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

kidney transplant outcomes.

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 I^2 statistics; an I^2 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

(GFI) was used in 1 study, and the Kihon checklist (KCL) was used in 1 study. The sample size varied from 87 to 1,113, the mean age was 51.8–54 years, and the proportion of female recipients was 34.3%–41%. Of the cohort studies, 11 were from the United States of America, 1 from Japan, 1 from Brazil, and 1 from the Netherlands. All included studies provided effect measures adjusted for at least age.

Frailty and post-transplantation 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; $P = 0.02$; $I^2 = 73\%$). 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 ($P < 0.00001$, $I^2 = 95\%$). 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.

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FIGURES AND TABLES

Figure 1. PRISMA flow diagram for study selection.

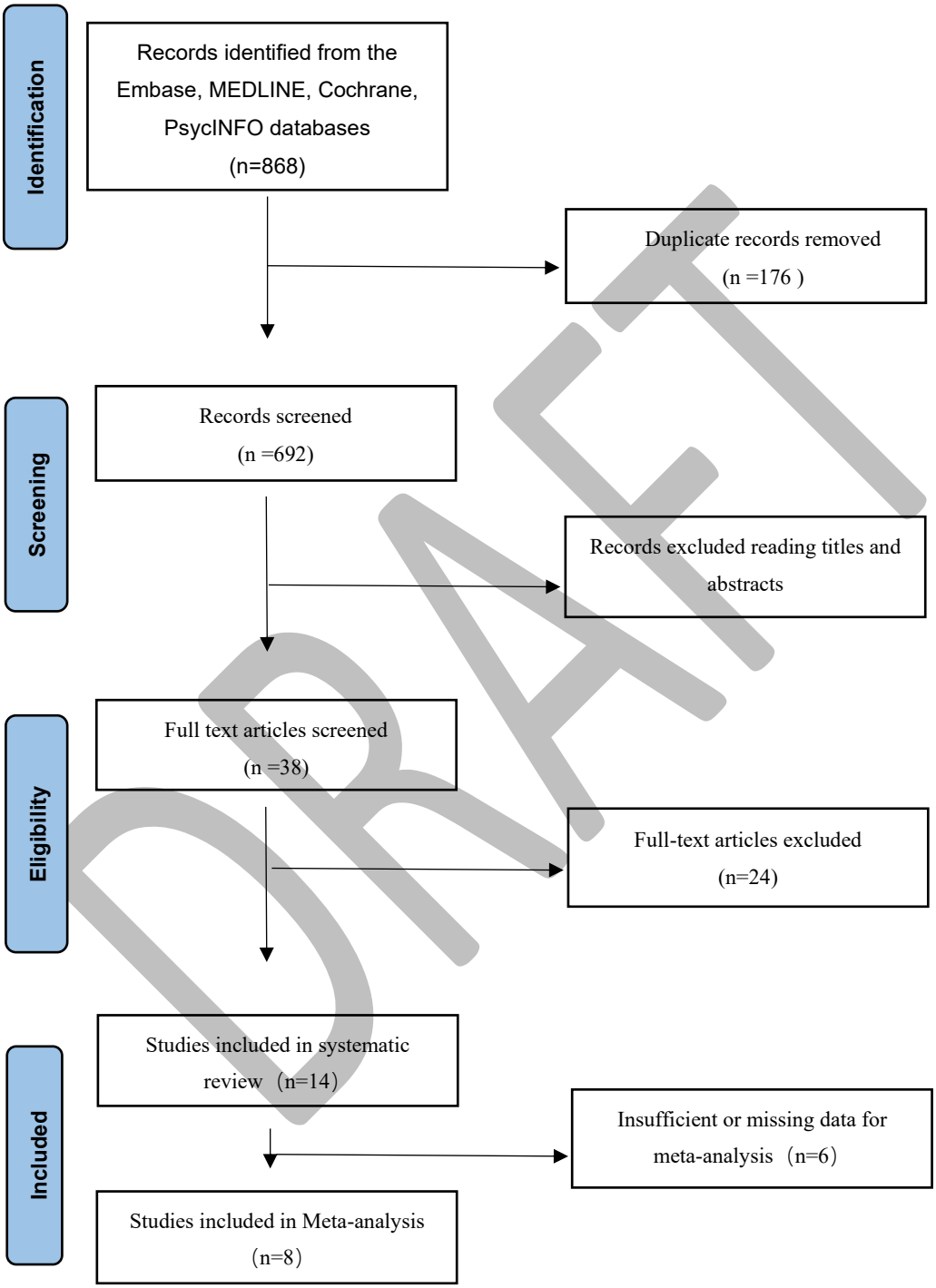

Figure 2. Meta-analysis of the effects of frailty on mortality among the kidney transplant recipients. CI: confidence interval.

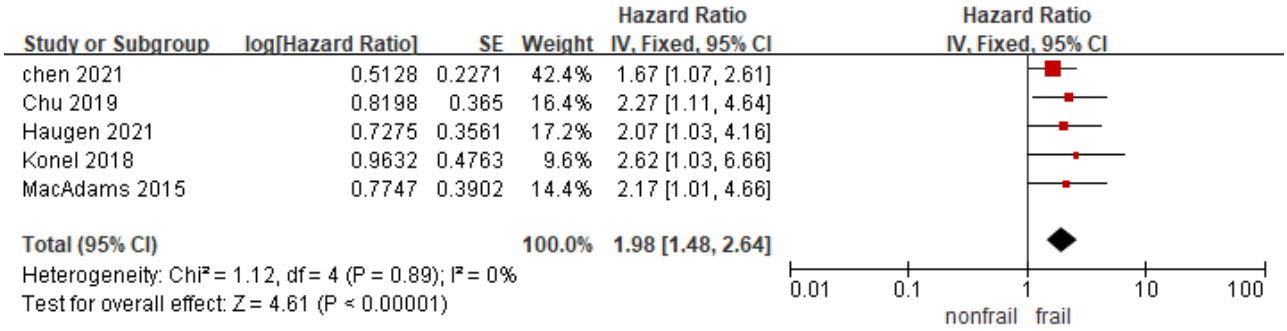

Figure 3. Meta-analysis of the effects of frailty on death-censored graft failure among the kidney transplant recipients. CI: confidence interval.

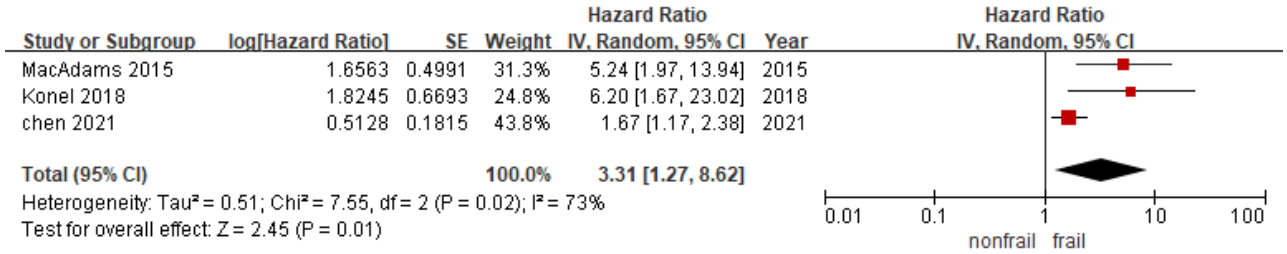

Table 1. Newcastle-Ottawa scale for quality assessment of included cohort studies

Author	Year	Selection				Comparability of cohorts on the basis of the design or analysis (age and other)	Outcome			Total points
		Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of study		Assessment of outcome	Was followup long enough for outcomes to occur?	Adequacy of followup of cohorts	
Kokosu	2022	*	_	*	_	**	*	*	*	7
Haugen	2021	-	*	_	*	**	*	*	*	8
Chen	2021	*	*	*	*	**	*	*	*	9
dos Santos	2020	*	*	*	*	**	*	-	*	8
Chu	2019	-	*	*	*	**	_	_	*	6
Chu	2019	*	*	*	-	**	*	*	-	7
Konel	2018	-	-	*	*	**	*	*	*	7
McAdams	2018	*	*	*	_	**	*	-	*	7

Schopmeyer	2018	*	*	*	*	*-	*	-	*	7
McAdams	2017	*	*	*	*	-*	-	-	-	5
McAdams	2015	*	*	*	*	**	*	*	*	9
McAdams	2015	*	*	*	*	**	*	*	*	9
McAdams	2013	*	*	*	*	**	–	–	*	7
Garonzik-Wang	2012	*	*	*	*	-*	*	*	*	8

Table 2. Summary of included studies on frailty and post-transplant outcomes among kidney transplant recipients

Author	Year	Country	Study design	Age	Sample size	Female (%)	Frailty definition	Number frail/non-frail	Outcomes assessed	Risk estimate HR/OR/RR (95%CI)/others	Adjustment	Followup period
Kosoku	2022	Japan	Cohort	Mean age 55 (range 46–66)	211	41%	KCL	Non-frail:201 Frailty:20	Hyperpolyphaymacy	OR 5.7	Age, sex, and BMI	84 months (43-145)
Haugen	2021	USA	Cohort	Mean age 54 (SD 13)	378	34.3%	IL6+PFP	Frail: 55 non-frail: 323	5-year mortality	HR 2.07(1.03–4.19)	Age, sex, race (Black), donor type, CCI, cause of ESKD and smoking status	5 years
Chen	2021	USA	Cohort	Mean age 52.9 (SD 13.8)	1113	38.6%	PFP	Frail:207 Non-frail:906	Mortality and graft loss	HR1.67(1.07–2.62) HR 1.67(1.17–2.40)	Age, sex, race (Black), donor type and CCI	6.3 years (4–8.4)
Dos Santos	2020	Brazil	Cohort	>18 years old	87	NA	PFP	Frail:32 Non-frail:55	surgical complication	RR 2.14(1.01–4.54)	Age, sex, diabetes, time on dialysis before KTx, cardiovascular risk, BMI	3 months after the KTx, or until graft loss or death

											classification, panel reactive antibodies, type of donor, expanded criteria donor, and cold ischemia time	
Chu	2019	USA	Cohort	Mean age 51.7 (SD 14)	569	39.2%	PFP	NA	Mortality LOS ≥2 w	HR 2.27(1.11–4.65) HR 2.02 (1.20, 3.40)	Sex, age, race (Black), BMI, CVD, diabetes, dialysis modality, time on dialysis, and number of hospitalizations	1.1 year
Chu	2019	USA	Cohort	Mean age 52 (SD 14.2)	665	38.8%	PFP	Frail:100 Non-frail:565	Cognitive function	5.8 points lower for frail recipients compared with non-frail	Sex, age, race (Black), BMI, CVD, diabetes, dialysis modality, time on dialysis, and number of hospitalizations	4 year
Konel	2018	USA	Cohort	Mean age 54 (SD 14)	773	37.8%	PFP	Frail: 126 Non-frail: 647	LOS DCGF Mortality	RR 1.88 (1.70–2.08) HR 6.20 (1.67–	Age, sex, race (Black), education,	NA

										2.95) HR 2.62 (1.03–6.70)	BMI, mCCI, causes of ESRD, time on dialysis, donor type.	
Schopmeyer	2018	Netherlands	Cohort	Mean age 51.8 (SD 14.5)	139	37.4%	GFI	Fraily: 23 Non-frail: 116	30-day postoperative complications	B 13.3 (5.72–20.89)	Sex, age, ASA Score, CCI, hypertension, BMI, smoking, dialysis, duration of dialysis, type of transplant, and retransplant	30 days
McAdams	2018	USA	Cohort	Mean age 52 (SD 14.1)	443	37.3%	PFP	NA	Health-related quality of life	-6.31 points; 95% CI -8.16, -4.46	Recipient and donor factors	7.7 months
McAdams	2017	USA	Cohort	NA	589	NA	PFP	NA	LOS≥2w LOS	OR 1.57 (1.06–2.33) RR 1.15 (1.03, 1.28)	Donor, recipient, and transplant factors, DGF	1 year
McAdams	2015	USA	Cohort	Mean age 53 (SD 14)	525	39.8%	PFP	Frail: 19.5%	MDR	HR 1.29 (1.01–1.66)	Age, race (Black), sex, BMI, deceased donor	4 years

McAdams	2015	USA	Cohort	Mean age 53(SD 14)	537	40%	PFP	Frail: 107 Non-frail: 430	5year mortality	HR 2.17 (1.01–4.65)	age, sex, race (Black), diabetes, time on dialysis and preemptive KT, donor type, cold ischemia time	5 years
Mcadams	2013	USA	Cohort	Mean age 53.5 (SD 13.9)	383	39.7%	PFP	Frail: 72 Non-frail: 311	Early hospital readmission	RR 1.61(1.18–2.19)	Sex, age, race (Black), BMI, recipient diabetes, recipient heart disease, time on dialysis, donor type, donor age, use of induction therapy and HLA mismatches	30 days
Garonzik-Wang	2012	USA	Cohort	Mean age 53 (SD 14)	183	36%	PFP	Frail: 46 Non-frail: 137	DGF	RR 1.94 (1.13–3.36)	Age, donor creatine level, cold ischemia time, extended criteria donor, donor after	1 week

											cardiac death, BMI, race, diabetes, preemptive	

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.