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Frailty and Kidney Transplantation: A Systematic Review and Meta-analysis

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Background. Frailty is a multidimensional condition and is the result of the body's age-associated decline in physical, cognitive, physiological, and immune reserves. The aim of this systematic review is to assess the quality of evidence of the included studies, determine the prevalence of frailty among kidney transplant candidates, and evaluate the relationship between frailty and associated patient characteristics and outcomes after kidney transplantation. **Methods.** A systematic search was performed for relevant literature on frailty and kidney transplantation. This was followed by a meta-analysis for patient characteristics and outcomes reported by a minimum of 2 studies including mean age, gender, mean body mass index, type of kidney transplantation, dialysis, previous kidney transplantation, comorbidities, hypertension, race, preemptive kidney transplantation, delayed graft function, and length of stay. **Results.** A total of 18 studies were included in the systematic review and 14 of those studies were suitable for meta-analysis. The overall pooled prevalence of frailty before transplantation was estimated at 17.1% (95% confidence interval [CI], 15.4-18.7). Frailty was significantly associated with higher age (mean difference, 3.6; 95% CI, 1.4-5.9), lower rate of preemptive transplantation (relative risk, 0.60; 95% CI, 0.4-0.9), longer duration of delayed graft function (relative risk, 1.80; 95% CI, 1.1-3.0), and length of stay longer than 2 wk (odds ratio, 1.64; 95% CI, 1.2-2.3). **Conclusions.** One in 6 kidney transplant recipients is frail before transplantation. The presence of frailty is associated with lower rates of preemptive transplantation, older recipient age, higher rates of delayed graft function, and longer length of stay. Future research is required to explore the association of frailty with other adverse outcomes after kidney transplantation and the effects of intervention programs to improve the different frailty domains.

(*Transplantation Direct* 2021;7: e701; doi: 10.1097/TXD.0000000000001156. Published online 18 May, 2021.)

Received 5 March 2021.

Accepted 22 March 2021.

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The authors declare no funding or conflicts of interest.

E.E.Q. and D.Z. participated in acquiring the data, data analysis, interpretation, drafting of the article, and critical revision of the article. L.B.D.B., S.B., C.A., S.J.L.B., M.M.D, and D.L.S participated in interpretation and critical revision of the article. R.A.P. participated in the study and its design and critical revision of the article.

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001156

INTRODUCTION

Kidney transplantation is the preferred treatment modality for patients with end-stage renal disease (ESRD), as it is associated with reduced risk of mortality and improved quality of life compared with dialysis.[1] The kidney transplant recipient population is changing immensely due to the population. The annual number of transplants performed in patients aged 60 y and older has tripled between 1998 and 2016.[2-4]

Frailty is a multifactorial, age-related condition caused by a decline in physical, cognitive, physiological, and immune reserves.[5,6] As a result, a diminished ability to cope with acute or everyday stressors occurs. Frailty is associated with increased mortality, hospitalization, functional impairment, disability, and reduced quality of life in the general population.[7-9] Also, in the surgical population, frailty is associated with increased postoperative morbidity and mortality.[10-12] Therefore, it is important to measure frailty to distinguish which patients are at risk for adverse outcomes after transplantation. In addition, identification of specific patient characteristics associated with frailty is imperative, so preventative interventions can be implemented to combat unfavorable consequences.[13]

To improve long-term patient and graft outcome, healthcare professionals must gain a better understanding of frailty in the

context of kidney transplantation. The aim of this systematic review and meta-analysis is to provide a comprehensive overview of the published evidence regarding the prevalence of frailty in kidney transplant recipients, the demographic and clinical characteristics associated with frailty in kidney transplant recipients, and the impact of frailty on outcomes after kidney transplantation.

MATERIALS AND METHODS

Protocol and Registration

The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42020187221).[14] This systematic review and meta-analysis was conducted in accordance with the guidelines for observational studies as described in the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols and the Meta-analysis of Observational Studies in Epidemiology checklist.[15,16]

Eligibility Criteria

Observational studies, cross-sectional studies, case-control studies, longitudinal studies, and randomized-control trials that analyzed the relationship between kidney transplantation and frailty were included. Articles were included in the systematic review if: (1) articles were available as full text, (2) articles were published in the English or Dutch language, (3) patients were kidney transplantation recipients, and (4) frailty scores were based on multidomain instruments (muscle mass, gait speed, grip strength, cognition, physical activity, psychosocial, and nutrition) or frailty assessment tools. Studies were included in the meta-analysis if data were reported for both frail and nonfrail patients.

Search Strategy

PubMed, EMBASE, The Cochrane Library, OvidSP, Web of Science, and Google Scholar were searched for articles that analyzed the relationship between kidney transplantation and frailty. Search strings were built verified by the medical library department. The search included the following Mesh terms: kidney transplantation, frailty, sarcopenia, and cognition. Identification of potential unpublished works was not performed. Our final search was performed on May 26, 2020. Detailed search strings, ordered per database, can be found in Appendix S1 (SDC, http://links.lww.com/TXD/A330).

Study Selection and Data Extraction

Studies were selected by 2 independent reviewers (E.Q. and D.Z.) using the CADIMA evidence synthesis tool and database.[17] Titles and abstracts of articles retrieved from all databases were reviewed to determine whether they met the eligibility criteria. Full-text articles were reviewed by the same 2 independent reviewers (E.Q. and D.Z.). Disagreements between individual judgment were either resolved by consensus or by an independent third reviewer (L.B.). The following study and patient characteristics were extracted from the included studies: first author, publication year, study design, sample size, prevalence of frailty at kidney transplantation (baseline frail), frailty tool used, mean age (y), gender (% female), mean body mass index (body mass [kg]/height [m^2]), type of kidney transplantation (% deceased donor kidney transplantation), pretransplant dialysis (%), mean time on dialysis (y), diabetes mellitus before kidney transplantation (%), and previous kidney transplantation (%). The meta-analysis included the following additional data: comorbidities ([%] Charlson Comorbidity Index), hypertension (%), race (% African American), preemptive kidney transplantation (%), delayed graft function (DGF) (%), length of stay (LOS) (% >2 wk). The Charlson Comorbidity Index is a score (0–24), which predicts the 1-y mortality of a patient based on age and coexisting medical conditions.[18] DGF was defined as the need for dialysis during the first 7 d posttransplantation.[19] The following frailty domains were extracted from the different frailty tools used: physical fitness, vision, hearing, cognition, psychosocial well-being, nutrition, comorbidities, mobility, strength, and balance. When data were unavailable, the corresponding author was contacted via email with the request to provide additional data.

Quality Assessment

A quality assessment of all included cohort studies was performed by 2 independent reviewers (E.Q. and D.Z.) using a modified Newcastle-Ottawa Scale specified for cohort studies investigating frailty.[20-22] Disagreements in quality assessment were either resolved by consensus or an independent third reviewer (L.B.). The scale consisted of the following domains: representativeness, validation of frailty assessment, determination of frailty status, loss to follow-up, missing data, and prediction model validation. Per domain, 1 point was given when the domain was adequate, 0.5 points when it was partially adequate, and 0 points when it was not adequate. An overall score was calculated with a score of ≥4 points indicating a low risk of bias, a score of ≥3 and <4 indicating a moderate risk of bias, and a score of <3 points indicating a high risk of bias.

Statistical Analysis

Meta-analyses were performed for all patient characteristics and outcomes reported by 2 or more studies if data for frail patients as well as nonfrail patients were reported. Variables that did not have the same unit of measurement were converted or excluded from the meta-analysis if conversion was not possible. The data regarding patient characteristics and outcomes were either continuous or dichotomous. Continuous variables were expressed as standardized mean differences (MDs) with 95% confidence intervals (CIs) or odds ratios (ORs) with 95% CIs. Dichotomous variables were expressed as risk ratios with 95% CI. The chi-square heterogeneity test was used to report heterogeneity among studies, presented as I^2. A low chance of heterogeneity was shown by an I^2 of <25%. A high chance of heterogeneity was shown by an I^2 of >50%.[23] Random-effects models were used for the pooled data when heterogeneity was expected to be high. When heterogeneity was expected to be low, a fixed-effects model was used. Effect estimates were illustrated as forest plots. Funnel plots were used to assess publication bias. Subgroup analyses were performed for all significant outcomes to adjust for the overlapping cohorts from all studies conducted at the Johns Hopkins Hospital, Baltimore, MD and the University of Michigan Medical Center, Ann Arbor, MI. Review Manager (RevMan, Version 5.4, The Cochrane Collaboration, 2020, Copenhagen, Denmark) was used to perform all statistical analyses in our study.

RESULTS

A total of 3686 potentially relevant articles were identified. After applying the eligibility criteria, a total of 18 full-text articles remained (Figure 1). All studies were published in English between 2012 and 2020.[24-41] Research for these publications was perfomed between 2008 and 2018. Quality assessment identified 15 studies with a low risk of bias and 3 studies with a moderate risk of bias (Table 1). Funnel plots showed no significant publication bias. Seven studies were excluded from the meta-analysis because of unavailability of number of frail and nonfrail patients.

Study Characteristics and Population Demographics

Fourteen prospective cohort studies,[24-37] 3 retrospective cohort studies,[38-40] and 1 cross-sectional study[41] were included in this systematic review (Table 2). All studies combined resulted in a cohort of 9545 patients. The mean age of kidney transplant recipients across studies ranged from 44 to 54 y and 35%–43% of patients were female individuals. The percentage of African American recipients included in the studies ranged from 28.5% to 41.4%. The mean BMI ranged from 22 to 27 kg/m^2 and 13.8%–42% of patients had diabetes before transplantation. Frequency of deceased donor kidney transplantation ranged from 18.7% to 78.2%. Fourteen studies included data from patients from a single center during overlapping time frames, as shown in Table S1 (SDC, http://links.lww.com/TXD/A330).[24,26,28-39]

Frailty Tools

Four different multidomain frailty tools were used to assess frailty status, for which an overview is shown in Table 3. The majority of studies (n = 15) used the Fried frailty phenotype to determine frailty.[24-26,28-39] The Kihon Checklist (KCL),[41] the Frailty Risk Score,[40] and the Groningen Frailty Indicator[27] were used in 1 study each.

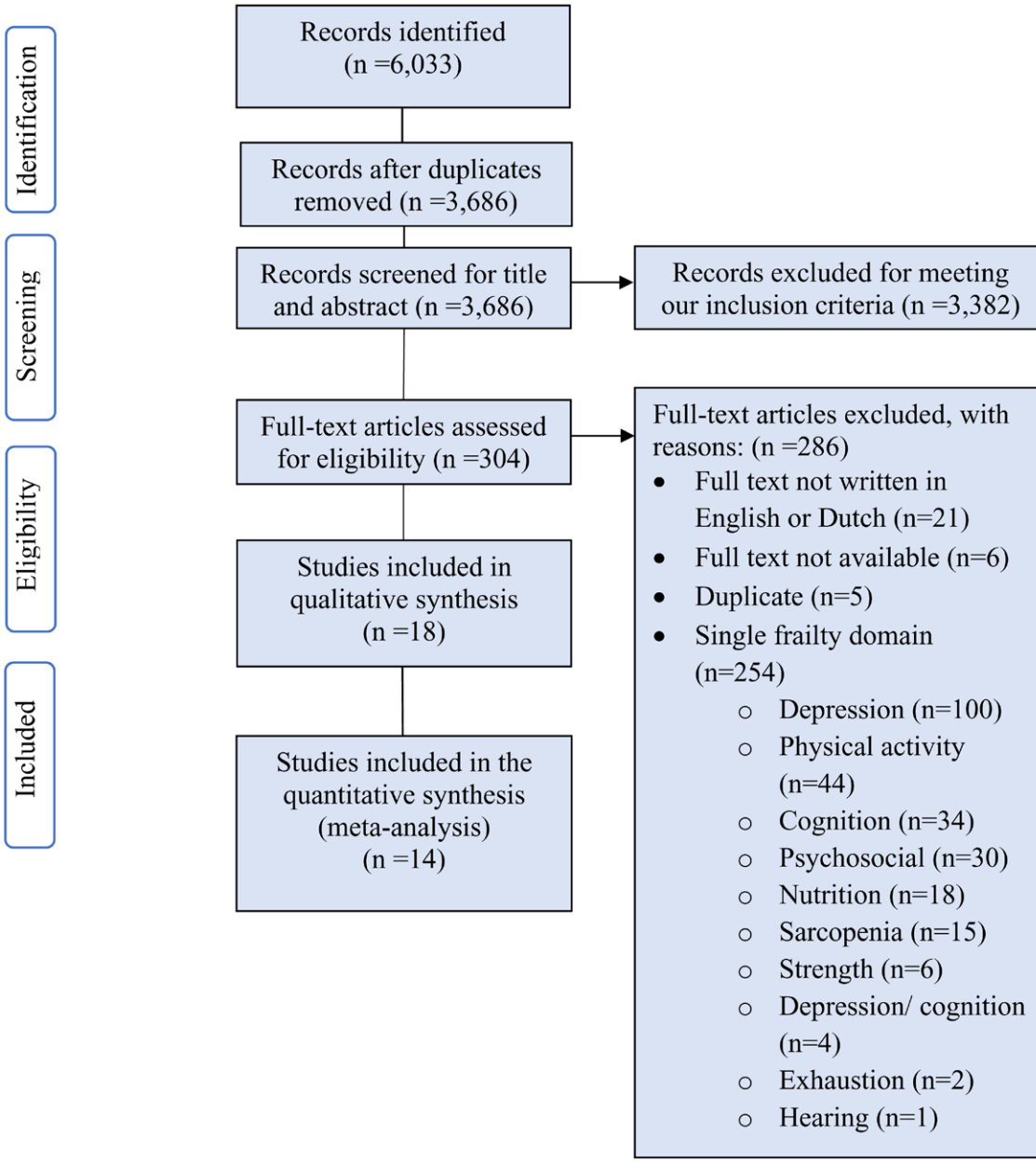

FIGURE 1. Study selection.

TABLE 1.

Modified Newcastle-Ottawa Scale for quality assessment of included cohort studies

Author	Year	Representativeness	Validation of frailty assessment	Determination of frailty status	Loss to follow-up	Missing data	Prediction on model validation	Overall risk of bias
Chu	2019	●	●	●	●	●	●	Low
Chu	2019	●	●	●	●	●	●	Low
Dos Santos Mantovani	2020	●	●	●	●	●	●	Low
Garonzik-Wang	2012	●	●	●	●	●	●	Low
Haugen	2018	●	●	●	●	●	●	Moderate
Haugen	2020	●	●	●	●	●	●	Low
Konel	2018	●	●	●	●	●	●	Low
Kosoku	2020	●	●	●	●	●	●	Moderate
McAdams-DeMarco	2013	●	●	●	●	●	●	Low
McAdams-DeMarco	2015	●	●	●	●	●	●	Low
McAdams-DeMarco	2015	●	●	●	●	●	●	Low
McAdams-DeMarco	2015	●	●	●	●	●	●	Low
McAdams-DeMarco	2017	●	●	●	●	●	●	Low
McAdams-DeMarco	2017	●	●	●	●	●	●	Low
McAdams-DeMarco	2018	●	●	●	●	●	●	Low
Nastasi	2018	●	●	●	●	●	●	Low
Schaenman	2019	●	●	●	●	●	●	Moderate
Schopmeyer	2019	●	●	●	●	●	●	Low

Each component was assigned 1 point for adequate (green), 0.5 points for partially adequate (yellow), and 0 points for inadequate (red). Overall score of ≥4 points low risk of bias, ≥3 points for a moderate risk of bias, and <3 points for a high risk of bias.

TABLE 2.

Study characteristics and patient demographics

Author	Year	Design	Sample size	Baseline frail (%)	Frailty tool	Age	% Female	BMI	DDKT %	Dialysis (%)	Dialysis duration (y)	Pre-KT diabetes	Previous KT
Chu	2019	P	569	–	FFP	52 ± 14.0	39.2	28.4	–	72.5	2.1 ± 3.3/2.6 ± 2.5[b]	30.4	–
Chu	2019	R	665	15.0	FFP	52 ± 14.2	38.8	–	59.2	–	2.6 (1.1–5.0)[d]	–	–
Dos Santos Mantovani	2020	P	87	16.1	FFP	44 ± 12/ 46 ± 13[b]	41.4	–	78.2	96.6	2.2 ± 1.8/3.0 ± 2.3[b]	13.8	3.5
Garonzik-Wang	2012	P	183	25.1	FFP	53 ± 14	36.0	26.6 ± 5.6	58.5	85.2	2.5	–	15.0
Haugen	2018	R	893	16.4	FFP	52 ± 14.2	39.0	28.4	62.2	–	2.9	–	–
Haugen	2020	P	1763	13.3	FFP	53[c]	39.9	28.2	53.7	–	2.2	–	16.1
Konel	2018	P	773	16.3	FFP	54 ± 14	37.8	–	38.0	–	–	–	–
Kosoku	2020	C	205	11.2	KCL	54 (45–65)[d]	42.9	22 (20–25)[d]	11.0	–	1.8 (0.5–5.8)[d]	–	–
McAdams-DeMarco	2013	P	383	18.8	FFP	54 ± 13.9	39.7	27.4	53.3	–	4.4	–	–
McAdams-DeMarco	2015	P	537	19.9	FFP	53 ± 14.0	39.9	–	55.1	81.9	1.9	–	16.4
McAdams-DeMarco	2015	P	525	19.5	FFP	53 ± 14	39.8	27.5 ± 5.9	55.6	18.1	3.0 ± 4.0	17.9	16.4
McAdams-DeMarco	2015	P	349	19.8	FFP	53 ± 14.2	38.1	27.5	62.7	80.0	2.1	–	–
McAdams-DeMarco	2017	P	663	19.5	FFP	53 ± 13.9	38.0	–	38.9	76.0	–	–	–
McAdams-DeMarco	2017	P	589	–	FFP	–	36.0/50.0[f]	–	–	–	–	15.8/22.1[f]	–
McAdams-DeMarco	2018	P	443	37.0[a]	FFP	52 ± 14.1	37.3	–	65.2	85.6	–	–	–
Nastasi	2018	P	719	15.7	FFP	52 ± 14.2	37.7	–	62.3	80.8	–	–	19.1
Schaenman	2019	R	60	–	FRS	43/67[e]	40.5/26.1[e]	–	45.0	80.0	–	–	–
Schopmeyer	2019	P	139	16.55	GFI	52 ± 14.5	37.4	25.5 (5.4)	18.9	58.3	0.58	–	18.0

[a]Intermediate frail and frail.
[b]Reported as nonfrail/frail.
[c]Reported as mean.
[d]Reported as median (interquartile range).
[e]Reported as age group <60 y/age group >60 y.
[f]Reported as LOS <2 wk group/LOS >2 wk group.
BMI, body mass index; C, cross-sectional study; FFP, Fried frailty phenotype; FRS, Frailty Risk Score; GFI, Groningen Frailty Indicator; KCL, Kihon Checklist Criteria; KT, kidney transplantation; LOS, length of stay; P, prospective cohort study; R, retrospective cohort study.

Prevalence of Frailty Before Transplantation

Fourteen studies that reported prevalence for frail and nonfrail kidney transplant recipients were included in the analysis of pretransplant frailty prevalence.[24-29,31-35,37,39,41] Overall pooled prevalence for frailty was estimated at 17.1% (95% CI, 15.4-18.7) with a high level of heterogeneity ($I^2 = 70\%$, $P < 0.01$) (Figure 2). In the subgroup analysis, we found that the prevalence of frailty was higher in the 14 studies conducted at Johns Hopkins Hospital (17.5%; 95% CI, 15.8-19.2) than in the 4 other studies (13.4%; 95% CI, 8.2-18.6).

TABLE 3.

Frailty assessment tools and their different domains

Tool	Physical activity	Vision	Hearing	Cognition	Psychosocial	Nutrition	Comorbidity	Mobility	Strength	Balance	Score	Frailty	Validated in KTR
FFP	•					•			•		0–5	≥3	Yes
FRS		•			•	•			•		N/A	>3	No
GFI	•	•	•	•	•	•	•	•			0–15	≥4	Yes
KCL	•				•	•		•	•	•	0–25	≥8	No

FFP, Fried frailty phenotype, physical activity, and strength are either self-reported or assessed by a clinician; FRS, frailty risk score, database; GFI, Groningen Frailty Indicator, questionnaire; KCL, Kihon Checklist Criteria, questionnaire; KTR, kidney transplant recipients.

Forest plots showing pooled standardized MD are to be found in Figures S1–S3 (SDC, http://links.lww.com/TXD/A330).

Demographic and Clinical Characteristics Associated With Pretransplant Frailty

Age

Twelve studies reported mean age among both nonfrail and frail kidney transplant recipients.[25,27-34,37,38,41] Frail patients were significantly older than nonfrail patients (MD, 3.64; 95% CI, 1.4-5.9). Significant heterogeneity was observed ($I^2 = 71\%$, $P < 0.01$), with no signs of publication bias. In the subgroup analysis, frail patients from the cohorts at Johns Hopkins hospital were older (MD, 4.14; 95% CI, 1.6-6.7) than the patients from the cohorts from other studies (MD, 1.66; 95% CI, –2.5 to 5.8). However, this difference between subgroups was not significant.

Preemptive Transplantation

Six studies reported an association between preemptive transplantation and frailty (relative risk, 0.60; 95% CI, 0.4-0.9).[25,28,29,32,33,37] Significant heterogeneity was observed ($I^2 = 69\%$, $P < 0.01$), with no signs for publication bias. Table 4 shows the meta-analysis results for patient factors.

Outcomes Associated With Pretransplant Frailty

Delayed Graft Function

Four studies reported data on the association between frailty and DGF for both frail and nonfrail patients.[25,27,28,32] All 4 studies defined DGF as the need for dialysis during the first 7 postoperative days.[19] Overall, frail patients had an increased risk of DGF compared with nonfrail patients (OR, 1.80; 95% CI, 1.1-3.0). Moderate heterogeneity was observed ($I^2 = 36\%$, $P = 0.02$), with no signs for publication bias. Subgroup analysis showed that frail patients from the cohort studies at Johns Hopkins Hospital had a lower risk of DGF (OR, 1.61; 95% CI, 0.9-3.0) than frail patients from other study cohorts (OR, 2.38; 95% CI, 0.9-6.3).

Length of Stay

The OR for a LOS >2 wk was determined in 2 studies.[29,30] Frail patients had a higher risk of LOS of >2 wk (OR, 1.64; 95% CI, 1.2-2.3). Neither heterogeneity ($I^2 = 0\%$, $P < 0.01$)

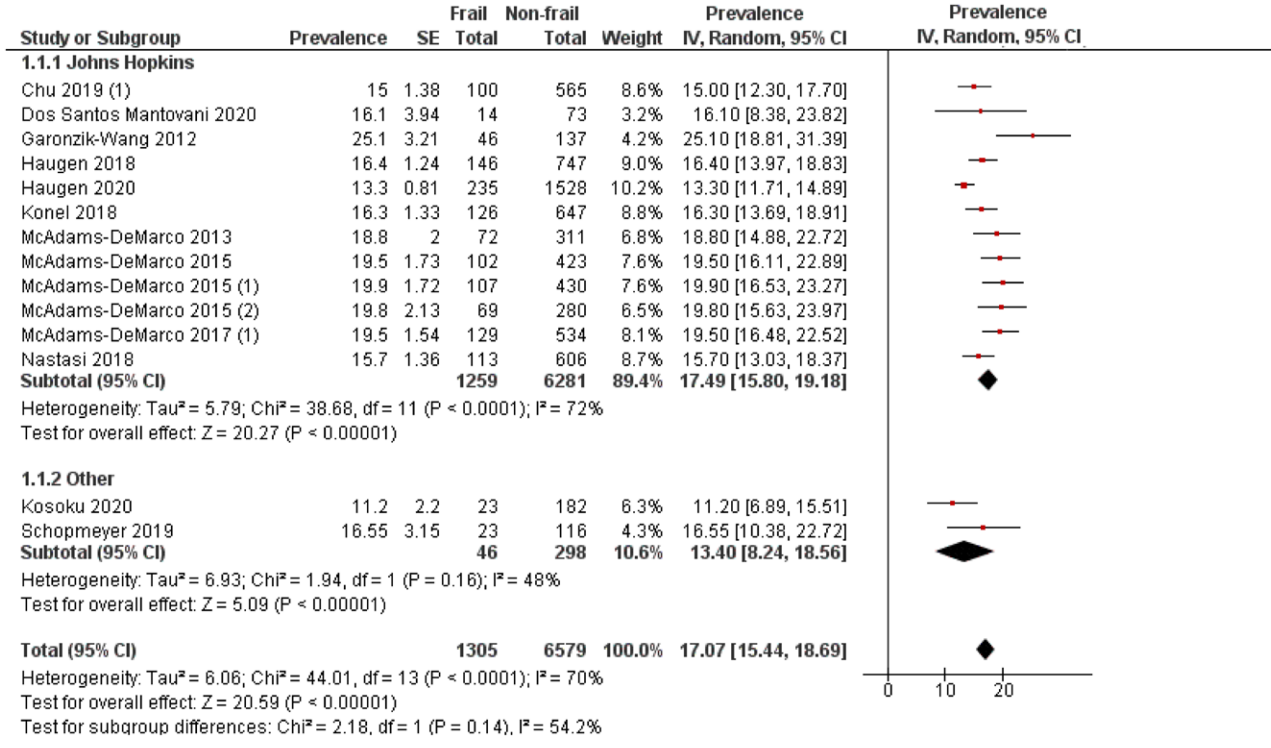

FIGURE 2. Pooled prevalence of frailty in kidney transplant recipients. CI, confidence interval; IV interval variable.

TABLE 4.

Summary of meta-analysis results of patient demographics and clinical characteristics

Patient factor	Studies	Frail patients	Nonfrail patients	Effect estimate[a]	I^2	*P*
Continuous variables						
Age	10	804	3742	MD, 3.64 (1.38-5.90)	72%	**<0.01**
BMI	7	546	2475	MD, 0.17 (−0.36 to 0.70)	7%	0.37
CCI	3	189	1187	MD, −0.23 (−1.39 to 0.92)	92%	0.69
Dialysis duration (y)	8	578	2530	MD, 0.03 (−0.48 to 0.54)	61%	0.92
Categorical variables						
Diabetes	8	684	2701	RR, 1.02 (0.66-1.58)	76%	0.92
Dialysis	5	248	980	RR, 1.08 (1.00-1.17)	49%	0.04
Hypertension	4	312	1400	RR, 1.48 (0.92-2.39)	91%	0.11
Preemptive KT	6	480	1840	RR, 0.60 (0.39-0.94)	69%	**<0.01**
Previous KT	4	397	1531	RR, 0.98 (0.76-1.28)	0%	0.90
Race (African American)	8	855	3768	RR, 1.10 (0.84-1.45)	88%	0.47
Sex (female)	11	933	4066	RR, 1.01 (0.85-1.21)	72%	0.89
Transplantation type (DDKT)	10	893	3642	RR, 1.10 (0.93-1.30)	83%	0.27

[a]Effect estimates are presented with 95% confidence intervals within parentheses.
Bold type indicates statistical significance.
BMI, body mass index; CCI, Charlson Comorbidity Index; DDKT, dead donor kidney transplantation; KT, kidney transplantation; MD, mean difference; RR, risk ratio.

nor signs of publication bias were observed. The results of the meta-analysis of patient factors are presented in Table 5, with corresponding forest plots of significant patient factors shown in Figures S1 and S2 (SDC, http://links.lww.com/TXD/A330).

DISCUSSION

This systematic review and meta-analysis showed that the pooled prevalence of preoperative frailty in kidney transplant recipients was 17.1%. In this patient population, frailty was associated with a higher recipient age and a lower rate of preemptive transplantation. With the meta-analysis on transplant outcomes, we identified an association between frailty, increased LOS, and prolonged duration of DGF.

When prevalence of frailty in kidney transplant recipients in this meta-analysis was compared with that of patients with ESRD (36.8%), there was a pronounced difference.[42] One factor may be that mean age among ESRD patients was 54–65 y compared with 44–54 y among kidney transplant recipients.[42] As the preferred treatment method for ESRD is kidney transplantation, one can expect that frailty prevalence decreases after transplantation as a consequence of cured chronic kidney disease. Many ESRD patients require dialysis, which in itself is a risk factor for being frail.[1] Our results show that preemptive transplantation was significantly associated with a reduced frailty risk.

We also found that frail patients are older than nonfrail patients. This could be foreseen as frailty is the result of the body's age-associated decline in physiologic reserve.[5,6] A systematic review on the association between frailty and outcomes in vascular surgery patients reported that frail patients were approximately 4 y older than nonfrail patients, which is similar to our results.[10]

Preoperative frailty is associated with an increase in LOS after kidney transplantation. Individuals who are frail may not swiftly return to homeostasis and spend a longer period of time recovering in the hospital. Multiple studies have found that frailty is associated with increased LOS in surgical populations.[11,12,43] This increase in LOS could be due to the fact that frail patients more often develop complications and require more extensive care.[27] Though all patients undergo a decline in functional capacity after surgery, frail patients experience a greater decline and experience more difficulty regaining their preoperative capacity.[44] Because of this weakened balance in physical reserve, the critical zone for impaired recovery is reached much faster and initiates a process in which the baseline condition is no longer achievable or the decline continues, resulting in a permanent need for care or even death. The level of baseline physical functioning, partly but not exclusively, determined by the frailty domains, therefore requires a timely assessment and, if possible, improvement through physical and cognitive training. This can potentially prevent a dip below that "critical zone."[44]

Another interesting outcome of this meta-analysis was the increased risk of developing DGF in frail patients. Although the exact underlying cause of DGF is not completely understood, the variety of risk factors reported for DGF underscores a complex and multifactorial pathophysiological mechanism.[45] Ischemia and reperfusion injury (IRI), inevitable in kidney transplantation most likely is one of the most important underlying mechanisms for non- or delayed function immediately after transplantation.[46,47] It is accompanied by tissue injury and a proinflammatory response, resulting in posttransplantation oliguria, increased allograft immunogenicity and risk of acute rejection episodes, and decreased long-term survival.[48,49] Cell injury and death initiated by renal IRI lead to the release of danger-associated molecular patterns and activation of the innate and subsequently the adaptive immune system, which result in an increase in chemokines, cytokines, complement factors, and immune cells.[46] Eventually, the inflammatory processes result in damage to the renal tubular epithelial cells.[49] Frailty is associated with inflammageing, a form of immune dysregulation accompanied by a chronic low-grade proinflammatory state, resulting in higher serum levels of interleukin-6, C-reactive protein, tumor factor-α-receptor-1, and complement proteins C3 and C1q.[50] In parallel, inflammageing is associated with an impaired effective immune response to immunogenic stimulations and inability to dispose cellular debris accurately.[50] Therefore, it could be hypothesized that frail patients experience extended IRI and its consequences, hence DGF.

TABLE 5.

Summary of meta-analysis results of patient outcomes after kidney transplantation

Patient factor	Studies	Frail patients	Nonfrail patients	Effect estimate[a]	I^2	*P*
Categorical variables						
DGF	4	227	955	RR, 1.80 (1.09-2.97)	36%	**0.02**
Generic inverse variance						
LOS > 2 wk	2	–	–	OR, 1.64 (1.18-2.28)	0%	**<0.01**

[a]Effect estimates are presented with 95% confidence intervals within parentheses
Bold type indicates statistical significance.
DGF, delayed graft function; LOS, length of stay; OR, odds ratio; RR, relative risk.

Multiple domains define the presence of frailty and, in turn, can lead to various adverse outcomes. These multiple domains are embedded in frailty assessment tools. Out of the 4 frailty assessment tools used in our study, only the Fried's frailty phenotype and the Groningen Frailty Indicator have been validated in kidney transplant populations. De Vries et al[51] concluded that the choice for a frailty tool depends on many factors such as the aim, the setting, and available time. Ultimately, it would be preferable if a universal, validated assessment tool, which is easy to administer and covers all frailty domains, would be used to assess frailty in kidney transplant recipients worldwide. This would allow for a better comparison between countries and different cohort compositions. In a recent survey among physicians, surgeons, and health professionals active in the field of kidney transplantation, it was reported that 98.9% of respondents believed that frailty was a useful tool to evaluate candidates for kidney transplantation.[52] However, only 23.9% performed a standardized frailty assessment as part of evaluation for kidney transplantation. Interestingly, there was no consistency in which tools they used to measure frailty.

Multidomain frailty assessment tools are preferred because they also point out which domains need improvement. This information could be used to improve frailty status before transplantation in prehabilitation programs by targeting these specific domains. A pilot study on prehabilitation in kidney transplant recipients reported that a prehabilitation program is associated with an increase in objectively measured physical activity and a decrease in LOS.[13] Additionally, rehabilitation exercise programs could be offered posttransplantation to increase exercise tolerance and quality of life in kidney transplant recipients.[53,54]

This is the first systematic review and meta-analysis to investigate frailty status and kidney transplantation. However, this study has some limitations that need to be addressed. First, 14 out of 18 studies included in this systematic review were performed by the same study group at the Johns Hopkins Hospital or the University of Michigan Medical Centre, resulting in a potential overlap in patient cohorts and overestimating the size and precision of our estimates. However, we performed subgroup analyses to combat a possible overestimation and we provided a table (Table S1, SDC, http://links.lww.com/TXD/A330) to clearly illustrate the medical centers or registries involved in the studies. Second, we had to exclude 7 studies from the meta-analysis because data regarding number of frail and nonfrail patients were not available. Also, different measurement methods were used for a number of variables, which we could not convert. For example, mortality was measured after 30 d in one study[27] and after 1, 3, and 5 y in another study.[37] Although we contacted the corresponding authors of multiple studies to retrieve additional data, we were not able to obtain the requested data. Third, there is a high rate of heterogeneity among the included studies. This needs to be taken into consideration when interpreting the results. The causes for heterogeneity in our study may be due to varying and global patient populations between studies. We experimented with subgroup analyses by omitting studies from our meta-analysis to determine whether this would have an effect on the heterogeneity. However, we opted not to do this, as this exclusion would lead to a bias. Furthermore, the random-effects meta-analysis assumes that underlying effects follow a normal distribution that allows for heterogeneity.[55] Fourth, different frailty tools were used to measure frailty, which could have led to a misclassification of frailty. Ultimately, the use of a single frailty tool would be most optimal when performing a meta-analysis as each tool encompasses different domains, which could lead to heterogeneity. However, all but 1 instrument has been validated to measure frailty, and the use of a frailty tool provides us with a variation or approximation of the syndrome.

In conclusion, approximately 1 in 6 kidney transplant recipients were frail before transplantation. The presence of frailty was associated with lower rates of preemptive transplantation, older age, higher DGF rates, and longer LOS. Efforts are needed to reach consensus on which frailty tool to use in kidney transplant recipients. Future research is required to explore frailty and adverse outcomes such as surgical complications, patient survival, and graft survival after kidney transplantation among frail and nonfrail patients. This information is deemed pivotal to implement programs to tackle and decrease the rate of frailty among this group of patients.

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