distinct outcomes that were examined across all studies. Mortality was the most frequently examined outcome, appearing in 28 studies, followed by hospital readmission after transplantation (n = 11 studies), graft loss (n = 14 studies), hospital length of stay (n = 8 studies), and DGF (n = 8 studies). Additional outcomes included waitlisting denial/removal (n = 8 studies) and kidney transplantation (n = 7 studies). Supplementary Table S3 outlines the remaining outcomes.

Critical Appraisal of Quality

The quality assessment of the studies is summarized in Supplementary Table S4. Four studies (8%) were assessed as having a low risk of bias across all 6 categories, and 6 studies (12%) had a low risk of bias across 5 of the categories. There were 20 studies (40%) assessed to have a high risk of bias in at least 1 of the categories. Overall, the studies performed the best in the outcome measurement category, with 34 studies (68%) identified as low risk of bias in this category.

Mortality

Table 1 provides an overview of the association between various frailty and functional status instruments and mortality. Overall, there were 45 assessments across 28 studies. The majority of studies examined the association in kidney transplant recipients, whereas some were in kidney transplant candidates while on the waitlist. Results were overall consistent between the 2 populations.

There were 14 categorical assessments examining overall frailty. Among these, 71.4% (n = 10) reported a statistically significant association, where being frail prior to transplantation was associated with a 2- to 7- fold increased risk of mortality among waitlisted and transplanted patients (Figure 2). An additional 7 assessments examined sarcopenia, in which 5 unique instruments were used. A single assessment evaluating sarcopenia as a continuous measure reported an increased risk of mortality (Supplementary Figure S1), whereas 3 of 6 categorical assessments of sarcopenia revealed a positive association between sarcopenia and mortality. When the remaining domains of frailty were examined, there was no consistent association with mortality.

The relationship between functional status and mortality was examined among 16 assessments in 13 studies (Figure 3). Overall, individuals with impaired functional status based on categorical measures of ADL, Karnofsky, and SF-36 physical functioning scale had up to a 2.5-fold increased risk of mortality. Similarly, impaired function using ADL and Karnofsky as continuous measures was also associated with an increased risk of mortality.

Supplementary Table S3 provides an overview of the association between various frailty and functional status instruments and the remaining outcomes.

Graft Loss

There were 13 assessments of frailty that examined graft loss outcome among transplanted patients (Figure 4). These assessments measured all domains of frailty, with a primary focus on overall frailty, as determined by the Physical Frailty Phenotype, and the domain of sarcopenia. Frailty by the Physical Frailty Phenotype was associated with a 2-fold increased risk of graft loss. Frailty as determined by sarcopenia also showed an increased risk for graft loss when used as a categorical measure (n = 3) but not as a continuous one (n = 1). The remaining domains of frailty revealed no association with graft loss.

There were 7 assessments of functional status that examined graft loss. Functional status by level of assistance with ADL showed a 2-fold increased risk of graft loss (n = 2). Similarly, the point estimates for most assessments of Karnofsky and SF-36 physical functioning were above 1.0, suggesting a positive association between poor physical functioning and graft loss (Figure 5).

Hospital Readmission

The relationship between frailty and hospital readmission after transplantation was examined in 13 assessments across 5 studies. Various frailty instruments were examined and covered every domain of frailty. Among these, 9 assessments

Table 1. Overview of the Association Between Frailty and Functional Status Instruments and Mortality.

Author, year	N	Tool	Follow-up	Analysis[a]	Main findings
Frailty tools					
McAdams-Demarco, 2015[24]	537	Fried Frailty Index	2.7 years[b]	Not frail (referent) vs: intermediately frail: aHR 1.49 (0.73-3.06) frail: aHR 2.17 (1.01-4.65)	Frailty was associated with ↑ risk of mortality among kidney transplant recipients.
McAdams-DeMarco, 2017[27]	663	Fried Frailty Index	3.1 years[c]	(a) Absence of each component (referent) vs presence of at least 1 component: aHR 2.43 (1.17-5.03) (b) Absence of each component (referent) vs presence of at least 1 component: aHR 2.61 (1.14-5.97)	(a) Kidney transplant recipients with exhaustion and slowed walking speed were at ↑ risk of mortality (regardless of whether they were defined as frail). (b) Kidney transplant recipients with poor grip strength, exhaustion and slowed walking speed were at ↑ risk of mortality (regardless of whether they were defined as frail).
McAdams-DeMarco, 2018	1975	Fried Frailty Index	1.6 years[c]	Not frail (referent) vs: intermediately frail: aHR 1.73 (1.04-2.89) frail: aHR 2.19 (1.26-3.79)	Frailty was associated with ↑ risk of mortality on the kidney transplant waitlist.
Nastasi, 2018[31]	719	Fried Frailty Index	2.0 years[b]	Not frail (referent) vs frail: aHR 2.17 (Confidence interval, not reported)[d]; *P*-value: not reported	Frailty was associated with ↑ risk of mortality after kidney transplant.
Haugen, 2019	4552	Fried Frailty Index	Up to 5 years	Not frail (referent) vs frail: aSHR 1.70 (1.36-2.14)	Frailty was associated with ↑ risk of mortality on the kidney transplant waitlist.
Lorenz, 2019	272	Fried Frailty Index	12.4 months[c]	Not frail (referent) vs frail: aHR 7.1 (1.6-32.4)[d,e]	Frailty was associated with ↑ risk of mortality on the kidney transplant waitlist.
Parajuli, 2022	825	Fried Frailty Index	24.1 months[c]	Sum <2 (referent) vs ≥ 2: aOR 1.34 (0.52-3.42)	Frailty was not associated with mortality among kidney transplant recipients.
Perez-Saez, 2022[33]	153	Frail Scale	26 months[b]	Not frail (referent) vs frail: aHR 1.51 (0.62-3.70)[d]	Frailty was not associated with mortality while on the kidney transplant waitlist.
Campbell, 2022	122	Geriatric assessment (GA)	Up to 9 years	Good/excellent (referent) vs poor/marginal/fair: HR 0.86 (0.32-2.27)[f,g]	Poor GA was not associated with mortality on the kidney transplant waitlist.
Chen, 2022	1113	New Physical Frailty Phenotype	6.3 years[b]	Not frail (referent) vs frail: aHR 1.68 (1.06-2.66)[d]	Frailty was associated with ↑ risk of all-cause mortality after kidney transplant.
Chen, 2022	1113	Physical Frailty Phenotype	6.3 years[b]	Not frail (referent) vs frail: aHR 1.67 (1.07-2.62)[d]	Frailty was associated with ↑ risk of all-cause mortality after kidney transplant.
Perez-Saez, 2022[34]	296	Physical Frailty Phenotype	1 year	Score 0-1 (referent) vs score ≥ 2: RR 5.49 (1.70-17.7)[f,h]	Frailty was associated with ↑ risk of 1-year mortality among kidney transplant recipients.
Perez-Saez, 2022[34]	217	Physical Frailty Phenotype	Not reported	Score 0 (referent) vs score 1: aHR 3.52 (1.03-15.9)[e]	Frailty was associated with ↑ risk of mortality among kidney transplant recipients.
Perez-Saez, 2022[33]	153	Physical Frailty Phenotype	26 months[b]	Score 0 (referent) vs score $\geq$ 1: aHR 4.07 (0.78-21.1)[d]	Frailty was not associated with mortality while on the kidney transplant waitlist.
Morel, 2022	200	Muscle density (MD)	1322 days[b]	Normal MD (referent) vs low MD: aHR 2.12 (1.06-4.24)[e]	Myosteatosis (low MD) was associated with ↑ risk of mortality after kidney transplant.
Norris, 2022	465	Psoas cross-sectional area	1207 days[b]	Per unit change (either increase or decrease): aHR 0.99 (0.996-1.001)	Sarcopenia was not associated with mortality among kidney transplant recipients.
Beetz, 2022	42	Skeletal muscle index (SMI)	5 years	Not sarcopenic (referent) vs sarcopenic: aOR 1.79 (1.26-2.40)[d,i]; *P*-value: 0.68	Sarcopenia was not associated with worse patient survival at 5-year post-kidney transplant, as per *P*-value.
Morel, 2022	200	SMI	Low SMI: 992 days[b] Normal SMI: 1158 days[b]	Normal (referent) vs low SMI: RR 1.15 (0.32-4.13)[f,h]	SMI was not associated with of mortality after kidney transplant.

(continued)

Table 1. (continued)

Author, year	N	Tool	Follow-up	Analysis[a]	Main findings
Druckmann, 2022	183	Sarcopenia	Not reported	Per 1cm^2 decrease in cross-sectional area of psoas muscle at L3 level: aHR 1.16 (1.02-1.43)[e,g]	Sarcopenia was associated with ↑ risk of mortality after kidney transplant.
Harhay, 2019	94 465	Weight loss	5.0 years[b]	<5% pre-kidney transplant weight change (referent): weight loss ≥10%: aHR 1.18 (1.11-1.25)[d] weight loss 5%-9.9%: aHR 1.04 (0.99-1.25)[d]	Weight loss (≥10%) was associated with ↑ risk of all-cause mortality after kidney transplant.
Parajuli, 2022	825	Weight loss	24.1 months[c]	No weight loss (referent) vs weight loss: aOR 0.47 (0.11-2.07)	Weight loss was not associated with mortality among kidney transplant recipients.
Nastasi, 2018[31]	719	Gait speed	2.0 years[b]	Per 1-point decrease: aHR 1.21 (0.89-1.65)	Gait speed was not associated with mortality after kidney transplant.
Campbell, 2022	122	Gait speed	Up to 9 years	10m in ≤ 10s (referent) vs 10 min > 10 s: HR 1.10 (0.36-3.37)[f]	Gait speed was not associated with mortality on the kidney transplant waitlist.
Parajuli, 2022	825	Gait speed	24.1 months[c]	Not slow (referent) vs slow: aOR 1.72 (0.55-5.40)	Gait speed was not associated with mortality among kidney transplant recipients.
Cheng, 2020	305	6-Minute Walk Test (6MWT)	362 days[b]	Per 100 m decrease: aHR 1.66 (1.12-2.5)[j]	Decrease in 6MWT was associated with ↑ risk of mortality on the kidney transplant waitlist.
Nastasi, 2018[31]	719	Chair stand	2.0 years[b]	Per 1-point decrease: aHR 1.28 (1.02-1.60)	Decreasing chair stand performance was associated with ↑ risk of mortality after kidney transplant.
Parajuli, 2022	825	Handgrip strength	24.1 months[c]	Normal (referent) vs low grip strength: aOR 0.80 (0.37-1.74)	Grip strength was not associated with mortality among kidney transplant recipients.
Cheng, 2020	304	Sit to stand (STS)	362 days[b]	Per 5 repetitions lower: aHR 1.23 (0.92-1.66)	Lower STS results were not associated with mortality on the kidney transplant waitlist.
Parajuli, 2022	825	Exhaustion	24.1 months[c]	No exhaustion (referent) vs exhaustion ≥3 days/week: aOR 0.72 (0.21-2.45)	Exhaustion was not associated with mortality among kidney transplant recipients.
Functional status tools					
Yango, 2006	64	Activity level	3 years	Active (referent) vs inactive: log-rank *P*-value < 0.001[f]	Inactivity was associated with greater mortality after kidney transplant.
Pieloch, 2014[35]	30 132	Functional status-level of assistance with activities of daily living	3 years	No assistance (referent) vs: some assistance: aHR 1.18 (1.10-1.29) total assistance: aHR 1.56 (1.12-2.16)	Lower functional status was associated with ↑ risk of mortality among kidney transplant recipients.
Brar, 2021	DD: 19 539 LD: 7182	Functional status—level of assistance with activities of daily living	3 years	No assistance (referent) vs: <u>DD</u> moderate assistance: aHR: 1.17 (1.08-1.28) total assistance: aHR: 2.06 (1.74-2.43) <u>LD</u> moderate assistance: aHR: 1.37 (1.14-1.65) total assistance: aHR: 1.38 (0.78-2.42)	Lower functional status was associated with ↑ risk of mortality among kidney transplant recipients.
Campbell, 2022	122	Katz' Activities of Daily Living (ADL)	Up to 9 years	ADL score 6 (referent) vs <6: HR 0.99 (0.13-7.30)[f]	ADL was not associated with mortality on the kidney transplant waitlist.
Campbell, 2022	122	Lawton and Brody's Instrumental Activities of Daily Living Scale (IADL)	Up to 9 years	IADL score 8 (referent) vs <8: HR 0.23 (0.03-1.69)[f]	IADL was not associated with mortality on the kidney transplant waitlist.
Nastasi, 2018[31]	719	Short Physical Performance Battery (SPPB)	2.0 years[b]	Unimpaired (score 11-12) (referent) vs impaired (score <11): aHR 2.28 (1.08-4.84)[d] Per 1-point decrease: aHR 1.19 (1.09-1.30)[d]	SPPB impairment was associated with ↑ risk of mortality after kidney transplant.

(continued)

Table 1. (continued)

Author, year	N	Tool	Follow-up	Analysis[a]	Main findings
Lorenz, 2019	272	SPPB	12.4 months[c]	Per 1-point decrease: aHR 1.37 (1.1-1.72)[d,e,g]	Low physical performance was associated with ↑ risk of mortality on the kidney transplant waitlist.
Haugen, 2020	1951	SPPB	up to 5 years	No impairment (referent) vs impairment: aSHR 1.56 (1.18-2.06)	Impairment was associated with ↑ risk of mortality on the kidney transplant waitlist.
Veasey, 2018	736	Karnofsky Performance Status (Karnofsky)	5.5 years	High functional status (referent) vs low functional status: RR 2.19 (1.1-4.36)[f,h]	Low functional status was associated with ↑ risk of mortality among kidney transplant recipients.
Bui, 2019	97 321	Karnofsky	up to 5 years	Karnofsky unknown (referent) vs: Karnofsky score 80-100: aHR 0.96 (0.92-1.01) Karnofsky score 50-70: aHR 1.13 (1.07-1.19) Karnofsky Score 10-40: aHR 2.45 (2.25-2.66)	Lower functional status was associated with ↑ risk of mortality on the kidney transplant waitlist.
Chu, 2021	224 832	Karnofsky	5 years	Per 10% decrease in Karnofsky: aHR 1.11 (1.10-1.11)	Lower Karnofsky was associated with ↑ risk of mortality after kidney transplant.
Parajuli, 2022	825	Karnofsky[k]	24.1 months[c]	Karnofsky scale ≥60% (referent) vs <60%: aOR 0.99 (0.13-7.88)	Physical activity was not associated with mortality among kidney transplant recipients.
Reese, 2014	10 875	SF-36 physical functioning scale	1631 days[b]	Score >85 (Q4) (referent) vs: score 60-85 (Q3): aHR 1.09 (0.94-1.77)[d] score 40-60 (Q2): aHR 1.28 (1.12-1.46)[d] score <40 (Q1): aHR 1.66 (1.45-1.89)[d]	Decreased physical function was associated with ↑ risk of mortality after kidney transplant.
Reese, 2015	11 050	SF-36 physical functioning scale	5.8 years[b]	Highest physical function (Q1) (referent) vs: Q2: RR 1.37 (1.17-1.61)[f,h] Q3: RR 1.62 (1.38-1.91)[f,h] lowest physical function (Q4): RR 2.00 (1.71-2.33)[f,h]	Decreased physical function was associated with ↑ risk of mortality on the kidney transplant waitlist.
Harhay, 2016	8788	SF-36 physical functioning scale	5.0 years[b]	Highest physical function (Q4) (referent) vs: Q3: aHR 1.07 (0.92-1.25)[d] Q2: aHR 1.21 (1.05-1.40)[d] lowest physical function (Q1): aHR 1.52 (1.31-1.75)[d]	Decreased physical function was associated with ↑ risk of mortality after kidney transplant.
von der Lippe, 2016	140	SF-36 physical functioning scale	102 months[b]	Better physical function (T2 and T3) vs poor physical function (T1): log-rank *P*-value= 0.019[f]	Decreased physical function was associated with mortality after kidney transplant.

Note. 6MWT = 6-Minute Walk Test; ADL = Activities of Daily Living; aHR = adjusted hazard ratio; aOR = adjusted odds ratio; aSHR = adjusted subhazard ratio; CI = 95% confidence interval; DD = deceased donor; GA = geriatric assessment; HR = unadjusted hazard ratio; IADL = instrumental activities of daily living; Karnofsky = Karnofsky Performance Status; LD = living donor; MD = muscle density; nPFP = new physical frailty phenotype; OR = unadjusted odds ratio; Q = quartile; RR = unadjusted relative risk; SMI = Skeletal Muscle Index; SPPB = Short Physical Performance Battery; STS = Sit to Stand Test.
[a]All models adjusted for a minimum of age and sex, unless otherwise noted. Where a choice of models exists, the most fully adjusted model is presented.
[b]Median.
[c]Mean.
[d]Multiple adjusted models available.
[e]Model not adjusted for sex.
[f]Unadjusted model.
[g]Scale inverted.
[h]RR calculated from event data, or cumulative survival event data.
[i]Model not adjusted for age.
[j]Scale change.
[k]For this study, Karnofsky was used to assess physical activity, instead of functional status.

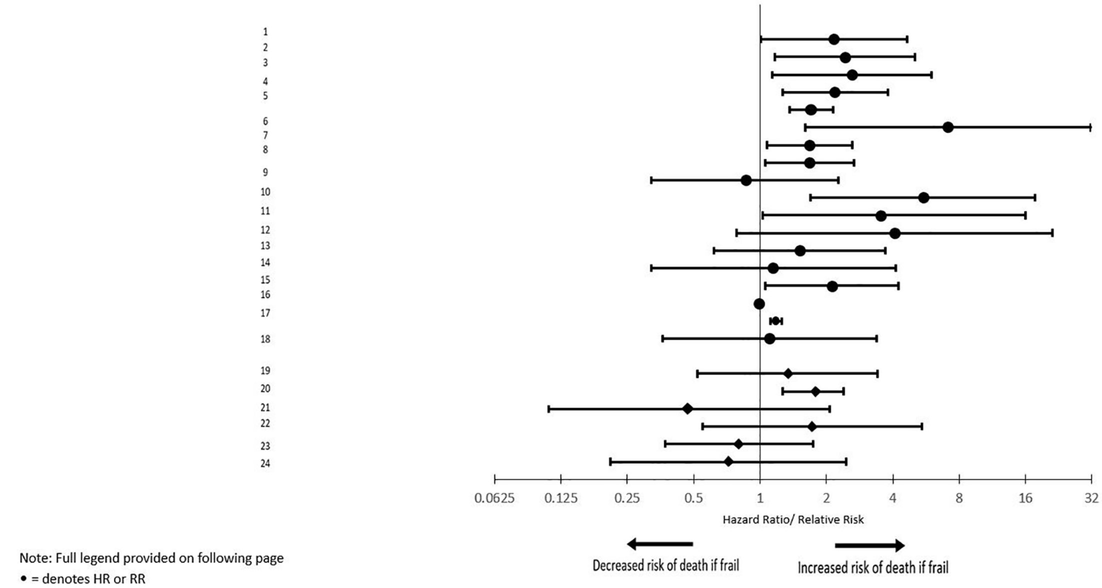

Figure 2. Forest plot of the association between frailty as a categorical variable and mortality.§

1	McAdams-Demarco, 2015	Fried Frailty Index	HR	Frail vs. not frail
2	McAdams-Demarco, 2017[27]	Fried Frailty Index (a)	HR	Presence of at least 1 component vs. absence of each component
3	McAdams-Demarco, 2017[27]	Fried Frailty Index (b)	HR	Presence of at least 1 component vs. absence of each component
4	McAdams-Demarco, 2018	Fried Frailty Index	HR	Frail vs. not frail
5	Haugen, 2019	Fried Frailty Index	HR	Frail vs. not frail
6	Lorenz, 2019	Fried Frailty Index	HR	Frail vs. not frail
7	Chen, 2022	Physical Frailty Phenotype	HR	Frail vs. not frail
8	Chen, 2022	New Physical Frailty Phenotype	HR	Frail vs. not frail
9	Campbell, 2022	Geriatric assessment recommendation	HR¥, unadj.	Poor vs. good
10	Perez-Saez, 2022[36]	Physical Frailty Phenotype	RR*, unadj.	≥2 vs. 0-1
11	Perez-Saez, 2022[36]	Physical Frailty Phenotype	HR	1 vs. 0
12	Perez-Saez, 2022[35]	Physical Frailty Phenotype	HR	≥1 vs. 0
13	Perez-Saez, 2022[35]	Frail Scale	HR	Frail vs. not frail
14	Morel, 2022	Skeletal muscle index (SMI)	RR*, unadj.	Low vs. normal SMI
15	Morel, 2022	Muscle density	HR	Low vs. normal muscle density
16	Norris, 2022	Psoas cross sectional area	HR	Per unit change (either direction)
17	Harhay, 2019	Weight loss	HR	Weight loss ≥10% vs. <5% pre kidney transplant weight change
18	Campbell, 2022	Gait speed	HR, unadj.	10 m in > 10s vs. 10m in ≤10s
19	Parajuli, 2022	Fried Frailty Index	OR	Score ≥2 vs. <2
20	Beetz, 2022	SMI	OR	Sarcopenic vs not sarcopenic
21	Parajuli, 2022	Weight loss	OR	Weight loss vs no weight loss
22	Parajuli, 2022	Gait speed	OR	Slow vs. not slow
23	Parajuli, 2022	Grip strength	OR	Low vs. normal grip strength
24	Parajuli, 2022	Exhaustion	OR	Exhaustion ≥ 3days/week vs. no exhaustion

Abbreviations: HR= hazard ratio; OR, Odds ratio; RR*= relative risk calculated from event data; SMI= Skeletal Muscle Index; Unadj; unadjusted model;
¥ = comparison was inverted

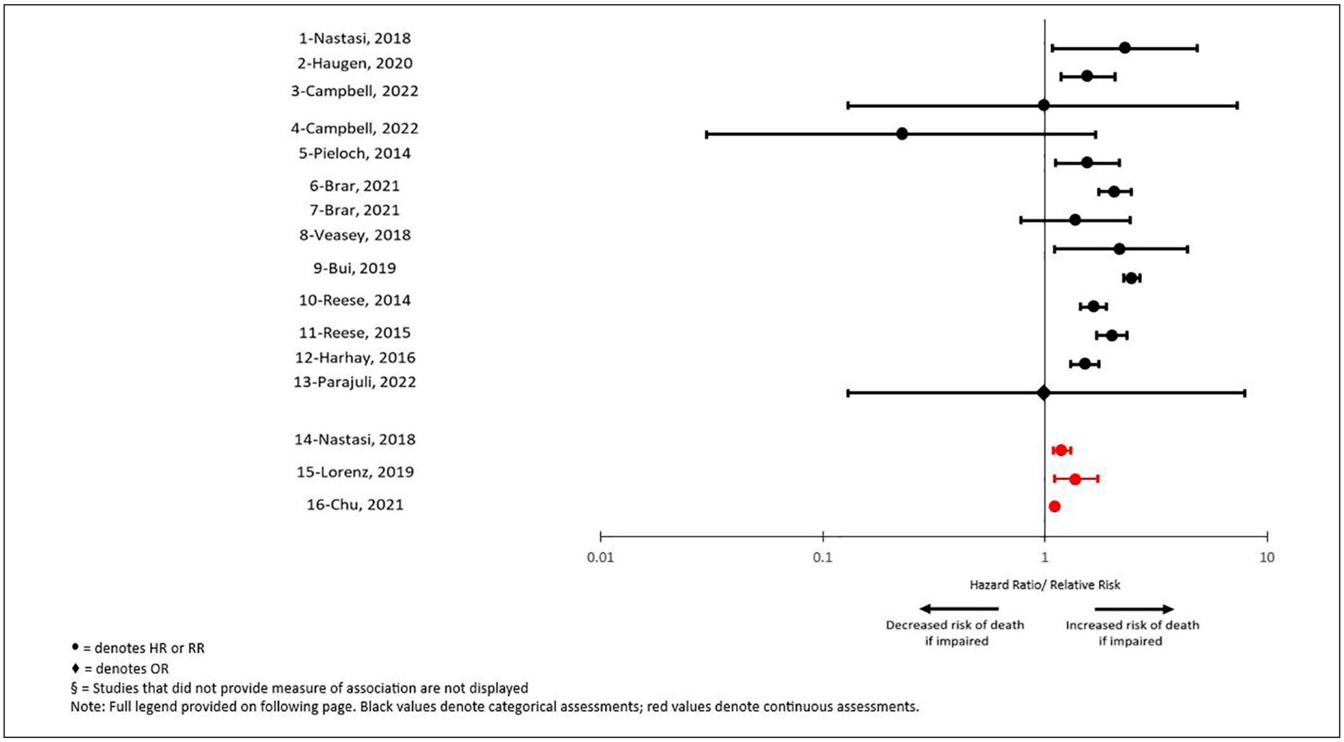

Figure 3. Forest plot of the association between functional status and mortality.[§]

1	Nastasi, 2018	Short Physical Performance Battery (SPPB)	HR	Impaired vs. not impaired
2	Haugen, 2020	SPPB	HR	Impaired vs. not impaired
3	Campbell, 2022	Katz' Activities of Daily Living (ADL)	HR, unadj.	ADL score <6 vs. 6
4	Campbell, 2022	Lawton & Brody Instrumental Activities of Daily Living (IADL)	HR, unadj.	IADL score <8 vs. 8
5	Pieloch, 2014[38]	Functional status-level of assistance with ADL	HR	Total assistance vs. no assistance
6	Brar, 2021	Functional status-level of assistance with ADL (DD)	HR	Total assistance vs. no assistance
7	Brar, 2021	Functional status-level of assistance with ADL (LD)	HR	Total assistance vs. no assistance
8	Veasey, 2018	Karnofsky Performance Status (Karnofsky)	RR*, unadj.	Low vs. high functional status
9	Bui, 2019	Karnofsky	HR	Karnofsky score 10-40 vs. unknown
10	Reese, 2014	SF-36 physical functioning scale	HR	Score <40 vs. >85
11	Reese, 2015	SF-36 physical functioning scale	RR*, unadj.	Lowest vs. highest physical function
12	Harhay, 2016	SF-36 physical functioning scale	HR	Lowest vs. highest physical function
13	Parajuli, 2022	Karnofsky	OR	Karnofsky scale <60% vs. ≥ 60%
14	Nastasi, 2018	SPPB	HR	Per 1-point decrease
15	Lorenz, 2019	SPPB	HR¥	Per 1 point decrease
16	Chu, 2021	Karnofsky	HR	Per 10% decrease

Abbreviations: ADL= Activities of Daily Living; DD= deceased donor; LD= living donor; Karnofsky = Karnofsky Performance Status; IADL, Instrumental Activities of Daily Living; OR, Odds ratio; RR*= relative risk calculated from event data; SPPB= Short Physical Performance Battery; Unadj; unadjusted model; ¥ = comparison was inverted

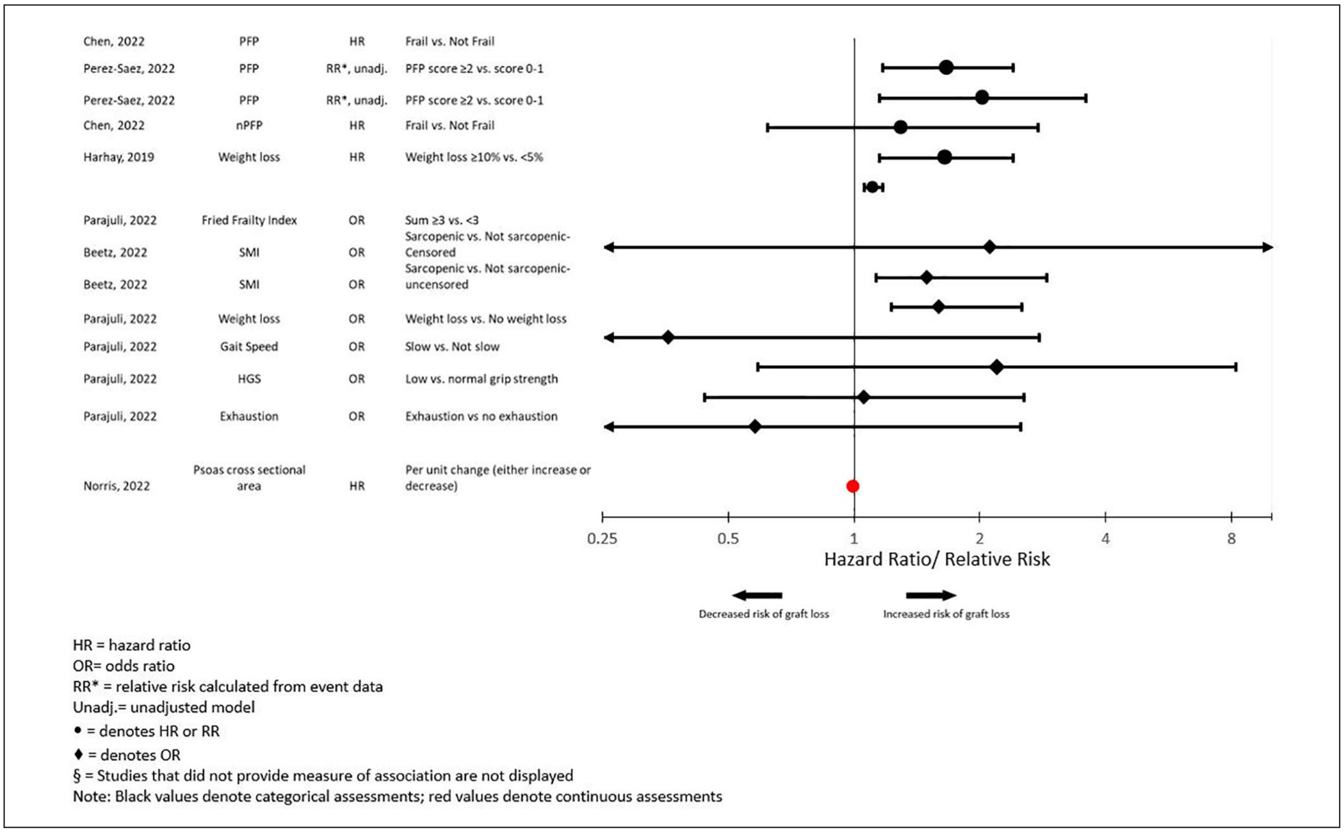

Figure 4. Forest plot of the association between frailty and graft loss.§

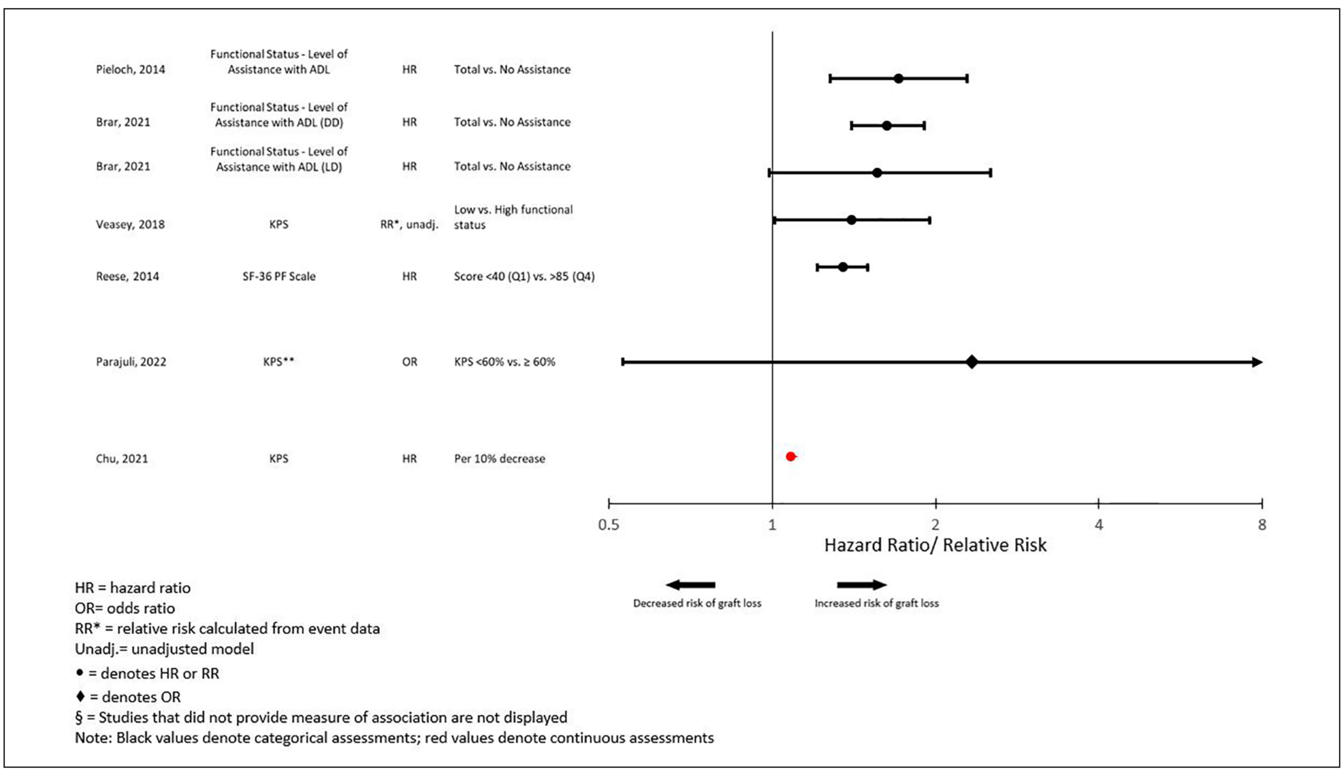

Figure 5. Forest plot of the association between functional status and graft loss.§

were examined categorically (Figure 6). For assessments measuring overall frailty, there was an increased risk for rehospitalization ranging from 2- to 4-fold among patients deemed frail prior to transplantation. When sarcopenia was examined, 2 of 3 assessments revealed a 4- to 7-fold increase in the risk of rehospitalization. A single assessment of strength found a 2-fold increased risk of rehospitalization among patients with weaker strength prior to transplantation. In contrast, frailty based on measurements of gait, physical activity, and fatigue were not significantly associated with rehospitalization. When frailty was examined as a continuous measure, only 2 of 4 assessments, which examined radiographically determined muscle attenuation prior to transplantation, found a statistically significant increased risk of rehospitalization after transplantation (Figure 7). Functional status was examined in 2 studies, with only 1 reporting significantly increased odds of rehospitalization among transplant patients with impaired functional status (Supplementary Figure S2). Finally, 6 assessments among 2 studies examined frailty and the risk of hospitalization while on the waitlist. Only 2 assessments found a statistically significant relationship.

Transplantation

The relationship between frailty and receiving a kidney transplant was examined in 8 assessments in 5 studies. Among these, 4 of the 8 assessments revealed a decreased likelihood (20%-61% reduction) of undergoing kidney transplantation among frail individuals (Figure 8). There were 4 assessments of functional status, with half reporting that impaired functional status was associated with a 16% to 26% decreased likelihood of undergoing kidney transplantation (Supplementary Figure S3).

Delayed Graft Function

Frailty's relationship with the occurrence of DGF post-kidney transplant was conducted through 10 categorical assessments (Supplementary Figure S4). Only 2 of 10 showed a significant association between frailty and DGF, with 1 study finding a 2-fold increased risk of DGF among patients identified as frail prior to transplantation, and another study finding an association between weight loss among transplant recipients prior to transplantation and decreased odds of DGF.

Three assessments examined functional status using Karnofsky and SF-36 physical functioning (Supplementary Figure S5). Two of these revealed an increased risk of DGF among patients with impaired functional status before transplantation.

Discussion

This systematic review identified 50 published studies using 36 unique instruments that examined the association between measures of frailty and functional status with key clinical outcomes in kidney transplant candidates. Both decreased functional status and frailty were associated with mortality. Similar trends were noted when examining graft loss and rehospitalization as outcomes. These findings reinforce the importance of considering frailty and functional status during the transplant evaluation process.

The magnitude of the effect of frailty on overall survival after kidney transplant is difficult to quantify. Given the heterogeneity of the studies included in this systematic review, we could not pool results nor perform a meta-analysis. However, the magnitude of the association of frailty with mortality in our study is in the same range as what our group has previously demonstrated for frailty in CKD patients[22] and what has been shown with diabetes pre-kidney transplant.[36] Therefore, the potential impact of frailty on kidney transplant outcomes and how to address this should be considered.

Although a growing number of studies have examined frailty's impact on kidney transplant outcomes,[6,8,37] there has been less focus on functional status. Our review adds to the available literature by summarizing the effects of pre-transplant frailty on relevant post-transplant outcomes. Our findings provide additional insights into the role of functional status in predicting adverse outcomes in transplant candidates, reinforcing its potential role as a prognostic factor and a possible assessment tool in the evaluation process.

Frailty has a long-reaching impact, not only affecting patients before surgery but also influencing an array of outcomes post-transplant.[7,20,33-35,38-40] Studies have shown that the prevalence of frailty among kidney transplant candidates is nearly 20%.[7,8,38] Kidney transplant guidelines highlight the need for studies to examine the utility of measuring frailty during the transplant evaluation process.[41] Despite the acknowledged importance of frailty in determining transplant eligibility, the use of standardized frailty assessment in clinical practice remains rare, suggesting a gap between its recognized importance and clinical implementation.[11,22,42] Standardizing frailty measures would facilitate more consistent risk stratification, enabling clinicians to make more informed decisions regarding transplant eligibility, potentially improving recovery times and overall outcomes. It would also enhance the comparability of research findings and serve as a benchmark for quality improvement initiatives. This study advances the understanding of frailty and its interplay with kidney transplantation outcomes. Our work supports the initiative to develop and adopt validated, standardized frailty assessment tools by underscoring the absence of standardization in this field.

Furthermore, by identifying and addressing poor physical functioning and frailty before transplantation, health care providers can design and implement prehabilitation strategies specific for transplantation that may lead to improved outcomes.[21,43] Identifying frailty and assessing functional capacity pre-operatively could offer opportunities to implement changes in approaches to care that have

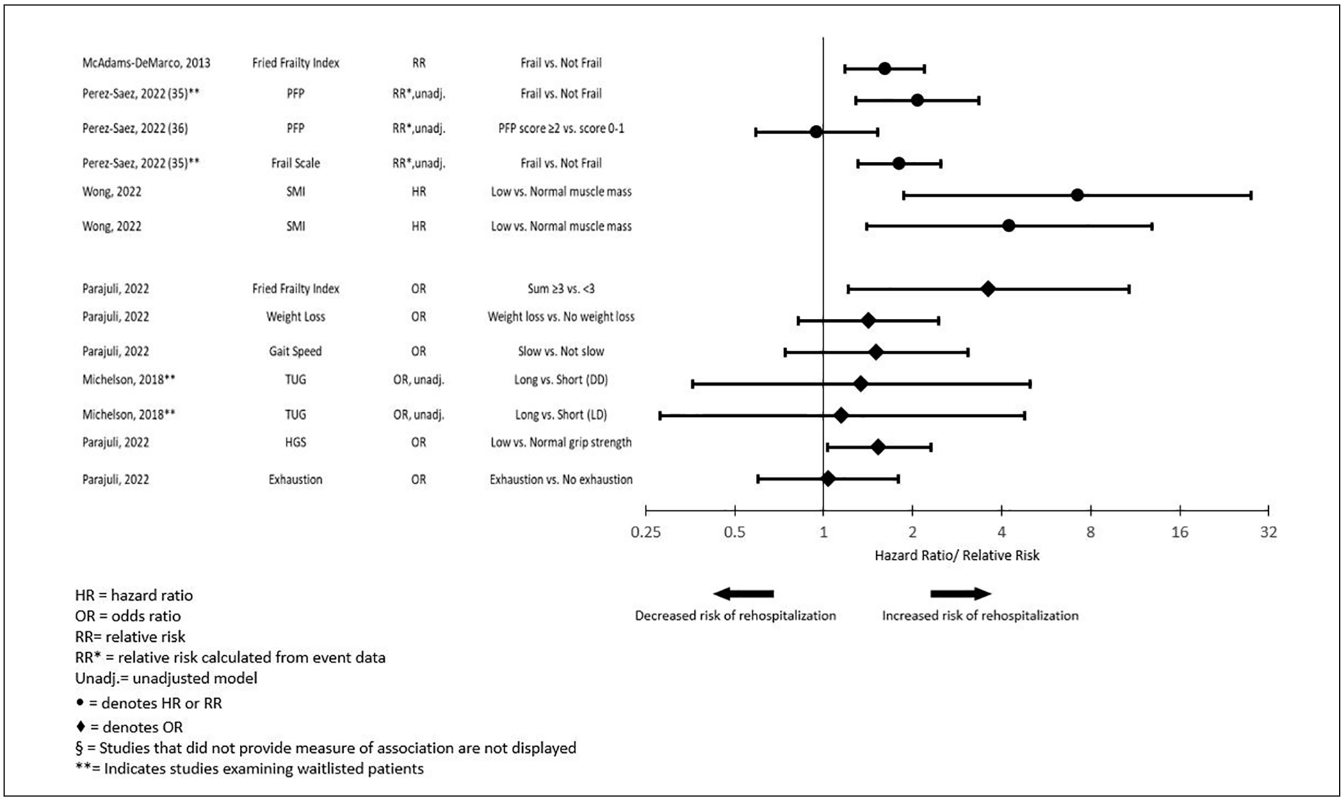

Figure 6. Forest plot of the association between frailty as a categorical variable and rehospitalization.§

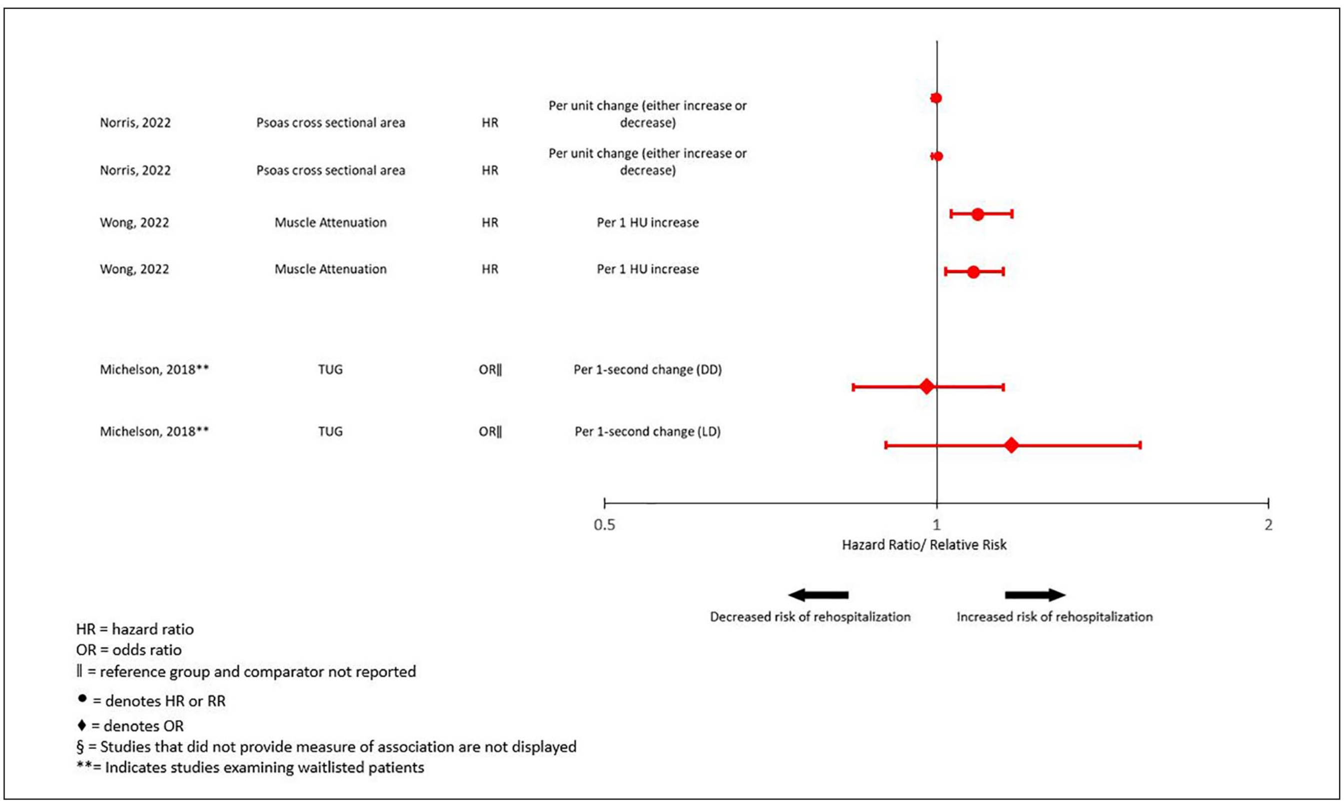

Figure 7. Forest plot of the association between frailty as a continuous variable and rehospitalization.§

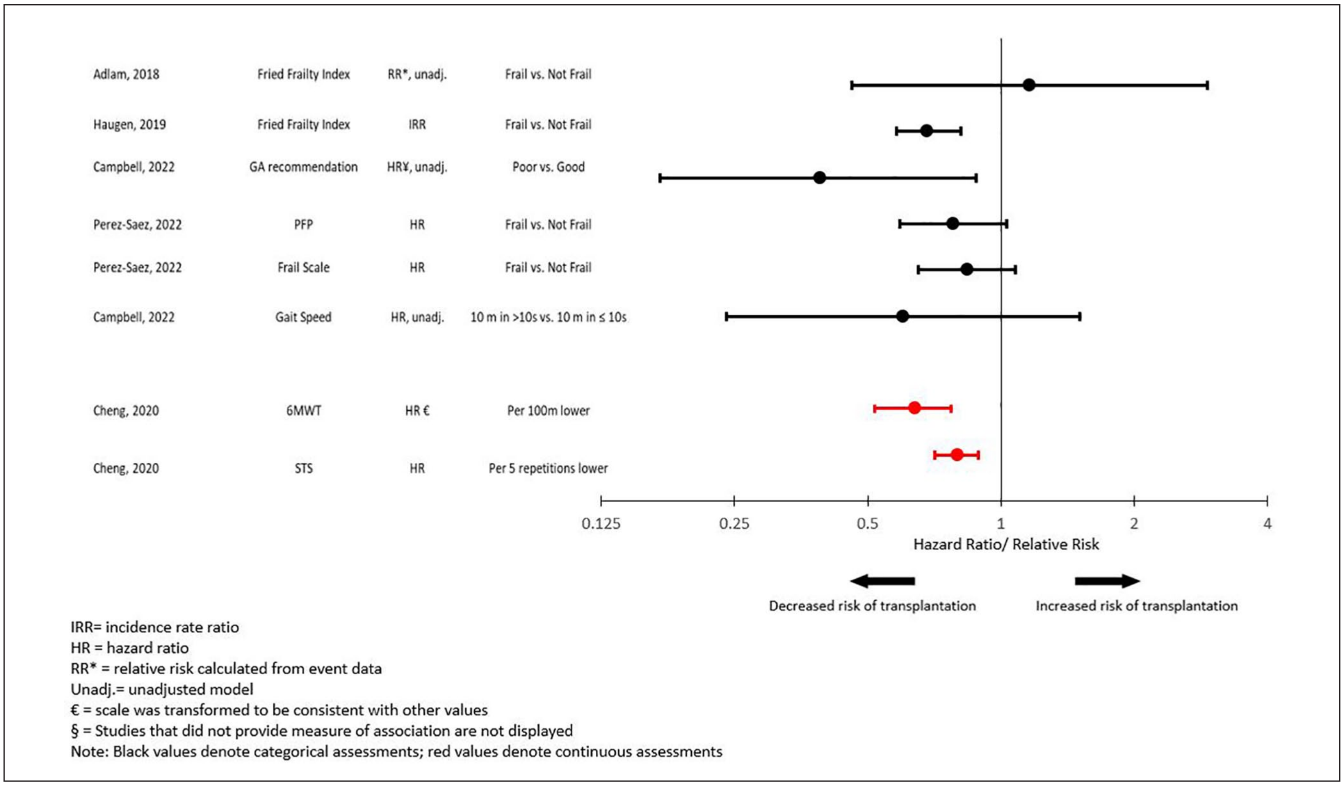

Figure 8. Forest plot of the association between frailty and transplantation.§

the potential to improve post-operative outcomes. Kidney transplant candidates generally have time to intervene with prehabilitation given the current waiting times for deceased donor kidney transplantation.[44] A pilot study by McAdams-Demarco examined center-based rehabilitation involving weekly physical therapy sessions on 5 transplant candidates.[21] Although the study reported improvements in overall health status and feasibility of the intervention, the small sample size and lack of control group limit the ability to draw definitive conclusions about its impact on post-operative outcomes such as hospital length of stay.[21] Although this preliminary work is hopeful, hard evidence is lacking on the effectiveness of such strategies in kidney transplant candidates. However, evidence from other surgical populations, such as colorectal, cardiac, and orthopedic surgery, suggests prehabilitation may improve post-operative outcomes, including reduced complications and shorter hospital stays.[45-47] These findings indicate a potential for similar benefits in kidney transplantation. By focusing on improving patients' strength, endurance, and physical functioning, implementing such programs could enhance outcomes after transplantation, but further research is needed to determine the efficacy of prehabilitation strategies in this specific patient population.

Although transplantation generally offers survival and quality of life advantages over remaining on dialysis, it is unclear whether there exists a threshold of frailty or diminished functional status beyond which the absolute risk of adverse outcomes is prohibitively high, and an individual should not receive a kidney transplant. The heterogeneity of frailty assessment tools and the lack of standardized cutoff points in the studies we reviewed, and the various other clinical factors which must be considered when evaluating an individual's transplant candidacy would make it nearly impossible to define such a threshold. Even if there was an accurate, reliable, easy to implement assessment tool for frailty in transplant candidates, it is hard to see how it could be studied to determine one's transplant candidacy in a prospective, controlled fashion. Observational prospective cohort studies where outcomes are stratified by frailty status could be informative, despite selection bias and confounding that are difficult to control for. They could help identify patients who may not benefit from transplantation due to excessive risk. As the age of waitlisted transplant candidates continues to grow,[48] frailty is likely to play an ever-growing role in transplant candidacy evaluation. Future research is needed to improve assessment tools and determine its impact on the risk-benefit balance of kidney transplantation.

Major strengths of our review are its size and broad scope. Our findings draw from a pool of 50 studies encompassing 668 103 patients. These factors increase the clinical applicability of our findings. In addition, our study investigated the impact of all frailty domains on various clinical outcomes, including the effect of functional status on adverse events, something previous systematic reviews have not addressed. Also, measurement methods were not restricted in this review. Therefore, numerous instruments measuring functional status and all the domains of frailty were included. Although our study provides valuable insights, it is not without limitations. The heterogeneity in the measurement instruments and study designs included in the review may limit the generalizability of the findings. Furthermore, the majority of studies originated from the United States, and we only included studies published in English, further limiting generalizability. It is important to note that there were variations in the study designs and assessment instruments across the included studies. Moreover, there were discrepancies in the definition of outcomes across studies. These factors introduce heterogeneity influencing the comparability of findings, and as a result, conducting a meta-analysis and pooling statistics could not be performed. In addition, many studies relied on secondary data sources such as registries, hospital records, and previous cohorts. This may have impacted the validity of data collection, assessment of exposure and outcomes, and may have led to selection bias in some of these studies.

Conclusion

This systematic review highlights the significant impact of frailty and decreased functional status on key outcomes in kidney transplant candidates, including mortality, graft loss, and rehospitalization. Our findings suggest that further studies are needed to evaluate the best instrument(s) to assess frailty and functional status, and importantly, interventional studies are needed to determine whether prehabilitation strategies can improve post-transplant outcomes in appropriate kidney transplant candidates.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by peer-reviewed grant from the Canadian Institutes of Health Research (grant #FDN-143239).

Ethics Approval

Not Applicable.

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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Availability of Data and Materials

Not Applicable.

Supplemental Material

Supplemental material for this article is available online.

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