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An underestimated old friend: serum protein electrophoresis in the differential diagnosis of glomerulopathies

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ABSTRACT

Background Serum protein electrophoresis (SPEP) is an easy test separating serum proteins based on their physical and chemical properties. Although it is frequently used in the differential diagnosis of multiple myeloma and various chronic inflammatory diseases, its value in the etiologic classification of glomerular diseases has yet to be studied.

Material and Methods We retrospectively reviewed the medical records of patients who underwent renal biopsy from 2008 to 2016 at our institution. We excluded patients who can not be classified as primary (PGn) or secondary glomerulonephritis (SGn). Univariate and multivariate logistic regression analyses were performed for the prediction of SGn.

Results Four hundred thirty-two patients were included in the study. Of those, 57.9% had PGn. Rheumatological diseases, malignancies, and infections were the most common etiologic causes of SGn, accounting for nearly 75%. Univariate analysis revealed that alpha-1 (α1), gamma (Ɣ), and albumin fractions significantly differ between PGn and SGn groups. ROC curve analysis determined the cut-off value of (α1*Ɣ)/albumin ratio as 1.48. Multivariate analysis revealed that total serum protein and (α1*Ɣ)/albumin ratio were significantly independent predictors for SGn ($p = 0.020$ and $p < 0.001$, respectively).

Conclusions A ratio generated by multiplying α1 and Ɣ and dividing by albumin from SPEP, an easy, reliable, and cheap test, may help clinicians differentiate between PGn and SGn after validation in more extensive prospective studies.

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INTRODUCTION

Glomerular disease is a heterogeneous group of disorders affecting the functions of the glomeruli with various mechanisms.[1] Clinical manifestations of glomerular diseases vary from asymptomatic urinary abnormalities to life-threatening renal and extrarenal organ dysfunctions.[2] Although glomerular diseases are rare, considering each histopathologic type as a specific disorder, they constitute roughly 10% of patients receiving renal replacement therapy, according to the European Renal Association Registry Annual Report 2021.[3]

Serum protein electrophoresis (SPEP) is an easy and reliable laboratory technique for separating serum proteins into fractions based on their physical features, such as charge, shape, and molecular weight. Protein fractions in SPEP are as follows: albumin and alpha-1 globulin (α1), alpha-2 globulin (α2), beta globulin (β), and gamma globulin (Ɣ). Although the diagnostic instruments develop and improve over time, SPEP is still frequently preferred by clinicians, particularly since the second half of the 20th century.[4] In clinical practice, SPEP is a convenient laboratory test for differential diagnoses and follow-ups of numerous diseases.[5,6] Also, protein fractions in SPEP are reported to alter in various renal diseases.[7] However, there is no recommendation for its use in the differential diagnosis of glomerular diseases other than multiple myeloma.

Various classifications of glomerular diseases were proposed based on aetiology, histology, and pathogenesis.[8,9] According to the aetiology, glomerular diseases are classified as primary and secondary glomerular diseases.[10,11] Secondary glomerulonephritis (SGn) represents glomerular dysfunction secondary to an identifiable underlying or systemic cause. Although the differential diagnosis of primary and secondary glomerular disease is crucial for applying appropriate therapy to the patient, this classification sometimes becomes challenging in clinical practice despite recent biomarkers.[12,13] The etiological causes of histopathologically confirmed secondary glomerulonephritis are mostly rheumatological diseases, amyloidosis, infections, and malignancies.[14,15] These disorders are accompanied by monoclonal gammopathies or marked by chronic inflammation, causing characteristic changes in SPEP. Therefore, in the present study, we investigated the predictive value of SPEP for classifying glomerular diseases as primary glomerulonephritis (PGn) or SGn.

MATERIAL AND METHODS

We reviewed the electronic medical records of the patients who underwent renal biopsies between January 2008 and November 2016 in the Department of Nephrology Bursa Uludag University. The study was in accordance with the 1964 Declaration of Helsinki. The clinical research ethics committee of Bursa

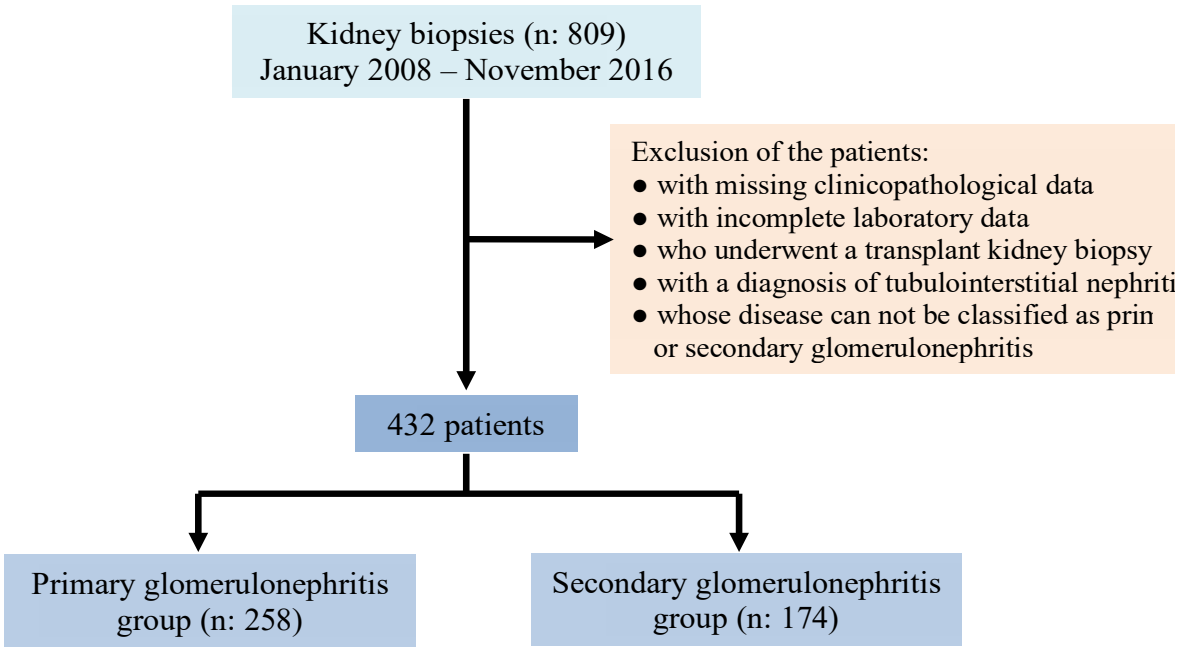

Figure 1. Flow chart of patient selection and study design.

Uludag University Faculty of Medicine approved the study (Approval number: 2017-14/30). We extracted the participants' demographic features, comorbidities, clinical manifestations, laboratory findings at admission, pathological results, treatments, and clinical courses. SPEP results and graphs at the time of admission were accessed from patient files or electronic medical records of our centre.

Figure 1 displayed the patient's flow chart. The patients were classified as PGn and SGn by two experienced nephrologists, evaluating their laboratory and histopathological findings and clinical courses. Histopathologic features of mesangial proliferation, tubulointerstitial polymorphonuclear inflammation, crescents in light microscopy, mesangial and/or diffuse staining in immunofluorescence microscopy, monoclonal light chain staining were considered a secondary aetiology. Patients with membranous glomerulonephritis (MGN) were considered primary MGN whose histopathologic features were consistent with typical findings and positive phospholipase A2 receptor (PLAR2) antibody. MGN patients with mesangial proliferation in their biopsy and negative anti-PLA2R were typed as secondary MGN. Patients with histopathological findings of amyloidosis, cast nephropathy, and monoclonal gammopathy of renal significance were also classified as SGn. We excluded patients with incomplete clinicopathological and lab-

Table 1. Clinicopathological characteristics of the patients (n: 432).

Parameters	Values
Age (years)	43.1 (14.0:84.0)
Gender (Male)	246 (56.9)
Serum urea (mg/dL)	43.0 (10.0:277.0)
Serum creatinine (mg/dL)	1.1 (0.2:13.6)
24-h urine protein (g/day)	4.5 (0.0:49.8)
Indications for biopsy	
Nephrotic syndrome	180 (41.6)
Nephritic syndrome	148 (34.3)
Isolated non-nephrotic proteinuria	96 (22.2)
Isolated glomerular hematuria	8 (1.9)
Histopathological diagnosis	
Primary glomerulonephritides	258 (59.7)
MGN	84 (19.4)
FSGS	77 (17.8)
IgA nephropathy	46 (10.7)
MPGN	25 (5.8)
MCD	24 (5.6)
Fibrillary GN	2 (0.4)
Secondary glomerulonephritides	174 (40.3)
AA amyloidosis	42 (9.7)
AL amyloidosis	6 (1.4)
Lupus nephropathy	34 (7.9)
Crescentic GN	25 (5.8)
MGN	10 (2.3)
FSGS	15 (3.5)
MPGN	12 (2.8)
Diabetic nephropathy	8 (1.8)
Hypertensive nephropathy	5 (1.2)
IgA nephropathy	4 (0.9)
MGRS	5 (1.2)
Cast nephropathy	3 (0.7)
Thrombotic microangiopathy	3 (0.7)
MCD	1 (0.2)
Fibrillary GN	1 (0.2)

MGN: membranous glomerulonephritis, FSGS: focal segmental glomerulosclerosis, MPGN: membranoproliferative glomerulonephritis; MCD: minimal change disease, GN: glomerulonephritis, MGRS: monoclonal gammopathy of renal significance.
The values were expressed as n (%) or median (minimum: maximum).

oratory data, those who underwent transplant kidney biopsy, and those who cannot be classified as PGn or SGn.

Statistical analysis

Statistical analyses were conducted operating SPSS, version 28.0 (IBM, NY, USA). Descriptive statistics were presented as percentages for categorical variables and mean with standard deviation or median with ranges according to the distribution of variables for continuous variables. Student t-test or Mann–Whitney U test for continuous variables and Pearson's Chi-squared test for categorical variables were used to compare the variables between groups. The optimal cut-off point for α1*Ɣ/albumin ratio was determined using receiver operating characteristic (ROC) curve analysis. Enter method was employed for multivariate binary logistic regression analysis, including factors with a *p* - value below 0.20 in univariate analysis. A *p* - value of 0.05 was set for statistical significance.

RESULTS

A total of 432 patients (43.1 [14.0-84.0] years old, 56.9% male) were enrolled in our study. Demographic and clinicopathological characteristics were shown in Table 1. The leading cause of kidney biopsy was nephrotic syndrome (41.6%), followed by nephritic syndrome. Approximately 60% of the cases were patients with PGn, and 174 had SGn. The most common histopathological diagnosis was MGN in PGn, accounting for 32.6% of PGn cases, and amyloidosis (11.1%) in SGn. The etiological causes of SGn were presented in Table 2. Approximately half of the patients with SGn (49.4%) had rheumatological diseases, and systemic lupus erythematosus was the leading aetiology. Malignancy and infection were common for the following reasons. Nine patients were included in the SGn group due to clinicopathological and laboratory findings (mostly amyloidosis patients), but etiological reasons could not be revealed.

Clinical and laboratory parameters of PGn and SGn were compared in Table 3. Female patients were more common in the SGn group than in the PGn group. Haemoglobin level, 24-hour urine protein and serum total cholesterol, complement 3 (C3) and complement 4 (C4) levels were significantly higher in patients with PGn. Conversely, serum urea, creatinine, total protein, C-reactive protein, and immunoglobulin G levels were significantly higher in the SGn group than in the PGn group. Analysis of protein fractions in SPEP revealed that the percentage of albumin was significantly higher in patients with PGn. However, α1 and Ɣ percentages were significantly higher in patients with SGn.

We calculated the (α1*Ɣ)/albumin ratio ([% of α1 fraction multiplied by % of Ɣ fraction] divided by % of albumin fraction) using SPEP fractions, which differed significantly between PGn and SGn to determine the value of SPEP in distinguishing PGn and SGn. Figure 2A demonstrated the Box-and-whisker plot showing (α1*Ɣ)/albumin ratio in PGn and SGn groups. Figure 2B showed the ROC curve of (α1*Ɣ)/albumin ratio, taking the presence of SGn as the endpoint of interest. In ROC curve analysis, the cut-off value for (α1*Ɣ)/albumin ratio was determined as ≥ 1.48 (AUC: 0.680, sensitivity: 70.7%, specificity: 61.2%, $p < 0.001$).

The results of binary logistic regression analysis were exhibited in Table 4. Multivariate analysis revealed that serum total protein level (odds ratio [OR], 1.768; 95% confidence interval [CI], 1.093-2.861; *p* =

Table 2. Etiological causes of secondary glomerulonephritides (n: 174).

Etiological reasons	Frequency
Systemic lupus erythematosus	36 (20.7)
Vasculitides	27 (15.5)
Malignancy	13 (7.5)
Infection	13 (7.5)
Familial Mediterranean fever	10 (5.7)
Multiple myeloma	8 (4.6)
Diabetes mellitus	8 (4.6)
Hypertension	7 (4.0)
Rheumatoid arthritis	7 (4.0)
Obesity	5 (2.9)
Monoclonal gammopathy of renal significance	5 (2.9)
Bronchiectasis	4 (2.3)
Thrombotic thrombocytopenic purpura	4 (2.3)
Lymphoproliferative disorders	4 (2.3)
Myeloproliferative disorders	2 (1.1)
Ankylosing spondylitis	4 (2.3)
Psoriasis	3 (1.7)
Mixed connective tissue disease	1 (0.6)
Behcet's disease	1 (0.6)
Obstructive uropathy	1 (0.6)
Inflammatory bowel disease	1 (0.6)
Fabry disease	1 (0.6)
Unknown*	9 (5.1)

*Histopathological diagnoses of patients whose etiological cause could not be found were AA amyloidosis, membranous glomerulonephritis and membranoproliferative glomerulonephritis.

Table 3. Comparison of clinical and laboratory parameters of primary and secondary glomerulonephritides.

Parameters	Primary GN	Secondary GN	*P* - value
Age (years)	42.3 (17.0:84.0)	45.2 (14.0:78.7)	0.057
Gender (male)	162 (62.8%)	84 (48.3%)	0.003
Serum urea (mg/dL)	39.5 (11.0:277.0)	54.0 (10.0:268.0)	< 0.001
Serum creatinine (mg/dL)	1.1 (0.2:13.6)	1.4 (0.4:13.0)	< 0.001
Serum total protein (g/dL)	5.6 (2.8:8.3)	5.9 (2.9:8.7)	0.048
Serum albumin (g/dL)	3.0 (0.3:4.9)	3.0 (0.7:4.9)	0.792
Total cholesterol (mg/dL)	255.0 (80.0:892.0)	200.5 (73.0:642.0)	< 0.001
Haemoglobin (g/dL)	12.9 ± 2.0	11.1 ± 2.2	< 0.001
24-h urine protein (g/day)	4.9 (0.0:49.8)	3.9 (0.0:29.1)	0.066
SPE-albumin (%)	51.2 (6.6:79.0)	47.3 (6.2:64.9)	< 0.001
SPE-alpha-1 (%)	5.6 (1.4:15.5)	6.2 (1.3:14.2)	0.005
SPE-alpha-2 (%)	15.8 (2.9:39.7)	14.0 (1.5:46.2)	0.087
SPE-beta (%)	12.7 (5.9:28.0)	12.2 (5.5:31.4)	0.210
SPE-gamma (%)	13.1 (3.8:27.6)	16.1 (3.2:42.7)	< 0.001
ESR (mm/hour)	26.5 (2.0:120.0)	41.0 (2.0:133.0)	< 0.001
CRP (mg/dL)	0.35 (0.02:18.0)	0.8 (0.03:26.8)	< 0.001
C3 (mg/dL)	126.0 (13.0:223.0)	114.0 (13.0:260.0)	< 0.001
C4 (mg/dL)	29.4 (6.5:138.0)	25.5 (1.7:59.8)	0.008
IgG (mg/dL)	742.0 (143.0:2320.0)	988 (190.0:3380.0)	< 0.001
IgM (mg/dL)	98.3 (16.0:434.0)	95.7 (16.0:1070.0)	0.883

GN: glomerulonephritis, SPE: serum protein electrophoresis, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, C3: complement 3, C4: complement 4, Ig: immunoglobulin.
The values were expressed as median (minimum:maximum), n (%) or mean ± standard deviation.

0.020), and (α1*Ɣ)/albumin ratio (OR, 4.235; 95% CI, 1.739–10.310; $p < 0.001$) were independent predictors for SGn. Other variables lost statistical significance in multivariate analysis.

DISCUSSION

To our knowledge, this is the first study assessing the predictive value of SPEP in classifying glomerular diseases as PGn and SGn. We found that α1, Ɣ, and albumin fractions in SPEP differ significantly between PGn and SGn, and the (α1*Ɣ)/albumin ratio produced from the percentages of SPEP fractions was higher in the SGn group than in the PGn group. Furthermore, serum total protein level was an independent predictor for SGn.

SPEP separates the serum proteins into albumin

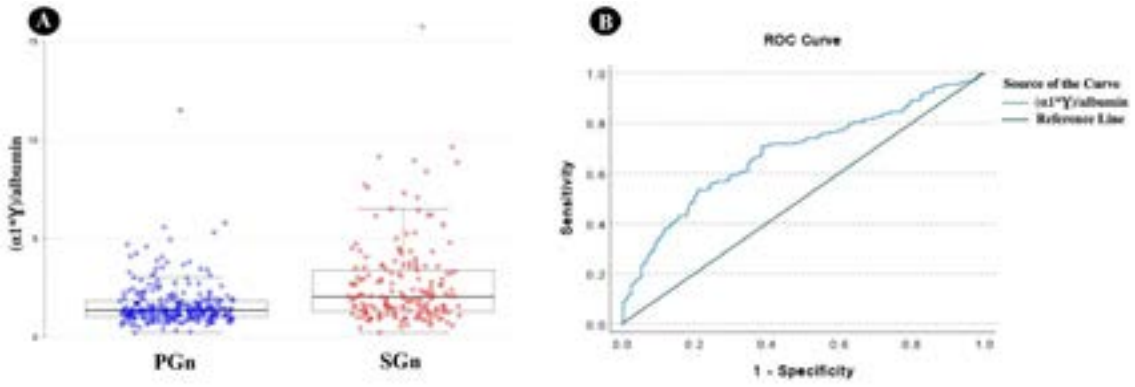

Figure 2. A: Boxplot scheme of (α1*Ɣ)/albumin ratio in primary (PGn) and secondary (SGn) glomerulonephritis groups. The median was indicated as the black line, and circles expressed all individual data. B: The ROC curve (α1*Ɣ)/albumin ratio.

Table 4. Univariate and multivariate logistic regression analysis for the predictors of secondary glomerulonephritides.

Factor	Univariate analysis				Multivariate analysis			
	OR	95% CI		*p* - value	OR	95% CI		*p* - value
		Lower	Upper			Lower	Upper	
Age (years)	1.011	0.998	1.024	0.086	1.016	0.991	1.042	0.222
Gender (male [RC] vs female)	1.818	1.224	2.671	0.003	0.478	0.202	1.127	0.092
Serum urea (mg/dL)	1.011	1.006	1.015	< 0.001	0.991	0.978	1.042	0.228
Serum creatinine (mg/dL)	1.280	1.150	1.424	< 0.001	1.384	0.975	1.964	0.069
Serum total protein (g/dL)	1.184	1.006	1.392	0.042	1.768	1.093	2.861	0.020
Serum albumin (g/dL)	0.981	0.796	1.208	0.854				
Total cholesterol (mg/dL)	0.995	0.992	0.997	< 0.001	1.001	0.996	1.006	0.732
Haemoglobin (g/dL)	0.657	0.589	0.732	< 0.001	0.856	0.665	1.102	0.228
24-h urine protein (g/day)	0.959	0.925	0.994	0.024	0.996	0.909	1.092	0.936
ESR (mm/hour)	1.019	1.011	1.027	< 0.001	1.011	0.994	1.028	0.223
CRP (mg/dL)	1.219	1.109	1.340	< 0.001	1.063	0.900	1.257	0.472
C3 (mg/dL)	0.990	0.984	0.996	< 0.001	0.988	0.974	1.001	0.074
C4 (mg/dL)	0.971	0.953	0.989	0.002	0.981	0.949	1.014	0.260
IgG (mg/dL)	1.001	1.001	1.002	< 0.001	0.999	0.998	1.001	0.304
IgM (mg/dL)	1.001	0.999	1.004	0.279				
(α1*Ɣ)/albumin ratio (low [RC] vs high)	3.811	2.525	5.750	< 0.001	4.235	1.739	10.310	< 0.001

OR: odds ratio, CI: confidential interval, RC: reference category, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

and globulin fractions based on charge-by-mass ratio under an electrical field. Albumin constitutes the most prominent fraction of SPEP. The liver produces albumin, the primary determinant of plasma oncotic pressure. Also, it functions as a transporter of various substances in the blood.16 Numerous clinical conditions accompany hypoalbuminemia in which either decreased production or increased loss results. Due to its low molecular weight and glomerular loss, hypoalbuminemia is frequently encountered in nephrotic syndrome and acute glomerulonephritis.6,17 In addition, clinical conditions driven by inflammation are among the most noteworthy disorders causing hypoalbuminemia. In the case of inflammation, several mechanisms result in hypoalbuminemia: (1) the inhibition of the hepatic secretion of albumin mediated by the proinflammatory cytokine-IL6 and (2) the increase in interstitial volume secondary to the increased capillary permeability by proinflammatory cytokines such as vascular endothelial growth factor and (3) the decrease in circulatory half-life of albumin.18,19 Duration and severity of inflammation have been associated with the severity of hypoalbuminemia.18 Rheumatological diseases, malignancies, and infections, which constitute nearly 3/4 of SGn in our study, are accompanied by severe inflammation at the whole-body level.18 In this context, we attributed the low albumin fraction in SPEP in SGn to the more prolonged and severe inflammation due to the underlying disease.

The α1 fraction of SPEP consists of alpha-1 antitrypsin (A1T), alpha-1-chymotrypsin, transcortin, and thyroid-binding globulin.[5,20] A1T is a plasma serine protease inhibitor and a significant component of the α1 band. It increases after initiating inflammation and is vital in limiting tissue injury mediated by proteases during inflammation.[21] In inflammatory conditions such as infection and tissue damage, A1T may increase up to six times above steady-state levels.[22] Furthermore, it has been reported that A1T can be used as a biomarker for evaluating the efficacy of chronic infections such as tuberculosis since it regresses after treatment.[22,23] Malignancy can also increase the α1 protein band in SPEP.20 The gamma fraction includes mainly serum immunoglobulins. Clonal proliferation of plasma cells, as occurred in multiple myeloma and plasmacytoma, results in monoclonal gammopathy. Overproducing more than one class of immunoglobulins by plasma cells prompts polyclonal gammopathy, associated with liver disease, malignancies, chron-

ic inflammation, and autoimmune disorders such as rheumatological diseases.[24] All these data support the finding in our study that α1 and γ bands are more prominent in SGn.

Although the absolute serum albumin levels in the two groups in our study were similar, significantly lower albumin fractions in SPEP in the SGn group can be explained by the global evaluation of all serum proteins in SPEP because it has been reported that total protein increases in chronic inflammation and malignancies, consistent with our results.[4] With this regard, evaluation of total protein increase using fractional distribution, as in SPEP, maybe more valuable in the differential diagnosis of glomerular diseases.

Glomerulonephritis is a heterogeneous group of diseases causing around 20% of ESRDs, although uncommon.[25] To control the disease in SGn, it is necessary to eliminate the underlying condition in addition to the anti-inflammatory and immunosuppressive therapy used in PGn. Therefore, it is crucial to differentiate between PGn and SGn to direct the most appropriate treatment.[11] However, classifying glomerulonephritis according to aetiology is sometimes challenging because histopathological findings can only sometimes identify secondary causes. Although some recent biomarkers can help the clinician in this distinction, especially in certain types of histopathological glomerulonephritis, new biomarkers are still needed.[12,13] In this context, we proclaim that the (α1*γ)/albumin ratio generated from SPEP, an easy, inexpensive, and easily accessible test, may help differentiate PGn and SGn. By confirming our results with studies investigating the (α1*γ)/albumin ratio in patients with certain glomerulonephritis types and more extensive prospectively designed analyses, this ratio may meet the urgent need for biomarkers.

The strengths of our study were that all patients were followed for at least five years after diagnosis due to the possibility of underlying systemic reasons for the PGn group and a relatively high number of participants. Nevertheless, our study had limitations: a retrospective design and an inability to test the predictive value of SPEP by performing particular analyses for each etiological reason of SGn. Additionally, accompanying conditions that may change SPEP findings, such as acute infection, A1T deficiency, and iron deficiency anaemia, may have impacted our findings. Therefore, prospective studies that exclude patients with such confounding conditions must confirm our results.

CONCLUSIONS

We conclude that the (α1*γ)/albumin ratio generated from fractions of SPEP may differentiate glomerular diseases between PGn and SGn. This ratio may help clinicians in this regard after confirmation of our results in more extensive prospective studies.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Bursa Uludag University, Bursa, Turkey. (Decision number: 2017-14/30, date: 03.10.2017).

Authors' Contribution

Study Conception: MG, ABS; Study Design: MG, ABS, AM; Supervision: MG, AM, AE, AO; Funding: N/A; Materials: N/A; Data Collection and/or Processing: ABS, SB, SEGB; Statistical Analysis and/or Data Interpretation: GO, ABS, AM; Literature Review: ABS, AO, AE, SB, SEBG; Manuscript Preparation: ABS, AO, SEGB, SB; and Critical Review: MG, AE, AM, AO, GO.

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