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Growth Differentiation Factor 15 as a Promising Biomarker for Kidney Transplant Evaluation

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Abstract

While kidney transplantation substantially improves patient outcomes, early post-transplant mortality remains a concern. Growth differentiation factor 15 (GDF-15) has recently been explored as a biomarker for predicting mortality in various clinical contexts. This study investigates whether pretransplant GDF-15 levels can serve as a prognostic indicator in kidney transplant candidates. The analysis included 395 recipients with stored serum samples obtained prior to transplantation. The median GDF-15 level was 5331.3 pg/mL (range: 50.49–16,242.3). Over an average follow-up of 90.6 ± 41.5 months, 82 patients (20.8%) died. Patients in the highest GDF-15 tertile faced approximately double the mortality risk, even after adjusting for clinical variables ($p = 0.009$). When accounting for the Estimated Post Transplant Survival (EPTS) score, elevated GDF-15 remained significantly associated with mortality: medium-risk tertile HR = 3.24 (95% CI: 1.2–8.8; $p = 0.021$) and high-risk tertile HR = 4.3 (95% CI: 1.65–11.54; $p = 0.003$). Addition of GDF-15 to the EPTS score improved predictive accuracy for 1-year ($\Delta AUC = 0.09$, $p = 0.039$) and 3-year mortality ($\Delta AUC = 0.11$, $p = 0.036$). These results suggest that higher pretransplant GDF-15 concentrations independently predict mortality and can enhance the prognostic performance of established risk assessment tools for kidney transplant candidates.

Keywords: Kidney transplant, Mortality prediction; Growth differentiation factor 15, Pretransplant evaluation, Patient survival

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Introduction

Growth differentiation factor 15 (GDF-15) is a stress-responsive cytokine belonging to the transforming growth factor β (TGF-β) superfamily. This multifunctional protein is involved in regulating inflammation, metabolic processes, and oncogenic pathways. Although GDF-15 is minimally expressed under normal physiological conditions, its levels rise in response to tissue injury, ischemia, oxidative stress, and metabolic disturbances, highlighting its potential as a biomarker in various human diseases [1–3].

Elevated circulating GDF-15 has been strongly associated with cardiovascular disorders. In patients with heart failure, GDF-15 provides prognostic information beyond

conventional risk factors, predicting both all-cause and cardiovascular mortality [3, 4]. Higher GDF-15 levels correlate with lower ejection fraction, diastolic dysfunction, and more severe clinical symptoms [5, 6]. Following myocardial infarction, GDF-15 levels rise, not necessarily reflecting the extent of myocardial necrosis, but rather indicating chronic disease burden and poorer outcomes. In this context, elevated GDF-15 has been linked to higher risks of mortality and recurrent infarction, suggesting its potential utility for patient stratification and therapeutic decision-making in acute coronary syndromes [7–9]. Beyond the heart, GDF-15 has been implicated in other vascular conditions, including peripheral artery disease and stroke [10–12].

GDF-15 has also emerged as a potential marker in oncology. Its involvement in angiogenesis, cell proliferation, apoptosis, and tissue remodeling supports its relevance in cancer biology. Elevated GDF-15 expression has been reported across multiple malignancies, including breast, colorectal, prostate, and head and neck cancers [13–16].

In nephrology, higher GDF-15 concentrations have been associated with an increased risk of chronic kidney disease (CKD) onset and faster progression of renal dysfunction across diverse conditions, such as diabetic nephropathy, IgA nephropathy, and primary membranous nephropathy [17–20]. Recent studies have evaluated GDF-15 as a prognostic biomarker in CKD populations, demonstrating that elevated levels predict mortality and cardiovascular events across all CKD stages, including in patients on hemodialysis [21–26]. While GDF-15 generally decreases after kidney transplantation—reflecting reduced cardiovascular risk—its levels remain linked to anemia and the severity of ischemia-reperfusion injury in transplant recipients [27–31].

Cardiovascular disease remains the leading cause of death among kidney transplant recipients, followed by infections and malignancies [32, 33]. The risk of major adverse cardiac events (MACE) is particularly high in the early post-transplant period, although it subsequently declines compared to dialysis patients [34, 35]. Nevertheless, cardiovascular morbidity and mortality continue to pose significant challenges, emphasizing the need for accurate pretransplant cardiovascular assessment [36, 37]. Current evaluation methods often lack sufficient predictive power to prevent adverse events effectively [38–40]. Consequently, there is a clear need for non-invasive, reliable biomarkers to improve risk stratification, reduce reliance on aggressive procedures, and guide pretransplant clinical decision-making. Given GDF-15's associations with the pathophysiological conditions prevalent in transplant candidates, it represents a promising biomarker for pretransplant evaluation. Therefore, this study aims to identify factors influencing GDF-15 levels in patients with advanced CKD and to assess its potential utility as a predictor of post-transplant survival.

Experimental Section

This study included all adult kidney transplant procedures performed at our institution between 2005 and 2015. As part of standard practice since 1985, pretransplant serum samples have been routinely collected and stored at low temperatures. Only samples with at least 150 µL remaining for GDF-15 measurement were eligible for inclusion. The study protocol complied with the Declaration of Helsinki and received approval from the hospital Ethics Committee.

GDF-15 concentrations were measured using a commercially available enzyme-linked immunosorbent assay (Quantikine, R&D Systems, Minneapolis, MN, USA). Samples with high GDF-15 values were diluted to allow accurate quantification, and each sample was analyzed in duplicate to ensure measurement reliability. For statistical purposes, GDF-15 was evaluated as a continuous variable after logarithmic transformation due to non-normal distribution, and as a categorical variable by dividing patients into tertiles.

Demographic and clinical information for recipients, donors, and transplant procedures was retrieved from a prospectively maintained renal transplant database. Collected variables included age, sex, race, primary cause of CKD, dialysis history, number of prior transplants, and history of other solid organ transplants. Cardiovascular comorbidities included documented coronary artery disease confirmed by imaging and clinically significant peripheral artery disease requiring intervention. Pretransplant diabetes was defined as requiring pharmacologic treatment.

For first-time transplant recipients, the Estimated Post Transplant Survival (EPTS) score was calculated using age, dialysis duration, diabetes status, and prior transplant history, following the official OPTN online calculator (https://optn.transplant.hrsa.gov/resources/allocation-calculators/epts-calculator/).

Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR) for skewed distributions. Categorical variables were presented as frequencies and percentages. Logistic regression, both univariate and multivariate, was used to identify clinical factors associated with higher GDF-15 levels.

The main outcome was all-cause mortality. Associations between GDF-15 (log-transformed and tertile-based) and survival were evaluated using Cox proportional hazards models. Covariates for adjustment were selected based on prior literature. Variables significant in univariate analyses were included in multivariate models, and results were

reported as hazard ratios (HR) with 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$. Predictive performance of GDF-15, EPTS, and their combination was assessed using receiver operating characteristic (ROC) curves and area under the curve (AUC) for mortality at 1, 3, and 5 years post-transplant. All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) and MedCalc® version 19.6 (MedCalc Software Ltd., Ostend, Belgium).

Results and Discussion

Between January 2005 and December 2015, a total of 450 kidney transplants were performed at our center. Of these, 395 patients had pretransplant serum samples available and were included in the analysis. For hemodialysis patients, samples were obtained after a short dialysis vintage, whereas for peritoneal dialysis and preemptive transplant candidates, samples were collected immediately prior to transplantation. Baseline characteristics of the cohort are summarized in **Table 1**.

Among the study population, 31 patients (7.8%) had received prior non-renal transplants, including liver (n = 5), heart (n = 8), lung (n = 4), and pancreas (n = 14). A majority of patients (n = 264; 66.8%) were receiving their first kidney transplant, while 131 patients underwent retransplantation. The overall duration of renal replacement therapy, encompassing both dialysis and previous transplants, was 1.76 years (IQR 0.56–5.06).

Regarding sensitization status, 319 recipients (80.8%) were unsensitized, with a virtual panel-reactive antibody (PRA) of 0%. Among the 76 sensitized patients, the median peak PRA was 65% (IQR 36.7–93.3). Immunosuppressive therapy predominantly included calcineurin inhibitors (91.4%), mTOR inhibitors (4.6%), mycophenolate or azathioprine (93.9%), and prednisone (93.4%). Induction therapy was not administered in 275 patients (69.6%), while 18 patients (4.6%) received basiliximab and 100 patients (25.4%) received thymoglobulin.

Concerning donor characteristics, most patients (94.2%) received kidneys from deceased donors, with the majority from brain-death donors (92.4%) and a smaller proportion from cardiac-death donors (1.8%). Living donor transplants accounted for 5.8% of the cohort.

Table 1. Baseline characteristics

Number of patients	395
Donor age (years)	57.1 (47.6–66.6)
Cold Ischemia Time (min)	19 (15–23)
Recipient age (years)	52 ± 12.4
Recipient sex (%)	68.1 males/31.9 females
Recipient race (% Caucasian)	96.5
Diabetes (%)	23
Type I	7.8
Type II	15.2
Coronary artery disease (%)	10.4
Peripheral vascular disease (%)	8.6
Non renal solid organ transplant (%)	7.8
Primary renal diagnosis	
Glomerular (%)	27.4
Diabetes (%)	14.7
Hypertension/vascular (%)	24.2
Polycystic kidney disease (%)	12.4
Other (%)	15.7
Unknown (%)	5.6
Preemptive transplant (%)	15.9
Time of renal replacement therapy (years)	1.76 (0–5.1)
Retransplant (%)	33.2
GDF-15 (pg/mL)	5331.3 (4071.8–6819.9)
Hemoglobin (g/dL)	11.9 (10.8–13)
Serum albumin (g/dL)	4 (3.8–4.3)
Creatinine (mg/dL)	6.4 (4.9–8.3)
Uric acid (mg/dL)	6.3 (5.2–7.8)
C-reactive protein (mg/L)	0.5 (0.2–1.1)
Phosphorus (md/dL)	5.1 (4.0–6.1)
Parathyroid hormone (pg/mL)	290 (149–495)

Among the 395 kidney transplant recipients included in this study, the median pretransplant GDF-15 concentration was 5331.3 pg/mL (IQR 4071.8–6819.9), with only six patients (1.5%) exhibiting values within the normal range for healthy adults (≤2000 pg/mL) [1, 15]. For analysis, participants were divided into tertiles: low (<4612.1 pg/mL), medium (4612.1–6296.5 pg/mL), and high (>6296.5 pg/mL) GDF-15 levels.

In univariate logistic regression, higher GDF-15 concentrations (>4612.1 pg/mL) were associated with older age (OR 1.04, 95% CI 1.02–1.06, $p < 0.001$), presence of coronary artery disease (OR 2.66, 95% CI 1.14–6.16, $p = 0.02$), peripheral artery disease (OR 2.51, 95% CI 1.01–6.2, $p = 0.048$), and longer duration of renal replacement therapy (OR 1.04, 95% CI 1.01–1.10, $p = 0.02$). No significant relationship was found with sex, race, diabetes, underlying renal disease, hemoglobin, albumin, creatinine, uric acid, C-reactive protein, phosphorus, parathyroid hormone, preemptive transplant status, dialysis modality, or history of non-renal solid organ transplants. In multivariate analysis, only age (OR 1.04, 95% CI 1.02–1.06, $p < 0.001$) and renal replacement therapy duration (OR 1.04, 95% CI 1.01–1.07, $p = 0.02$) remained independently associated with elevated GDF-15.

During a mean follow-up of 90.6 ± 41.5 months, 82 patients (20.8%) died. Higher GDF-15 levels were significantly linked to increased mortality in univariate Cox regression (log-transformed GDF-15: HR 3.88, 95% CI 1.18–12.78, $p = 0.026$). Mortality risk increased progressively across tertiles, with medium (HR 2.16, 95% CI 1.14–4.44, $p = 0.018$) and high-risk groups (HR 3.28,

95% CI 1.79–6.10, p < 0.001) showing worse survival compared to the low tertile **(Figure 1)**.

Other factors significantly associated with post-transplant mortality included older age (HR 1.07, 95% CI 1.04–1.09, p < 0.001), diabetes (HR 2.34, 95% CI 1.49–3.67, p < 0.001), coronary artery disease (HR 2.99, 95% CI 1.75–5.13, p < 0.001), peripheral arterial disease (HR 2.24, 95% CI 1.24–4.06, p = 0.008), prior non-renal solid organ transplantation (HR 1.97, 95% CI 1.02–3.84, p = 0.044), and renal graft loss (HR 1.61, 95% CI 1.03–2.53, p = 0.038). Variables not significantly associated with survival included sex, race, dialysis modality, pretransplant lab parameters (albumin, creatinine, uric acid, CRP, phosphorus, parathyroid hormone, hemoglobin), PRA, donor type, induction therapy, and immunosuppressive regimen.

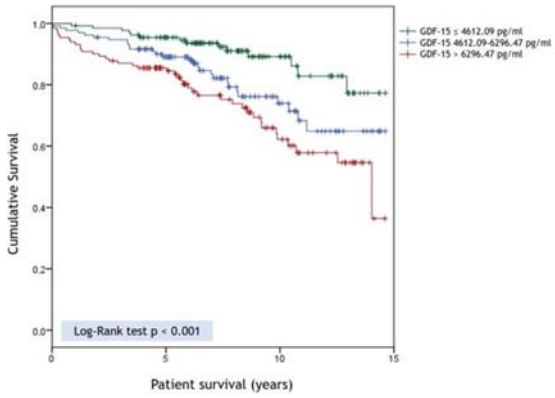

Figure 1. Kaplan–Meier survival estimates stratified by GDF-15 tertiles

In multivariate Cox regression, the association between elevated GDF-15 and mortality remained significant for the high-risk tertile (HR 2.29, 95% CI 1.24–4.24, p = 0.009), after adjusting for age (HR 1.07, 95% CI 1.04–1.09, p < 0.001), history of coronary artery disease (HR 2.20, 95% CI 1.26–3.82, p = 0.005), censored graft loss (HR 1.95, 95% CI 1.23–3.09, p = 0.005), and previous non-renal solid organ transplants (HR 2.64, 95% CI 1.32–5.28, p = 0.006). A summary of variables associated with mortality in both univariate and multivariate analyses is provided in **Table 2**.

Table 2. Variables associated with mortality in univariate and multivariate Cox regression analysis

	Univariate		Multivariate			
	HR (CI)	***p*-Value**	**HR (CI) Model 1**	***p*-Value**	**HR (CI) Model 2**	***p*-Value**
Age (per year)	1.07 (1.04–1.09)	<0.001	1.07 (1.04–1.09)	<0.001		
Diabetes	2.34 (1.49–3.67)	<0.001		ns		
Coronary artery disease	2.99 (1.75–5.13)	<0.001	2.2 (1.26–3.82)	0.005		
Peripheral arteriopathy	2.24 (1.24–4.06)	0.008		ns		
Other solid transplants	1.97 (1.02–3.84)	0.044	2.64 (1.32–5.28)	0.006		
Graft loss censored by death	1.61 (1.03–2.53)	0.038	1.95 (1.23–3.09)	0.005		
GDF-15 medium risk tertile	2.16 (1.14–1.44)	0.018		ns	3.24 (1.2–8.8)	0.021
GDF-15 high risk tertile	3.28 (1.79–6.1)	0.001	2.29 (1.24–4.24)	0.009	4.3 (1.65–11.54)	0.003
EPTS	1.03 (1.02–1.04)	<0.001			1.02 (1.01–1.03)	<0.001

Model 1 included: Age, diabetes, coronary artery disease, peripheral arteriopathy, graft loss censored by death, and GDF-15 tertiles (growth differentiation factor 15). Model 2 included: Estimated Post Transplant Survival (EPTS) score and GDF-15 tertiles. HR: hazards ratios; CI: confidence interval.

For all first-time kidney transplant recipients in the cohort (n = 264), the median EPTS score was 31% (IQR 11.5–50.5). Incorporating the EPTS score into multivariate analyses did not diminish the prognostic significance of GDF-15. Elevated GDF-15 levels remained independently associated with mortality, whether considered as a continuous variable (logGDF-15 HR 9.46, 95% CI 1.78–40.41, p = 0.008) or stratified into tertiles (medium-risk tertile HR 3.24, 95% CI 1.2–8.8, p = 0.021; high-risk tertile HR 4.3, 95% CI 1.65–11.54, p = 0.003).

Observed mortality rates among first-time recipients were 3% (n = 8) at 1 year, 5.7% (n = 15) at 3 years, and 7.2% (n = 19) at 5 years. In multivariate logistic regression models, both EPTS and the high-risk GDF-15 tertile were significantly associated with death within 1 and 3 years post-transplant, while only the EPTS score predicted mortality at 5 years. ROC curve analyses further demonstrated that combining GDF-15 tertiles with EPTS enhanced the accuracy of mortality prediction at 1 and 3 years **(Figure 2)**.

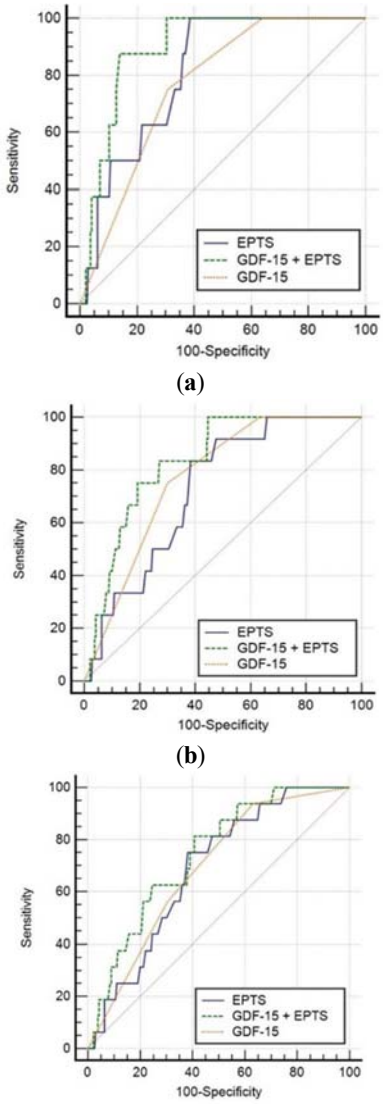

Figure 2. ROC curves illustrating predicted mortality probabilities using logistic regression models with EPTS, GDF-15 tertiles, and the combination of both. (a) 1-year mortality: AUC EPTS = 0.81 (CI95% 0.67–0.89) vs. EPTS + GDF-15 = 0.90 (CI95% 0.81–0.94), ΔAUC = 0.09, p = 0.039; EPTS vs. GDF-15 alone = 0.766 (CI95% 0.71–0.81), ΔAUC = 0.04, p = 0.55. (b) 3-year mortality: AUC EPTS = 0.73 (CI95% 0.59–0.82) vs. EPTS + GDF-15 = 0.83 (CI95% 0.71–0.90), ΔAUC = 0.11, p = 0.036; EPTS vs. GDF-15 = 0.77 (CI95% 0.71–0.82), ΔAUC = 0.04, p = 0.56. (c) 5-year mortality: AUC EPTS = 0.69 (CI95% 0.56–0.78) vs. EPTS + GDF-15 = 0.74 (CI95% 0.61–0.83), ΔAUC = 0.06, p = 0.22; EPTS vs. GDF-15 = 0.69 (CI95% 0.62–0.74), ΔAUC = 0.002, p = 0.98. EPTS: estimated post-transplant survival; GDF-15: growth differentiation factor 15

Assessment of mortality causes indicated that cardiovascular events accounted for 35.4% of deaths (n = 29), whereas malignancy and related treatment complications represented 22.0% (n = 18). Univariate Cox regression demonstrated a strong association between higher GDF-15 levels and cardiovascular mortality: medium-risk tertile HR = 5.95 (CI95% 1.32–26.88), p = 0.02; high-risk tertile HR = 7.91 (CI95% 1.78–35.10), p = 0.006. This association remained significant after adjustment for age, coronary artery disease, diabetes, and censored graft loss, with the highest tertile showing HR = 5.55 (CI95% 1.24–24.7), p = 0.025. In contrast, no statistically significant correlation was observed between GDF-15 and cancer-related mortality (high-risk tertile HR = 0.54, CI95% 0.16–1.76, p = 0.32).

Risk stratification for mortality following kidney transplantation remains complex [36]. In this retrospective cohort of 395 renal transplant recipients, pre-transplant GDF-15 levels were independently associated with post-transplant mortality. This relationship persisted after controlling for clinical and laboratory factors previously linked to adverse outcomes [41–44]. Participants in the highest GDF-15 tertile experienced more than double the mortality risk. Additionally, combining GDF-15 with the EPTS score enhanced early post-transplant mortality prediction, highlighting its potential as a useful biomarker in evaluating transplant candidates and optimizing organ allocation, especially during the first critical post-transplant years.

Although prior research has evaluated GDF-15 in general populations and in CKD patients [1], this study is the first, to our knowledge, to investigate its prognostic value specifically in kidney transplant candidates. Previous studies in CKD and hemodialysis populations reported that elevated GDF-15 was associated with increased mortality, particularly in the early post-transplant period [24, 25, 45]. Similarly, our findings indicate that GDF-15 improves early post-transplant mortality prediction. Recent reports also suggest a substantial decrease in GDF-15 after kidney transplantation, which correlates with improved renal function and reduced myocardial stress as indicated by NT-proBNP levels [27, 29].

Our analysis of cause-specific mortality confirmed the strong relationship of GDF-15 with cardiovascular death, the leading cause of mortality among kidney transplant recipients [32, 33]. In contrast, no significant association was observed for cancer-related mortality, possibly due to the limited number of malignancy-related deaths or the predominant influence of cardiovascular burden on GDF-15 levels in this population.

In healthy individuals, GDF-15 increases with aging (the primary determinant in most studies) and with smoking, whereas its relationship with BMI appears variable [1]. In CKD cohorts, higher levels have been linked with female sex, older age, active smoking, and diabetes [24]. In our study, elevated GDF-15 was associated with older age and

longer renal replacement therapy duration, but not with other clinical or laboratory parameters, including sex or diabetes. These observations are consistent with prior dialysis studies, highlighting the influence of cumulative renal history and nutritional status on GDF-15, which in turn may contribute to cardiovascular events and mortality [25, 26]. Notably, our study did not find an independent association between GDF-15 and dialysis modality, contrasting with prior findings [29], suggesting further research is warranted to clarify this aspect.

In addition, several questions regarding the pathophysiological role of GDF-15 remain unresolved. As previously noted, this protein is minimally expressed in healthy tissues and is upregulated in response to diverse forms of cellular injury. However, the precise source of GDF-15 production in patients with chronic kidney disease (CKD) is not well defined, as most prior studies have focused on its utility as a biomarker rather than as a mediator of biological responses. Nair *et al.* [19] reported GDF-15 expression in renal tissue, correlating with circulating levels and associating with a higher risk of CKD progression. In our cohort, GDF-15 did not correlate with renal history, including primary kidney disease, preemptive transplant status, or modality of renal replacement therapy (RRT). Given that all participants had advanced CKD, it is plausible that variations in GDF-15 levels may originate from other tissues, such as the myocardium or vascular system. Therefore, further investigations are necessary to delineate the molecular pathways involving GDF-15 and determine whether it functions solely as a prognostic marker or also plays a causal role in mortality. Clarifying this distinction is essential for translating these findings into clinical practice.

Numerous markers of post-transplant mortality have been studied to date, yet their practical utility remains uncertain [37]. Considering the potential benefits of risk stratification in this high-risk population, advances in this field are crucial for improving transplantation outcomes. Imaging modalities, including echocardiography and cardiac CT scans, are commonly employed pre-transplant, although their effectiveness in reducing cardiovascular morbidity and mortality post-transplant has not been conclusively demonstrated [36, 46]. Combining laboratory biomarkers with imaging may enhance prognostic accuracy, enable more targeted use of imaging studies, and provide objective metrics less prone to observer variability. Among laboratory biomarkers, candidates such as cardiac troponin and soluble ST2 have shown promise, though their incremental value over established clinical risk models remains to be demonstrated [47–50]. In our study, GDF-15 fulfilled this role, likely due to its pleiotropic effects on multiple pathogenic pathways relevant to kidney transplant candidates. Additionally, a recently developed fully automated electrochemiluminescence immunoassay for GDF-15 has demonstrated robust performance under clinical conditions, potentially facilitating widespread, cost-effective measurement [51].

The strengths of this study include several factors: first, a relatively large cohort with standardized sample collection and GDF-15 analysis performed in a single laboratory; second, use of a prospectively maintained renal transplant database with a minimum five-year follow-up and no patient loss during the study; and third, demonstration that GDF-15 enhances the prognostic utility of the widely validated EPTS score for kidney transplant candidates.

Several limitations must also be acknowledged. Our cohort was relatively homogenous, predominantly Caucasian, with grafts primarily from donors after brain death, which limits generalizability. Additionally, we could not compare GDF-15 with imaging or anthropometric measures (e.g., echocardiography, intima-media thickness, ankle–brachial index, pulse wave velocity) as these are not routinely performed in all transplant candidates at our center. Finally, GDF-15 was measured only once per patient, precluding assessment of post-transplant changes in biomarker levels and the prognostic significance of such dynamics.

In conclusion, our findings support an independent association between elevated pre-transplant GDF-15 levels and post-transplant mortality, while also enhancing the predictive accuracy of the EPTS score, a validated risk assessment tool currently used in kidney transplant candidates. As an emerging biomarker, further research is warranted to validate these results, elucidate the mechanisms underlying GDF-15 regulation, and explore potential therapeutic implications, ultimately aiming to improve outcomes in this population.

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