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ORIGINAL ARTICLE

Transitions in frailty state 12 months after kidney transplantation: a prospective cohort study

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Abstract

Background Frailty is associated with several unfavorable outcomes after kidney transplantation (KTx). However, limited information is available regarding the transitions in frailty state and its components after KTx. This study aimed to evaluate the transitions in physical frailty phenotype and its components over a period of 12 months after KTx.

Methods In this prospective single-center cohort study, we measured physical frailty phenotype (PFP) and its components at the time of admission for KTx and 12 months after KTx. The evaluation includes five components: weakness (grip strength analysed by sex and body mass index quartiles), physical activity (kcals/week based on the Minnesota Leisure Time Physical Activity questionnaire), exhaustion (self-report using the Center for Epidemiological Studies Depression Scale), gait speed (time taken to walk 15 feet based on sex and height-specific cutoff), and unintentional weight loss (self-report of unintentional weight loss > 10 lbs in the last year). The exhaustion and physical activity components are validated in the Brazilian population. Each component is scored as 0 or 1 according to its presence or absence, and a PFP score of 3–5 defines frailty, 2 is intermediate, and 0–1 is rated as non-frail. We used the McNemar and Wilcoxon test to compare physical frailty phenotype and its components between the two periods.

Results Among 87 patients included in the study, 16.1% were classified as frail, 20.7% as intermediately frail, and 63.2% as non-frail. Sixty-four patients were included in the analysis to evaluate transitions in frailty. At the time of admission for KTx, 15.6% of patients were defined as frail compared to 4.7% of patients at 12 months after KTx ($p = 0.023$). Among the physical frailty phenotype components, the proportion of patients who scored in the weight loss category 12 months after KTx was significantly lower than that at the time of KTx (6.3% vs 34.4%, $p < 0.001$).

Conclusions There was a 69.9% reduction in the prevalence of frail patients at the end of the 12-month follow-up after KTx. Among the components of frailty, weight loss showed a significant improvement.

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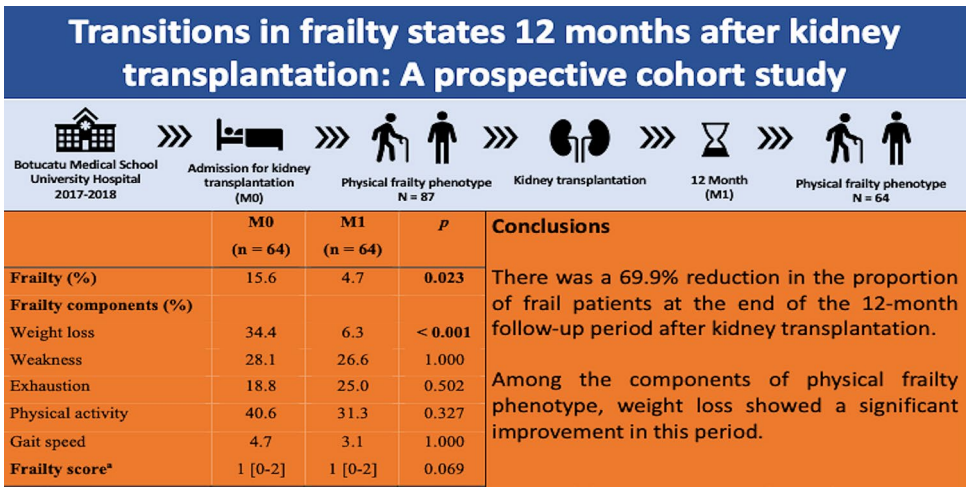
Graphical abstract



Keywords Frailty · Physical frailty phenotype · Kidney transplantation · Chronic kidney disease

Introduction

Frailty is a condition characterized by a multidimensional decline in physiological systems. It results in functional, cognitive, and immunological impairment, accelerated aging, and, consequently, an inability to deal with stressors. Frailty overlaps with comorbidities and aging; however, it is independently associated with adverse outcomes such as disabilities, falls, decreased mobility, hospitalization, postoperative complications, reduced quality of life, cognitive decline, and death [1–7].

Frailty has been described and validated in geriatric populations, and additionally, in patients with chronic end-stage kidney disease transplantation (KTx) recipients [8–18]. These populations share many pathogenic mechanisms of frailty, including a pro-inflammatory state and dysregulation of the immune, neuroendocrine and neuromuscular systems. These factors can lead to protein-energy malnutrition, sarcopenia, and anorexia, thereby resulting in accelerated aging [8, 10, 19, 20].

Frailty is also associated with several adverse outcomes after KTx, such as delayed graft function, longer hospital stay, early hospital readmission, development of delirium, intolerance to immunosuppressants, surgical complications, and mortality [10, 12–15, 17, 18, 21, 22]. However, few studies have evaluated the transitions in frailty states and its components after KTx [23–25], thus generating conflicting results. Two of these previous studies [23, 25] used the physical frailty phenotype (PFP), a tool developed by Fried et al. [6]. The most appropriate methodology for assessing frailty before and after KTx has not yet been identified [22, 26]; however, the PFP [6] is the most commonly used tool in the literature for KTx patients.

Most of the available data on transitions in frailty states after KTx are derived from a single group of researchers [23, 25] and two American centers. Therefore, it is necessary to conduct studies in populations with different characteristics. This study aimed to evaluate the transitions in PFP states and its components after a follow-up period of 12 months post KTx.

Methods

Study design

We performed a prospective cohort study in which the PFP and its components were measured in patients at the time of admission for KTx and 12 months after KTx.

Study setting

This study included recipients of KTx at Botucatu Medical School University Hospital (HCFMB), Botucatu, SP, Brazil. The HCFMB is a tertiary care teaching and research center with 417 beds, covering approximately 75 municipalities and 2 million people. The HCFMB Kidney Transplant Service performs 140 transplants per year on average, with approximately 80% using kidneys from deceased donors.

Eligibility criteria

Patients of both sexes aged 18 years or older who underwent KTx between March 2017 and March 2018 were included. However, patients undergoing combined organ transplantation, those with amputations and other physical conditions that precluded the walk test or handgrip strength test, as well as patients with considerable cognitive impairments who were unable to understand and respond to the frailty score questionnaires were excluded from the study.

Study protocol

All patients were evaluated at the time of admission for KTx (M0). Demographic, clinical, anthropometric, laboratory, and KTx data were collected from medical records and interviews with the patients; the physical frailty phenotype was simultaneously assessed. It was assessed again 12 months after KTx (M1). M1 data collection was performed in the interval between 11 and 13 months after KTx.

Two authors collected data for evaluating the physical frailty phenotype: a dietitian performed 90.8% of the assessments, and a nursing student performed 9.2% of the evaluations. PFP [6] consists of five components: weakness (grip strength quantified by sex and body mass index quartiles), physical activity (kcals/week based on the Minnesota Leisure Time Physical Activity questionnaire), exhaustion (self-report using the Center for Epidemiological Studies Depression Scale), gait speed (time taken to walk 15 feet based on sex and height-specific cutoff), and unintentional weight loss (self-report of unintentional weight loss > 10 lbs in the last year). The exhaustion and physical activity components were adapted and validated for the Brazilian population [27, 28]. Each component was scored as 0 or 1 according to its presence or absence, and the PFP score was calculated by adding the scores of its components. A score of 3–5 was defined as frail, 2 as intermediate frail, and 0–1 as non-frail [25].

Definitions of study variables and protocols of the transplantation service

The definitions of study variables and outcomes, as well as descriptions of the prophylactic protocols of the HCFMB Transplantation Service, can be found in the supplementary material (Supplementary Text 1).

Statistical analysis

The present study is a subanalysis of a cohort with 87 patients at baseline that evaluated frailty as a predictor of infectious and non-infectious outcomes in KTx recipients. Therefore, the sample size calculation in the present study was 68, based on that reported by Dos Santos Mantovani et al. [17].

Data are expressed as mean ± SD, median (interquartile range), or percentage. The groups were compared using the Student's *t* test or Mann–Whitney *U* test for continuous variables, and the χ^2 test or Fisher's exact test for categorical variables. The comparison between PFP and its components before and 12 months after KTx was performed using the McNemar or Wilcoxon test.

Data analysis was performed using SigmaPlot v12.0 (Systat Software Inc., San Jose, CA, USA) for Windows, and p values < 0.05 were considered statistically significant.

Ethical consideration

The Institutional Review Board of Botucatu Medical School approved this study (IRB approval number: CAAE 59232316.2.0000.5411). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All participants provided written informed consent.

Results

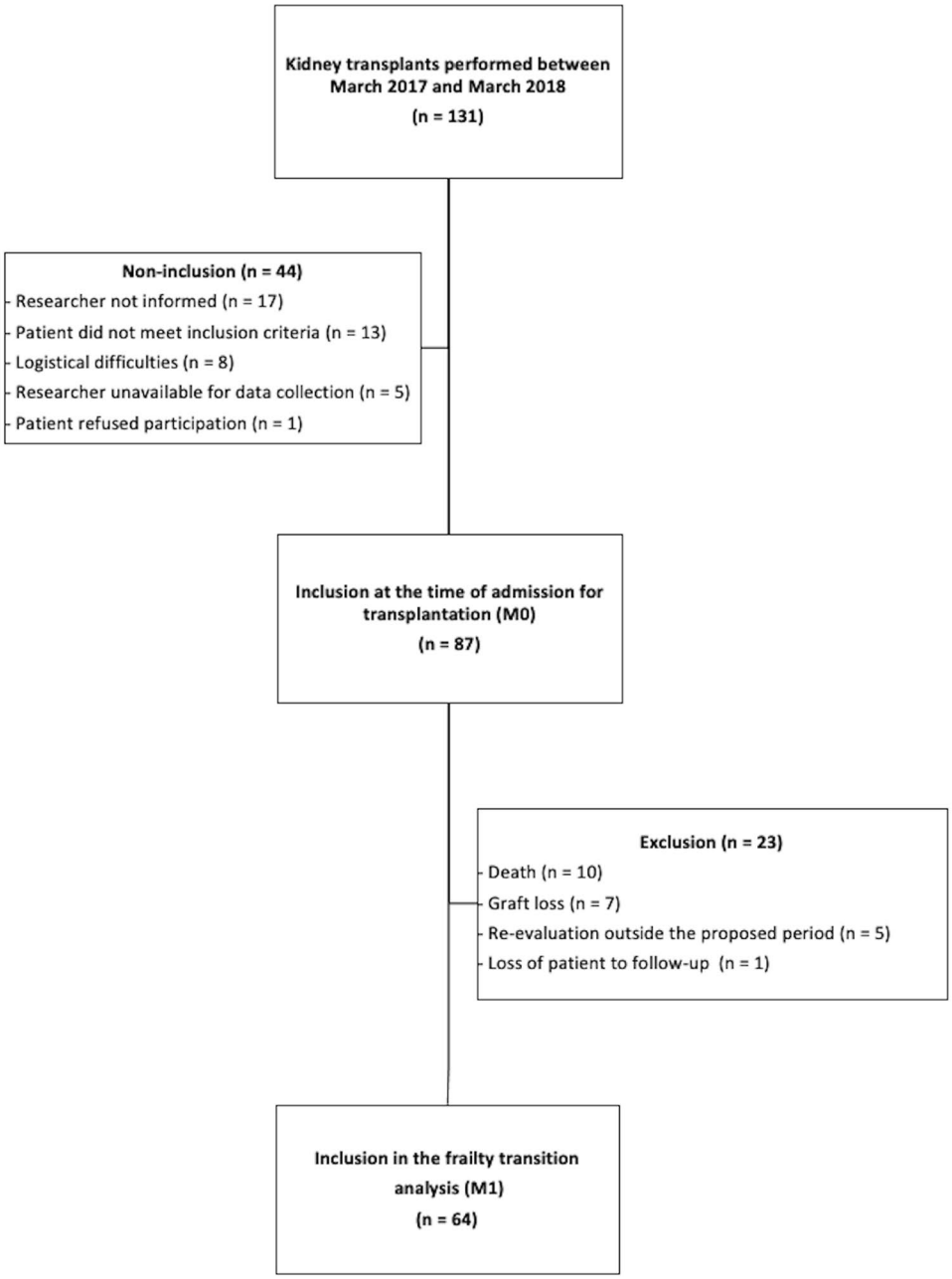
Study population

From March 2017 to March 2018, 131 patients underwent KTx at the HCFMB. Of these, 87 (66.4%) were included in the study (M0). Twelve months after KTx (M1), 64 patients were included in the frailty transitions analysis. Figure 1 shows the patient flowchart.

Table 1 shows the demographic, anthropometric, clinical, laboratory, and transplant-related data of the patients, according to the presence or absence of frailty. There was a predominance of White (51.7%) and multiracial Black and White (33.3%) patients. Men represented 58.6% of the patients, with a mean age of 44.9 ± 12.2 years. The predominant etiology of end-stage kidney disease was undefined (33.3%). The most commonly used kidney replacement therapy (KRT) was hemodialysis (81.6%), with a median pre-KTx KRT time of 28 months. In addition, transplants from deceased donors predominated (78.2%). Other general characteristics of the patients and their donors are also presented in Table 1. There was no significant difference concerning the data evaluated in Table 1 when frail and non-frail patients (grouped as intermediate frail and non-frail patients) were compared.

The only statistical difference in the baseline characteristics between the 64 patients who had a 12-month follow-up and the 23 patients lost to follow-up was the age of the patients. The mean age of the patients lost to follow-up

Fig. 1 Patient disposition



(49.2 ± 9.7) was higher than that of the 64 patients who had a 12-month follow-up (43.3 ± 12.7) (Supplementary Table 1).

Pre-KTx frailty

Table 2 shows data on physical frailty phenotype and its components of the patients at the time of admission for KTx.

Among the 87 patients included in the study, 16.1% were classified as frail, 20.7% as intermediately frail, and 63.2% as non-frail. Among the frailty components, low physical activity (46.0%), weight loss (32.2%), and weakness (32.2%) were predominant. The median frailty score was 1.

Transitions in frailty 12 months after KTx

Table 3 shows the transitions in physical frailty phenotype and its components from the time of admission for KTx to 12 months after KTx.

Among the 64 patients included in the final analysis, there was a significant reduction in the proportion of frail patients. At the time of admission for KTx, 15.6% of patients were frail, while 12 months after KTx, 4.7% were classified as frail ($p = 0.023$). When considering the median frailty score, no significant difference was identified between the M0 and M1 time points.

Table 1 Demographic, anthropometric, clinical, laboratory and transplant-related data of the patients included in the study, according to the presence or absence of frailty

Characteristics	Overall	Frailty state		*p*
	(*n* = 87)	Yes (*n* = 14)	No[d] (*n* = 73)	
Age (y)[a]	44.9 ± 12.2	47.6 ± 15.3	44.4 ± 11.6	0.372
Male (%)	58.6	35.7	63.0	0.109
Race and ethnicity (%)				
White	51.7	57.1	50.7	
Black	12.6	14.3	12.3	
Multiracial Black and White	33.3	28.6	34.2	0.960
Asian	1.1	0.0	1.4	
Brazilian Indian	1.1	0.0	1.4	
Cause of ESKD (%)				
Undefined	33.3	21.4	35.6	
Other	27.6	35.7	26.0	
Hypertension	21.8	28.6	20.5	0.342
Diabetes	10.3	0.0	12.3	
Glomerulonephritis	6.9	14.3	5.5	
Dialysis modality (%)				
Hemodialysis	81.6	92.9	79.4	0.469
Peritoneal	14.9	7.1	16.4	
Preemptive (none)	3.4	0.0	4.1	
Time on dialysis (m)[b]	28 [14–45]	24 [13–57]	29 [14–44]	0.790
Pre-KTx diabetes (%)	13.8	7.1	15.1	0.681
Cardiovascular risk (%)				
Low	70.1	57.1	72.6	0.339
Moderate + high	29.9	42.9	27.4	
Retransplantation (%)	3.4	7.1	2.7	0.413
HLA mismatches (*n*)[b]	3 [2–4]	3 [3–3.3]	3 [2–4]	0.890
PRA class I (%)[b]	0 [0–10]	0 [0–67.3]	0 [0–2]	0.198
Type of donor (%)				
Living	21.8	21.4	21.9	1.000
Deceased	78.2	78.6	78.1	
BMI (kg/m^2)[a]	25.7 ± 4.6	25.6 ± 5.4	25.8 ± 4.4	0.915
Expanded criteria donor (%)[c]	29.4	36.4	28.1	0.719
Cold ischemia time (h)[ac]	23.2 ± 3.7	22.8 ± 3.3	23.2 ± 3.7	0.735
Induction therapy (%)				
Anti-thymocyte globulin	96.6	92.9	97.3	0.413
No induction	3.4	7.1	2.7	
Maintenance therapy (%)				
FK + mTORi + PDN	64.4	64.3	64.4	
FK + MPS + PDN	32.2	28.6	32.9	0.695
Other	3.4	7.1	2.7	
DGF (%)	53.0	61.5	51.4	0.713

y years, *ESKD* end-stage kidney disease, *m* month, *KTx* kidney transplantation, *HLA* human leukocyte antigen, *n* number of participants, *PRA* panel reactive antibody, *BMI* body mass index, *h* hours, *FK* tacrolimus, *mTORi* mammalian target of rapamycin inhibitor, *MPS* mycophenolate sodium, *PDN* prednisone, *DGF* delayed graft function

[a]Mean ± standard deviation

[b]Median [interquartile range]

[c]Only deceased donors

[d]Intermediate frailty + non-frail

Table 2 Frailty state and its components at the time of admission for kidney transplantation

Frailty	$n=87$
Frailty state (%)	
Frail	16.1
Intermediate frailty	20.7
Non-frail	63.2
Frailty components (%)	
Weight loss	32.2
Weakness	32.2
Exhaustion	20.7
Physical activity	46.0
Gait speed	4.6
Frailty score[a]	1 [1, 2]

[a]Median [interquartile range]

Table 3 Transitions of the frailty states and its components from the time of admission for kidney transplantation (M0) to 12 months after kidney transplantation (M1)

	M0 ($n=64$)	M1 ($n=64$)	p
Frailty (%)	15.6	4.7	0.023
Frailty components (%)			
Weight loss	34.4	6.3	< 0.001
Weakness	28.1	26.6	1.000
Exhaustion	18.8	25.0	0.502
Physical activity	40.6	31.3	0.327
Gait speed	4.7	3.1	1.000
Frailty score[a]	1 [0–2]	1 [0–2]	0.069

M0 admission for kidney transplantation, *M1* 12 months after kidney transplantation

[a]Median [interquartile range]

The proportion of patients who scored in the weight loss category was significantly lower at 12 months after KTx than at the time of admission for KTx (6.3% vs 34.4%, $p < 0.001$). The mean body mass index (BMI) at M1 was significantly higher than at M0 (27.6 ± 4.8 vs 25.5 ± 4.7, $p < 0.001$).

The number of patients with each number of frailty components at M0 and M1 is presented in Supplementary Fig. 1.

Supplementary Table 2 shows the proportion of patients who transitioned between frail and non-frail states during the study period. Overall, 84.4% of patients remained non-frail, no patient transitioned to frailty, 4.7% remained frail, and 10.9% were no longer frail at the end of the study period.

Supplementary Table 3 shows the proportion of patients who had a stable, worsening, or improving frailty state during the follow-up. The frailty state remained stable for 54.7% of patients, improved in 26.5% of patients, and worsened in 18.8% of patients. In addition, the frailty score remained stable in 29.7% of patients, reduced in 48.4% of patients, and increased in 21.9% of patients.

Discussion

In this prospective observational study of 87 patients in a single Brazilian center, there was a significant reduction in the proportion of frail individuals at the end of the 12-month follow-up period.

The mean age of the study population was at the lower limit among patients included in the systematic review by Quint et al. [9]. Most of the patients were male, similar to the findings noted in the literature [9]. In addition, the proportion of patients who received a deceased donor transplant was higher than that in other studies on frailty in the American kidney transplant population [12, 14, 23]. Diabetes mellitus was present in 13.8% of patients during the pre-transplant period, a proportion lower than that reported in the literature [9].

The prevalence of frail patients at the time of admission for KTx in the present study was similar to that identified in the meta-analysis by Quint et al. [9]. McAdams-DeMarco et al. [18] reported that 37.0% of 443 patients evaluated at the time of admission for KTx were classified as frail or intermediately frail, which is similar to that found in the present study. The similar proportion of pre-KTx frail patients in our younger population probably can be justified by the higher proportion of patients on dialysis, the longer time on KRT, and the socioeconomic status.

McAdams-DeMarco et al. [23] evaluated 349 KTx recipients from a single American center. They showed that the prevalence of frailty increased from 19.8% before KTx to 33.3% after 1 month and to 27.7% after 2 months of KTx. Three months after KTx, the proportion of frail patients dropped to 17.2%, a significant reduction compared with that immediately before KTx, thus suggesting that frailty in this population is not an irreversible state.

McAdams-DeMarco et al. [23] also found that 44.8% of patients were less frail and 25.0% were more frail 3 months after KTx. These data are very similar to those in the present study, which considered a longer follow-up period of 12 months.

We identified only one study that evaluated the long-term trajectory of frailty and its components in KTx recipients [25]. This study observed 1,336 KTx recipients at two American centers and showed that frailty significantly decreased in the first 2.5 years after KTx. There were significant improvements in the weight, physical activity, and exhaustion components. However, after 2.5 years of transplantation, there was a reduction in strength and physical activity thus increasing the possibility of developing frailty in this population. Although the aforementioned study

[25] did not present specific data for the follow-up period of 12 months after KTx, the data from the present study corroborate the significant improvement in frailty during the initial years after KTx. Differences in follow-up time, sample size, and population characteristics may justify the absence of improvement in components other than weight loss in the present study.

Quint et al. [24] analyzed the transitions in frailty states in a population of 176 KTx recipients in the first 12, 24, and 36 months using the Groningen Frailty Indicator. The proportion of frail patients at the time of admission for KTx was similar to that in the present study and the meta-analysis by Quint et al. [9]. However, while evaluating the transitions in the frailty states after KTx, these authors observed conflicting results compared with Chu et al. [25] and those of the present study. After 22.8 months of mean follow-up, 19.3% of patients progressed to frailty, 71.0% remained stable, and 9.7% were no longer frail. The proportion of frail patients at the time of KTx, which was 17.0%, increased to 26.7% after the mean follow-up period. When the follow-up period up to 12 months after KTx was considered, 17.7% of patients developed frailty and 10.0% were no longer frail. One possible explanation for this unfavorable result is the differences between the frailty assessment tools used in the studies. Another finding highlighted by Quint et al. [24] is the high proportion of patients pre-emptively transplanted (40.9%). Among these patients, 44.1% progressed to frailty after KTx. The Groningen Frailty Indicator evaluates both cognitive and psychosocial factors, which were strongly associated with the transition to frailty in this study. Cognitive and psychosocial conditions would be better preserved before KTx when patients are not undergoing dialysis. The natural complications associated with KTx and the need to use immunosuppressants would affect the cognitive and psychosocial aspects, thus increasing the proportion of frail patients. Another parameter is the different characteristics, such as the average age and proportion of deceased donors, of the populations included in the studies by Quint et al. [24], Chu et al. [25], and the present study.

The only component of frailty that underwent a significant change in the present study was unintentional weight loss. In fact, there was a weight gain during follow-up. We expected this result because the literature shows that most KTx recipients gain weight in the first year after KTx [29]. The weight gain has multiple contributing factors, including the immunosuppressive treatment, age, sex, genetics, ethnicity, pre-transplant BMI, physical activity, socioeconomic status, graft function, and the disappearance of dietary restrictions [29–31].

Chang et al. [29] showed that a 10% to 19% weight gain in the first year after KTx was associated with the best outcomes. On the other hand, weight gain greater than or equal to 20% resulted in higher mortality. Obesity was also associated with other complications in KTx, such as delayed graft function, surgical complications, acute rejection, decreasing estimated glomerular filtration rate, dyslipidemia, diabetes mellitus, and cardiovascular diseases [31, 32]. Therefore, we should better study the repercussions of reducing frailty in this context of weight gain.

As visceral obesity and sarcopenia are associated with unfavorable outcomes, we should use methods to identify these metabolic changes in patients who gain weight after KTx. These methods include dual-energy X-ray absorptiometry, bioimpedance analysis, and waist circumference [30, 33–36].

It is important to note that the frailty in patients undergoing KTx is different from that found in other chronic diseases or acute conditions such as stroke and other critical illnesses. [37–39]. In chronic kidney disease, the incidence of frailty increases as the stage of the disease progresses. In addition, dialysis and uremia impact frailty. Therefore, KTx can, in most cases, improve frailty in a population with end-stage kidney disease, which is less common than in other diseases [40–42].

This study has some limitations. The cohort study was performed only at one Brazilian center, and we used only one frailty assessment tool [6]. Furthermore, the sample size is relatively limited and may have reduced the statistical power of the study.

Despite these limitations, this study has significant strengths. It is novel, as it includes patients from a developing country with specific demographic, economic, and health characteristics. In this study, physical frailty phenotype [6] was used, which is the most commonly used tool among the population of KTx patients and, above all, we measured frailty when the patients were hospitalized for the kidney transplant, thus reflecting the actual pre-KTx state.

Conclusion

In conclusion, there was an important (69.9%) reduction in the prevalence of frail patients at the 12-month follow-up period after KTx. Among the components of frailty, weight loss showed a significant improvement in this period.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40620-022-01436-4.

Author contributions Conceptualization and methodology: MSM, MFM, LGMA, RSC, GBA, NAC, JFS, RAMBA; Data collection: MSM, NCC, RSC, GBA, RAMBA; Formal analysis: MFM, LGMA; Writing the initial draft: MSM, MFM, NAC, RAMBA; Supervision:

RAMBA; Funding acquisition: RAMBA; All authors approved the final version of the manuscript.

Data Availability The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors of this study declare no conflict of interest.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. The Institutional Review Board of Botucatu Medical School approved this study (IRB approval number: CAAE 59232316.2.0000.5411). All participants provided written informed consent.

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