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ORIGINAL ARTICLE

Elevated leucine-rich alpha-2 glycoprotein levels and mortality risk in end-stage renal disease: evidence for gender differences

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ABSTRACT

Background. Leucine-rich α-2 glycoprotein (LRG) is an inflammation-related serum protein implicated in cardiovascular pathology. Its prognostic role in patients with end-stage renal disease (ESRD) remains unclear. We investigated the association between serum LRG levels and all-cause mortality in maintenance haemodialysis patients, with a focus on sex-specific effects.

Methods. In this prospective cohort study, 313 stable haemodialysis patients (206 males, 107 females) were enrolled and followed for 5 years. Baseline serum LRG concentrations were quantified by ELISA. Receiver operating characteristic (ROC) analysis identified an optimal mortality risk cut-off (45.5 μg/ml). Survival analyses used Kaplan–Meier curves and multivariable Cox regression models adjusted for demographic, clinical, and laboratory covariates. Analyses were stratified by sex.

Results. During follow-up, 103 deaths occurred (78 males, 25 females). Higher LRG levels were significantly associated with increased mortality risk in males (log-rank $P < .001$), but not females ($P = .17$). In adjusted Cox models, male patients with LRG >45.5 μg/ml had a ∼2-fold higher mortality risk [hazard ratio (HR) = 2.07; 95% confidence interval (CI) 1.32–3.23] compared to those below the cut-off. The association remained robust after further adjustment for C-reactive protein, albumin, dialysis vintage, and comorbidities. No significant association was observed in females (HR = 1.24; 95% CI = 0.65–2.34). ROC analysis yielded an AUC of 0.604 for LRG in predicting mortality.

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Conclusions. Elevated serum LRG independently predicts all-cause mortality in male, but not female, haemodialysis patients. These findings highlight the potential of LRG as a sex-specific biomarker for risk stratification in ESRD and underscore the need for mechanistic studies on sex differences in LRG-related pathways.

Keywords: all-cause mortality, end-stage renal disease, gender-specific analysis, haemodialysis, serum LRG

KEY LEARNING POINTS

What was known:

- Leucine-rich α-2 glycoprotein (LRG) is an inflammation-related circulating protein implicated in cardiovascular pathology and fibrotic remodelling (e.g. via TGF-β–related pathways), and is elevated in several chronic inflammatory diseases.
- Patients with ESRD on maintenance haemodialysis have very high mortality risk, and existing clinical risk markers do not fully capture the underlying cardio-inflammatory/fibrotic burden driving outcomes.
- Before our study, the prognostic value of serum LRG for mortality in haemodialysis patients—especially with sex-stratified analyses—was insufficiently defined, creating a need for prospective evidence.

This study adds:

- In a 5-year prospective cohort of 313 stable haemodialysis patients, higher baseline LRG was associated with increased all-cause mortality, with an ROC-derived cut-off of 45.5 μg/ml (AUC ≈ 0.60).
- Sex-specific finding: Elevated LRG predicted mortality in men (≈2-fold higher risk above the cut-off in adjusted models), but not in women, highlighting meaningful gender differences in LRG-related prognostication.
- LRG showed a moderate correlation with CRP and remained prognostic after multivariable adjustment, suggesting LRG captures risk information beyond routine inflammation/nutrition markers in male ESRD patients.

Potential impact:

- Measuring LRG could help improve risk stratification in male haemodialysis patients, complementing established clinical and laboratory markers to identify individuals who may benefit from closer surveillance or intensified management.
- The clear sex difference supports sex-stratified interpretation of biomarkers in ESRD and may influence future guideline discussions towards more personalized risk assessment.
- Findings motivate follow-up studies to validate thresholds, test longitudinal LRG monitoring, and clarify mechanisms, potentially informing targeted strategies addressing cardio-inflammatory/fibrotic pathways in ESRD.

INTRODUCTION

Leucine-rich alpha-2 glycoprotein 1 (LRG) is a multifunctional matricellular protein increasingly recognized for its role in inflammation, fibrosis, and cardiovascular disease. Initially characterized as an acute-phase reactant, LRG has been implicated in several pathological conditions, including cancer, autoimmune diseases, and organ fibrosis. In the kidney, LRG expression is notably upregulated under inflammatory and fibrotic conditions, suggesting a role in the pathogenesis of chronic kidney disease (CKD), particularly in diabetic nephropathy and glomerular injury [1, 2].

Recent studies have identified LRG as a potential modulator of transforming growth factor beta (TGF-β) signalling, a key pathway in tissue fibrosis. By binding to specific integrins and influencing downstream SMAD signalling, LRG facilitates extracellular matrix (ECM) remodelling and fibrogenesis, particularly in renal and cardiac tissues. This makes LRG1 not only a biomarker of inflammation and tissue injury, but also a potential therapeutic target [3–5].

In patients with end-stage renal disease (ESRD) undergoing maintenance haemodialysis, cardiovascular complications remain the leading cause of morbidity and mortality. Traditional risk factors do not fully explain the high mortality rates observed in this population, prompting the search for novel biomarkers that reflect underlying pathophysiological processes. Given LRG1's involvement in inflammation, endothelial dysfunction, and myocardial fibrosis, it may serve as a mechanistic link between renal dysfunction and cardiovascular outcomes in ESRD. Importantly, emerging evidence suggests that LRG1 expression and its downstream effects may vary by sex. Hormonal regulation of TGF-β and associated fibrotic pathways could explain observed sex-specific differences in cardiovascular risk and survival in ESRD populations. However, the prognostic value of LRG1, especially in a sex-stratified context, remains poorly defined [6–10].

In this prospective cohort study, we aimed to investigate whether baseline serum LRG1 levels are associated with all-cause mortality in a large population of patients undergoing haemodialysis. We further explored potential sex-specific differences in this association because sex-specific effects of LRG1 were described in previous studies.

MATERIALS AND METHODS

Research population

In this prospective cohort study, we enrolled 313 clinically stable patients (206 males and 107 females) with ESRD undergoing maintenance haemodialysis at outpatient dialysis centres across Berlin, Germany. We required all patients to have established ESRD (defined by the need for long-term renal replacement therapy) and stable haemodialysis regimens for ≥3 months before enrollment. We followed patients for 5 years to

assess all-cause mortality. All participants received standard bicarbonate dialysis three times weekly (4–5 hours/session), using biocompatible membranes, a dialysate flow rate of 500 ml/min, and a blood flow rate of 250–300 ml/min. We included only clinically stable patients without recent hospitalizations or acute medical events. We obtained written informed consent from each participant. The local ethics committee approved the study protocol (approval no. S-20090061), and we conducted the study in accordance with the Declaration of Helsinki.

Data collection

We collected baseline demographic and clinical data at study entry, including age, sex, height, weight, primary renal disease, dialysis vintage, blood pressure, comorbidities (e.g. diabetes mellitus, coronary heart disease, hypertension), and current medications (specifically noting use of angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, and erythropoietin). Before the midweek haemodialysis session, we drew venous blood samples and analysed them for laboratory parameters such as serum albumin, cholesterol, triglycerides, urea, creatinine, calcium, potassium, phosphate, and C-reactive protein, using standard clinical laboratory methods.

Measurement of serum LRG

We measured serum LRG levels using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit (cat. no. BI-LRG, Biomedica, Austria). We performed the assay strictly according to the manufacturer's protocol. In brief, we thawed serum samples on ice and pre-diluted them 1:4000 as recommended. We prepared standards as instructed and generated a standard curve by plotting known concentrations against their optical density readings. We added each sample and standard in duplicate to a 96-well microtitre plate precoated with a polyclonal capture antibody specific to human LRG. After an initial incubation period at room temperature, we removed unbound components by multiple washing steps. We then added an HRPO-labelled detection antibody specific to human LRG to the wells. After another incubation and washing step, we added tetramethylbenzidine substrate solution and allowed it to react, producing a colorimetric change proportional to the amount of captured LRG. We terminated the reaction by adding stop solution and measured absorbance at 450 nm with a reference wavelength of 630 nm using a microplate reader.

The assay's detection limit was 0.26 ng/ml. We observed mean intra- and inter-assay coefficients of variation of 3.0% and 6.0%, respectively, indicating good assay precision [11]. We provide detailed reagent volumes, incubation times, and washing conditions in Supplementary Table 1. We performed data analysis, including standard curve construction and sample concentration calculations, using a four-parameter logistic regression model, as the kit manufacturer recommended.

Data analysis

We expressed continuous variables as medians with interquartile range and presented categorical variables as frequency (percentage). Using the Shapiro–Wilk test, we assessed normality, which indicated the data were non-normally distributed ($P < .001$). Consequently, for group comparisons, we used nonparametric tests: the Mann–Whitney *U*-test for continuous variables and the χ^2 test for categorical variables. To determine the optimal LRG cut-off value for predicting all-cause mortality, we performed receiver operating characteristic (ROC) analysis.

We compared survival distributions according to LRG levels using Kaplan–Meier curves and log-rank tests. Patients were followed from baseline until death, kidney transplantation, loss to follow-up, or the end of the observation period, whichever occurred first; deaths were treated as events, whereas kidney transplantation and loss to follow-up were treated as censoring events at the corresponding dates. Univariable Cox proportional hazards regression analyses were first performed to identify variables associated with all-cause mortality. Variables that were significant in univariable analyses or deemed clinically relevant were then entered into multivariable Cox models. To illustrate the impact of progressive adjustment for potential confounders, we specified three hierarchical models, and all multivariable models were additionally adjusted for age and sex. Model A included comorbidities and medications [diabetes mellitus, hypertension, coronary heart disease (CHD), history of malignancy, and use of renin–angiotensin–aldosterone system (RAAS) inhibitors, beta-blockers, calcium channel blockers, and erythropoietin]. Model B included dialysis- and laboratory-related covariates [dialysis vintage, dialysis dose, transferrin, haemoglobin, C-reactive protein, serum albumin, leukocyte and platelet counts, intact parathyroid hormone (iPTH), LRG, and serum creatinine]. Model C combined all covariates from Models A and B. Results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). To control for multiple comparisons, we applied false discovery rate adjustments. Missing baseline data were handled using complete-case analysis without imputation, and the sample size in each model corresponds to patients with complete data for the variables included. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA), and two-sided *P* values <.05 were considered statistically significant.

RESULTS

Patient cohort and baseline characteristics

Baseline characteristics of the study population are summarized in Table 1. A total of 313 patients on maintenance haemodialysis (183 men, 130 women) were included, with a median age of 62.0 years (IQR 54.0–70.0) and median dialysis vintage of 3.4 years (IQR 1.8–6.1). Men were significantly more likely than women to have diabetes (36% vs. 24%, $P = .007$) and to be current smokers (28% vs. 15%, $P = .004$). Inflammatory burden differed by sex, with higher hsCRP levels in men [3.1 (1.2–5.8) vs. 1.4 (0.7–3.15) mg/l, $P < .001$]. Serum creatinine was also higher in men than in women [6.90 (4.56–8.71) vs. 5.74 (3.76–7.46) mg/dl, $P = .004$], which probably reflects differences in muscle mass rather than true differences in residual renal function; detailed data on urine output were not available. Conversely, women had higher lipid levels, with total cholesterol 185 vs. 172 mg/dl ($P = .020$) and high-density lipoprotein (HDL) 52 vs. 44 mg/dl ($P < .001$). There were no sex differences in 5-year survival (67.5% vs. 69.2%, $P = .633$).

Association between LRG, hsCRP, and diabetes

In our cohort, hsCRP levels were significantly higher in men than in women [median (IQR) 3.1 (1.2–5.8) vs. 1.4 (0.7–3.15) mg/l; $P < .001$). Serum LRG showed a moderate positive correlation with hsCRP (Spearman $r = 0.53$; $P < .001$), consistent with its role

Table 1: Baseline characteristics of all study indicators.

	All ($N = 313$)	Male ($N = 206$)	Female ($N = 107$)	P value
Age, y	66.00 (56.00–75.00)	66.00 (56.00–74.00)	67.00 (57.00–76.00)	.617
Primary kidney diseases, *n* (%)				.722
Hypertensive nephropathy	107 (34.19%)	76 (36.89%)	31 (28.97%)	.182
Diabetic nephropathy	97 (30.99%)	57 (27.67%)	40 (37.38%)	.078
Glomerulonephritis	25 (7.99%)	13 (6.31%)	12 (11.21%)	.130
Polycystic kidney disease	9 (2.88%)	7 (3.40%)	2 (1.87%)	.443
Other or unknown cause	75 (23.96%)	53 (25.73%)	22(20.56%)	.310
Diabetes mellitus, %	117 (37.38%)	66 (32.04%)	51 (47.66%)	.007**
Hypertension, %	246 (78.59%)	160 (77.67%)	86 (80.37%)	.581
CHD, %	148 (47.28%)	99 (48.06%)	49 (45.79%)	.704
Tumour, %	70 (22.4%)	45 (21.8%)	25(23.4%)	.760
Smoker, %	97 (30.99%)	75 (36.41%)	22 (20.56%)	.004**
Alcohol, %	56 (17.9%)	49 (23.8%)	7 (6.5%)	.001**
Medication, %				
RAAS inhibitors	82 (26.20%)	54 (26.21%)	28 (26.17%)	.993
Beta-blockers	186 (59.42%)	116 (56.31%)	70 (65.42%)	.120
Calcium channel blockers	98 (31.31%)	65 (31.55%)	33 (30.84%)	.897
Erythropoietin	158 (50.48%)	104 (50.49%)	54 (50.46%)	.998
Body mass index, kg/m^2	24.53 (22.01–27.55)	24.91 (22.25–27.35)	24.12 (21.60–28.51)	.306
Dialysis vintage, days	243 (31–1172)	271 (31–1347)	227 (31–919)	.180
Dialysis dose, Kt/V	1.19 (1.07–1.33)	1.16 (1.06–1.31)	1.24 (1.11–1.44)	.017*
Ferritin ng/ml	516.50 (243.50–1074.00)	513.00 (239.00–1150.50)	520.00 (243.00–914.00)	.762
Transferrin mg/dl	138.00 (107.00–173.00)	138.00 (104.00–172.00)	142.00 (116.25–177.00)	.286
Haemoglobin, g/dl	10.20 (9.05–11.45)	10.10 (9.00–11.20)	10.20 (9.15–11.60)	.593
Serum albumin, g/dl	3.30 (2.90–3.70)	3.30 (2.90–3.70)	3.20 (2.80–3.60)	.565
Total cholesterol, mg/dl	150.60 (127.40–187.00)	146.70 (119.70–182.25)	166.00 (134.15–204.00)	.020*
Triglycerides, mg/dl	159.30 (109.50–247.80)	159.30 (106.20–247.80)	162.80 (112.40–247.80)	.708
LDL, mg/dl	92.70 (72.35–120.08)	92.70 (70.40–114.23)	103.00 (75.78–128.60)	.101
HDL, mg/dl	39.80 (32.00–50.20)	36.45 (30.90–46.32)	43.80 (36.43–56.68)	<.001***
iPTH, ng/l	50.18 (18.96–129.60)	47.71 (18.96–131.88)	52.79 (18.85–127.40)	.769
Periostin, pmol/l	835.00 (591.5–1149.5)	822.5(588.00–1147.75)	873.00 (600.00–1164.00)	.781
Leukocytes 10^9/l	8.04 (5.98–10.26)	8.11 (6.27–10.28)	7.92 (5.54–10.45)	.274
Thrombocytes 10^9/l	223.00 (174.00–283)	224.00 (170.25–275.00)	223.00 (181.00–304.00)	.336
C-reactive protein, mg/l	2.60 (1.00–5.00)	3.10 (1.15–5.95)	1.40 (0.67–3.33)	<.001***
Blood urea nitrogen, mg/dl	195.52 (147.31–268.57)	205.09 (145.94–279.53)	183.18 (150.67–242.39)	.110
Serum creatinine, mg/dl	6.66 (4.25–8.39)	6.90 (4.56–8.71)	5.74 (3.76–7.46)	.004**
Serum potassium, mmol/l	4.70 (4.10–5.26)	4.80 (4.10–5.30)	4.60 (4.00–5.20)	.186
Serum calcium, mmol/l	2.22 (2.09–2.40)	2.25 (2.08–2.40)	2.20 (2.10–2.44)	.774
Serum phosphorus, mg/dl	1.61 (1.20–2.10)	1.63 (1.21–2.10)	1.59 (1.17–2.01)	.485
LRG, μg/ml	56.00 (45.00–69.00)	57.50 (45.00–70.00)	55.00 (44.00–64.00)	.459
Death, %	157 (50.16%)	102 (49.51%)	55 (51.40%)	.633

Data shown as median (interquartile range) or frequency (%). Comparisons: Mann–Whitney U-test (continuous), χ^2 test (categorical).
Abbreviation: LDL, low-density lipoprotein.
Significance markers: *$P < .05$, **$P < .01$, ***$P < .001$.

as an acute-phase protein. LRG levels were only slightly higher in patients with diabetes mellitus than in those without diabetes [median (IQR) 56 (48–70) vs. 56 (44–67) μg/ml; $P = .48$], indicating no clear association between LRG and diabetes status.

Association between LRG and cardiovascular comorbidities

We next explored whether serum LRG levels were associated with baseline cardiovascular comorbidities. LRG levels were similar in patients with and without CHD [median (IQR) 56 (47–66) vs. 56 (42–70) μg/ml; $P = .83$]. Patients with peripheral arterial disease (PAD) tended to have higher LRG levels than those without PAD [61 (47–75) vs. 56 (45–67) μg/ml], although this difference did not reach statistical significance ($P = 0.13$). A combined indicator capturing the presence of either CHD or PAD also showed no significant difference in LRG levels (both groups: median 56 μg/ml; $P = .73$; Supplementary Table S1). The correlations between LRG and other baseline variables, including hsCRP, albumin, haemoglobin, transferrin, and age, are summarized in Supplementary Table S2.

Determinants of baseline LRG levels

To identify which baseline characteristics were independently associated with higher LRG levels, we fitted a multivariable linear regression model with log-transformed LRG as the dependent variable and age, sex, hsCRP, albumin, haemoglobin, diabetes, CHD, and PAD as covariates. Higher hsCRP, older age, and lower haemoglobin were independently associated with higher LRG levels, whereas sex, diabetes, CHD, and PAD were not significant predictors (Supplementary Table S3). These findings

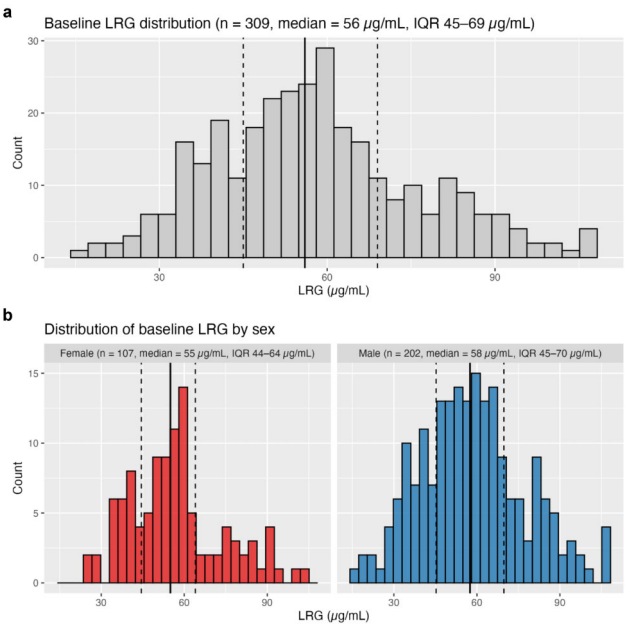

Figure 1: Distribution of baseline serum LRG levels. **(a)** Histogram of LRG concentrations in the overall cohort ($n = 309$). The panel title reports the sample size and the median and interquartile range (IQR), and vertical lines indicate the median (solid line) and IQR (dashed lines). **(b)** Sex-stratified histograms of baseline LRG for women (red) and men (blue). Panel titles report the sample size and LRG median and IQR for each sex, and vertical lines again indicate the median (solid) and IQR (dashed) within each group.?

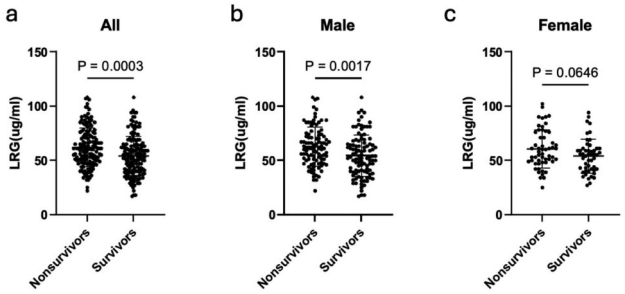

Figure 2: Serum LRG in survivors versus non-survivors, overall and by sex. (a) Comparison of baseline LRG levels between all survivors and non-survivors (Mann–Whitney *U*-test). (b) Male patients: survivors versus non-survivors. (c) Female patients: survivors versus non-survivors.?

support the concept that LRG primarily reflects an inflammatory and haematologic risk profile in this ESRD population.

Distribution of serum LRG and correlations

Baseline serum LRG concentrations were right-skewed, ranging from 9.3 to 2638 μg/ml (overall median 56, IQR 45–69 μg/ml; Fig. 1a). Sex-stratified histograms are shown in Fig. 1b, with vertical lines indicating the median and interquartile range for women (median 55, IQR 44–64 μg/ml) and men (median 58, IQR 45–70 μg/ml). LRG did not differ significantly by sex ($P = .412$). LRG did not differ by sex ($P = .412$). Exploratory Spearman correlation analyses showed that higher LRG tended to co-occur with elevated CRP and serum creatinine, whereas no meaningful relationship was seen with HDL or total cholesterol.

LRG levels and mortality outcomes

Over a median follow-up of 4.7 years, 102 patients (32.5%) died. The remaining 211 patients (67.5%) were alive at the end of follow-up or were censored because of kidney transplantation or loss to follow-up. Non-survivors had significantly higher baseline LRG than survivors (61.0 vs. 54.0 μg/ml, $P = .002$; Fig. 2a). When stratified by sex, this difference persisted in men (62.5 vs. 55.0 μg/ml, $P = .002$; Fig. 2b) but was not statistically significant in women (59.0 vs. 53.0 μg/ml, $P = .065$; Fig. 2c), suggesting a sex-specific prognostic pattern.

Survival analyses by LRG tertiles and cut-off

Patients were divided into LRG tertiles: low (9.3–45), mid (45–69), and high (69–2638 μg/ml). Kaplan–Meier curves demonstrated a graded decrease in 5-year survival across tertiles (78.2%, 68.7%, and 55.4%; log-rank $P = .020$; Fig. 4a). ROC analysis identified an AUC of 0.602 ($P < .001$) for LRG predicting mortality and an optimal cut-off of 45.5 μg/ml (Fig. 3). In sex-stratified ROC analyses, serum LRG predicted mortality with modest discrimination in both men and women. The AUC was 0.63 in men and 0.60 in women. The optimal sex-specific cut-offs, determined by the Youden index, were 54 μg/ml in men (sensitivity 0.69, specificity 0.51) and 60 μg/ml in women (sensitivity 0.49, specificity 0.74). These thresholds were slightly higher than the overall cut-off of 45.5 μg/ml derived from the pooled cohort and illustrate a trade-off between sensitivity and specificity in each sex (Supplementary Table S4).

Dichotomized at this threshold, patients with LRG ≥45.5 μg/ml had significantly lower survival than those below (56.3% vs. 75.8%; $P = .016$). Sex-stratified KM analyses confirmed that elevated LRG predicted worse survival in men ($P = .023$; Fig. 4b) but not in women ($P = .335$; Fig. 4c).

Cox regression and mechanistic insights

In univariable Cox models, each 1 μg/ml increase in LRG was associated with mortality in the overall cohort (HR 1.012; $P = .006$) and in men (HR 1.014; $P = .006$), whereas in women the estimated association was weaker and did not reach statistical significance (HR 1.008; $P = .089$). As a binary variable (≥45.5 μg/ml), high LRG predicted death overall (HR 1.65; $P = .016$) and in men (HR 1.85; $P = 0.017$), but was not statistically significant in women (HR 1.37; $P = .335$). In multivariable Cox models adjusting for age, sex, comorbidities, and laboratory parameters as specified in Models A–C, LRG remained an independent risk factor for mortality (overall adjusted HR 1.52; $P = .039$; men adjusted HR 1.73; $P = .038$), whereas sex itself was not an independent predictor of mortality after full adjustment ($P > .05$ in all multivariable models).

To contextualize these findings, we propose a sex-specific mechanism (Fig. 5): elevated LRG amplifies TGF-β1 signalling via $\alpha V\beta 3$ integrin, promoting myocardial fibrosis and extracellular matrix remodelling [2, 12–17]. In men, androgen-mediated upregulation of TGF-β1 enhances these pro-fibrotic effects, contributing to cardiac stiffness and diastolic dysfunction. In women, oestrogen's antifibrotic actions may attenuate TGF-β1 signalling, mitigating LRG's impact on survival.

DISCUSSION

In this prospective cohort study, we investigated the prognostic significance of baseline serum LRG levels in patients undergoing

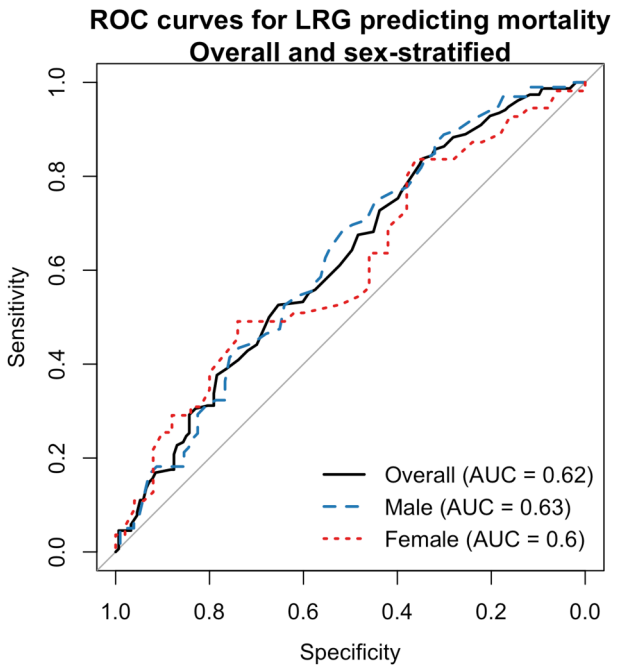

Figure 3: ROC curves for baseline serum LRG predicting 5-year all-cause mortality in the overall cohort and stratified by sex. The solid black line represents the overall cohort, the dashed red line represents men, and the dotted blue line represents women. For the overall cohort, LRG predicted mortality with an AUC of 0.62 (95% CI 0.54–0.66; $P < .001$). The optimal prognostic cut-off derived from this pooled ROC curve was 45.5 μg/ml, which was used for subsequent survival and Cox regression analyses.?

haemodialysis for ESRD. Our findings demonstrate that elevated LRG levels independently associate with increased all-cause mortality, particularly in male patients. This observation supports the hypothesis that LRG could serve as a novel biomarker with sex-specific implications in ESRD-related outcomes.

Previous studies suggest that LRG expresses minimally in healthy renal tissue but markedly upregulates under chronic inflammatory and fibrotic conditions, such as diabetic nephropathy and glomerular disease [1–3]. Our findings align with these reports and further indicate that elevated serum LRG in ESRD patients likely reflects a systemic inflammatory state and contributes to adverse cardiovascular outcomes.

From a mechanistic standpoint, LRG has been implicated in cardiovascular pathology beyond its role as an acute-phase protein. Previous studies suggest that LRG is upregulated in chronic inflammatory states and may enhance transforming growth factor-β1 (TGF-β1) signalling and extracellular matrix remodelling, thereby promoting myocardial fibrosis and adverse cardiac remodelling [3, 21, 22]. In ESRD, where systemic inflammation, vascular calcification, and volume overload are highly prevalent, elevated LRG may therefore reflect a cardio-inflammatory and pro-fibrotic milieu that predisposes to cardiovascular events and death.

In our cohort, however, baseline LRG levels were not significantly different between patients with and without CHD, and only a modest, non-significant trend towards higher LRG levels was observed in patients with PAD. These cross-sectional findings do not strongly support a simple one-to-one relationship between LRG and documented cardiovascular comorbidities, but they are compatible with the notion that LRG reflects a broader burden of inflammation and fibrosis-related risk that

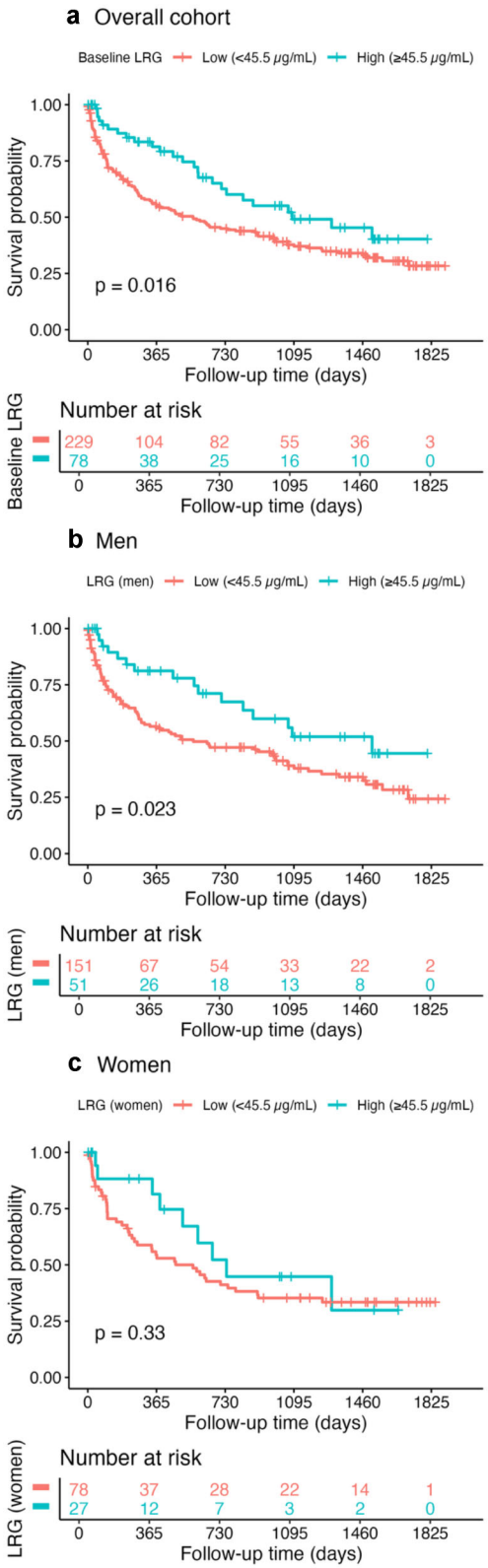

Figure 4: Kaplan–Meier curves for 5-year all-cause mortality according to dichotomized baseline LRG. (a) Overall cohort. (b) Men. (c) Women. In each panel, patients are stratified into low (<45.5 μg/ml, red) and high (≥45.5 μg/ml, blue) baseline LRG groups; *P* values are from log-rank tests. The number of patients at risk at selected time points is shown below each curve.?

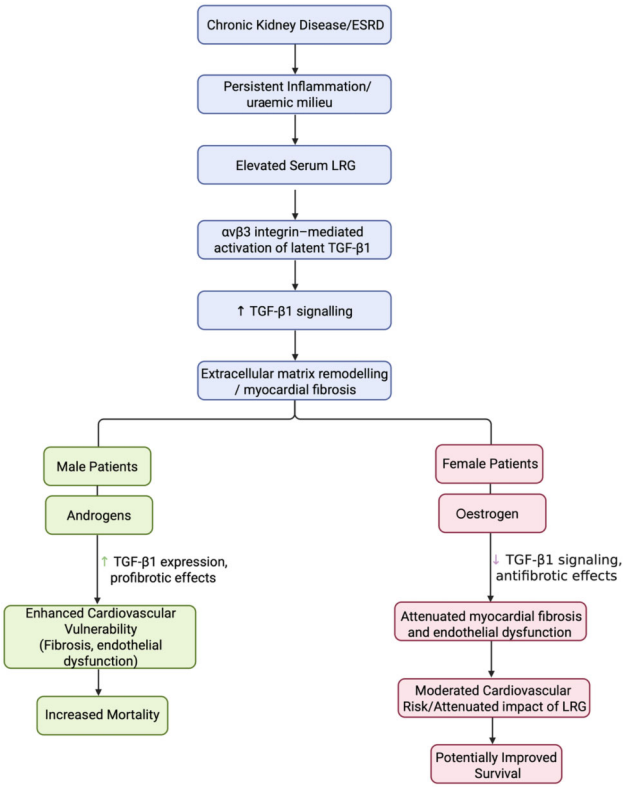

Figure 5: Proposed sex-specific mechanisms linking elevated LRG to myocardial fibrosis and mortality in ESRD. Chronic kidney disease/ESRD is characterized by persistent inflammation and a uraemic milieu, leading to elevated circulating LRG. LRG amplifies TGF-β1 signalling via αvβ3 integrin-mediated activation of latent TGF-β1, promoting extracellular matrix remodelling and myocardial fibrosis. In men, androgens upregulate TGF-β1 expression and favour a more pronounced pro-fibrotic response, thereby strengthening the LRG–TGF-β1–fibrosis axis and enhancing cardiovascular vulnerability and mortality. In women, oestrogens exert antifibrotic effects and attenuate TGF-β1 signalling, which may mitigate the impact of elevated LRG on myocardial fibrosis, moderate cardiovascular risk, and contribute to relatively better survival. The figure summarizes a hypothesis-generating mechanistic model that integrates our sex-stratified findings with existing experimental and clinical data.?

may not be fully captured by traditional diagnostic labels. Importantly, because cause-specific mortality was not available, the link between LRG, cardiovascular events, and mortality in ESRD remains hypothesis-generating and should be confirmed in future studies with adjudicated cardiovascular outcomes.

In line with this interpretation, our multivariable regression analyses showed that higher hsCRP, older age, and lower haemoglobin were independently associated with higher LRG levels, whereas sex, diabetes, CHD, and PAD were not significant determinants. This pattern suggests that LRG captures an inflammatory and haematologic/nutritional risk profile rather than being directly driven by diabetes or established cardiovascular diagnoses. However, we did not have measurements of sex hormones (e.g. testosterone or oestradiol), and thus could not directly test the hormone-dependent aspects of the mechanistic model depicted in Fig. 5. The proposed interplay between LRG, TGF-β1 signalling, and sex hormones should therefore be regarded as hypothesis-generating and warrants confirmation in future studies with detailed hormonal profiling.

In our cohort, hsCRP levels were higher in men than in women, which contrasts with several large dialysis cohorts where women tended to have slightly higher CRP values. This discrepancy may reflect differences in case mix, centre-specific referral patterns, and the distribution of comorbidities, such as diabetes and cardiovascular disease, in our single-centre study. The moderate correlation between LRG and hsCRP suggests that part of the sex difference in LRG may be driven by a higher inflammatory burden in men. However, the absence of a strong difference in LRG levels between patients with and without diabetes, and the persistence of the prognostic association of LRG with mortality in men after adjustment for CRP and diabetes in multivariable models, indicate that inflammation and diabetes alone are unlikely to fully explain the sex-specific prognostic impact of LRG. Additional mechanisms, such as sex hormone-dependent modulation of TGF-β1 signalling and myocardial fibrosis, are therefore likely to contribute.

Kaplan–Meier survival analysis and multivariable Cox regression modelling revealed that elevated LRG levels associate with lower 5-year survival rates in male but not female patients. This sex-specific difference is biologically plausible and may involve hormonal influences on fibrotic pathways. Androgens enhance transforming growth factor-beta1 (TGF-β1) expression via androgen response elements, while oestrogens exert protective, antifibrotic effects [25]. LRG itself promotes myocardial fibrosis by amplifying TGF-β signalling through αVβ3-integrin-mediated activation of latent TGF-β1 [3, 21, 22]. This creates a pathogenic feedback loop, in which LRG both induces and responds to TGF-β1 activity, potentially exacerbating fibrotic remodelling in the myocardium.

These findings are consistent with studies showing that myocardial fibrosis, driven by imbalanced extracellular matrix remodelling, plays a critical role in the pathophysiology of heart failure in CKD and ESRD patients [18–20]. In our cohort, we propose that elevated LRG accelerates fibrotic processes in the heart, contributing to the high burden of cardiovascular mortality in male dialysis patients.

By contrast, the lack of a statistically significant association in female patients suggests that oestrogen modulates TGF-β1 signalling to counteract the fibrogenic effects of LRG. Preclinical studies support this hypothesis, demonstrating reduced myocardial fibrosis following oestrogen treatment or orchiectomy in animal models [25]. Figure 5 illustrates a hypothetical model for these sex-specific mechanisms. Nonetheless, future studies should investigate the interaction between sex hormones and LRG signalling in humans.

Beyond its fibrotic roles, LRG may also reflect systemic inflammation and oxidative stress, both hallmarks of ageing and uremic toxicity [5, 9]. Elevated LRG levels may indicate impaired protein clearance, oxidative injury, or subclinical infection, all of which associate with poor outcomes in haemodialysis patients. Thus, LRG could serve as a composite marker capturing the multifactorial nature of morbidity in ESRD.

Limitations

Our study has several limitations. First, the analysis was observational, and while we accounted for many confounders, residual bias cannot be excluded. Second, only baseline LRG levels were analysed; longitudinal assessment of LRG trends might better reflect disease progression and treatment response. Third, the sample size of female participants was relatively small, possibly limiting the statistical power to detect effects in women.

In addition, we did not have adjudicated cause-specific mortality or detailed information on cardiovascular versus non-cardiovascular causes of death. As a result, we cannot

Table 2: Univariable Cox regression analysis for predicting all-cause mortality.

	All (N = 313)		Male (N = 206)		Female (N = 107)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Diabetes mellitus	1.209 (0.882–1.659)	.238	0.992 (0.657–1.498)	.969	1.697 (0.983–2.930)	.058
Hypertension	0.771 (0.517–1.149)	.202	0.754 (0.465–1.221)	.251	0.803 (0.392–1.643)	.548
CHD	1.435 (1.040–1.978)	.028*	1.632 (1.087–2.450)	.018*	1.158 (0.681–1.970)	.588
Tumour	1.615 (1.136–2.297)	.008**	1.604 (1.032–2.494)	.036*	1.552 (0.865–2.785)	.140
Smoker	0.930 (0.662–1.306)	.674	1.074 (0.721–1.598)	.726	0.614 (0.278–1.358)	.228
Alcohol	1.161 (0.780–1.729)	.462	1.263 (0.813–1.962)	.300	0.952 (0.297–3.051)	.934
RAAS inhibitors	0.790 (0.552–1.132)	.199	0.804 (0.515–1.255)	.337	0.757 (0.412–1.389)	.369
Beta-blockers	0.482 (0.352–0.661)	<.001***	0.410 (0.275–0.610)	<.001***	0.596 (0.347–1.023)	.060
Calcium channel blockers	0.721 (0.506–1.028)	.071	0.588 (0.374–0.925)	.022*	1.082 (0.608–1.923)	.789
Erythropoietin	0.959 (0.700–1.312)	.792	1.041 (0.705–1.538)	.839	0.823 (0.485–1.398)	.471
Body mass index, kg/m^2	0.990 (0.957–1.024)	.556	0.975 (0.927–1.025)	.321	1.001 (0.961–1.043)	.964
Dialysis vintage, days	0.929 (0.809–1.067)	.298	0.880 (0.736–1.052)	.160	1.018 (0.818–1.267)	.873
Dialysis dose, Kt/V	0.968 (0.904–1.036)	.346	1.018 (0.926–1.119)	.713	0.896 (0.787–1.020)	.096
Ferritin, ng/ml	1.000 (0.992–1.008)	.976	0.997 (0.987–1.007)	.607	1.005 (0.991–1.020)	.471
Transferrin, mg/dl	0.957 (0.926–0.989)	.009**	0.970 (0.934–1.007)	.112	0.886 (0.814–0.963)	.005**
Haemoglobin, g/dl	0.942 (0.859–1.033)	.204	0.947 (0.850–1.055)	.319	0.937 (0.785–1.118)	.470
Serum albumin, g/dl	0.721 (0.546–0.954)	.022*	0.411 (0.282–0.601)	<.001***	1.096 (0.923–1.303)	.296
Total cholesterol, mg/dl	0.970 (0.939–1.003)	.076	0.961 (0.923–1.000)	.051	0.990 (0.932–1.052)	.752
Triglycerides, mg/dl	0.926 (0.855–1.004)	.063	0.888 (0.801–0.984)	.024*	0.995 (0.874–1.132)	.941
LDL, mg/dl	0.987 (0.942–1.035)	.602	0.975 (0.918–1.035)	.399	1.011 (0.934–1.095)	.786
HDL, mg/dl	1.074 (0.975–1.183)	.150	1.173 (1.066–1.291)	.001**	0.831 (0.682–1.013)	.067
iPTH, ng/l	0.966 (0.923–1.011)	.137	0.969 (0.912–1.031)	.322	0.964 (0.900–1.032)	.288
LRG, μg/ml	1.130 (1.037–1.233)	.005**	1.124 (1.017–1.244)	.023*	1.160 (0.978–1.376)	.089
Leukocytes, 10^9/l	1.009 (0.969–1.050)	.671	0.987 (0.940–1.037)	.608	1.081 (0.993–1.176)	.072
Thrombocytes, 10^9/l	0.945 (0.861–1.037)	.229	0.980 (0.866–1.109)	.750	0.899 (0.777–1.039)	.150
C-reactive protein, mg/l	1.022 (0.996–1.049)	.097	1.020 (0.990–1.051)	.189	1.044 (0.986–1.105)	.137
Blood urea nitrogen, mg/dl	1.003 (0.970–1.038)	.846	1.026 (0.974–1.081)	.332	0.982 (0.928–1.039)	.533
Serum creatinine, mg/dl	0.877 (0.819–0.939)	<.001***	0.865 (0.796–0.941)	<.001***	0.890 (0.785–1.008)	.066
Serum potassium, mmol/l	0.889 (0.733–1.079)	.234	0.945 (0.753–1.187)	.629	0.767 (0.531–1.108)	.158
Serum calcium, mmol/l	0.990 (0.938–1.044)	.704	1.005 (0.944–1.069)	.884	0.943 (0.847–1.051)	.288
Serum phosphorus, mg/dl	0.898 (0.784–1.028)	.117	0.912 (0.776–1.073)	.267	0.868 (0.680–1.106)	.252

Cox regression results are shown as HRs with 95% CIs. For continuous variables, HRs are expressed per clinically meaningful unit change (e.g. LRG per 10 μg/ml, ferritin per 50 ng/ml, iPTH per 50 ng/l, dialysis dose per 0.1 Kt/V), as indicated in the variable labels.
Abbreviation: LDL, low-density lipoprotein.
Significance markers: *P < .05, **P < .01, ***P < .001.

determine to what extent the observed association between LRG and all-cause mortality, particularly in men, is driven by cardiovascular events versus other causes such as infections or malignancies. It is conceivable that a larger proportion of deaths in women may have been due to causes less tightly linked to inflammation and myocardial fibrosis, whereas deaths in men may have more often reflected cardiovascular events in which LRG-related pathways are more relevant. Without cause-specific data or competing-risk analyses, however, this remains speculative, and our mechanistic interpretation linking LRG, TGF-β1 signalling, and sex-specific cardiovascular mortality should be regarded as hypothesis-generating. Furthermore, residual renal function was not systematically assessed (e.g. by urine volume or clearance measurements), and serum creatinine differences between sexes probably reflect variation in muscle mass rather than true differences in residual renal function.

Conclusion and outlook

This study identifies serum LRG as a promising prognostic biomarker in haemodialysis patients with ESRD. Our data reveal a significant, independent association between elevated LRG levels and all-cause mortality, particularly among male patients. This sex-specific effect underscores the complex interplay between inflammation, fibrosis, and hormonal regulation in CKD and its cardiovascular complications.

Clinically, integrating LRG measurement into routine risk stratification protocols could enhance early identification of high-risk individuals, especially men. LRG may provide a valuable adjunct to established biomarkers (e.g. CRP, NT-proBNP, troponins) by offering insights into fibrotic and inflammatory pathways. We could also use LRG to monitor treatment responses, particularly for interventions targeting TGF-β signalling, oxidative stress, or myocardial remodelling.

The observed gender differences necessitate deeper investigation into hormonal modulation of LRG expression and its downstream effects. Oestrogen's protective role against fibrosis and its potential to counteract LRG-driven TGF-β amplification may explain the lack of significant association in female patients. Future studies should incorporate hormonal status, menopausal state, and oestrogen therapies as stratifying variables to refine risk assessment.

Furthermore, longitudinal studies should assess whether LRG level changes over time reflect cardiovascular/fibrotic

Table 3: Cox regression analysis of LRG levels for predicting all-cause mortality.

	All (N = 313)		Male (N = 206)		Female (N = 107)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Continuous LRG (per 10 μg/ml), univariable	1.130 (1.037–1.233)	.005**	1.124 (1.017–1.244)	.023*	1.160 (0.978–1.376)	.089
Continuous LRG (per 10 μg/ml), Model A	1.149 (1.049–1.259)	.003**	1.175 (1.047–1.319)	.006**	1.173 (0.980–1.404)	.082
Continuous LRG (per 10 μg/ml), Model B	1.193 (1.025–1.390)	.023*	1.210 (0.992–1.475)	.060	1.069 (0.819–1.395)	.625
Continuous LRG (per 10 μg/ml), Model C	1.284 (1.089–1.515)	.003**	1.423 (1.121–1.805)	.004**	0.967 (0.691–1.351)	.843
Binary LRG (≥45.5 vs <45.5 μg/ml), univariable	1.681 (1.095–2.580)	.018*	1.848 (1.082–3.157)	.025*	1.422 (0.696–2.909)	.334

Binary LRG was defined according to the optimal ROC-derived cut-off of 45.5 μg/ml (≥45.5 vs. <45.5 μg/ml). In multivariable Cox models (Models A–C), LRG was entered as a continuous variable and HRs for continuous LRG are expressed per 10 μg/ml increase. Model A was adjusted for comorbidities and medications (diabetes mellitus, hypertension, CHD, history of malignancy, and use of RAAS inhibitors, beta-blockers, calcium channel blockers, and erythropoietin). Model B was adjusted for dialysis vintage, dialysis dose, transferrin, haemoglobin, C-reactive protein, serum albumin, leukocyte and platelet counts, iPTH, and serum creatinine. Model C included all covariates from Models A and B. Only unadjusted P values are shown; false discovery rate correction using the Benjamini–Hochberg procedure was applied in secondary analyses as described in the Methods.
Abbreviation: LDL, low-density lipoprotein. Significance markers: *P < .05, **P < .01, ***P < .001.

disease progression or response to clinical interventions. Mechanistic studies using cellular and animal models must elucidate the exact pathways through which LRG influences cardiac/renal fibrosis, including modulation by sex hormones, oxidative stress, or the uremic milieu (Tables 2 and 3).

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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