International Journal of Nephrology and Renovascular Disease

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ORIGINAL RESEARCH

Growth Differentiation Factor-15 as a Potential Biomarker for Renal Involvement in POEMS Syndrome

Yuan Huang[1,*], Jia Chen[2,*], Yanlan Yao[3,*], Lu Zhang[2], Yongzhe Li[1], Jian Li[2]

[1]Department of Clinical Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China; [2]Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China; [3]Department of Clinical Laboratory, The First People's Hospital of Longquanyi District Chengdu, Chongqing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yongzhe Li; Jian Li, Email yongzhelipumch@126.com; Lijian@pumch.cn

Introduction: Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare plasma cell dyscrasia. Growth differentiation factor-15 (GDF-15) is related with renal function, but few studies have focused on it in renal impairment of POEMS syndrome.

Objective: To evaluate the potential of circulating GDF-15 concentration as a biomarker for renal function in POEMS syndrome.

Methods: 150 Chinese patients, diagnosed with POMES syndrome, were enrolled and divided into three subgroups according to their chemotherapy stage. All the patients' medical records were retrospectively analyzed and plasma VEGF and GDF-15 were measured using ELISA kits. Treatment-naïve patients were followed up for 13±6 months.

Results: Plasma GDF-15 concentration positively correlated with serum creatinine (r=0.4048; $P<0.0001$), blood urea nitrogen (r=0.3302; $P<0.0001$), risk stratification (r=0.3949; $P<0.0001$), while negatively correlating with eGFR (r=−0.5057; $P<0.0001$) and albumin (r=−0.3800; $P=0.0014$). GDF-15>547.8 pg/mL provided an AUC of 0.8541 in diagnosing renal impairment (eGFR<60mL/min/1.73m^2) in POEMS syndrome. With a prevalence of renal impairment of 16.7%, GDF-15>547.8 pg/mL showed a prominent NPV (94.9%) for the diagnosis of renal impairment in POEMS syndrome. Moreover, treatment-naïve patients with serous effusion had higher plasma GDF-15 concentration ($P=0.0004$) and lower eGFR ($P=0.0001$) than those without serous effusion. Noteworthy, baseline GDF-15 was positively correlated with ΔeGFR (r=0.4694, $P=0.0044$).

Conclusion: Circulating GDF-15 concentration is associated with serous effusion, renal function and risk stratification, while a plasma GDF-15 < 547.8 pg /mL can help rule out renal impairment in POEMS syndrome. Baseline plasma GDF-15 is associated with renal remission after chemotherapy.

Keywords: POEMS syndrome, growth differentiation factor 15, renal impairment, biomarker, risk stratification

Introduction

Polyneuropathy, Organomegaly, Endocrinopathies, Monoclonal protein, Skin changes (POEMS) syndrome is a rare, multisystem paraneoplastic disorder driven by an aberrant plasma cell clone.[1] Renal involvement, presenting as proteinuria, hematuria and renal dysfunction, is a common occurrence in POEMS, even though not present in the acronym. Various kidney pathological changes such as membranoproliferative glomerulonephritis-like lesions and microangiopathic lesions, have been observed from the renal biopsy of patients with POEMS syndrome.[2,3] In a retrospective analysis, 22.4% of Chinese POEMS syndrome patients had renal impairment (defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2) at baseline.[4] With a median follow-up of 27.4 months, a renal response predicted an improved survival rate.[4] Thus, an accurate assessment of renal function is very important for the diagnosis and treatment of POEMS syndrome.

Received: 10 December 2024
Accepted: 1 May 2025
Published: 20 May 2025

Growth differentiation factor-15 (GDF-15), considered a divergent member of the transforming growth factor-β (TGF-β) superfamily, was found to be associated with renal function.[5] Ho et al were able to demonstrate an association between incident chronic kidney disease (CKD) and GDF-15. Furthermore, a similar association was observed between GDF-15 and the decline in renal function.[6] Moreover, preclinical research revealed that intrarenal expression of GDF-15 in the tubule compartment correlates with its circulating levels, for which an increase in the latter may independently reflect renal function deterioration.[7] GDF-15 was found to play a role in enhancing the proliferation of renal tubular epithelial cells,[8] as well as enhancing tubular repair.[9] Further association was observed between GDF-15 and kidney impairment in plasma cell diseases such as light chain amyloidosis (AL) and multiple myeloma (MM). In AL, serum GDF-15 was revealed as the most significant prognostic measure for dialysis and a valuable addition to renal risk stratification.[10] Moreover, circulating GDF-15 was found to be associated with the involved monoclonal light chains, in addition to renal function in MM patients.[5] These findings suggest that GDF-15 is not only a marker, but a direct participant in kidney pathogenesis. However, the relationship between circulating GDF-15 and renal function in POEMS syndrome remains to be studied.

Herein, we performed a retrospective study to evaluate the potential of GDF-15 as an indicator of renal function in patients with POEMS syndrome.

Methods

Study Design and Patients

This is a retrospective cross-sectional study. Patients with POEMS syndrome were recruited at the Department of Hematology of the Peking Union Medical College Hospital in Beijing, China, between August 2022 and July 2024. The diagnosis of POEMS was made according to Dispenzieri et al[11] with the presence of two mandatory criteria (polyneuropathy and monoclonal plasma cell proliferating disorder), at least one major criterion (sclerotic bone lesion, Castleman disease or VEGF elevation), and one minor criterion (organomegaly, extravascular volume overload, endocrinopathy, skin change, papilledema, or thrombocytosis).

Neurological assessment was performed by the "Overall Neuropathy Limitations scale" (ONLS), which evaluates patient disability caused by neuropathy. The scores range from 0–12, with 0 representing no patient disability and 12 maximum disability. Patients with pleural effusion or ascites were regarded as having serous effusion. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[12] Renal impairment was defined as an eGFR < 60 mL/min/1.73m^2 using the CKD-EPI formula, based on the definition of at least moderate renal dysfunction by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative.[13]

For patients who had multiple visits during recruitment, only the first plasma sample and relevant medical records were included. Exclusion criteria: (1) patients undergone autologous hematopoietic stem cell transplantation rather than chemotherapy prior enrollment. (2) patients had finished chemotherapy more than 2 years prior enrollment. 34 patients were excluded and 150 patients were enrolled and divided into 3 subgroups: ① the before treatment (BT) subgroup (n=50); ② the chemotherapy (CT) subgroup (n=63); ③ and the stop treatment (ST) group, which consisted of POEMS syndrome patients who had finished chemotherapy less than 2 years prior enrollment (n=37). The medical records of all the patients were retrospectively analyzed. A retrospective cohort study was conducted in the BT subgroup. Patients in the BT subgroup were followed up until August 2024, with a mean follow-up of 13±6 months. Baseline eGFR ($eGFR_B$) and the last follow-up of eGFR ($eGFR_L$) and baseline BUN (BUN_B) and last follow-up BUN (BUN_L) were used to calculate the ΔeGFR ($eGFR_L$-$eGFR_B$) and ΔBUN (BUN_L-BUN_B). The patients in the CT subgroup received the initiation therapy (lenalidomide 25mg/day orally at days 1–21 a month and dexamethasone orally 40 mg weekly for 12 cycles) or the maintain therapy (lenalidomide 25mg/day orally at days 1–21 a month for 12 cycles).

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital, in accordance with the Declaration of Helsinki.

Risk Stratification

Patients were stratified to low, medium, or high-risk groups using four baseline characteristics: age > 50 years, presence of pulmonary hypertension, presence of pleural effusion, and an eGFR < 30 mL/min/1.73m^2. The first three characteristics had a value of 1; the last had a value of 2. Patients with total scores of 0, 1, and 2–5 were assigned to low, medium, and high-risk groups, respectively.[14]

Blood Samples and Laboratory Test

EDTA-anticoagulated blood samples were obtained from patients at the time of enrollment. The plasma samples were frozen and stored at −80°C. Plasma VEGF was measured using the Human VEGF ELISA Kit (JianPing, China) according to manufacturer's instructions, with the minimum detectable dose of 6.25pg/mL. Plasma GDF-15 was measured using the Human GDF-15 ELISA Kit (Multi Sciences, China) according to manufacturer's instructions, with the minimum and maximum detectable doses of 1.24 pg/mL and 10000.00 pg/mL.

Statistical Analysis

Mean ± standard deviation was reported for normally distributed quantitative variables. Non-normally distributed quantitative variables were reported by median values and inter-quartile range. Shapiro–Wilk test was used to assess normal distribution. Fisher exact test or χ^2 test was used for the analysis of contingency table. Ordinary one-way ANOVA or Kruskal–Wallis was used to analyze differences between the three subgroups (BT, CT and ST) in quantitative variables. Unpaired *t*-test or Kruskal–Wallis test was used to compare quantitative variables between patients with or without serous effusion. Receiver operator characteristic curve (ROC) was used to evaluate the diagnostic value of plasma GDF-15 in kidney failure. The statistical tests were two-tailed. The Spearman`s Rank Correlation was used to measure the correlation between two variables. Bonferroni correction was used for multiple testing. Prism 9.3.1 (GraphPad Software) was used for all the computations.

Results

Demographic and Clinical Characteristics of the Studied Patients with POEMS Syndrome

The study recruited 184 patients diagnosed with POEMS syndrome during their ambulatory visits between August 2022 and July 2024. 150 patients with POEMS syndrome (52 women, 98 men) aged 54±11 years, at the time of inclusion, were enrolled in the study (Table 1). These were then divided according to their chemotherapy stage, where 50, 63 and 37 patients were included in the BT, CT and ST subgroups, respectively. The median ONLS score was 1. 129 (86%) patients had monoclonal immunoglobulin with λ light chain, and 1(1%) patient had monoclonal κ light chain. The remaining 20 (13%) were negative for monoclonal immunoglobulin in serum and urine by immunofixation electrophoresis. So, they were regarded as suspicious non-secretory. A monoclonal plasma cell disorder was confirmed in 11 of these cases through bone marrow biopsy and 9 targeted plasmacytoma biopsy. Risk stratification resulted in 34 low-risk (23%), 102 medium-risk (68%), and 14 high-risk (9%) patients.

As shown in Table 1, there were significant differences in ONLS score, plasma VEGF, serum IgA, ALT and Alb between the BT, CT and ST subgroups (all $P < 0.05$). Moreover, the proportions of organomegaly, endocrinopathy, skin changes, serous effusion, and distribution of risk stratification were also significantly different among the three subgroups. On the contrary, no significant difference was observed in the age, gender composition, and monoclonal immunoglobulin concentration (tested by serum protein electrophoresis) (all $P > 0.05$). This lack of significance, among the three subgroups, was also observed for the kidney function, serum creatinine (Cr) and eGFR (all $P > 0.05$).

Circulating GDF-15 Concentration is Associated with Renal Function and Risk Stratification in POEMS Syndrome

A correlation analysis was performed between GDF-15 plasma concentration and clinical parameters related to the patients. A significantly low, positive correlation was observed between plasma GDF-15 concentration and serum Cr

Table 1 Demographic and Clinical Characteristics of POEMS Patients

Characteristic	Total (n=150)	BT (n=50)	CT (n=63)	ST (n=37)	*P* value
Age, years	54±11	53±10	54±12	56±11	0.3528
Male sex, n (%)	98(65)	33(66)	40(63)	25(68)	0.9113
Immunophenotype					
IgG λ, n (%)	35 (23)	6(12)	19(30)	10(27)	
IgA λ, n (%)	89 (59)	32(64)	35(56)	22(59)	
λ, n (%)[#]	2(1)		2(3)		
IgG κ, n (%)	1(1)		1(2)		
Biclonal IgG λ+IgA λ, n (%)	3 (2)	3(6)	0	0	
Suspicious nonsecretory, n (%)*	20 (13)	9(18)	6(9)	5(14)	
ONLS score	1 (0, 3)	2 (1, 4)	1 (0, 3)	0 (0, 1)	0.0001
Organomegaly, n (%)	53 (35)	34(68)	16(25)	3(8)	<0.0001
Endocrinopathy, n (%)	59 (39)	38(76)	18(29)	3(8)	<0.0001
Skin changes, n (%)	100 (67)	48(96)	41(65)	11(30)	<0.0001
Serous effusion, n (%)	28 (19)	20(40)	7(11)	1(3)	<0.0001
Risk stratification					0.2803
Low-risk, n (%)	34 (23)	8(16)	18(29)	8(22)	
Medium-risk, n (%)	102 (68)	32(64)	41(65)	29(78)	
High-risk, n (%)	14 (9)	10(20)	4(6)	0(0)	
M protein (g/L)	0.4(0, 1.7)	1.2(0, 3.1)	0.4(0, 1.6)	0(0, 0.6)	0.0010
Ig A (g/L)	2.7(1.9, 4.0)	3.4(2.3, 5.1)	2.5(1.6, 3.5)	2.3 (1.7, 3.2)	0.0020
ALT (U/L)	18(10, 27)	11(6, 18)	23(14, 36)	18(12, 27)	<0.0001
Alb (g/L)	42±4	40±4	42±4	44±3	<0.0001
Serum creatinine, μmol/L	76 (63, 93)	76(61, 106)	76(64, 93)	78(62, 86)	0.9691
VEGF(pg/mL)	$137\pm28^{88+}$	$225\pm54^{37+}$	$78\pm31^{38+}$	$56\pm15^{13+}$	<0.0001
eGFR (mL/min/1.73m^2)	93 (69, 104)	94(66, 108)	93(70, 102)	95(81, 104)	0.9445
<60 mL/min/1.73m^2, n (%)	25(17)	10(20)	10(16)	5(14)	0.7070
≥60 mL/min/1.73m^2, n (%)	125(83)	40(80)	53(84)	32(86)	

Notes: Data are shown as median (lower, upper quartile) or means ± standard deviation unless otherwise specified. # means that only urinary lambda light chain was found by immunofixation electrophoresis. Asterisk * means that no monoclonal immunoglobulin was detected by immunofixation electrophoresis in both serum and urine. Superscript $^+$ shows the number of patients who had plasma VEGF detection. *P* values were calculated between groups of BT, CT and ST by Ordinary one-way ANOVA, Kruskal–Wallis, Fisher exact test or Chi-square test. *P*<0.05 was considered to be statistically significant.
Abbreviations: BT, before treatment; CT, chemotherapy treatment; ST, stop treatment; ALT, Alanine transaminase; Alb, albumin.

concentration (r = 0.4048; *P*<0.0001), as well as blood urea nitrogen (BUN) (r = 0.3302; *P*<0.0001) (Table 2). While a significantly moderate, negative correlation was observed between plasma GDF-15 concentration and eGFR (r = −0.5057; *P*<0.0001). Furthermore, GDF-15 concentration showed a low, positive correlation with risk stratification (r = 0.3949; *P*<0.0001), and a low, negative correlation with albumin (Alb) concentration (r = −0.3800; *P* = 0.0014). However, no correlation was observed between GDF-15 concentration and IgA, thyroid stimulating hormone (TSH), age, ONLS score, monoclonal (M) immunoglobulin concentration, or plasma VEGF concentration (all *P*>0.0045).

GDF-15 Is Helpful in Monitoring Renal Function in Patients with POEMS Syndrome

Since circulating GDF-15 concentration has a significant association with eGFR, we tried to establish a cut-off value for the GDF-15 level to differentiate POEMS syndrome patients with and without renal impairment. We observed that a GDF-15 concentration > 547.8 pg/mL can help diagnose renal impairment (eGFR < 60mL/min/1.73m^2) in POEMS syndrome (Figure 1). Considering that therapy may affect the circulating level of GDF-15, the diagnostic value of GDF-15 > 547.8 pg /mL was analyzed in the three subgroups. The AUCs of GDF-15 > 547.8 pg /mL in the total subjects, the BT, CT, and ST subgroups were 0.8541, 95% CI (0.7769, 0.9313); 0.8775, 95% CI (0.7442, 1.000); 0.8509, 95% CI (0.7511, 0.9508); and 0.8063, 95% CI (0.6133, 0.9992); respectively (Figure 1). As shown in Table 3, the prevalence of renal impairment was 16.7%, and utilizing the GDF-15 cut-off of > 547.8 pg /mL showed an outstanding NPV in the

Table 2 Correlations Between GDF-15 and Other Parameters in POEMS Syndrome

	r	*P* value
eGFR (mL/min/1.73m^2)^{150}*	−0.5057	<0.0001
Alb (g/L)^{150}*	−0.3800	<0.0001
Cr (μmol/L)^{150}*	0.4048	<0.0001
BUN (mmol/L)^{150}*	0.3205	<0.0001
Risk stratification^{150}*	0.3949	<0.0001
IgA (g/L)^{144}*	0.2212	0.0077
TSH (μIU/mL)^{145}*	0.2019	0.0149
Age (years)^{150}*	0.1526	0.0622
ONLS score^{150}*	0.0816	0.3206
M immunoglobulin (g/L)^{150}*	0.0380	0.6450
VEGF (pg/mL)^{88}*	−0.1628	0.1295

Notes: Asterisk * shows the number of patients that included in the analysis. *Spearman`s rank* correlation was used for the correlation test, and *Bonferroni* correction was used for multiple analysis. *P*<0.0045 was considered to be statistically significant.

Abbreviations: eGFR, estimated glomerular filtration rate; Cr, creatinine; GDF-15, growth differentiation factor-15; ONLS, overall neuropathy limitations scale score; TSH, thyroid stimulating hormone; M, monoclonal; Alb, albumin; VEGF, vascular endothelial growth factor; BUN, blood urea nitrogen.

diagnosis of renal impairment in POEMS syndrome (94.9% in all subjects, 93.8% in the BT subgroup, 100% in the CT subgroup, and 89.3% in the ST subgroup, respectively). However, the sensitivity and specificity were relatively lower for all patient classifications: 80.0% and 75.2% in all subjects, 80% and 75.0% in the BT subgroup, 100.0% and 71.7% in the CT subgroup, and 40% and 78.1% in the ST subgroup.

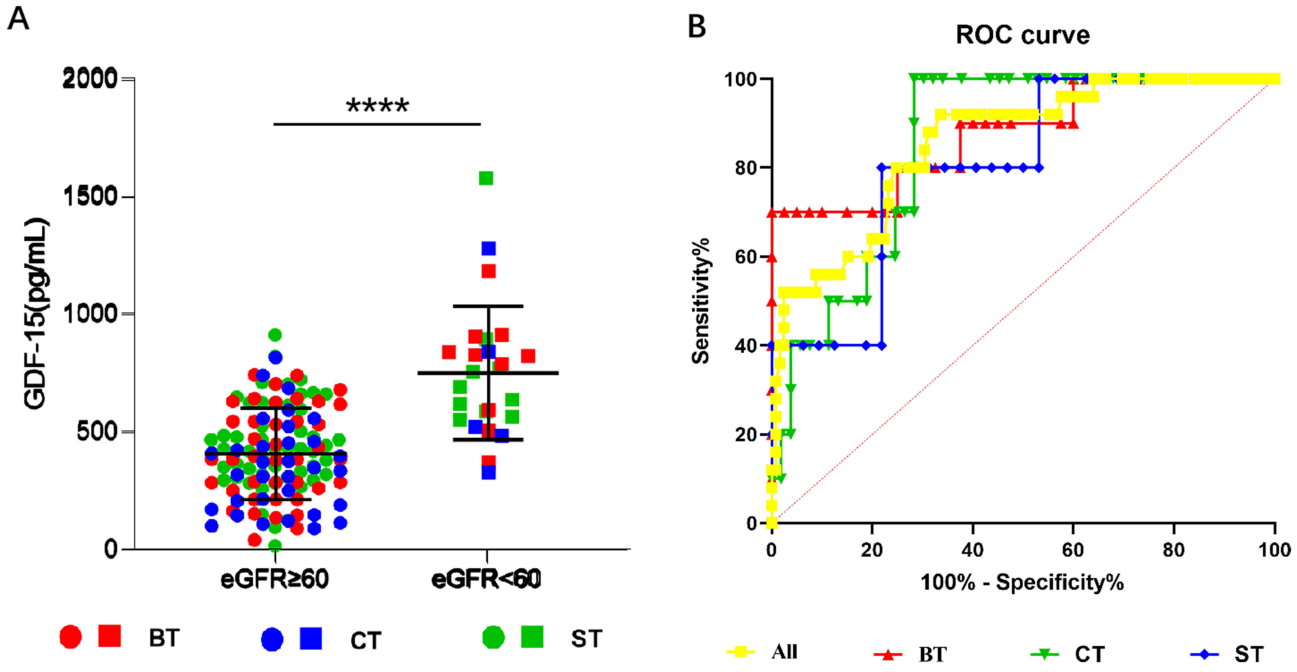

Figure 1 ROC analysis of plasma GDF-15 concentration in all participants and subgroups. (**A**) Comparison of plasma GDF-15 concentration between patients with eGFR < 60mL/min/1.73m^2 and eGFR ≥ 60mL/min/1.73m^2. (**B**) ROC curve of plasma GDF-15 concentration diagnosing renal dysfunction in the overall POEMS syndrome patients (n = 150), BT subgroup (n = 50), CT subgroup (n = 63), and ST subgroup (n = 37). The *P* values were calculated using unpaired *t*-test and ROC analysis. Statistical significance is displayed as **** *P*<0.0001.

https://doi.org/10.2147/IJNRD.S507148

Table 3 Diagnostic Efficacy of GDF-15 Cut-off of > 547.8 pg /mL to Determine Renal Impairment (eGFR < 60mL/min/1.73m^2) in POEMS Syndrome

	AUC, 95% CI	P value	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
All patients (n=150)	0.8541 (0.7769, 0.9313)	<0.0001	80.0	75.2	94.9	39.2
BT (n=50)	0.8775 (0.7442, 1.000)	0.0002	80.0	75.0	93.8	44.4
CT(n=63)	0.8509 (0.7511, 0.9508)	0.0005	100.0	71.7	100.0	40.0
ST(n=37)	0.8063 (0.6133, 0.9992)	0.0295	40.0	78.1	89.3	22.2

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; BT, before treatment; CT, chemotherapy treatment; ST, stop treatment.

GDF-15 is Associated with Serous Effusion in Treatment-Naive POEMS Syndrome Patients

When looking at the results of the renal function tests within patients in the BT subgroup, patients with serous effusion showed significantly higher serum N-terminal pro B-type natriuretic peptide (NT-proBNP) (1506 pg/mL vs 234 pg/mL, *P*=0.0017), plasma GDF-15 (381.7±206.1 pg/mL vs 625.1±243.0 pg/mL, *P*=0.0004) and BUN (6.630 mmol/L vs 5.575 mmol/L, *P*=0.0011), as well as significantly lower eGFR (67.7 mL/min/1.73m^2 vs 102.4 mL/min/1.73m^2, *P*=0.0001), as compared to those without serous effusion (Figure 2A–D). Moreover, those with serous effusion had significantly lower hemoglobin (120±26 g/L vs 150±18 g/L, *P*<0.0001) and albumin concentration (39 g/L vs 41 g/L, *P*=0.0016) as compared to those without serous effusion, while no significant difference was observed in WBC (5.09×10^9/L vs 7.23×10^9/L, *P*=0.0147) after *Bonferroni* correction (Figure 2E–G). Of note, the risk stratification of patients with serous effusion was higher than those without (1.5 vs 1, *P*<0.0001) (Figure 2H).

Furthermore, a correlation analysis, within the BT subgroup, showed that GDF-15 concentration had a moderate positive correlation with NT-proBNP (r=0.6414, *P*<0.0001), BUN (r=0.5685, *P*<0.0001) and risk stratification (r=0.5172, *P*=0.001), while a moderate negative correlation was observed with eGFR (r=−0.6229, *P* < 0.0001). NT-proBNP showed a moderate negative correlation with eGFR (r=0.6414, *P* < 0.0001) in the BT subgroup (Figure S1A–E).

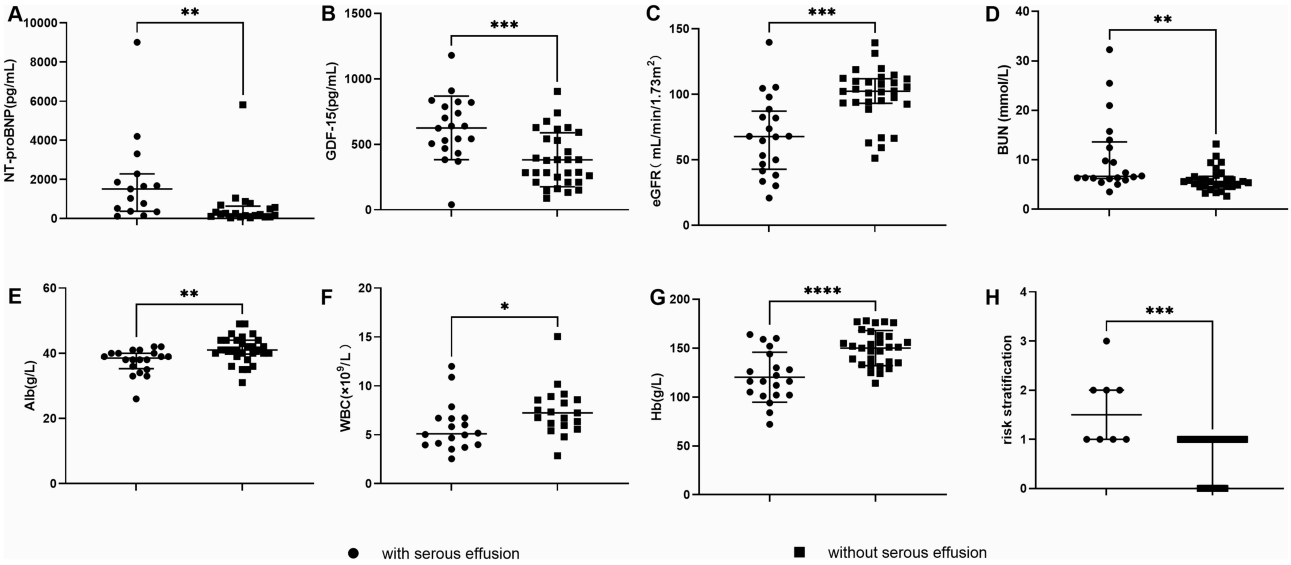

Figure 2 Differences in clinical parameters between those with or without serous effusion in treatment-naive POEMS syndrome patients. (**A**–**H**) Comparison of NT-proBNP, GDF-15, eGFR, BUN, Alb, WBC, Hb, and risk stratification of POEMS syndrome patients with and without serous effusion. The sample size was 36 for NT-proBNP comparison because it was not measured for 14 patients and 50 for GDF-15, eGFR, BUN, Hb, Alb, and WBC comparison. *P*-values of GDF-15 and Hb were calculated using Unpaired *t*-test, and those for NT-proBNP, eGFR, BUN, Alb, and WBC were calculated using Mann–Whitney test. And *Bonferroni* correction was used for multiple comparison. *P* < 0.00625 was considered to be statistically significant. Statistical significance is displayed as * *P* < 0.05, ** *P* < 0.01, *** *P* < 0.001, **** *P* <0.0001.
Abbreviations: NT-proBNP, N-terminal pro-brain natriuretic peptide; GDF-15, growth differentiation factor 15; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; Hb, hemoglobin; Alb, albumin; WBC, white blood cell.

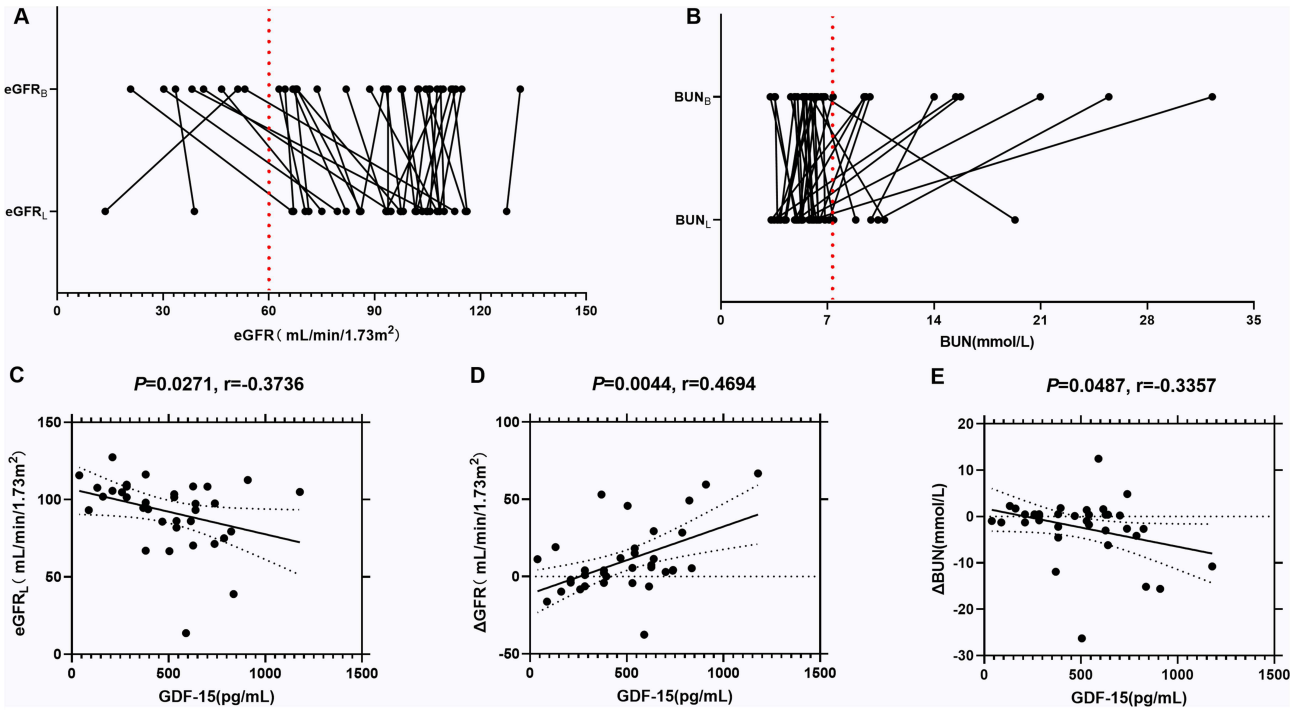

Figure 3 Association between baseline GDF-15 and renal remission. (**A** and **B**) Comparison of eGFR and BUN at baseline and last follow-up time (average 13 months) in POEMS syndrome patients (n=35). (**C–E**) Correlations between GDF-15 and $eGFR_L$, ΔeGFR ($eGFR_L$- $eGFR_B$), and ΔBUN (BUN_L- BUN_B) in POEMS syndrome patients (n=35). The Spearman rank test was used for correlation analysis. *Bonferroni* correction was used for multiple analyses. $P < 0.017$ was considered to be statistically significant. **Abbreviations**: GDF-15, growth differentiation factor 15; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; $eGFR_L$, eGFR at last follow-up; $eGFR_B$, eGFR at baseline; BUN_L, BUN at last follow-up; BUN_B, BUN at baseline.

Circulating GDF-15 Concentration is Associated with Renal Remission in POEMS Syndrome Patients

BT patients were followed up, with a mean time, for 13±6 months. 8 out of the 10 patients with renal dysfunction, in the BT subgroup, were followed up for more than 3 months. As shown in Figure 3A and B, 6 out of the 8 patients (75%) had achieved renal remission (eGFR ≥ 60 mL/min/1.73m^2). The BUN level returned to normal range (<7.14mmol/L) in 5 out of the 8 (62.5%) patients, who had renal dysfunction. Of interest, baseline plasma concentration of GDF-15 showed a low positive correlation with ΔeGFR (r=0.4694, P=0.0044), while no correlation was observed between baseline GDF-15 and $eGFR_L$ or ΔBUN after Bonferroni correction (all $P > 0.017$) (Figure 3C–E).

Discussion

Renal impairment in Chinese patients with POEMS syndrome is not uncommon.[4,15] Its main manifestation is decreased glomerular filtration rate rather than proteinuria. The exact mechanism of renal impairment in POEMS syndrome is unclear. A recent study showed that circulating GDF-15 concentration correlates with intrarenal GDF-15 messenger RNA transcript level and an increase in circulating GDF-15 level was independently associated with adverse renal outcome.[7] In our current study, we have provided evidence, in treatment-naïve POEMS syndrome patients, that GDF-15 plasma concentration could be utilized as a new biomarker associated with renal function, serous effusion, risk stratification and renal remission. Furthermore, GDF-15 > 547.8 pg/mL can help diagnose renal impairment (eGFR < 60mL/min/1.73m^2) in POEMS syndrome.

Borrowing the definition of renal impairment (eGFR < 60mL/min/1.73m^2) from MM studies, we found that 20% of untreated POEMS patients (BT) in the current cohort had renal impairment, from which 75% had achieved renal remission (eGFR > 60mL/min/1.73m^2) after chemotherapy. These results are consistent with a previous study in the Chinese population.[4] Our study also provided evidence that circulating GDF-15 concentration was positively correlated with serum Cr, BUN, and risk stratification, while negatively correlated with eGFR and Alb; consistent with previous

https://doi.org/10.2147/IJNRD.S507148

studies in non-POEMS syndrome patients with renal impairment, where a correlation was observed between GDF-15 and renal function related indicators.[16–18] We speculate that this may contribute to the correlation between GDF-15 and the risk stratification score, because the risk stratification consists of an eGFR < 30 mL/min/1.73m^2 (2 points). Indeed, previous study has confirmed that poor renal remission was associated with poor prognosis in POEMS syndrome.[4]

It is noteworthy that no correlation was observed in POEMS syndrome patients between circulating GDF-15 concentration and IgA, ONLS score, and monoclonal immunoglobulin level. This suggests that in POEMS syndrome, circulating GDF-15 mainly reflects renal function and is not directly affected by tumor burden, which is different from previous studies in MM[5,19] while similar to studies in AL.[10] In MM, apart from renal impairment and several prognostic markers, myeloma burden was also associated with GDF-15.[5] Moreover, GDF-15 was found to be able to enhance the tumor-initiating and self-renewal potential of MM cells.[19] In AL,[10] GDF-15 was found to be a new biomarker for survival and renal outcomes, while there was no correlation of GDF-15 level with the level of free light chain or with the extent of bone marrow plasma cell infiltration. Therefore, GDF-15 may play different roles in different subtypes of plasma cell disease. Renal damage in POEMS syndrome is a complex phenomenon. Underlying mechanisms include glomerular alterations and vasculopathy mediated by various cytokines and growth factors. Our findings support GDF15 as a marker of renal damage rather than POEMS activity. And the role of GDF-15 in POEMS syndrome needs to be clarified by further mechanistic studies.

Of note, no correlation was observed, in the current study, between GDF-15 concentration and age. This is inconsistent with a previous study, which found that age was one of the independent predictors of circulating GDF-15 in obese patients.[20] This divergence might be related to the difference in subject characteristics between the two studies. Most of the POEMS syndrome patients are emaciated, which is completely different from the obese patients.

We further evaluated the cut-off of GDF-15 concentration in the diagnosis of renal impairment. The results showed that plasma GDF-15 > 547.8 pg /mL had a high NPV in the diagnosis of renal impairment in all the different treatment stages of POEMS syndrome patients. Indeed, such an NPV is related to the relatively low prevalence of renal impairment in POEMS syndrome. In comparison to the sensitivity and specificity, at plasma GDF-15 concentration > 547.8 pg /mL, the specificity in diagnosing renal impairment is suboptimal but stable at different treatment stages, while the sensitivity varied greatly at different treatment stages. This may be related to the relatively small sample size of each subgroup. Nevertheless, plasma GDF-15 > 547.8 pg /mL has good diagnostic potential for renal impairment in POEMS syndrome patients who are newly diagnosed or undergoing chemotherapy (AUC>0.85).

Furthermore, by focusing on treatment-naive POEMS syndrome patients, we found out that those with serous effusion had higher plasma GDF-15, poorer kidney function, lower serum albumin, and higher risk stratification score. A correlation of plasma GDF-15 with renal function and risk stratification scores was observed. Serous effusion is regarded as a sign of extravascular overload in POEMS syndrome.[11] In the current study, the presence of ascites, pleural effusion or pericardial effusion was considered to be the presence of serous effusion. Pleural effusion, ascites, lower serum albumin, and reduced eGFR are believed to be clinical surrogate markers for the disease severity of POEMS syndrome.[4,11] A previous study[4] has found that renal impairment is strongly associated with ascites, which is considered to be exudation caused by cytokine-induced vascular hypermeability in POEMS syndrome.[21] This is consistent with our finding that the plasma GDF-15 concentration, an indicator of renal function, was significantly higher in POEMS syndrome patients with serous effusion.

Of interest, our study also showed that baseline plasma GDF-15 was associated with renal remission after chemotherapy. The positive correlation between baseline plasma GDF-15 and ΔeGFR indicates that higher baseline plasma GDF-15 may be an indicator of better renal function recovery after chemotherapy in POEMS syndrome patients with renal impairment. This is consistent with previous studies that revealed the protective role of GDF-15 in renal function.[22–26] It has been shown that the loss of GDF-15 is harmful for lipopolysaccharide-induced (LPS-induced) kidney damage, while overexpression of GDF-15 improves LPS-induced kidney dysfunction.[23] In addition, GDF-15 is related to early renal protective injury responses by altering the behavior of immune cells[24] and promoting podocyte survival.[22] GDF-15 protects the renal interstitial and tubule compartments.[25,26] Therefore, we speculate that, in POEMS syndrome, GDF-15 is not only a biomarker for kidney impairment but also plays a role in helping kidney remission.

There are some limitations to this study. The first and most important point is the shortness of cross-sectional study. Prospective studies are needed to validate the protective role of GDF-15 in POEMS syndrome patients with kidney impairment. In addition, the reference intervals (185 to 439 pg/mL) of plasma GDF-15 in our study is different from those detected by Cobas e801 (463 to 652 pg/mL)[27] or by another quantitative sandwich enzyme immunoassay technique (292 to 533 pg/mL)[28] in other studies.[27,28] Accordingly, it is necessary to establish the cut-off values of plasma GDF-15 for diagnosing renal impairment (eGFR < 60mL/min/1.73m^2) separately.

We conclude that plasma GDF-15 concentration is associated with serous effusion, renal impairment and risk stratification. As a biomarker for renal impairment (eGFR < 60mL/min/1.73m^2) in POEMS syndrome patients, GDF-15 > 547.8 pg /mL had a prominent NPV. For patients with renal impairment, baseline plasma GDF-15 can help indicate renal remission after chemotherapy. Overall, measuring plasma GDF-15 concentration has the potential to be used as an additional biomarker for renal function and help in the prognosis of POEMS syndrome.

Data Sharing Statement

The raw data supporting the conclusions of this article are available from authors upon request.

Ethics Statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Peking Union Medical College Hospital (K23C3946, December 11, 2023). Written informed consent for participation was not required for this study in accordance with the institutional requirements of Guidelines for the Construction of Ethical Review Committees for Clinical Research Involving Humans (2020 edition): The subject may not be exposed to more than minimal risks; The exemption from the subject's informed consent will not adversely affect the subject's rights and interests; The use of identifiable human material or data for research does not involve personal privacy and commercial interests; The donor of the biological sample has signed an informed consent, agreeing that the donated sample and related information can be used for all medical research; Exemption from informed consent does not imply exemption from ethical review committee review.

Acknowledgments

This study was supported by the National High Level Hospital Clinical Research Funding (2022-PUMCH-B-124), and Beijing Natural Science Foundation (M23008).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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