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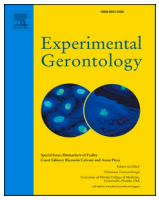

Single nucleotide polymorphism *SULT2A1* rs4149448 and genetic risk score as biomarkers of frailty and progression of chronic kidney disease

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ABSTRACT

Background: Frailty is a multifactorial condition highly prevalent in patients with chronic kidney disease (CKD), increasing with disease progression. Identifying genetic determinants associated with frailty may aid in risk stratification. We aimed to identify whether single nucleotide polymorphisms (SNPs), individually or combined into a genetic risk score (GRS), are associated with the frailty phenotype and adverse clinical outcomes in CKD patients.

Methods: This is a longitudinal study that evaluated patients with CKD 3b-5 non-dialysis dependent [69 (57–72) years; 59,1 % men; body mass index, 27.2 ± 5.3 kg/m^2]. Clinical, anthropometric, and biochemical variables, including 25(OH)D concentration, were evaluated. Eight SNPs associated with low vitamin D levels were genotyped using qPCR. The genetic risk score (GRS) was calculated by summing the number of risk alleles for vitamin D deficiency across the SNPs, resulting in values ranging from 0 to 16. Frailty was assessed using the physical frailty phenotype. The outcomes considered were non-elective hospitalization and changes in CKD stage.

Results: Around 36 % of patients were frail, and 68 % had 25(OH)D levels below 20 ng/mL and were considered deficient. The higher GRS [9 (7–10) versus 6 (5–7); $p = 0.034$] occurred in patients who developed CKD progression. After the adjusted logistic regression analysis, the *SULT2A1* genotype of rs4149448 was associated with a greater chance of frailty (OR: 8.8 IC95% 1.048–74.733; $p = 0.045$).

Conclusion: Specific genetic variants, including a higher GRS and the SNP *SULT2A1* rs4149448 genotype, were associated with CKD progression and frailty, suggesting their potential role in risk stratification.

1. Introduction

Frailty is characterized by the deterioration of multiple body systems, leading to a decreased physiological response to stressors (Fried et al., 2001). In patients with non-dialysis dependent chronic kidney disease (CKD), this condition has been widely recognized and is associated with adverse outcomes such as progression to dialysis, hospitalizations, and mortality (Gordon et al., 2021; Hoogendijk et al., 2019; Li et al., 2022).

In addition to the consequences caused by frailty itself, patients with CKD face chronic inflammation, uremia, metabolic acidosis, mineral-bone loss, and hormonal disorders, such as vitamin D deficiency (Gungor et al., 2021). Studies indicate that vitamin D affects skeletal muscle health, a critical component of frailty (Alvarez Mejía et al., 2023; Gungor et al., 2021; Ju et al., 2018). Although higher serum concentrations of vitamin D are associated with a reduced risk of frailty, the response to supplementation varies among individuals (Ju et al., 2018; Prokopidis et al., 2022). One possible explanation for this variability may be the presence of single nucleotide polymorphisms (SNPs), which can influence both the response to supplementation and serum concentrations of vitamin D (Al-Daghri et al., 2019; Bahrami et al., 2019; Jiang et al., 2019).

Genome-wide association studies (GWAS) have identified SNPs strongly linked with serum vitamin D concentrations despite not being

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located in genes traditionally associated with vitamin D metabolism (Manousaki et al., 2020; Revez et al., 2020).

Studies have investigated the relationship between genetics and frailty, identifying SNPs related to the musculoskeletal system (Inglés et al., 2019; Willems et al., 2017), apoptosis (Ho et al., 2011), inflammation (Mekli et al., 2016), and the immune system (Inglés et al., 2019; Jiang et al., 2018). However, no research has been conducted to evaluate vitamin D deficiency-related SNPs. Given the complexity of frailty, exploring the genetic basis involved in both vitamin D deficiency and its pathophysiology in patients with CKD can elucidate unresolved issues ranging from the variability in how frailty manifests to the development of targeted nutritional strategies. Genetic markers with diagnostic and prognostic value would be useful in monitoring and could direct actions to prevent progression to an irreversible state of frailty in CKD patients.

Considering that low vitamin D concentrations may contribute to the development of frailty, we hypothesize that specific SNPs may impair vitamin D metabolism. Given that vitamin D deficiency is a known risk factor for sarcopenia and osteopenia, such polymorphisms could be linked to the onset or worsening of frailty and, consequently, to an increased risk of adverse clinical outcomes. We aimed to evaluate whether SNPs related to vitamin D concentrations, individually or combined into a genetic risk score (GRS), are associated with the frailty phenotype and hospitalization and CKD progression.

2. Methods

2.1. Study design, ethical statements, and participants

This longitudinal study was approved by the Human Research Ethics Committees and the two nephrology care centers involved in the study (UFG: CAAE: 47217721.9.0000.5083; Approval Number: 4.918.708; Hospital 1: CAAE: 47217721.9.3001.5078; Approval Number: 5.053.031; Hospital 2: CAAE: 47217721.9.3004.0035; Approval Number: 5.112.682). Baseline data collection took place between August and December 2022 in the outpatient clinics, following the nephrology consultations. All participants were informed about the research objectives and signed an informed consent form following the Declaration of Helsinki.

Patients with CKD stages 3b to 5 undergoing non-dialysis treatment (Levey et al., 2009), of both sexes and with a median age of 69 years (57–72), were prospectively included in the study. Bedridden patients, those diagnosed with active neoplasia and liver disease, previous diagnosis of immunological diseases, kidney transplantation, clinical signs of acute infection, pregnancy, limb amputation, or physical limitation, and those who refused to participate or were lost to follow-up in the study were not included.

This study is an exploratory analysis with the aim of generating new hypotheses. The sample of this study consisted of 22 participants selected and balanced according to sex and age among the patients who completed the parent study approved by the opinion cited above. Patients were followed for 18 months, and the development of non-elective hospitalization and progression of kidney disease during the period were assessed (Fig. 1). Non-elective hospitalization was considered any cause that required urgent or emergency admission with a stay in the hospital for at least 24 h. The progression of CKD was considered the evolution from one stage to a more advanced one.

2.2. Study variables

When the participant first entered the study, clinical, demographic, and biochemical data were recorded, including the most recent exams available in the medical record. Anthropometric assessment, and frailty screening were also carried out. For the anthropometric assessment, weight (kg) and height (m) were measured. Body mass index (BMI) was calculated by dividing body mass (kg) by the square of height (m). Waist circumference and calf circumference were measured with an inelastic and inextensible tape. Waist circumference was considered the smallest circumference between the lowest rib and the iliac crest, and for calf measurement, the largest circumference was considered according to standardized procedures (Lohman et al., 1988).

2.3. Frailty

To assess frailty, we used the Physical Frailty Phenotype scale proposed by Fried et al. (Fried et al., 2001). The evaluation was carried out by trained nutritionists and employing standardized procedures when patients were included in the study. The Physical Frailty Phenotype scale is based on weight loss, exhaustion, level of physical activity, muscle strength, and gait speed. Patients were classified as “non-frail” when the score was zero, “pre-frail” when they scored between 1 or 2 criteria, and

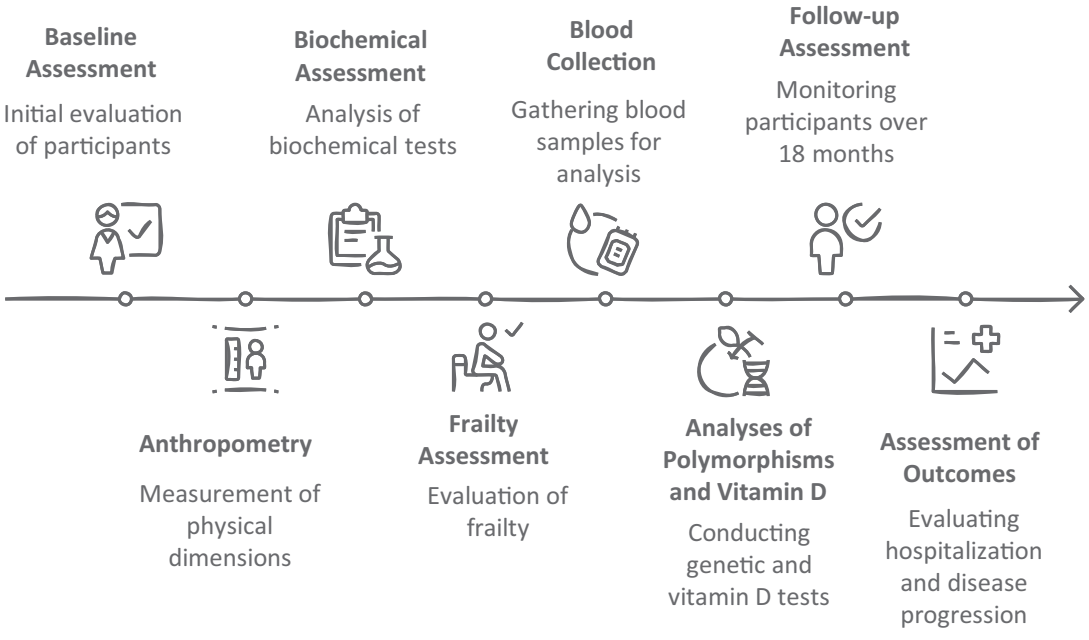

Fig. 1. Data collection and assessment process.

"frail" when they scored three or more criteria.

2.4. Biological samples

Blood samples were collected for analysis of SNPs and plasma vitamin D concentration. Blood collection (4 mL) was carried by a trained professional and without the need for overnight fasting. To obtain plasma, the blood was centrifuged for 10 min at 3200 rpm (4 °C). Plasma and whole blood were placed in microtubes and stored in an ultra-freezer at −80 °C until analysis.

2.5. Selection of SNPs

The selection of SNPs for this study was based on a search in the GWAS catalog ("GWAS Catalog,", n.d.), which indicated two GWAS (Manousaki et al., 2020; Revez et al., 2020) as major data contributors for the SNPs most strongly associated with vitamin D levels. Eight SNPs that presented allele frequencies of at least 10 % in the Brazilian population were selected (Naslavsky et al., 2022): rs10832254 *(COPB1);* rs10859995 *(HAL);* rs11608138 *(ACTE1P);* rs4149448 *(SULT2A1);* rs2011331 *(FLG);* rs3755967 *(GC);* rs8018720 *(SEC23A);* rs8121940 *(CYP24A1)*.

2.6. DNA extraction and genotyping

DNA extraction was performed with the Kasvi 50 Mini Spin Kit (K9–0050, KASVI, Prolab, Brazil) as recommended by the manufacturer. After extraction, DNA quantification and quality were performed using Nanodrop Lite (Thermo Fisher Scientific, USA). The DNA was eluted to a final concentration of 50 ng/μL and stored at −20 °C until genotyping.

Genotyping was performed by real-time polymerase chain reaction (StepOne™ Real-Time PCR System, Applied Biosystems, Foster City, CA, USA), using TaqMan Assays (Thermo Fisher, Waltham, MA, USA). Allelic discrimination plots were generated using StepOne™ v2.1 software, allowing the identification of genotypes based on the fluorescence intensity of the probes. Negative controls were included to monitor any potential contamination.

2.7. Determination of the genetic risk score (GRS)

To calculate the GRS, we assumed that each risk allele for vitamin D deficiency contributed equally and additively to the change in vitamin D concentrations. Each SNP was assigned a value of 0, 1, or 2 based on the number of risk alleles present in the individual genotype. Thus, the GRS was obtained by summing the frequencies of the risk alleles of all SNPs, with the minimum score being zero (no risk alleles) and the maximum score being 16 (presence of all risk alleles).

2.8. Vitamin D

The concentrations of 25(OH)D were analyzed in blood plasma using the chemiluminescence method- Architect 25-OH Vitamin D assay (Abott®, Germany). As there is no consensus for the ideal concentration of 25(OH)D specifically in patients with CKD, the recommendation of the Endocrine Society was considered, which classifies concentrations lower than 20 ng/mL as vitamin deficiency (Holick et al., 2011).

2.9. Statistical analysis

Data distribution was assessed using the Shapiro-Wilk test. Data are presented as mean and standard deviation or median and interquartile range. Categorical variables are expressed as absolute (n) and relative (%) values.

In the analysis between the two groups, the Student's T-test for independent samples or the Mann-Whitney test was applied. Fisher's Exact-tests were used to compare the percentages of frailty, hospitalization, and CKD progression as well for each genotype of the selected SNPs (rs10832254; rs10859995; rs11608138; rs4149448; rs2011331; rs3755967; rs8018720; rs8121940). Furthermore, linear regression was used to assess the association between vitamin D concentrations and genotypes.

The Hardy-Weinberg equilibrium (HWE) was evaluated by the exact chi-square test for adjustment quality, which demonstrated the adherence of all SNPs to the established conditions. Linear regression was used to evaluate the association between genotypes and vitamin D concentrations. Unadjusted and adjusted logistic regression models were used to examine the association between the SNP rs4149448, diagnosis of frailty (baseline), and outcomes (non-elective hospitalization and progression of CKD). Model 1 was adjusted by sex and waist circumference; Model 2 by sex and presence of cardiovascular disease.

All statistical analyses were performed using STATA v12.0 and R v4.3.3 software. The significance level was set at $p < 0.05$ two-tailed.

3. Results

The participants analyzed had a median of 69 (57–72) years old and 40.9 % women. Hypertension was the most prevalent comorbidity (85 %). Of the patients included, 36.4 % ($n = 8$) of patients were considered living with physical fragility, 68.2 % ($n = 15$) had 25(OH)D deficiency, 18.2 % experienced at least one hospitalization, and 22.2 % showed

Table 1
Characterization non-dialysis-dependent CKD patients according to frailty status.

Variables	All	Frailty		*p*-Value
	($n = 22$)	Yes ($n = 8$)	No ($n = 14$)	
Age (years)	69 (57–72)	62.5 (57–69.5)	70 (67–75)	0.182
Women n (%)	9 (40.9)	4 (50)	5 (35.7)	0.416
Men n (%)	13 (59.1)	4 (50.0)	9 (64.3)	
GFR (mL/min/1.73m^2)	36.9 ± 16.3	36.2 ± 17.3	37.2 ± 16.4	0.887
Hypertension n (%)	17 (85.0)	6 (85.7)	11 (84.6)	0.730
Diabetes n (%)	13 (65.0)	5 (71.4)	8 (61.5)	0.526
CVD n (%)	9 (45.0)	3 (42.9)	6 (46.2)	0.630
Anthropometry				
BMI (kg/m^2)	27.2 ± 5.3	26.8 ± 3.8	27.5 ± 6.1	0.792
CC (cm)	35.4 ± 4.0	34.2 ± 2.0	36.0 ± 4.7	0.318
WC (cm)	95.1 ± 16.2	94.2 ± 18.1	95.6 ± 15.9	0.863
Biochemical Analysis				
Urea (mg/dL)	70.2 ± 31.4	69.2 ± 29.6	70.8 ± 34.1	0.916
Creatinine (mg/dL)	2.1 ± 1.0	2.3 ± 1.3	2.1 ± 0.8	0.660
Potassium (mEq/L)	4.7 ± 0.6	4.7 ± 0.4	4.8 ± 0.8	0.761
Phosphorus (mg/dL)	3.9 ± 0.8	3.8 ± 0.7	3.9 ± 0.9	0.953
Calcium (mg/dL)	9.1 ± 0.7	8.9 ± 0.6	9.3 ± 0.8	0.259
PTH (pg/mL)	72.0 (54.2–180.2)	105.8 (57.8–164.7)	72 (54.2–253.5)	0.850
Vitamin D (ng/mL)	15.2 (13.6–20.9)	14.2 (13.6–18.0)	17.9 (13.5–20.9)	0.453
Outcomes				
Hospitalization n (%)	4 (18.2)	2 (25.0)	2 (14.3)	0.465
CKD Progression (%)	4 (22.2)	1 (25.0)	3 (21.4)	0.673

BMI: Body Mass Index. CC: Calf Circumference. CVD: Cardiovascular disease. CKD: Chronic Kidney Disease. GFR: Glomerular filtration rate. PTH: Parathyroid hormone. WC: Waist circumference. Data expressed as mean ± standard deviation or median (p25-p75) or absolute (%) values. Student's T-test or Mann-Whitney test or Fisher Exact test. Values $p < 0.05$ were considered significant.

progression in CKD stage over 18 months (Table 1).

The mean score of the calculated GRS was 6 (5–7) points. Higher GRS occurred in patients who developed CKD progression [9 (7–10) versus 6 (5–7); $p = 0.034$]. (Fig. 2). Data on the prevalence of genotypes for each SNP and vitamin D status are presented in Tables S1 and S2.

Although we did not identify associations between the higher prevalence of outcomes and the SNPs evaluated, there was a marginal association ($p = 0.072$) between rs4149448 and frailty, with AG genotype carriers showing a higher percentage of frailty than AA genotype carriers (Table 2). After the adjusted logistic regression analysis, we observed that carrying the AG genotype of rs4149448 was associated with a greater chance of frailty (OR: 8.8 CI95% 1.048–74.733; $p = 0.045$) (Table 3).

4. Discussion

This study aimed to identify whether vitamin D SNPs, individually or combined in a GRS, are associated with the frailty phenotype and unfavorable clinical outcomes in non-dialysis CKD patients. To the best of our knowledge, this was the first study that analyzed the association between SNPs individually and through a GRS with frailty, hospitalization, and progression of CKD. Our results show that a higher GRS and the *SULT2A1* rs4149448 genotype are associated with frailty and CKD progression, indicating a potential pathway for more robust research to confirm these genotypes in stratifying frailty risk in CKD patients.

Most patients evaluated had low concentrations of vitamin D. In its active form, this vitamin is responsible for optimizing renal and intestinal calcium absorption. Its deficiency can lead to changes in serum calcium concentrations, which can stimulate parathyroid hormone and compromise the mineral-bone matrix (Holick, 2007). Among other problems, the immune response may be compromised (Fernandez et al., 2022), and muscle weakness may occur because the muscle appears to depend on vitamin D to exert its maximum capacity (Gungor et al., 2021; Holick, 2007). Together, these events could contribute to physical frailty. In patients with CKD, this may be worse since the kidney is the main site of 25(OH)D activation (Chen et al., 2019).

SNPs have been identified as associated with the biological functions of vitamin D and could interfere with its metabolism and activation (Manousaki et al., 2020; Revez et al., 2020). A Mendelian randomization study that evaluated SNPs associated with vitamin D concentrations did not identify an association with CKD. However, it found that genetically lower vitamin D levels were inversely associated with bone mineral density and other metabolic health markers such as total cholesterol and triglycerides (Xu et al., 2023). However, GWAS have identified SNPs in genes that have no known function in vitamin D metabolism but are associated with deficiency risk. Our results showed that carrying the heterozygous AG genotype at SNP *rs4149448* was a factor associated with greater chances of frailty, probably due to the presence of the risk allele G. The frequency of this SNP in Brazilians was estimated to be around 12 % (Naslavsky et al., 2022); however, no patient in our study presented the GG genotype that may have strengthen this association.

The SNP *rs4149448* is located in the *SULT2A1* gene, which encodes one sulfotransferase (PubChem, n.d.). These enzymes help in the metabolism of medications and endogenous compounds (neurotransmitters, hormones, lipids, and proteins), making these substances soluble in water so that they can be excreted (Gamage et al., 2006; PubChem, n.d.). The sulfonation carried out by these enzymes contributes to the detoxification process and the maintenance of homeostasis of endogenous compounds (Lindsay et al., 2008). SULT2A1 is the main enzyme involved in sulfonation that occurs predominantly in the liver, where part of vitamin D metabolism also occurs. The 25(OH)D3-3-O-sulfate is an important circulating metabolite generated in sulfonation and, when undergoing hydrolysis, could be regenerated into 25(OH)D (Wong et al., 2018). Therefore, the 25(OH)D3-3-O-sulfate might represent an important form of 25(OH)D storage. Interindividual differences in the sulfonation of 25(OH)D, due to the presence of SNPs, could explain the reduction in circulating concentrations of 25(OH)D (Kurogi et al., 2017; Wong et al., 2018). In addition, sulfotransferases as phase 2 enzymes, once compromised, may be associated with the development of multifactorial conditions.

Understanding the context of varying vitamin D concentrations is relevant because it can contribute to frailty (Bollen et al., 2022; Buchebner et al., 2019), which is associated with worse clinical outcomes (Hannan et al., 2024). The literature shows that frailty stands out as a predictor of postoperative complications in post-kidney transplant patients (Mantovani et al., 2020), adversely affecting the onset of dialysis (Bao et al., 2012). In non-dialysis dependent patients, frailty was associated with a two to three times higher risk of mortality from all causes compared to the absence of frailty (Hannan et al., 2024). Therefore, interventions that improve 25(OH)D concentrations can help prevent and treat frailty.

Although no significance was identified between vitamin D deficiency, GRS, and frailty status, higher GRS was observed in patients with CKD progression. Therefore, an individual living with frailty, with low concentrations of vitamin D, and with more risk alleles may have worse clinical progression, requiring dialysis intervention. Mitigating frailty in non-dialysis patients with CKD is essential, as frailty in this population increases the risk of mortality, hospitalization, and progression to dialysis by two- to six-fold (Karnabi et al., 2023). Moreover, the initiation of dialysis itself significantly reduces life expectancy. Therefore, advancing knowledge to support strategies aimed at improving diagnosis, risk prediction, and overall quality of life is crucial by ensuring that patients not only survive, but live with dignity and well-being. In this context, the GRS could be useful to stratify the risk of frailty and promote more assertive interventions, especially for individuals at high risk (Torkamani et al., 2018). A study that aimed to personalize vitamin D supplementation according to genetic factors identified that explaining to patients about the individual GRS and serum concentrations of 25 (OH)D can be used to personalize vitamin D supplementation with more efficient responses (Sallinen et al., 2021). These results suggest that individuals with CKD should not receive 25(OH)D supplementation in a standardized manner and based solely on disease burden. Thus, personalized interventions according to the GRS may present greater supplementation effectiveness and should be considered.

Our study has some limitations. First, our small sample to establish an association between SNPs and frailty is insufficient to extrapolate the results to all SNPs evaluated here. Second, a longer follow-up period is needed to observe different clinical outcomes, including mortality. Furthermore, since we did not assess frailty at the second time point, our analyses did not allow for the evaluation of associations between SNPs and frailty transitions. The assessment of other markers of nutritional status in a longitudinal manner should also be included in future studies.

This study offers a new perspective to further explore the interconnections between vitamin D, genetics, and frailty. The assessment of GRS in patients with CKD may support the development of more targeted strategies, such as determining the appropriate dose of vitamin D supplementation. This is because patients with a higher genetic risk may benefit from different interventions compared to those without such risk. In addition, the SNP rs4149448 could be validated in larger studies as a potential screening marker for frailty. The results of this study indicate that SNPs may partly explain the presence of frailty, and that they may be useful markers for detecting conditions such as CKD progression.

5. Conclusion

Specific genetic variants, including a higher GRS and the SNP *SULT2A1* rs4149448 genotype, were associated with CKD progression and frailty, suggesting their potential role in risk stratification. Taken together, our data suggest that frailty can be partly explained by the genetic component, and risk alleles in SNPs related to vitamin D predispose the individual to worse health outcomes. Understanding this

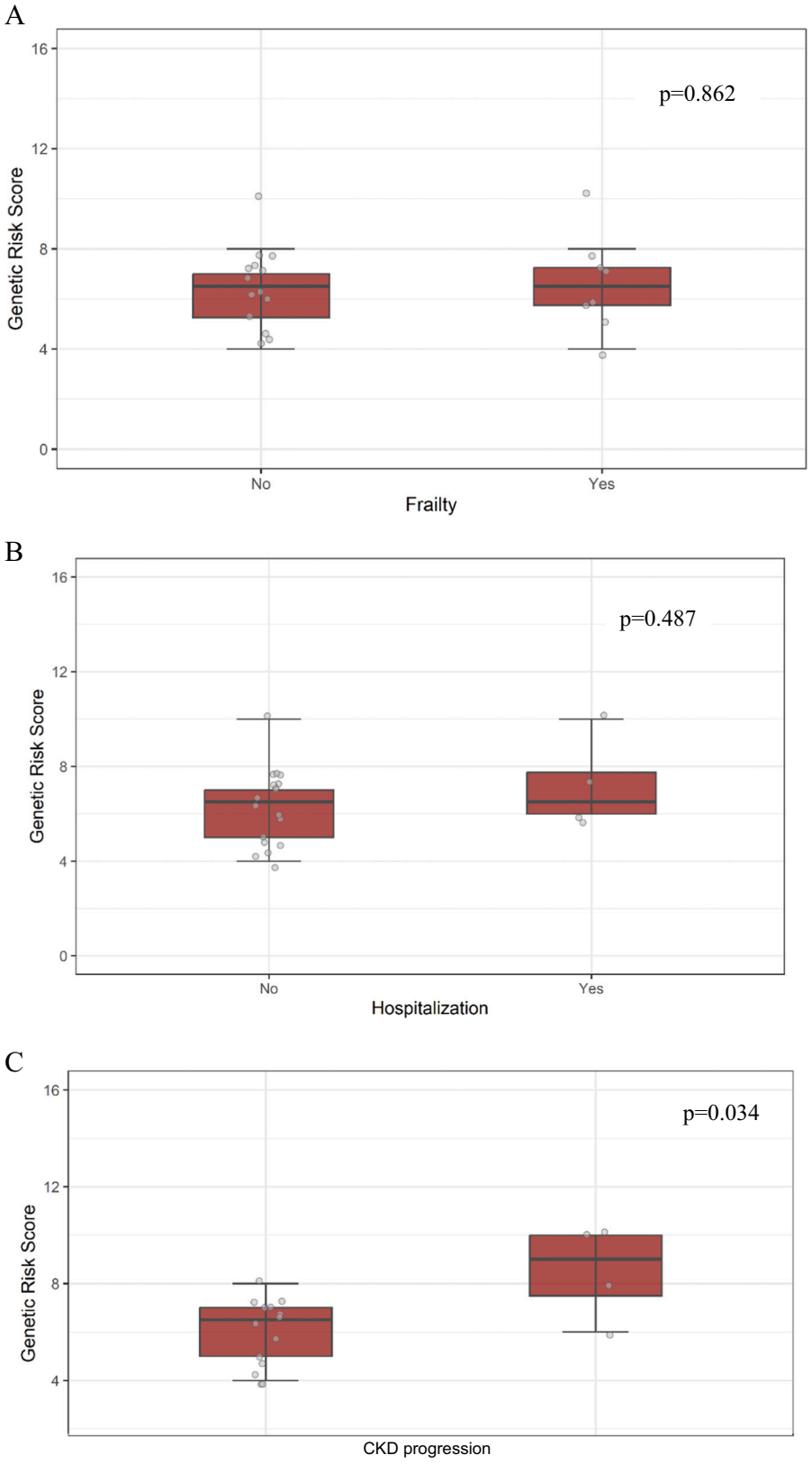

Fig. 2. A Assessment of genetic risk score (*GRS*) according to frailty status. Mann-Whitney test.
B Assessment of genetic risk score (GRS) according to the occurrence of non-elective hospitalization. Mann-Whitney test.
C Assessment of genetic risk score (GRS) according to chronic kidney disease (CKD) progression. Mann-Whitney test.

Table 2
Assessment of genotypes according to frailty status and clinical outcomes.

SNP	All	Frailty		p-Value	Hospitalization		p-Value	CKD progression[a]		p-Value
Genotype	(n = 22)	Yes (n = 8)	No (n = 14)		Sim (*n* = 4)	Não (*n* = 18)		Sim (n = 4)	Não (n = 14)	
COPB1 (rs10832254)										
AA	11 (50.0)	3 (37.5)	8 (57.1)	0.610	1 (25.0)	10 (55.6)	0.436	1 (25.0)	8 (57.1)	0.192
AG	10 (45.4)	5 (62.5)	5 (35.7)		3 (75.0)	7 (38.9)		2 (50.0)	6 (42.9)	
GG	1 (4.6)	0 (0)	1 (7.1)		0 (0)	1 (5.6)		1 (25.0)	0 (0)	
HAL (rs10859995)										
CC	5 (22.7)	3 (37.5)	2 (14.3)	0.461	0 (0)	5 (27.8)	0.631	0 (0)	3 (21.4)	0.060
CT	8 (36.4)	2 (25.0)	6 (42.9)		2 (50.0)	6 (33.3)		0 (0)	7 (50.0)	
TT	9 (40.9)	3 (37.5)	6 (42.9)		2 (50.0)	7 (38.9)		4 (100)	4 (28.6)	
FLJ42102 (rs11608138)										
CC	13 (59.1)	5 (62.5)	8 (57.1)	0.584	1 (25.0)	12 (66.7)	0.167	1 (25.0)	9 (64.3)	0.206
CT	9 (40.9)	3 (37.5)	6 (42.9)		3 (75.0)	6 (33.3)		3 (75.0)	5 (35.7)	
FLG (rs2011331)										
CC	4 (18.2)	1 (12.5)	3 (21.4)	0.511	0 (0)	4 (22.2)	0.803	1 (25.0)	3 (21.4)	1.000
TC	8 (36.4)	2 (25.0)	6 (42.9)		2 (50.0)	6 (33.3)		1 (25.0)	6 (42.9)	
TT	10 (45.4)	5 (62.5)	5 (35.7)		2 (50.0)	8 (44.4)		2 (50.0)	5 (35.7)	
GC (rs3755967)										
CC	12 (54.6)	3 (37.5)	9 (64.3)	0.254	3 (75.0)	9 (50.0)	0.783	2 (50.0)	9 (64.3)	1.000
CT	6 (27.3)	4 (50.0)	2 (14.3)		1 (25.0)	5 (27.8)		1 (25.0)	2 (14.3)	
TT	4 (18.2)	1 (12.5)	3 (21.4)		0 (0)	4 (22.2)		1 (25.0)	3 (21.4)	
SULT2A1 (rs4149448)										
AA	14 (63.6)	3 (37.5)	11 (78.6)	0.072	2 (50.0)	12 (66.7)	0.465	3 (75.0)	10 (71.4)	0.701
AG	8 (36.4)	5 (62.5)	3 (21.4)		2 (50.0)	6 (33.3)		1 (25.0)	4 (28.6)	
SEC23A (rs8018720)										
CC	14 (63.6)	5 (62.5)	9 (64.3)	0.584	3 (75.0)	11 (61.1)	0.100	2 (50.0)	10 (71.4)	0.263
CG	7 (31.8)	2 (25.0)	5 (35.7)		0 (0)	7 (38.9)		1 (25.0)	4 (28.6)	
GG	1 (4.6)	1 (12.5)	0 (0)		1 (25.0)	0 (0)		1 (25.0)	0 (0)	
CYP24A1 (rs8121940)										
CC	14 (63.6)	5 (62.5)	9 (64.3)	0.584	2 (50.0)	12 (66.7)	0.652	3 (75.0)	8 (57.1)	0.485
CG	7 (31.8)	2 (25.0)	5 (35.7)		2 (50.0)	5 (27.8)		1 (25.0)	6 (42.9)	
GG	1 (4.6)	1 (12.5)	0 (0)		0 (0)	1 (5.6)				

CKD: Chronic Kidney Disease. SNPs: Single nucleotide Polymorphism. Data expressed as absolute (%) values. Fisher's Exact test. $P < 0.05$ were considered significant values.
[a] $n = 18$.

Table 3
Logistic regression between SULT2A1 rs4149448, frailty and clinical outcomes.

	Frailty		p-Value	Hospitalization		p-Value	CKD progression[a]		p-Value
	OR	IC95%		OR	IC95%		OR	IC95%	
Crude	6.1	0.898–41.598	0.064	2.0	0.224–17.894	0.535	0.8	0.066–10.597	0.888
Model 1	9.4	1.069–83.214	0.043	4.0	0.284–56.016	0.304	1.0	0.028–34.680	0.991
Model 2	8.8	1.048–74.733	0.045	1.5	0.104–21.210	0.772	1.2	0.047–33.200	0.894

CKD: Chronic Kidney Disease. CI: Confidence Interval. OR: *Odds Ratio*. Model 1: adjusted for sex and waist circumference. Model 2: adjusted for sex and cardiovascular disease. Values in bold were considered significant ($p < 0.05$).
[a] n = 18.

relationship may help explain the variability and complexity of frailty and support the development of targeted treatments for non-dialytic CKD patients.

Research ethics board statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Board of the Federal University of Goias (no. 4.918.708). In addition, this study was approved by the Human Research Ethics Committees of the participating hospitals (no 5.053.031 and no 5.112.682).

CRediT authorship contribution statement

Hellen Christina Neves Rodrigues: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alexandre Siqueira Guedes Coelho:** Writing – original draft, Methodology, Formal analysis. **Ana Tereza Vaz de Souza Freitas:** Writing – original draft, Methodology. **Maria do Rosário Gondim Peixoto:** Writing – original draft, Methodology. **Maria Aderuza Horst:**

Writing – review & editing, Methodology, Investigation, Funding acquisition. **Nara Aline Costa:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nara Aline Costa reports financial support was provided by Goias Research Support Foundation - FAPEG. Nara Aline Costa reports a relationship with Goias Research Support Foundation - FAPEG that includes: funding grants. Maria Aderuza Horst reports a relationship with National Council for Scientific and Technological Development that includes: funding grants. Hellen Christina Neves Rodrigues reports a relationship with Coordination of Higher Education Personnel Improvement that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2025.112836.

Data availability

Data will be made available upon request.

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