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Anemia in FSGS patients: Incidental Comorbidity or a Neglected Contributor?

Anemia en pacientes con GEFS: ¿Comorbilidad incidental o un contribuyente desatendido?

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RESUMEN

Introducción: La esclerosis glomerular focal y segmentaria (FSGS) es una de las glomerulonefritis más comunes. Se han propuesto varios mecanismos que podrían contribuir a la falta de respuesta al tratamiento en la FSGS primaria, tales como la cantidad de proteinuria basal, la tasa de esclerosis histopatológica y la presencia de pacientes no diagnosticados con FSGS secundaria. En este estudio, nuestro objetivo fue investigar los posibles factores que afectan la respuesta al tratamiento en la FSGS primaria. **Métodos**: Nuestro estudio es una cohorte retrospectiva de un solo centro que incluye pacientes diagnosticados con esclerosis glomerular focal y segmentaria mediante biopsias renales entre 2008 y 2018. Se identificaron un total de 185 pacientes diagnosticados con FSGS. Se registraron los subtipos de FSGS de estos pacientes. Se incluyeron 57 pacientes con un seguimiento y antecedentes de tratamiento completos. Cuarenta y uno de estos pacientes tenían FSGS primaria y 16 FSGS secundaria. Se analizaron las características basales, los parámetros de laboratorio, los hallazgos histopatológicos y los tratamientos iniciales en pacientes con FSGS primaria. Se compararon los respondedores y no respondedores a los tratamientos iniciales, y se analizaron los factores de riesgo para la falta de respuesta a los seis meses del tratamiento inicial. **Resultados**: No se encontraron diferencias en las características basales de los pacientes respondedores y no respondedores, ni en la mayoría de los parámetros de laboratorio o características histopatológicas. Los respondedores presentaron niveles de hemoglobina basal significativamente más altos que los no respondedores [13.5 (±1.5) en comparación con 12.1 (±2.9), respectivamente; p=0.003]. La anemia aumentó significativamente el riesgo de no respuesta al tratamiento [OR: 8.12 (mínimo: 1.12 – máximo: 66.16), p=0.048]. **Conclusiones**: Los resultados de nuestro estudio sugieren que la presencia de anemia puede ser un factor de riesgo para la falta de respuesta al tratamiento inicial en la FSGS. Aunque se conoce la relación entre la anemia y la fibrosis orgánica, existe incertidumbre sobre la eventual relación fisiopatológica de la anemia con la FSGS o si es incidental debido a su alta prevalencia. Se necesitan más estudios para aclarar estos hallazgos.

Palabras Clave: Esclerosis glomerular segmentaria focal, anemia, fibrosis

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ABSTRACT

Introduction: Focal segmental glomerulosclerosis (FSGS) is one of the most common glomerulonephritis. Several mechanisms have been proposed that may lead to treatment non-response in primary FSGS, such as the baseline proteinuria amount, histopathological sclerosis rate, and undiagnosed patients with secondary FSGS. This study investigated the possible factors affecting treatment response in primary FSGS. **Methods**: Our study is a single-center retrospective cohort study that included patients diagnosed with focal segmental glomerulosclerosis by renal biopsies between 2008 and 2018. A total of 185 patients diagnosed with FSGS were identified. The FSGS subtypes of these patients were recorded. There were 57 patients with complete follow-up and treatment histories. Forty-one of these patients were primary FSGS, and 16 were secondary FSGS. Baseline characteristics, laboratory parameters, histopathologic findings, and initial treatments were analyzed in patients with primary FSGS. Responders and non-responders to initial treatments were compared, and risk factors for nonresponsiveness were analyzed in the sixth month of the initial treatment. **Results**: No difference existed in the responder and non-responder patients' basal characteristics, most laboratory parameters, or histopathologic features. Responders had significantly higher baseline hemoglobin levels than non-responders [13.5 (±1.5) and 12.1 (±2.9), respectively; p=0.003]. Anemia significantly increased the risk of treatment nonresponsiveness [OR: 8.12 (min: 1.12 – max: 66.16), p=0.048]. **Conclusions**: The results of our study suggest that the presence of anemia may be a risk factor for FSGS initial treatment nonresponsiveness. Although the relationship between anemia and organ fibrosis is known, uncertainty exists about whether anemia is pathophysiologically related to FSGS or incidental due to its high prevalence. More studies are needed to clarify this uncertainty.

Keywords: Focal segmental glomerulosclerosis, anemia, fibrosis.

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is one of the most common histopathologic glomerular lesions in adult and pediatric patients. Primary FSGS is the most common cause of adult end-stage renal failure among glomerulonephritis [1,2]. FSGS is a heterogeneous disease. Severe proteinuria, hypertension, interstitial fibrosis, glomerular sclerosis, and decreased renal function have been evaluated both clinically and pathologically as poor prognostic factors in FSGS [3]. FSGS is an immunological abnormality and is a glomerular lesion that develops due to podocyte damage rather than a disease. Previous studies have suggested that molecules defined as "soluble circulating permeability factors" may be involved in the pathogenesis of FSGS [4]. In the last decade, mutations detected in gene series encoding podocyte-specific molecules (such as NPHS1, NPHS2, ACTN4, TRPC6, and INF2) have been identified as genetic causes of FSGS [5].

FSGS is classified into primary, secondary, and genetic forms. FSGS occurs when multiple pathways directly or indirectly cause podocyte damage. Secondary FSGS is an adaptive phenomenon due to decreased nephron mass and direct toxicity of drugs or viral agents [6]. The presence of an FSGS lesion on renal biopsy has no diagnostic value but indicates the need for investigation to detect a specific etiology. Distinguishing the different forms of FSGS is essential regarding treatment and prognosis. Our study aimed to investigate the possible factors affecting the treatment response in primary FSGS.

MATERIALS AND METHODS

Ethical Statements

The institute's committee on human research approved the study protocol.

Study Design

Our hypothesis-generating study is a single-center, retrospective cohort of patients diagnosed with FSGS with renal biopsies between January 2008 and January 2018 in our institute. A total of 185 patients diagnosed with FSGS were identified. The FSGS subtypes of these patients were recorded.

In our institute, the distinction between primary and secondary FSGS was made according to the histopathological features of the renal biopsies (e.g., immunofluorescence features), accompanying secondary conditions (e.g., obesity, drug exposure, genetic causes, pyelonephritis,

vesicoureteral reflux, unilateral renal agenesis, and systemic inflammatory diseases), and clinical features suggesting secondary condition such as a slowly progressing disease with a normal serum albumin level and lipid profile at the time of diagnosis. The team measured body mass indexes (BMI) to evaluate obesity. Patients with a BMI of ≥ 30 kg/m2 were considered obese based on the World Health Organization (WHO) BMI classification [7].

We analyzed the initial treatment response of the patients with primary FSGS in the sixth month. Baseline characteristics, related comorbidities, laboratory parameters, histopathological findings, and medical treatments were also analyzed. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. We calculated the total global and segmental sclerosis glomeruli ratio to all glomeruli in the biopsy material. Tubulointerstitial fibrosis scores were logged as mild, moderate, or severe. Anemia was defined according to values accepted by the World Health Organization (WHO) (hemoglobin below 12 g/dl for females, hemoglobin below 13 g/dl for males) [8]. Conservative treatment consisted of antiproteinuric treatment (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in maximum tolerated doses), adequate blood pressure control, hyperlipidemia treatment, and lifestyle changes such as weight loss and exercise, especially in patients with a high BMI. All patients receiving immunosuppressive treatment also received the conservative treatment. Daily urinary protein excretion, serum creatinine, and albumin levels were measured six months after the treatment initiation.

Based on the current studies in the literature and the kidney disease: Improving Global Outcomes guidelines, patients with urinary proteinuria <300 mg/day and stable eGFR after the treatment initiation were defined as "complete responders." Patients with more than 50% regression in daily proteinuria and stable eGFR were "partial responders." Patients with less than 50% proteinuria regression were defined as "nonresponsive." In the design of our study, patients with a complete response and partial response were included in the "responders" group and compared with"non-responders" to the initial treatment. The differences between the groups' baseline demographic characteristics, health parameters, and laboratory values were evaluated. The risk factors for nonresponsiveness in the sixth month were determined.

Statistical Analysis

The study's numeric values were shown with 1) mean and standard deviation or 2) medians with ranges, categorical data, frequency, and percentage. We compared categorical data with the T Chi-square Test. The Unpaired Student's T-Test was used to compare two groups for data normally distributed. The Kruskal-Wallis test was performed for abnormally distributed data. We used the Paired Samples T-test for normally distributed data to compare each group's baseline and sixth-month values and the Wilcoxon Test for non-normally distributed data. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis, with the backward selection, to determine the independent predictors of patient outcome. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Science (SPSS, Chicago, IL, USA) for personal computers, version 21.0.

RESULTS

Baseline Characteristics, Laboratory Parameters, and Initial Treatments of Patients

One hundred eighty-five patients with FSGS were analyzed; 93 (50.3%) were female and 92 (49.7%) were male. The mean age was 45.9±14.8 (20-84 years). The mean number of glomeruli in renal biopsy specimens is 20.5±12.1. When the histologic subgroups of FSGS were analyzed, 125(67.6%) patients were NOS variant, 21 (11.4%) were cellular variant, 23 (12.4%) were collapsing variant, 8 (4.3%) were tip lesion and 8 (4.3%) were perihilar variant. There were 57 patients with complete follow-up and treatment histories. Forty-one of these patients were primary FSGS, and 16 were secondary FSGS.

Forty-one patients with primary FSGS treatment responses were evaluated in the sixth month. While 30 (73.1%) patients were responders (complete or partial), 11 (26.9%) were non-responders. **Table 1** summarizes the primary FSGS patients' baseline characteristics.

When comparing the patients with or without

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Table 1: Baseline characteristics of the patients with primary FSGS (n=41)

Age, mean (±SD)	40.07 (±15.1)
Sex F/M (n)	23/18
BMI, mean (±SD) (kg/m2)	25.1 (±3.4)
Hypertension, n (%)	21 (51.2%)
Diabetes Mellitus, n (%)	3 (7.3%)
Smoking, n (%)	7 (17.1%)
Hematuria, n (%)	6 (14.6%)
Proteinuria (mg/d), median (min-max)	5093 (min:407 - max:20248)
eGFR, mean (±SD) (ml/min/1.73m2)	81.6 (±32.9)
Albumin, mean (±SD) (g/dl)	3.3 (±0.8)
Hemoglobin, mean (±SD) (g/dl)	13.1 (±2.06)
LDL cholesterol, mean (±SD) (mg/dl)	157.07 (±72.3)
Triglyceride, mean (±SD) (mg/dl)	212.1 (±145.4)

BMI: Body mass index, **Proteinuria:** 24-hour urine protein excretion at the time of diagnosis, **eGFR:** estimated glomerular filtration rate, **LDL:** low-density lipoprotein

a complete or partial response to the initial treatments, we found no difference in their baseline characteristics, comorbidities, most laboratory parameters, or histopathologic features (**Table 2**).

Treatment regimens of patients diagnosed with primary FSGS are shown in Table 3.

Table 2: Comparison based on initial treatment response after six months of therapy

	Responders (n=30)	Nonresponders (n=11)	P-value
Age	41.07 (±13.9)	37.3 (±18.2)	0.823
Sex F/M (n)	17/13	6/5	0.082
BMI, mean (±SD) (kg/m2)	24.5 (3.07%)	26.8 (4.05%)	0.828
Hypertension, n (%)	14 (46.7%)	7 (63.6%)	0.173
Diabetes Mellitus, n (%)	6 (20%)	1 (9.1%)	0.192
Smoking, n (%)	6 (20%)	1 (9.1%)	0.080
Proteinuria (mg/d), median (min-max)	3756 (min:407-max:20248)	4400 (min:1943-max:12130)	0.361
Hematuria	5 (16,6%)	1 (9.1%)	0.002
eGFR, mean (±SD) (ml/min/1.73m2)	85.3 (±31.8)	71.8 (±36.9)	0.473
Albumin, mean (±SD) (g/dl)	3.36 (±0.80)	3.22 (±0.81)	0.942
Hb baseline, mean (±SD) (g/dl)	13.5(±1.5)	12.1 (±2.9)	0.003
Hb 6th mo, mean (±SD) (g/dl)	13.6 (±1.5)	12.4 (±2.6)	0.001
LDL cholesterol, mean (±SD) (mg/dl)	153.8 (±61.4)	166 (±99.1)	0.071
Triglyceride, mean (±SD) (mg/dl)	197.1 (±143.9)	253 (±148.3)	0.581
Histological variant	NOS:22 (%73.3) Cellular:1 (%3.3) Tip:2 (%6.7) Perihilar:1 (%3.3) Collapsing:4 (%13.3)	NOS:8 (%72.7) Cellular:1 (%9.1) Tip:1 (%9.1) Collapsing:1 (%9.1)	0.413
Glomerulosclerosis (%)	31.2(±22.7)	42,6 (±31.2)	0.060
Tubulointerstitial fibrosis	Mild:14 Moderate:10 Severe:0	Mild:3 Moderate:5 Severe:1	0.201

Table 2: BMI: Body mass index, **Proteinuria**: 24-hour urine protein excretion at the time of diagnosis, **eGFR**: estimated glomerular filtration rate at the time of diagnosis, **Hb**: Hemoglobin, **mo**: months, **LDL**: low-density lipoprotein, **Glomerulosclerosis:** % of global or segmental sclerotic glomeruli on biopsy specimens

Table 3: Treatments of the patients with primary FSGS (n=41)

Medical treatment*	Patients without anemia (n=29)	Patients with anemia (n=12)
1mg/kg/d prednisolone	18	8
1mg/kg/d prednisolone plus CsA	3	1
CsA only	1	1
1mg/kg/d prednisolone plus Tac	1	0
Conservative only	6	2

CsA: Cyclosporine, **Tac**: Tacrolimus ***All patients who received immunosuppressive therapy also received conservative therapy**

The main difference between the two groups was the baseline hemoglobin levels. Those with a treatment response had significantly higher baseline hemoglobin levels than those without response [13.5(±1.5) and 12.1 (±2.9), respectively; p=0.003.] The hemoglobin value measured in the sixth month after the therapy initiation was significantly higher in responders compared to non-responders [13.6 (±1.5) and 12.4 (±2.6), respectively; p<0.001]. The frequency of patients with hematuria was significantly higher in the responder group than in the non-responder group (16.6% and 9.1%, respectively; p=0.002).

Comparison of Patient Characteristics and Initial Treatment Outcomes According to the Presence of Anemia

12 (29.2%) of 41 patients had anemia. The patients with or without anemia had similar baseline characteristics, laboratory parameters, and histopathologic features. **Table 4** shows the characteristics of the study population with or without anemia.

The etiological classification and treatments of patients diagnosed with anemia are given in **Table 5**.

Follow-up and treatment information regarding the anemia of 1 patient could not be obtained.

Comparison of Baseline and 6th-month Values of Anemic Patients

The baseline and the sixth-month hemoglobin levels of 12 patients with anemia are available in **Table 6.**

In the anemic patients, the mean baseline hemoglobin level was 10.7 (±1.6) g/dl and 10.8 (±0.9) g/dl in the sixth month (p=0.76). The mean proteinuria level was 3959.5 (min: 1785.0 - max: 11300.1) mg/day at the baseline and 3742.1 (min: 154.0 - max: 16867.2) mg/day at the sixth month (p=0.93). The mean baseline eGFR was 82.1 (±37.2) ml/min/1.73 m2, and the mean eGFR value in the sixth month was 78.8 (±35.3) ml/min/1.73 m2 (p=0.47). The mean baseline albumin value was 3.1 (±0.6) g/dl at baseline and 3.2 (±0.6) g/dlat the sixth month (p=0.86) (**Table 7**).

Initial Treatment Nonresponsiveness: The Logistic Regression Analysis of Possible Risk Factors

Logistic regression analysis was performed for the treatment response with the possible risk factors (age, tubulointerstitial fibrosis, proteinuria, glomerulosclerosis, and eGFR) and baseline hemoglobin value. Higher hemoglobin levels significantly decreased the risk of initial treatment nonresponsiveness when corrected for all possible risk factors [OR: 0.47 (min: 0.24 – max: 0.94), p=0.032]. When patients were classified and analyzed according to the presence of anemia, the presence of anemia significantly increased treatment nonresponsiveness risk [OR: 8.12 (min: 1.12 – max: 66.16), p=0.048]
(**Table 8**).

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Table 4: Comparison of primary FSGS patients without and with anemia

	Patients without anemia (n=29)	Patients with anemia (n=12)	P-value
Age, mean (±SD)	42.6 (±16.1)	33.9 (±10.2)	0.092
Sex F/M (n)	16/13	7/5	0.856
BMI, mean (±SD) (kg/m2)	24.6 (±2.9)	26.5 (±4.3)	0.112
Hemoglobin, mean (±SD) (g/dl)	14.1 (±1.2)	10.7 (±1.6)	<0.01
Proteinuria (mg/d), median (min-max)	3822 (min:407-max:20248)	3959.5 (min:1785-max:11300)	0.714
eGFR, mean (±SD) (ml/min/1.73m2)	81.5 (±31.6)	82.0 (±37.2)	0.962
Albumin, mean (±SD) (g/dl)	3.40 (±0.8)	3.12 (±0.59)	0.313
LDL cholesterol, mean (±SD) (mg/dl)	163.9 (±61.7)	140.5 (±94.2)	0.349
Triglyceride, mean (±SD) (mg/dl)	219.9 (±162.6)	193.2 (±94.9)	0.547
Histological variant	NOS: 22 Cellular:1 Tip:2 Perihilar:1 Collapsing:3	NOS:8 Cellular:1 Tip:2 Perihilar:0 Collapsing:2	0.642
Glomerulosclerosis (%)	30.9 (±25.1)	42.6 (±25.2)	0.191
Tubulointerstitial fibrosis	Mild:12 Moderate:10 Severe:7	Mild:4 Moderate:6 Severe:2	0.281
Medical treatment	1mg/kg/d prednisolone:18 1mg/kg/d prednisolone+CsA:3 CsA only:1 1mg/kg/d prednisolone+Tac:1 Conservative only:6	1mg/kg/d prednisolone:8 1mg/kg/d prednisolone+CsA:1 0,5mg/kg/d prednisone+CsA:1 Conservative only:2	-

BMI: Body mass index, **Proteinuria**: 24-hour urine protein excretion at the time of diagnosis, **eGFR**: estimated glomerular filtration rate at the time of diagnosis, **LDL**: low-density lipoprotein, **Glomerulosclerosis**: % of global or segmental sclerotic glomeruli on biopsy specimens

Table 5: Etiological Classification and Treatments of Patients Diagnosed with Anemia

	Female/Male (n)	Treatment (n)
Iron deficiency	4/0	Oral ferrous glycine sulfate (3) Oral ferrous ascorbate (1)
Vitamin B12 deficiency	0/1	Intramuscular cyanocobalamin
Iron + vitamin B12 deficiency	3/0	Oral ferrous glycine sulfate + oral methylcobalamin (1) Oral ferrous ascorbate + oral methylcobalamin (1) Oral ferrous glycine sulfate + Intramuscular cyanocobalamin (1)
Thalassemia trait	0/1	N/A
Negative work-up*	0/2	N/A
No work-up	1/0	N/A
Total	8/4	

***Including malabsorptive gastrointestinal disease and malignancy evaluation**

Table 6: Hemoglobin levels (baseline and sixth month) of patients diagnosed with primary FSGS and anemia

Patients	Gender	Hemoglobin (g/dl)- baseline	Hemoglobin (g/dl)- 6th month
Patient 1	Female	7,5	9,5
Patient 2	Female	8,0	9,6
Patient 3	Female	9,8	10
Patient 4	Female	10,1	10,4
Patient 5	Male	10,4	10,1
Patient 6	Female	11,3	11
Patient 7	Male	11,4	11,2
Patient 8	Female	11,5	11,1
Patient 9	Male	11,8	11,5
Patient 10	Female	11,8	11,9
Patient 11	Male	12,5	12
Patient 12	Male	12,5	12,1

Table 7: Results of anemic patients before primary treatment and in the sixth month

	Baseline	Sixth month	P-value
Hemoglobin, mean (±SD) (g/dl)	10.7 (±1.6)	10.8 (±0.9)	0.76
Proteinuria (mg/d), median (min-max)	3959.5 (min:1785.0-max:11300.1)	3742.1 (min:154.0-max:16867.2)	0.93
eGFR, mean (±SD) (ml/min/1.73m2)	82.1 (±37.2)	78.8 (±35.3)	0.47
Albumin, mean (±SD) (g/dl)	3.1 (±0.6)	3.2 (±0.6)	0.86

Table 8: Logistic regression analysis of possible risk factors for unresponsiveness to initial treatment

	OR (95% CI)	P-value		OR (95% CI)	P-value
Age	0.97 (0.90-1.04)	0.47	Age	0.98 (0.91-1.05)	0.632
Proteinuria (mg/d)	1.0 (1.0-1.001)	0.024	Proteinuria (mg/d)	1.00 (1.00-1.001)	0.022
Tubulointerstitial fibrosis	0.11 (0.003-4.29)	0.24	Tubulointerstitial fibrosis	0.22 (0.012-4.22)	0.314
Glomerulosclerosis (%)	1.03 (0.97-1.09)	0.26	Glomerulosclerosis (%)	1.02 (0.97-1.07)	0.308
eGFR (ml/min/1.73m2)	0.96 (0.93-1.007)	0.10	eGFR (ml/min/1.73m2)	0.98 (0.94-1.01)	0.213
Hemoglobin (g/dl)	0.47 (0.24-0.94)	0.032	Anemia	8.12 (1.12-66.16)	0.048

Proteinuria: 24-hour urine protein excretion at the time of diagnosis, **eGFR**: estimated glomerular filtration rate at the time of diagnosis, **Glomerulosclerosis**: % of global or segmental sclerotic glomeruli on biopsy specimens

DISCUSSION

The treatment response of patients with primary FSGS is shown to be less than 70%, regardless of extended immunosuppressive treatment [9]. Several risk factors for nonresponsiveness were identified. The amount of proteinuria at diagnosis is a significant risk factor. The response to the treatment is reported to be lower in cases presenting with nephrotic syndrome [10-13]. Another significant risk factor identified is the degree of renal dysfunction at diagnosis since the treatment response is reported more commonly in patients with normal

renal function [14-16]. The histological subtype is also essential. For example, the collapsing variant was described as having the worst prognosis, while the cellular variant is reported to be associated with the best prognosis [17]. Resistance to treatment is the most important known kidney survival risk factor. Renal survival is significantly increased in patients with a complete or partial response. The five-year renal survival for patients who are nonresponsive to treatment is less than 50%. This percentage increases by up to 80% for the patient responders [9,10,18,19].

Our study found no differences between the initial treatment responders and non-responders regarding age, gender, body mass index, or smoking status. The prevalence of diabetes mellitus and hypertension were similar in both groups. The non-responder group had insignificantly higher baseline proteinuria and lower baseline glomerular filtration rates than the responder group. The albumin values at diagnosis time were also similar in both groups. In our study, the frequency of hematuria was significantly higher in the responders group. This finding supports that the presence, or the amount of hematuria, is not a prognostic factor in primary FSGS [20]. No significant difference was found in the baseline biopsy specimens of glomerular sclerosis, tubulointerstitial sclerosis, and histological variant distribution.

Our study's most remarkable finding was the lower hemoglobin level and the higher anemia prevalence in nonresponsive patients compared to the patients with initial treatment responses. For non-responders, the proteinuria rates tend to be higher, and the glomerular filtration rates tend to be lower without statistical significance. Studies have reported that the amount of protein in the 24-hour urine specimen at the time of diagnosis, glomerular filtration rate, and the degree of glomerular and tubulointerstitial fibrosis in kidney biopsy specimens are the main risk factors for no responsiveness to FSGS treatment and progression to ESRD (9,21). In the regression analysis, we included the serum hemoglobin levels, the most significant difference between the groups in our study. In the logistic regression analysis, the higher hemoglobin levels seem protective regarding treatment nonresponsiveness.

Considering the results of our analysis, a model was created with the same risk factors. This time, anemia was added to the regression analysis as a possible risk factor, considering the WHO-accepted hemoglobin values. Similarly, all other factors lost significance in the regression analysis. Anemia was identified as a risk factor for 8.12-fold of patients' treatment nonresponsiveness.

Anemia and primary FSGS coexistence were reported in the literature. For example, in the study of Joardar et al., 69.2% of children with nephrotic syndrome were reported to be anemic at their first admission [22]. Park et al. reported a case of secondary FSGS in one patient with aplastic anemia [23]. Anemia was reported as an essential risk factor for the development of renal fibrosis and progression to ESRD in CKD patients. The correction of anemia was shown to slow the progression to ESRD [24-27]. However, to our knowledge, no study reports that anemia is an etiologic or a prognostic factor for FSGS.

Anemia was shown to impair oxygenation in the population without CKD. This concept was demonstrated by reducing microcirculatory red cells in all organs, including the kidneys [28,29]. Garrido et al. examined the effects of anemia on the renal tissue in the rodent model. Hypoxia-inducible factor-2α and β (HIF-2α and β) levels were significantly increased in the anemic rodents' kidneys. As a result, interleukin-6, interleukin-1β, and tumor necrosis factor-mRNA levels were increased. The nuclear factor kappa-B, connective tissue growth factor, and vascular endothelial growth factor levels were decreased. Lastly, and histopathologically, glomerular damage and tubulointerstitial fibrosis developed. No systemic inflammation was detected in this study. However, anemia causes an inflammatory response and is a contributing factor in the tissue-level fibrosis development. Proinflammatory cytokines such as interleukin-6, interleukin-1β, interferon-γ, and the macrophage migration inhibitory factor are essential in the anemia-inflammation relationship. These proinflammatory cytokines are generated in the early stages of infection due to the innate immune system's detection mechanisms. Nevertheless, in certain instances, the direct invasion of fully mature red blood cells (RBCs) or their precursor cells results in the destruction of RBCs or a reduction in the production of new RBCs, thereby causing anemia [30].

Hepcidin, a peptide synthesized in the liver, is the primary regulatory factor in iron absorption and distribution [31]. Inflammation increases

hepcidin levels, which facilitates functional iron deficiency by reducing iron availability at the bone marrow and myocardial levels. In the same way, inflammation affects the production of red blood cells by suppressing the synthesis of erythropoietin and its impact on erythropoiesis [32].

Reports demonstrate that chronic renal hypoxia can cause glomerulosclerosis before tubulointerstitial damage develops [33]. Inadequate glomerular capillary vascularization causes glomerulosclerosis, followed by decreased peritubular perfusion and tubulointerstitial fibrosis [33]. HIFs are the primary regulators of the hypoxic microenvironment [34]. HIF-1α plays a crucial role in vascular remodeling and consequently induces organ fibrosis. In this context, HIF inhibitors are developed to limit organ fibrosis and delay the progression of the disease [35].

FSGS is a disease associated with glomerular and tubulointerstitial fibrosis. Our study's results suggest that anemia may be a risk factor for treatment resistance in patients with FSGS. Anemia is a very prevalent condition in cases with FSGS. There are no reports of a relationship between FSGS and anemia in the literature on a pathophysiological basis. Pathophysiological interconnection can be suggested when considering the factors described above. The duration of the patient's anemia is unknown in our study. It can be hypothesized that long-term anemia leads to tissue fibrosis caused by long-term tissue hypoxia with the mechanisms described above. Also, the treatment response rates may be adversely affected due to persistent fibrotic changes in patients.

Our main limitation is the study's single-center retrospective observational method. Our study determined that anemia can be a risk factor for primary FSGS treatment nonresponsiveness. However, to support our findings, the effects of previous or simultaneous anemia treatment should be demonstrated in FSGS management. Our contribution to the literature is to draw attention to a possible related factor that can be undertreated while managing primary FSGS.

CONCLUSIONS

The results of our study suggest that anemia may be a risk factor for FSGS initial treatment nonresponsiveness. Although the relationship between anemia and organ fibrosis is well known, it is unknown whether anemia, due to its high prevalence, is pathophysiologically related to FSGS or is incidental. Further studies are required to elucidate this subject.

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