Frailty and post-transplant adverse outcomes among kidney transplant recipients: A systematic review and meta-analysis

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ABSTRACT

Introduction: Frailty is a good predictor of adverse outcomes among older patients, especially those who have undergone surgery. The prevalence of frailty among kidney transplant candidates is higher than the general population. This study aimed to explore the predictive value of frailty on post-transplant adverse outcomes among kidney recipients.

Methods: A systematic review was performed for relevant studies until May 20, 2022, using four databases (Embase, Medline, Cochrane, and PsycINFO) for prospective design studies (PROSPERP: CRD42022331022). Random-effect meta-analysis modeling was undertaken in RevMan 5.3 to estimate the predicting value of frailty on adverse outcomes after kidney transplant.

Results: This systematic review included 14 studies, eight of which were suitable for meta-analysis. Frailty increased the risk of mortality (pooled hazard ratio [HR] 1.98, 95% confidence interval [CI] 1.48–2.64), surgical complications (risk ratio [RR] 2.14, 95% CI 1.01–4.54), death-censored graft failure (DCGF) (pooled HR 3.31, 95% CI 1.27–8.62), length of stay (LOS) (pooled RR 1.59, 95% CI 1.05–2.39), length of stay ≥2 weeks (pooled odds ratio [OR] 1.72, 95% CI 1.26–2.35), and other common adverse outcomes among kidney transplant recipients.

Conclusions: Frailty is associated with adverse outcomes after kidney transplant. This
systematic review suggests the importance of assessing frailty among kidney transplant candidates prior to transplantation. Further research focusing on pretransplant assessment combined with frailty is warranted to improve kidney transplant management.

INTRODUCTION
Frailty is a biological syndrome presenting with decreased reserve and resistance to stressors resulting from a cumulative decline across multiple physiologic systems, thereby leading to vulnerability to adverse outcomes [1]. The majority of previous frailty studies focused on older patients and has been shown to be associated with increased mortality, falls, disability, and poor quality of life [1-5]. It has also been shown to predict postoperative complications, mortality, and length of stay (LOS) in hospitals for people who underwent surgery [6] and can enhance the efficiency of surgery risk assessment [7, 8]. Frailty has been associated with poor health outcomes in almost all populations, from community-dwelling older adults to solid organ transplant recipients [9]. Assessing frailty can aid physicians in identifying high-risk patients. The mean prevalence of frailty gradually increases with age [1, 10]. Nonetheless, frailty can occur due to a range of diseases and medical conditions [11]. According to a previous survey, lower levels of kidney function are independently associated with a higher risk of frailty [12, 13]. Among patients with chronic kidney disease (CKD) stages 1–4, the prevalence of frailty is more than twice as high as that among community-dwelling older adults [14]. Additionally, frailty is increasingly prevalent among patients with end-stage renal disease (ESRD). The prevalence of frailty when on dialysis was higher for patients of all ages than for older patients and that 69.4% of patients on peritoneal dialysis were frailty [15]. Moreover, frailty was associated with pretransplant dialysis duration [16]; and adverse clinical outcomes among patients on dialysis, including poor cognitive function, falls, hospitalizations, and mortality [14]. Frail participants were almost half as likely to be listed for KT [17].

Transplantation is the gold standard therapy for patients with ESRD. The latest UK Renal Registry report (up to December 31, 2019) revealed that 28,303 patients with kidney failure are managed through hemodialysis or peritoneal dialysis. Frailty is a common syndrome among these patients. Approximately one in six KT candidates were frail [18]. Recipients are more susceptible to post-transplant adverse outcomes, such as lower rates of preemptive transplantation. However, few studies have focused on the association between frailty and adverse outcomes after kidney transplant. Therefore, further research on frailty and surgical complications post-transplantation is needed. This systematic review and meta-analysis aimed to provide a comprehensive overview of published evidence on the impact of frailty on
METHODS

Protocol and registration
The review protocol is registered with the international prospective register of systematic reviews (PROSPERO) database (registration NO. CRD42022331022).

Inclusion and exclusion criteria
All cohort studies investigating the association between frailty and post-transplant outcomes for kidney transplant recipients were included. Studies that reported odds ratio (OR), risk ratio (RR), or hazard ratio (HR) were included in the meta-analysis.

The inclusion criteria were as follows:
- Articles available as full text;
- Prospective studies;
- Study population included kidney transplant recipients;
- Age ≥ 18 years;
- Frailty defined as per the original or modified versions of validated frailty criteria.

The exclusion criteria were as follows:
- Poster presentations, conference abstracts, case reports, or review articles and
- Kidney transplantation combined with other solid organ transplants.

Search strategy
We performed a systematic literature search to identify cohort studies that investigated the relationship between frailty and kidney transplantation till May 20, 2022. Two independent authors (Y.W. and L.X.) searched Medline (via the web of science), Embase (via Ovid), PsycINFO, and the Cochrane Library databases for studies from inception to the date of searching for published articles in English. The search terms used were “frailty or frail*” and “kidney transplantation OR renal transplant” OR kidney transplant*.”

Study selection
Two authors (Y.W. and L.X.) independently assessed the studies. Article titles and abstracts from all databases were reviewed to determine their eligibility; full-text articles were reviewed thereafter. Disagreements were resolved through discussion with a third reviewer (J.L.).

Data extraction
Data were extracted from the eligible studies using a standardized data collection sheet, which included details on the first author, publication year, study design, country, sample size, frailty tool, mean age (y), gender (% female), post-transplant outcome, risk estimate,
adjustment, and follow-up period. Delayed graft function (DGF) was defined as the need for dialysis during the first 7 days after transplant. HR, OR, and RRs of post-transplant outcomes, as well as a 95% confidence interval (CI), were collected. The effect measures with adjusted confounders were preferred over crude ones.

Assessment of study quality
Quality assessment of all included studies was conducted using the Newcastle–Ottawa Scale (NOS) for cohort studies independently by two authors (Y.W. and M.W.). This eight-item scale covered the selection, compatibility, and outcome domains of the cohort studies. The maximum score for NOS is 9; a score of ≥7 indicated that the study was of high quality, 4–6 indicated moderate quality, and ≤4 indicated low quality. A third reviewer helped with mediation (B.H.) when needed.

Statistical analyses
Meta-analysis was performed using Revman version 5.3. If an outcome was reported by two or more studies, pooled HR, OR, or RR and 95% CI were calculated using a fixed-effects model for dichotomous outcomes. The heterogeneity of the studies was evaluated using chi-square tests and I² statistics; an I² value of >50% or a P-value of <0.05 in Cochran’s Q testing indicated significant heterogeneity. Data with significant heterogeneity were subjected to the random-effects model to calculate the pooled effect size. A sensitivity analysis was conducted by removing one study and recalculating the values to estimate whether the results could have been markedly affected by a single study.

RESULTS

Literature search
A total of 868 potentially relevant articles were reviewed. The EndNote software was used to delete 176 duplicate articles. Articles that met the inclusion criteria but not the exclusion criteria were included. After analyzing the title, abstract, and full text, 14 articles were included in this analysis; these are shown in the PRISMA flowchart (Figure 1). The methodological quality of all studies was assessed using NOS. All studies met five or more of the eight scale items, and the average NOS score was 7.4 (range, 5–9) (Table 1). All studies were published between 2012 and 2022 in English. The study by Schaenman[19] demonstrated that pretransplant frailty among kidney transplant recipients was associated with increased LOS and the need for readmission; however, this article was excluded for its retrospective pilot nature. A total of 8 studies were included in the final meta-analysis.

Characteristics of the included studies
The characteristics of the included studies are summarized in Table 2. Frailty was assessed using the frailty physical phenotype (PFP) in 12 studies, the Groningen Frailty Indicator
Frailty and post-transplant adverse outcomes

Frailty and mortality

Six studies, including 3,457 kidney transplant recipients, reported post-transplant mortality [9, 20-23]. Of these, five studies were suitable to be included in the meta-analysis. The pooled OR for the association between frailty and post-transplant mortality was 1.98 RR (95% CI: 1.48–2.64; p < 0.00001). All studies indicated that frailty is a significant predictor of mortality. Notably, dos Santos [24] reported that the mortality rate was not significantly different between non-frail and frail groups. However, this was not included in the metanalysis because the HR was unavailable. (9.4% vs. 12.5%, p = 0.689).

Frailty and surgical complications

Data on surgical complications after kidney transplantation were only available in two studies. The study by dos Santos reported a 2.14-fold higher risk of surgical complications (95% CI: 1.01–4.54) (95% CI: 1.01–4.54). Another study demonstrated that frailty resulted in an increase of an average of 13.3 points on the Comprehensive Complication Index (CCI) for kidney transplant recipients (b = 13.3; 95% CI: 5.7–20.9; P = 0.0007) [25]. That is a big difference compared to other study, probably because the sample size is small leading to a wide range of confidence interval.

Frailty and DCGF

Three studies presented adjusted HR as a risk measure of DCGF. The pooled mean difference between the DCGF for frail and nonfrail patients was 3.31 (95% CI: 1.27–8.62). Meta-analysis revealed heterogeneity among the studies (Figure 3; P = 0.02; I² = 73%). A sensitivity analysis was performed by removing one study and recalculating the data to evaluate the stability of the results. Sensitivity analysis showed that the study by Chen et al. was the main source of heterogeneity; and there was no heterogeneity after excluding it.

Frailty and LOS

Three studies reported RR as a risk measure of LOS. The frail patients had an increased risk of LOS compared with non-frail patients (RR: 1.59; 95% CI:1.05 - 2.39). The meta-analysis results showed heterogeneity among the studies (P < 0.00001, I² = 95%). Sensitivity analysis was performed by removing one study and reevaluating the stability of the results. Sensitivity analysis showed that the study by McAdams-Demarco was the main source of heterogeneity; there was no heterogeneity after excluding it.
Two studies reported the OR as a risk measure for LOS ≥ 2 w [23, 26]. The pooled mean difference between the ≥ 2w LOS for frail and nonfrail patients was 1.72 (95% CI: 1.26–2.35). All the risk measures were obtained after adjusting for age and other common variables.

**Frailty and other post-transplant adverse outcomes**

Frailty was associated with other common adverse outcomes in kidney transplant recipients. One study reported that preoperative frailty was independently associated with a 1.94-fold increased risk of DGF (95% CI: 1.13–3.36; P = 0.02)[27]. One study confirmed that frailty independently predicted a 61% higher risk of early hospital readmission (adjusted RR: 1.61, 95% CI: 1.18–2.19, P = 0.002)[28]. Frailty decreased the post-transplantation quality of life[29]; and increased mycophenolate mofetil dose reduction (HR: 1.29, 95% CI: 1.01–1.66; P = 0.04) [30], delirium (OR: 2.05; 95% CI: 1.02–4.13; P = 0.04) [31], medium-term cognitive decline post-transplant [32], and polypharmacy [33].

**DISCUSSION**

Kidney transplant recipients with frailty tend to have poorer outcomes than nonfrail recipients, independent of their age or comorbidities [34]. This systematic review and meta-analysis indicated that frailty is a good predictor of adverse outcomes after kidney transplantation. The studies included in this analysis covered a wide range of post-transplant adverse outcomes in the recipients and identified frailty to be associated with an increased risk of mortality, post-transplant complications, LOS, DCGF, DGF, and other common clinical outcomes after kidney transplant.

A hallmark feature of CKD is a persistent state of low-grade inflammation [35], which is recognized as a major factor associated with CKD progression [36]. This may lead to the significantly higher prevalence in this population and in patients undergoing kidney transplantation. According to previous reports, 67% of patients on dialysis [37] and 69.4% of patients on hemodialysis [15] were frail. Notably, more than half of the patients with CKD are frail [38]. Thus, frailty is a common syndrome among all ages of candidates. These candidates are likely to have adverse outcomes.

Mortality and surgical complications are two challenges faced by kidney transplant recipients. We found evidence of an increased risk of mortality and surgical complications among frail recipients compared with non-frail recipients. Frailty is a strong predictor of mortality and surgical complications among older adults [6, 39], and kidney transplant is the gold standard therapy. As expected, frailty can significantly influence the management of kidney transplant candidates and recipients.

Graft failure is among kidney transplant recipients can be catastrophic. It is necessary to assess the risk of DCGF before transplant. Frailty is a good indicator of DCGF risk prior to
kidney transplant. DGF, a common acute surgical complication that occurs after kidney transplantation, increases the risk of graft immunogenicity and acute rejection, which is an independent risk factor affecting the long-term survival of the transplanted kidney. Rehabilitation should be considered for patients on the waitlist. In our study, frailty was observed to increase the risk of DGF, which is linked to the inflammatory state. Frailty is considered a pro-inflammatory state [27], and frailty assessment may help clinicians decide on pre-DGF prevention.

LOS of ≥ 2w is an important indicator of postoperative quality for kidney transplant recipients. Frail recipients are likely to encounter many clinical events after the transplantation. Therefore, longer LOS is common among frail individuals. PFP is a commonly used frailty assessment tool that was used in 11 of the 14 included studies. PFP is a measure of physiologic reserve based on five components: slowed gait speed, weakness, exhaustion, shrinking, and low physical activity. However, weight change (shrinking) is common among patients on dialysis. Clinicians should consider measuring shrinking using dry weight changes when measuring frailty using PFP. Post-transplant LOS and DCGF exhibited heterogeneity; however, we believe that it was because of the use of different assessment tools for frailty and sample sizes. Multimodal prehabilitation can be used to reverse frail patients before surgery. Frail patients benefit from targeted interventions (which focus on nutritional supplementation, feedback-based exercise regimens, and pulmonary optimization)[40].

**Limitations**

There are strengths and limitations to this systematic review. It included a diverse range of post-transplant adverse outcomes among kidney transplant recipients. The total sample size was large, comprising 5561 recipients. Most of the analyzed studies included data measured using PFP, whereas others used GFS or other tools. Potential heterogeneity was observed between studies. Unpublished results and articles that are not available in English were excluded from this systematic review; this may have led to a publication bias. Some of the included studies were performed by the same author group, thereby resulting in a potential overlap in patient cohorts and overestimating the size and precision of estimates.

**CONCLUSIONS**

Pretransplant risk assessment for kidney transplant candidates is necessary owing to its high predictive value of post-transplant adverse outcomes. Pretransplant assessments are not conducted to exclude patients from transplant consideration but to identify frail populations that need potential interventions, such as prehabilitation for patients on the waitlist and improvement of their physical status before transplantation. Thus, further research focusing on pretransplant assessment in combination with frailty assessment is warranted to improve the management techniques for kidney transplants.
REFERENCES


FIGURES AND TABLES

Figure 1. PRISMA flow diagram for study selection.

Records identified from the Embase, MEDLINE, Cochrane, PsycINFO databases (n=868)

Duplicate records removed (n =176 )

Records screened (n =692)

Records excluded reading titles and abstracts

Full text articles screened (n=38)

Full-text articles excluded (n=24)

Studies included in systematic review (n=14)

Insufficient or missing data for meta-analysis (n=6)

Studies included in Meta-analysis (n=8)
**Figure 2.** Meta-analysis of the effects of frailty on mortality among the kidney transplant recipients. CI: confidence interval.

**Figure 3.** Meta-analysis of the effects of frailty on death-censored graft failure among the kidney transplant recipients. CI: confidence interval.
Table 1. Newcastle-Ottawa scale for quality assessment of included cohort studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Selection Representativeness of the exposed cohort</th>
<th>Selection of the nonexposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Demonstration that outcome of interest was not present at the start of study</th>
<th>Comparability of cohorts on the basis of the design or analysis (age and other)</th>
<th>Outcome Assessment of outcome</th>
<th>Was followup long enough for outcomes to occur?</th>
<th>Adequacy of followup of cohorts</th>
<th>Total points</th>
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<td>Kokosu</td>
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<td>Chen</td>
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<td>McAdams</td>
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<td>Schopmeyer</td>
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<td>McAdams</td>
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<td>McAdams</td>
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<td>Garonzik-Wang</td>
<td>2012</td>
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Table 2. Summary of included studies on frailty and post-transplant outcomes among kidney transplant recipients

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Age</th>
<th>Sample size</th>
<th>Female (%)</th>
<th>Frailty definition</th>
<th>Number frail/non-frail</th>
<th>Outcomes assessed</th>
<th>Risk estimate Risk estimate</th>
<th>HR/OR/RR (95%CI)/others</th>
<th>Adjustment</th>
<th>Followup period</th>
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<tbody>
<tr>
<td>Kosoku</td>
<td>2022</td>
<td>Japan</td>
<td>Cohort</td>
<td>Mean age 55 (range 46–66)</td>
<td>211</td>
<td>41%</td>
<td>KCL Non-frail:201 Frailty:20</td>
<td>Hyperpolyphagamcy</td>
<td>OR 5.7</td>
<td></td>
<td>Age, sex, and BMI</td>
<td>84 months (43-145)</td>
<td></td>
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<tr>
<td>Haugen</td>
<td>2021</td>
<td>USA</td>
<td>Cohort</td>
<td>Mean age 54 (SD 13)</td>
<td>378</td>
<td>34.3%</td>
<td>IL6+PFP Frail: 55 non-frail: 323</td>
<td>5-year mortality</td>
<td>HR 2.07(1.03–4.19)</td>
<td></td>
<td>Age, sex, race (Black), donor type, CCI, cause of ESKD and smoking status</td>
<td>5 years</td>
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<tr>
<td>Chen</td>
<td>2021</td>
<td>USA</td>
<td>Cohort</td>
<td>Mean age 52.9 (SD 13.8)</td>
<td>1113</td>
<td>38.6%</td>
<td>PFP Frail:207 non-frail:906</td>
<td>Mortality and graft loss</td>
<td>HR1.67(1.07–2.62) HR 1.67(1.17–2.40)</td>
<td></td>
<td>Age, sex, race (Black), donor type and CCI</td>
<td>6.3 years (4–8.4)</td>
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<td>Dos Santos</td>
<td>2020</td>
<td>Brazil</td>
<td>Cohort</td>
<td>&gt;18 years old</td>
<td>87</td>
<td>NA</td>
<td>PFP Frail:32 non-frail:55</td>
<td>surgical complication</td>
<td>RR 2.14(1.01–4.54)</td>
<td></td>
<td>Age, sex, diabetes, time on dialysis before KTx, cardiovascular risk, BMI</td>
<td>3 months after the KTx, or until graft loss or death</td>
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<td>Study</td>
<td>Year</td>
<td>Country</td>
<td>Cohort Type</td>
<td>Mean Age (SD)</td>
<td>PFP</td>
<td>Mortality</td>
<td>LOS</td>
<td>Cognitive Function</td>
<td>Additional Factors Considered</td>
<td>Follow-up</td>
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<tr>
<td>Chu</td>
<td>2019</td>
<td>USA</td>
<td>Cohort</td>
<td>51.7 (SD 14)</td>
<td>39.2%</td>
<td>PFP</td>
<td>NA</td>
<td>LOS ≥2 w</td>
<td>Sex, age, race (Black), BMI, CVD, diabetes, dialysis modality, time on dialysis, and number of hospitalizations</td>
<td>1.1 year</td>
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<td>Chu</td>
<td>2019</td>
<td>USA</td>
<td>Cohort</td>
<td>52 (SD 14.2)</td>
<td>38.8%</td>
<td>PFP</td>
<td>Frail:100 Non-frail:565</td>
<td>5.8 points lower for frail recipients compared with non-frail</td>
<td>Sex, age, race (Black), BMI, CVD, diabetes, dialysis modality, time on dialysis, and number of hospitalizations</td>
<td>4 year</td>
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<td>Konel</td>
<td>2018</td>
<td>USA</td>
<td>Cohort</td>
<td>54 (SD 14)</td>
<td>37.8%</td>
<td>PFP</td>
<td>Frail:126 Non-frail:647</td>
<td>LOS DCGF Mortality</td>
<td>RR 1.88 (1.70–2.08)</td>
<td>Age, sex, race (Black), education,</td>
<td>NA</td>
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<td>Study</td>
<td>Country</td>
<td>Cohort</td>
<td>Mean age (SD)</td>
<td>Sample Size</td>
<td>Fraility</td>
<td>30-day Complications</td>
<td>Measure</td>
<td>Effect Size</td>
<td>OR/RR (95% CI)</td>
<td>Factors Considered</td>
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<td></td>
<td>2.95</td>
<td>BMI, mCCI, causes of ESRD, time on dialysis, donor type.</td>
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<tr>
<td>Schopmeyer</td>
<td>Netherlands</td>
<td>Cohort</td>
<td>Mean age 51.8 (SD 14.5)</td>
<td>139</td>
<td>37.4%</td>
<td>GFI</td>
<td>Fraily: 23 Non-frail: 116</td>
<td>B 13.3 (5.72–20.89)</td>
<td>Sex, age, ASA Score, CCI, hypertension, BMI, smoking, dialysis, duration of dialysis, type of transplant, and retransplant</td>
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<tr>
<td>McAdams</td>
<td>USA</td>
<td>Cohort</td>
<td>Mean age 52 (SD 14.1)</td>
<td>443</td>
<td>37.3%</td>
<td>PFP</td>
<td>NA</td>
<td>Health-related quality of life</td>
<td>-6.31 points; 95% CI -8.16, -4.46</td>
<td>Recipient and donor factors</td>
<td>7.7 months</td>
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<tr>
<td>McAdams</td>
<td>USA</td>
<td>Cohort</td>
<td>NA</td>
<td>589</td>
<td>NA</td>
<td>PFP</td>
<td>NA</td>
<td>LOS≥2w LOS</td>
<td>OR 1.57 (1.06–2.33) RR 1.15 (1.03, 1.28)</td>
<td>Donor, recipient, and transplant factors, DGF</td>
<td>1 year</td>
<td></td>
<td></td>
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<tr>
<td>McAdams</td>
<td>USA</td>
<td>Cohort</td>
<td>Mean age 53 (SD 14)</td>
<td>525</td>
<td>39.8%</td>
<td>PFP</td>
<td>Frail: 19.5%</td>
<td>MDR</td>
<td>HR 1.29 (1.01–1.66)</td>
<td>Age, race (Black), sex, BMI, deceased donor</td>
<td>4 years</td>
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</tbody>
</table>

*CUAJ – Original Research*
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Mean age (SD)</th>
<th>Percent Frail</th>
<th>Fraility Measure</th>
<th>Follow-up</th>
<th>Clinical Endpoints</th>
<th>Hazard Ratio (CI)</th>
<th>Risk Factors Considered</th>
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<tbody>
<tr>
<td>Wang et al</td>
<td>2015</td>
<td>USA</td>
<td>Cohort</td>
<td>537</td>
<td>53 (SD 14)</td>
<td>40%</td>
<td>PFP</td>
<td>5 years</td>
<td>5 year mortality</td>
<td>2.17 (1.01–4.65)</td>
<td>age, sex, race (Black), diabetes, time on dialysis and preemptive KT, donor type, cold ischemia time</td>
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<tr>
<td>McAdams</td>
<td>2013</td>
<td>USA</td>
<td>Cohort</td>
<td>383</td>
<td>53.5 (SD 13.9)</td>
<td>39.7%</td>
<td>PFP</td>
<td>30 days</td>
<td>Early hospital readmission</td>
<td>1.61 (1.18–2.19)</td>
<td>Sex, age, race (Black), BMI, recipient diabetes, recipient heart disease, time on dialysis, donor type, donor age, use of induction therapy and HLA mismatches</td>
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<tr>
<td>Garonzik-Wang</td>
<td>2012</td>
<td>USA</td>
<td>Cohort</td>
<td>183</td>
<td>53 (SD 14)</td>
<td>36%</td>
<td>PFP</td>
<td>1 week</td>
<td>DGF</td>
<td>1.94 (1.13–3.36)</td>
<td>Age, donor creatine level, cold ischemia time, extended criteria donor, donor after</td>
</tr>
</tbody>
</table>
**CUAJ – Original Research**

**Wang et al**

Frailty and post-transplant adverse outcomes

<table>
<thead>
<tr>
<th></th>
<th>cardiac death, BMI, race, diabetes, preemptive</th>
</tr>
</thead>
</table>

BMI: body mass index; CCI: Charlson comorbidity index; DCGF: death-censored graft failure; ESKD: end-stage renal disease; HR: hazard ratio; KTx: kidney transplant; LOS: length of stay; MDR: multidrug resistance. NA: not applicable; OR: odds ratio; RR: risk ratio; SD: standard deviation.