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Association of Frailty with Clinical Outcomes and Resource Use Following Kidney Transplantation

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Abstract:	**Introduction** Although not formalized into current risk assessment models, frailty has been associated with negative postoperative outcomes in many specialties. However, national analyses of the association between frailty and post-transplant outcomes following kidney transplantation are lacking. **Methods** This was a retrospective cohort study of adults undergoing kidney transplantation (KT) from 2016-2020 in the Nationwide Readmissions Databases. Frailty was defined using the Johns Hopkins Adjusted Clinical Groups frailty indicator. **Results** Of an estimated 95,765 patients undergoing KT during the study period, 4,918 (5.1%) were frail. After risk adjustment, frail patients were associated with significantly higher odds of in-hospital mortality (AOR 2.17, 95% CI: 1.33-3.57) compared to their non-frail counterparts. The presence of frailty was linked with incremental

	increase in postoperative length of stay (β +1.44 days; 95%CI: +1.36-1.52, p<0.001), hospitalization costs (β +$2,300; 95% CI: +$250-4,430, p=0.03), and development of major perioperative complications. Frailty was also associated with greater adjusted risk of non-home discharge. **Conclusions** Frailty, as identified by administrative coding, is independently associated with worse surgical outcomes, including increased mortality and resource use, in adults undergoing KT. Given the already limited donor organ pool, novel efforts are needed to ensure adequate optimization and timely post-transplantation care of the growing frail cohort undergoing kidney transplantation.

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Running Title: Frailty in Kidney Transplantation

Keywords: Kidney Transplantation, Frailty, Short-term Outcomes

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Abbreviations: KT, Kidney Transplantation; nFrail, non-Frail patients; ICD, International Classification of Diseases; IQR, Interquartile Range; LASSO, Least Absolute Shrinkage Selection Operator; pLOS, Postoperative Length of Stay; NRD, Nationwide Readmissions Database; SD, Standard Deviation; JHACG, Johns Hopkins Adjusted Clinical Groups; β, Beta Coefficients; AOR, Adjusted Odds Ratio

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Clin Transplant

ABSTRACT

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Although not formalized into current risk assessment models, frailty has been associated with negative postoperative outcomes in many specialties. However, national analyses of the association between frailty and post-transplant outcomes following kidney transplantation are lacking.

Methods

This was a retrospective cohort study of adults undergoing kidney transplantation (KT) from 2016-2020 in the Nationwide Readmissions Databases. Frailty was defined using the Johns Hopkins Adjusted Clinical Groups frailty indicator.

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Conclusions

Frailty, as identified by administrative coding, is independently associated with worse surgical outcomes, including increased mortality and resource use, in adults undergoing KT. Given the already limited donor organ pool, novel efforts are needed to ensure adequate optimization and timely post-transplantation care of the growing frail cohort undergoing kidney transplantation.

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Introduction

In part due to the continued rise in the prevalence of end-stage renal disease, additions to the kidney transplant waitlist continue to outpace rates of transplantation.[1,2] Thus, clinical care paradigms have persistently evolved to tackle the growing waitlist times and aging pool of transplant candidates.[3–6] While allocation schemes for other organs have considered both pre- and post-transplant survival, predicting post-transplant outcomes to guide clinical care and resource allocation in kidney transplantation remains particularly challenging.[7] With demand far exceeding the supply of suitable donor kidney organs, prior work has suggested the need and opportunity for improved performance of existing risk prediction models.[8,9]

While traditional factors such as chronologic age and comorbidities have been used to estimate operative risk, more recent work suggested frailty to be a better predictor of postoperative outcomes.[10] While an exact definition remains lacking, frailty is associated with reduced functional reserve and linked with inferior outcomes following a myriad of operations.[11–13] Considerable work has evaluated the prevalence of frailty among individuals with chronic kidney disease, with a recent study revealing up to 73% of dialysis patients to be frail.[14,15] Moreover, limited studies have linked frailty with unfavorable clinical outcomes following kidney transplantation.[9,16] Yet, these decade-old investigations have generally been limited to small cohorts and single centers, limiting their generalizability.

In the present work, we aimed to characterize the impact of frailty on short-term outcomes of kidney transplantation using a nationally representative cohort. We hypothesized frailty to be associated with increased in-hospital mortality, perioperative complications, resource utilization, and non-elective readmissions.

Methods

The Nationwide Readmissions Database (NRD) was queried to identify all adults (≥18 years) undergoing first-time, isolated kidney transplantation (KT) from 2016 to 2020. The NRD uses hospital-based discharge weights to provide accurate estimates for nearly 60% of all hospitalizations in the United States.[17] The NRD tracks readmission across hospitals within each calendar year using patient and hospital linkage numbers.

Records entailing KT were identified using relevant International Classification of Diseases, Tenth Revision (ICD-10) procedure codes (Appendix Supplementary Table I). Entries for multi-organ transplantation or re-transplantation, as well as those missing data (0.5%) for age, sex, or in-hospital mortality, were excluded from further analysis (Appendix Supplementary Figure I). The previously validated Johns Hopkins Adjusted Clinical Groups (JHACG), a binary tool that uses administrative codes to ascertain the presence of frailty, was used to divide patients into *Frail* and *nFrail* cohorts.[18–20]

Patient and hospital characteristics, including age, sex, income quartile, primary payer, and teaching status, were defined in accordance with the NRD data dictionary.[21] In line with previous work, hospitals were further classified into quartiles based on the annual volume of KT.[22] The modified Elixhauser Comorbidity index, a validated composite of 30 comorbidities, was used to quantify the burden of chronic conditions.[23]

Complications included for analysis were graft rejection and infection, renal artery or vein thrombosis, neurologic complications (stroke, transient ischemic attack), cardiac arrest, myocardial infarction (MI), hemoperitoneum, respiratory complications (pneumonia, acute respiratory distress syndrome, pneumothorax, empyema, prolonged ventilation (>96 hours), other thromboembolic complications (pulmonary embolism, deep vein thrombosis), and other infectious complications (sepsis, septicemia, surgical site infection, wound disruption, urinary tract infection). Graft failure using ICD-10 code T86.101 was not utilized as it performed poorly in previous studies using administrative data.[24] Hospital-specific cost-to-charge ratios were used to calculate index hospitalization costs, which were then adjusted for inflation using the 2020 Personal Health Index.[25]

The primary outcome of this study was mortality during index admission. Secondary endpoints included complications, postoperative length of stay (pLOS), hospitalization costs, non-home discharge, and nonelective readmissions within 30- and 90-days of discharge.

Categorical variables are reported as proportions (%), while continuous variables are shown as means with standard deviation (SD) if normally distributed, or medians with interquartile range (IQR), otherwise. The significance of temporal trends was analyzed using a non-parametric rank-based test (nptrend) developed by Cuzick.[26] The adjusted Wald and Pearson's χ^2 test were used for bivariate comparison of patient and hospital characteristics. Multivariable logistic models were used to identify the association of frailty with outcomes of interest. Model covariates were selected using the least absolute shrinkage and selection operator (LASSO). Briefly, LASSO is a regularization algorithm used to reduce the risk of model overfitting and enhance the out-of-sample generalizability.[27] The Stata margins command was used to calculate the average marginal effect of individual covariates on outcomes.[28] Models were optimized using Akaike and Bayesian Information Criteria as well as the receiver-operator characteristics (C-statistic), as appropriate. Regression outputs are reported as beta coefficients (β) for continuous variables, and adjusted odds ratios (AOR) for discrete variables, both with 95% confidence intervals (95% CI).

Statistical analysis was performed using Stata 16.0 with α set at 0.05 for significance.[29] This study was deemed exempt from full review by the Institutional Review Board at the University of California, Los Angeles.

Results

Of an estimated 95,765 patients undergoing KT during the study period, 4,918 (5.1%) were *Frail*. The proportion of *Frail* patients significantly increased from 4.5% in 2016 to 5.5% in 2020 (nptrend<0.001; Figure I).

Compared to *nFrail*, *Frail* were older (53.0 ± 14.9 vs 52.2 ± 13.7 years, p=0.04), more commonly female (42.8 vs 39.5%, p=0.002), and had a higher Elixhauser index (4.9 ± 1.7 vs 4.0 ± 1.5, p<0.001). Further, *Frail* demonstrated a higher prevalence of neurological disorders (8.2 vs 2.9%, p<0.001), peripheral vascular disease (7.2 vs 5.6%, p=0.01), chronic liver disease (5.3 vs 3.7%, p<0.001), and diabetes (48.1 vs 35.8%, p<0.001). While a higher proportion of *nFrail* had private insurance (29.6 vs 20.7%, p<0.001), *Frail* patients were more frequently insured by Medicare (71.9 vs

64.7%, *p*<0.001). Both cohorts primarily underwent surgery at large (91.1 vs 91.0%, p=0.79), metropolitan teaching hospitals (99.1 vs 99.1%, p=0.84). In addition, *Frail* and *nFrail* underwent surgery in centers with equivalent annual transplant volume (Appendix Supplementary Table II).

On unadjusted analysis (Table I), the *Frail* cohort faced significantly higher rates of in-hospital mortality (1.2 vs 0.2%, p<0.001) and all tabulated postoperative complications, compared to *nFrail*. *Frail* patients also had greater median pLOS (6 [4-10] vs 4 [4-6] days, p<0.001) and hospitalization costs (74,500 [57,700-98,600] vs 64,600 [50,500-79,600], p<0.001). The *Frail* cohort further exhibited higher rates of non-home discharge as well as 30- and 90-day unplanned readmissions, compared to others.

After risk adjustment (Table I), *Frail* was associated with significantly higher odds of in-hospital mortality (AOR 2.17, 95% CI: 1.33-3.57). Notably, *Frail* patients demonstrated increased adjusted risk of mortality at all ages compared to their nFrail counterparts (Figure II). *Frail* was similarly linked with higher odds of graft rejection (AOR 1.39, 95% CI: 1.12-1.74), and renal vein thrombosis (AOR 2.43, 95% CI: 1.43-4.12). Relative to *nFrail*, *Frail* patients also had higher adjusted odds of neurologic complications, cardiac arrest, MI, hemoperitoneum, respiratory complications, and all other thromboembolic and other infectious complications. After adjustment for intergroup differences, frailty was linked with incremental increase in pLOS (β +1.44; 95%CI: +1.36, +1.52, p<0.001) and hospitalization costs (β +$2,300; 95% CI: +$250-$4,430, p=0.03). The presence of frailty and development of major perioperative complications, including graft rejection (β +$4,800; 95% CI +$600-9,000, p=0.03), myocardial infarction (β +$4,500; 95% CI +$600-8,300, p=0.02), and respiratory complications (β +$7,400; 95% CI +$4,600-10,100, p<0.001), were independently linked with increased costs. Conversely, advanced age and female sex were linked with decreased adjusted costs (Figure III).

While frailty was associated with greater adjusted risk of non-home discharge across all ages (AOR 3.01, 95% CI: 2.18-4.17; Figure II), it did not alter the odds of 30- or 90-day readmission (Table I).

Discussion

In this national analysis, we evaluated the impact of frailty on clinical and financial outcomes of kidney transplantation and made several important observations. First, we noted a significant rise in the number of frail patients undergoing kidney transplantation. Frailty was associated with significantly increased in-hospital mortality, pLOS, and perioperative complications. Further, frailty was associated with a significant increase in adjusted hospitalization costs and >3-fold increase in the odds of non-home discharge. Several of our findings warrant further discussion.

We found frailty to be associated with significantly greater likelihood of in-hospital mortality. Our effect size aligns with a previous study conducted by McAdams-Demarco et al., which independently linked frailty to a 2.17-fold higher risk of death.[9] The greater in-hospital mortality rate among frail KT recipients may be attributed to altered immune response and loss of physiological reserve, which leave these patients more vulnerable to postoperative stressors.[30,31] Furthermore, recent literature has implicated epigenetic alterations, neurohormonal failure, and sarcopenia as contributors to increased mortality among the clinically frail.[32–34] However, recent work has suggested that frailty among kidney transplant recipients may improve within three months post-transplantation.[35] Thus, our findings do not discourage transplantation among these patients, but rather underscore the importance of early identification of frail patients, in order to provide adequate risk-assessment, counseling, and pre-transplantation optimization. Some studies have suggested the incorporation of rehabilitation into routine pre-transplantation practices to improve patient functional status and long-term outcomes.[36] Indeed, the ongoing FRAILMar trial is exploring the potential benefits of multimodal pre-rehabilitation in improving outcomes and reducing resource utilization in kidney transplant patients.[37] Yet, future prospective studies that investigate the impact of pre-transplant physical therapy and rehabilitation on post-transplant outcomes among frail patients, are warranted.

While kidney transplantation remains a relatively safe procedure, the frail cohort demonstrated higher rates of perioperative complications. Indeed, frailty was significantly associated with increased odds of experiencing graft rejection. Thus, our study agrees with previous work by Quint and Mantovani et al. who linked frailty with increased rates of delayed graft function, as well as vascular, and urologic complications following transplantation.[38,39] While the underlying mechanisms remain to be elucidated, some have suggested the altered immune response among frail patients to play a role. Indeed, frailty is associated with a chronic pro-inflammatory state, with patients exhibiting higher baseline levels of C-reactive protein and interleukin-6.[40] This so-called ‘inflammageing’ has been linked with a less effective response to immunogenic stimuli. As such, frail patients are thought to be at higher risk for prolonged ischemia and reperfusion injury, which can lead to post-transplantation delayed graft function or graft failure.[41,42] In addition, we found frail patients to demonstrate a two-fold increase in odds of developing post-transplantation renal artery and vein thrombosis. These vascular complications have been implicated in >60% of early graft loss.[43] Ultimately, both timely identification and treatment of postoperative complications are crucial, as delayed intervention can jeopardize both graft and patient survival.[43] Bepoke care pathways for the frail should incorporate active surveillance and timely interventions in the perioperative period. Moreover, additional studies that identify pathophysiological alterations linked with frailty could shape the development of targeted interventions to reduce the incidence of graft failure among these patients.

In our study, frailty was found to be associated with increased resource utilization, including longer duration of hospitalization, higher hospitalization costs, and greater likelihood of non-home discharge. Thus, our work aligns with prior studies of solid organ transplantation that reported frailty to be associated with longer hospital stays.[9,33,44] The observed increase in pLOS among frail patients may be attributed to their higher propensity for complications and the need for more extensive or higher levels of care, as detailed in prior studies.[38] These factors may also contribute to the increase in adjusted hospitalization expenditures we noted among the frail cohort. Given the growing frail population undergoing kidney transplantation, novel efforts are needed to reduce the rising cost burden on both patients and the healthcare system. Indeed, interventions that specifically aim to streamline care among this population could be significant in increasing both value and quality of care. Lastly, we noted a three-fold increase in odds of non-home discharge among frail patients. Discharge to non-home facilities has been linked with excess post-discharge care and non-elective readmission.[45] The development of standardized recovery pathways and earlier care coordination efforts may contribute to reducing rates of non-home discharge rates and their associated resource utilization.[46]

Our study has several limitations due to its use of an administrative database. The NRD lacks granularity in laboratory values, intraoperative events, and waitlist outcomes. In addition, the NRD relies on accurate ICD coding which may vary based on local or regional practices. While cost to charge ratios provide a valuable insight into total hospitalization cost, we are unable to assess costs associated with preoperative and postoperative outpatient care. Despite these limitations, we utilized the largest all-payer national database and adhered to appropriate data practices as recommended by HCUP to report nationally representative outcomes.

In conclusion, we found a rising proportion of frail patients are undergoing kidney transplantation. Frailty appears to be independently associated with increased in-hospital mortality, complications, resource expenditures, and non-home discharge rates. Pre-transplant frailty assessments should be implemented to better identify higher-risk patients and allow for thorough risk-assessment and shared decision-making. Given the already limited donor organ pool, novel efforts are needed to ensure adequate optimization and timely post-transplantation care of the growing frail cohort undergoing kidney transplantation.

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The authors of this manuscript have no related conflicts of interest to declare. All authors have reviewed and approved the final manuscript.

DATA STATEMENT

The data that support the findings of this study are available from the Healthcare Cost and Utilization Project**.** Restrictions apply to the availability of these data, which were used under license for this study.

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Table I: Unadjusted and adjusted perioperative outcomes for kidney transplantation stratified by frailty

*nFrail, non-Frail; IQR, interquartile range; pLOS, postoperative length of stay; TIA, transient ischemic attack

	Unadjusted			Adjusted		
Outcome	nFrail	Frail	p-value	Frail	95%CI	p-value
Mortality (%)	0.2	1.2	<0.001	2.17	1.33-3.57	0.002
Major Complications (%)						
Graft rejection	2.4	3.8	<0.001	1.39	1.12-1.74	0.003
Graft infection	0.3	0.7	0.003	1.55	0.96-2.51	0.07
Renal artery thrombosis	0.4	0.9	0.001	2.03	1.25-3.29	0.004
Renal vein thrombosis	0.3	0.8	<0.001	2.43	1.43-4.12	0.001
Neurologic complications	0.1	0.6	<0.001	2.46	1.35-4.47	0.003
Cardiac arrest	0.4	1.8	<0.001	2.14	1.38-3.31	0.001
Myocardial infarction	0.9	2.3	<0.001	1.54	1.08-2.20	0.02
Hemoperitoneum	0.5	1.8	<0.001	2.55	1.86-3.49	<0.001
Other thromboembolic complications	1.1	3.8	<0.001	2.68	2.12-3.37	<0.001
Respiratory complications	2.4	10.4	<0.001	2.78	2.32-3.33	<0.001
Other infectious complications	4.0	11.6	<0.001	2.44	2.08-2.85	<0.001
Resource Utilization						
Cost (USD $1000) (median [IQR])	64.6 [50.5-79.6]	74.5 [57.7-98.6]	<0.001	2.34	0.25-4.43	0.03
pLOS (median [IQR])	4 [4-6]	6 [4-10]	<0.001	1.44	1.36-1.52	<0.001
Non-home discharge (%)	1.3	10.2	<0.001	3.01	2.18-4.17	<0.001
30-day readmission (%)	19.4	25.5	<0.001	1.03	0.93-1.14	0.56
90-day readmission (%)	21.9	28.8	<0.001	1.06	0.95-1.18	0.29

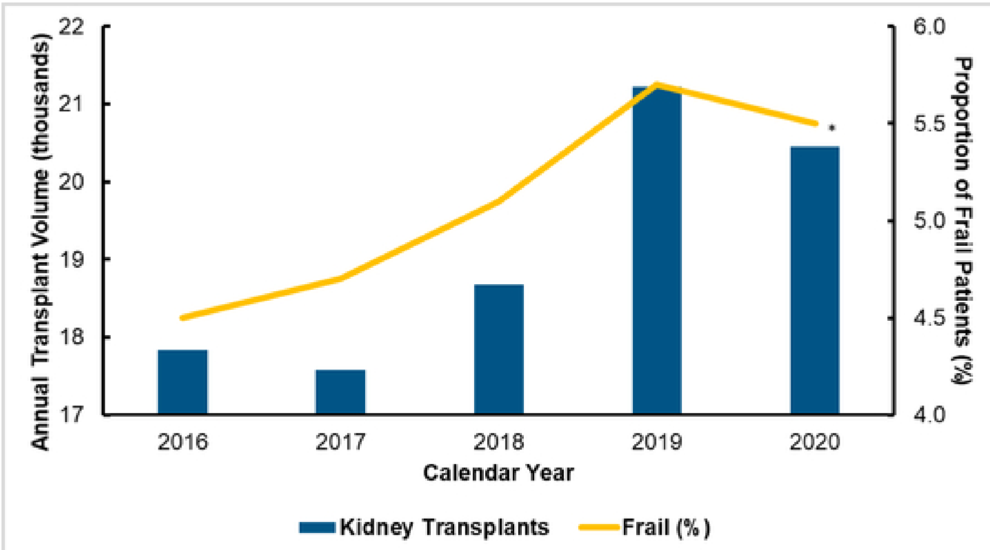
Figure Legends:

Figure I: National trends in kidney transplantation volume and frailty; *nptrend<0.001

Figure II: Predicted probability of mortality (Panel A) or non-home discharge (Panel B) by age and frailty status.

Figure III: Factors associated with differences in adjusted hospitalization costs

*ref, Reference



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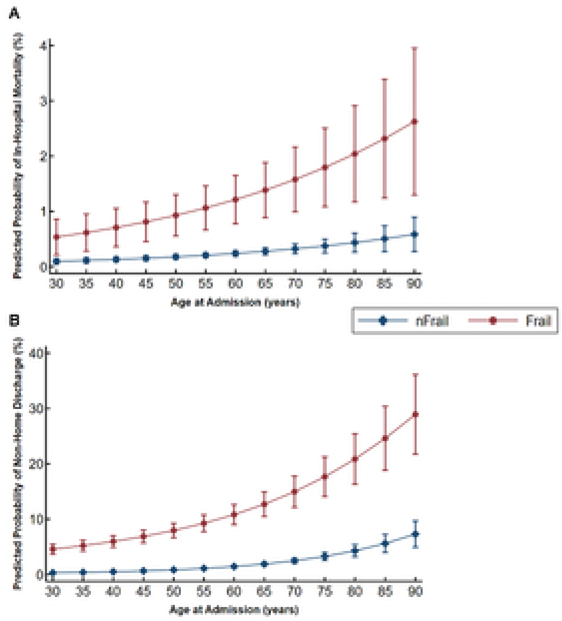

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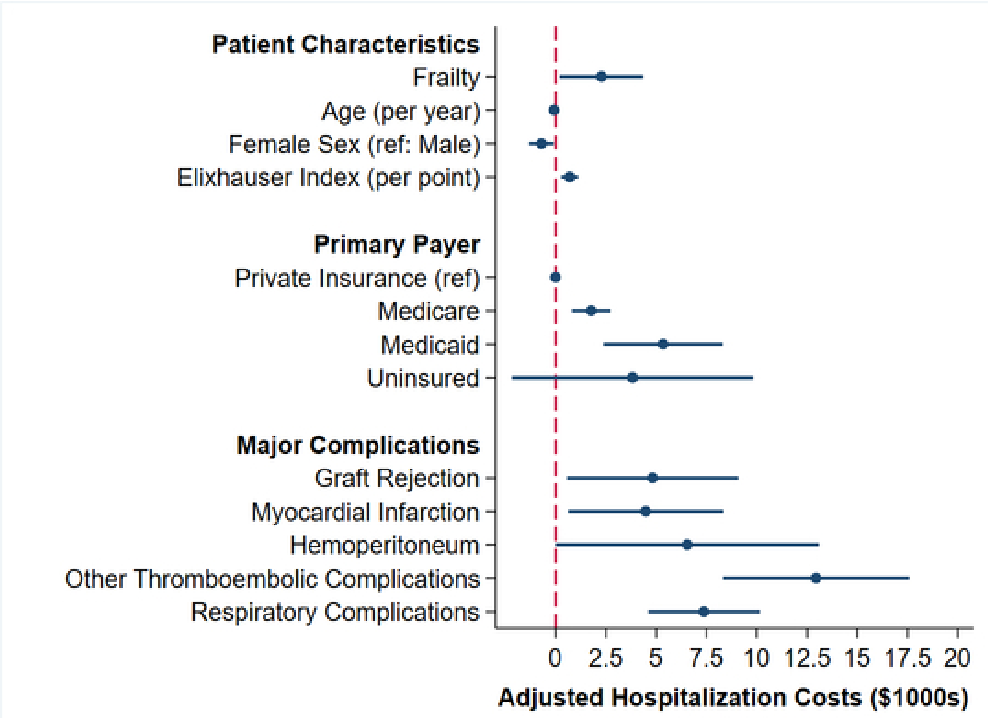

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Supplemental Tables

Supplementary Table I: International Classification of Diseases Code, Tenth Revision (ICD-10) procedure codes for kidney transplantation

Category	**ICD-10 Procedure Codes**
Transplantation of Right Kidney and Left Kidney	0TY10Z0, 0TY10Z1, 0TY00Z0, 0TY00Z1

Supplementary Table II: Demographic and hospital characteristics of patients undergoing kidney transplantation from 2016-2020

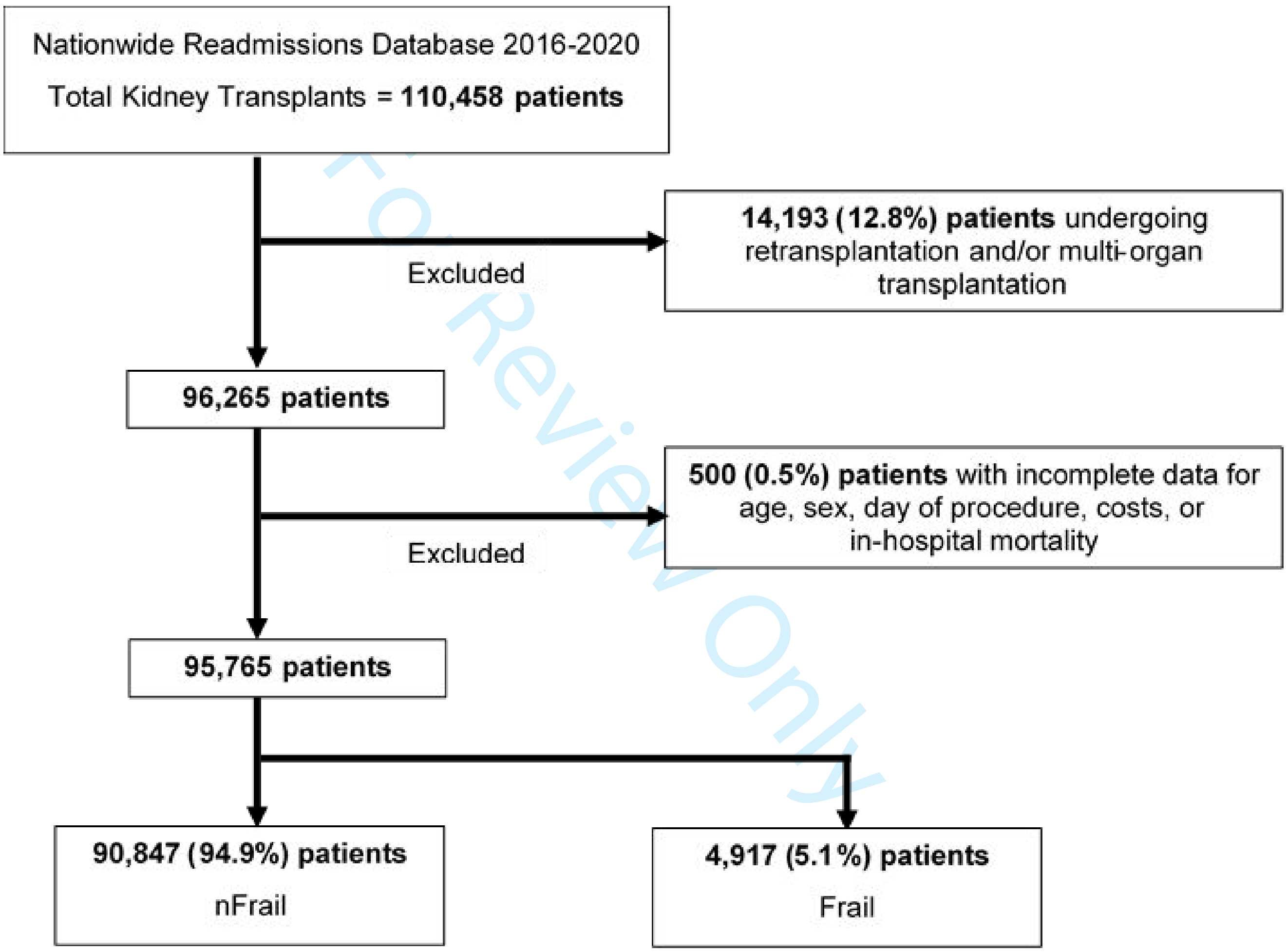
*nFrail, non-Frail; COPD, chronic obstructive pulmonary disease; SD, standard deviation; IQR, interquartile range

	nFrail (n=90,847)	Frail (n =4,918)	p-value
Patient Characteristics			
Age (years, mean ± SD)	52.2 ± 13.7	53 ± 14.9	0.04
Female (%)	39.5	42.8	0.002
Primary payer (%)			<0.001
Private	29.6	20.7	
Medicare	64.7	71.9	
Medicaid	3.9	5.4	
Uninsured	0.4	0.6	
Other payer	1.2	1.1	
Income quartile			0.01
>76%	25.8	27.9	
51-75%	26.1	28.2	
26-50%	25.3	23.5	
0-25%	21.7	19.5	
Elixhauser index (median [IQR])	4 [3-5]	5 [4-6]	<0.001
Comorbidities (%)			
Neurological disorders	2.9	8.2	<0.001
Cardiac arrhythmia	13.4	18.3	<0.001
Congestive heart failure	7.4	9.9	<0.001
Pulmonary hypertension	3.5	4.8	0.001
Peripheral vascular disease	5.6	7.2	0.01
Hypertension	95.4	93.9	0.002
COPD	8.2	8.5	0.64
Chronic liver disease	3.7	5.3	<0.001
Coagulopathy	12.3	20.8	<0.001
Obesity	19.9	19.0	0.41

Diabetes	35.8	48.1	<0.001
Hospital Characteristics			
Hospital teaching status (%)			0.84
Metropolitan teaching	99.1	99.1	
Metropolitan non-teaching	0.9	0.9	
Bed size (%)			0.79
Small	2.1	2.3	
Medium	6.9	7	
Large	91.0	91.1	
Hospital volume quartiles (%)			0.12
First (lowest volume)	25.9	24.8	
Second	22.9	22.8	
Third	25.9	30.5	
Fourth (highest volume)	25.3	21.8	

Supplemental Figures:

Supplementary Figure I: Exclusion criteria



Association of Frailty with Clinical Outcomes and Resource Use Following Kidney Transplantation