Risk factors associated with renal crescentic formation in pediatric Henoch–Schönlein purpura nephritis: a retrospective cohort study

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Abstract

Background

The long-term prognosis of Henoch-Schönlein purpura (HSP) depends on the severity of renal involvement, crescentic formation is considered to be an important risk factor for poor prognosis of Henoch-Schönlein purpura nephritis (HSPN). The objective of this study was to evaluate factors affecting crescent formation in children with HSPN.

Methods

Demographic factors, clinical characteristics, and laboratory data of children with HSPN with or without crescents were retrospectively analyzed. Univariate and multivariate logistic regression analyses were used to determine the risk factors of crescent formation in HSPN.

Results

A total of 191 children with HSPN were enrolled in the study. There were 107 (56%) males and 84 (44%) females, with a median age of 7 years (range: 2 years–15 years). International Study of Kidney Disease in Children (ISKDC) grading was used to divide subjects into two groups: those without glomerular crescent formation (ISKDC grades I–II, n = 146 cases) and those with glomerular crescentic formation (ISKDC grades III–V, n = 45 cases). Logistic regression analysis showed that higher urinary white blood cell (WBC) count (OR = 3.300; 95% CI, 1.119–9.739; P = 0.0306) and higher urinary microalbumin/creatinine ratio (ACR) (OR = 25.053; 95% CI, 1.354–463.708; P = 0.0305) were independent risk factors for the formation of crescents in HSPN. The area under the receiver operating characteristic curve of urinary WBC and ACR were 0.753 and 0.698 respectively, with the Hosmer and Lemeshow goodness-of-fit test (P = 0.0669, P > 0.05).

Conclusion

These results suggest that higher urinary WBC count and ACR should be strictly monitored for children with HSPN. Adequate clinical intervention for these risk factors may limit or prevent renal crescent formation.

Background

Henoch-Schönlein purpura (HSP), also known as IgA vasculitis, is the most common systemic vasculitis in children [1], with an incidence of 20 cases per 100,000 children annually [2]. It is considered to be a self-limiting disease; however, the long-term prognosis depends on the severity of renal involvement [3]. Renal involvement, particularly HSP nephritis (HSPN), may occur in 34% of HSP children [4], although

most children with HSPN have the opportunity to recover completely. HSPN may progress to renal failure in 2–20% of individuals [5, 6].

As the clinical symptoms and signs of HSPN vary greatly, it is difficult to predict the outcome and severity of HSPN [7]. Renal biopsy is the gold standard for evaluating the severity and prognosis of HSPN. Certain pathological features may be of value in predicting the prognosis of HSPN [7]. The existence of crescents is a prominent histological feature of HSPN and constitutes the basis of the pathological classification promulgated by the International Study of Kidney Disease in Children (ISKDC). Renal biopsy histological grade (grades I–II vs. grades III–V) score based on crescentic ISKDC pathological classification strongly predicts the prognosis of children with HSPN [8]. Also, in children, crescentic nephritis (ISKDC grades III–V) is considered to be an important risk factor for poor prognosis of HSPN [9, 10, 11]. Studies have reported the risk factors of renal involvement in HSP [12, 13]. However, the discovery of risk factors for progression to crescentic HSPN (ISKDC grades III–V) is an important issue for children with HSP with known renal involvement. To the best of our knowledge, risk factors in children for progression to crescentic HSPN have not been reported.

Methods

Patients

This study is a single-center, retrospective study of 191 children under the care of the Department of Nephrology and Immunology of the Children's Hospital of Soochow University from January 2016 to October 2019. The diagnosis of HSPN was by clinical presence of hematuria and/or proteinuria within 6 months of the course of Henoch-Schönlein purpura [14]. Hematuria was classified as either gross hematuria or microscopic hematuria (≥ five red blood cells/high power microscopic field three times a week). Proteinuria was diagnosed based on any of the following criteria: (1) routine urine qualitative analysis showing positive urine protein three times within one week; (2) 24-hour urine protein quantification > 150 mg or urinary protein/creatinine (mg/mg) > 0.2; or (3) a urine microalbumin above normal, three times within one week.

Renal biopsy and pathological examination was performed to further confirm the diagnosis of HSPN and to determine the severity of renal injury. Clinical treatment was carried out according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [14, 15].

Renal biopsies were obtained with the informed consent of the parents or guardians of the children. This study was reviewed and approved by the Ethics Committee of the Children's Hospital of Soochow University.

Procedures

Data collection included demographic data, clinical manifestations, laboratory data and renal biopsy characterization. Standard blood and chemistry studies, C-reactive protein (CRP) level, cellular and humoral immunity, hepatic and renal function indicators, mycoplasma antibody, antistreptolysin O test, and coagulation profiles were determined. Urine samples were collected for white blood (WBC) and red blood cell (RBC) counts, protein and creatinine, and qualitative examination of urinary occult blood and protein. This study had quantitative and qualitative variable data for 52 possible indicators.

All renal biopsy specimens were examined by light microscopy and immunofluorescence. Specimens were read by two pathologists (a chief physician and a deputy chief physician) who remained blind to clinical history and laboratory data. Two physicians,the chief in the department of pediatric nephrology and immunology, graded the pathological results. The biopsy results were graded according to the classification of the ISKDC [16]: (I) minimal alterations; (II) mesangial proliferation; (IIIa) focal or (IIIb) diffuse proliferation or sclerosis with < 50% crescents; (IVa) focal or (IVb) diffuse mesangial proliferation or sclerosis with 50–75% crescents; (Va) focal or (Vb) diffuse mesangial proliferation or sclerosis with > 75% crescents; and (VI) membranoproliferative-like lesions.

Statistical analysis

Univariate statistical analyses were performed using Statistics Analysis System (SAS) software version 9.2 (SAS Institute Inc., Cary, NC, USA). Variable data were grouped according to two histopathological categories: those without glomerular crescent formation (ISKDC grades I–II) and those with glomerular crescentic formation (ISKDC grades III–V). The quantitative data were analyzed using *t*-Test (homogeneity of variance) or Wilcoxon rank-sum test (heterogeneity of variance). The chi-square or Fisher's exact test (dichotomous data) and the Wilcoxon two-sample test (multi-categorical data) were carried out on the qualitative data. Stepwise logistic regression analysis, performed on SAS 9.2, was used for multivariate analysis to assess the risk factors for crescentic HSPN. The odds ratios (OR) and the 95% confidence intervals (CI) were calculated. The diagnostic efficacy of the logistic regression model was evaluated by the receiver operating characteristic curve (ROC) and the Hosmer and Lemeshow goodness-of-fit test. The confidence interval was 95%, and for all tests the level of statistical significance was defined as 0.05.

Results

A total of 191 children with HSPN received their first renal biopsy as part of this study, which included 107 (56%) males and 84 females (44%), with a median age of 7 years (range: 2–15 years). According to ISKDC criteria, subjects were divided into two groups: those without glomerular crescent formation (ISKDC grades I–II, n = 146 cases) and those with glomerular crescentic formation (ISKDC grades III–V, n = 45 cases). All patients in the crescent group were ISKDC grade IIIa–IIIb. There were no individuals classified as ISKDC grades IV–VI.

Among the 52 variables assessed by univariate analysis, there were significant differences in 18. The variables in the qualitative data set were abdominal pain, repeated rash more than three times per week, urinary occult blood, and urinary protein levels (Table 1). The variables in quantitative data were C-reactive protein, WBC, platelet, complement component 3, total cholesterol, triglyceride levels, 24-hour urinary microalbumin, 24-hour urinary total protein, urinary RBC count, urinary WBC count, N-acetylglucosaminidase (NAG), α1-microglobulin, urinary transferrin (TRU), and urinary ACR (Table 2).

Table 1
Univariate analysis of the factors associated with qualitative data in HSPN patients with and without crescent formation

Variable	Grade I-II n = 146	Grade III-V n = 45	X^2	P
Gender, Male/Female	79/67	28/17	0.9033	0.3491
Age, ≥ 8/<8 years	87/59	28/17	0.0414	0.8389
Age, ≥ 10/<10 years	50/96	17/28	0.0786	0.7792
Food intolerance, Severe/<Severe	51/80	16/24	0.0147	0.9035
Upper respiratory tract infection, Yes/No	22/118	11/34	1.7709	0.1833
Joint pain, Yes/No	60/82	20/24	0.1404	0.7079
Abdominal pain, Yes/No	46/96	25/20	7.7830	0.0053
Occult blood in stool, Yes/No	40/103	17/27	1.8058	0.1790
Recurrence of HSP, Yes/No	22/120	12/33	2.8679	0.0904
Season, Winter-Sping/Summer-Autumn	80/65	23/22	0.2282	0.6329
Recurrence of skin rash, ≥ 3/<3 times	9/136	7/39	3.6940	0.0383*
Recurrence of skin rash, Yes/No	61/84	26/19	3.4140	0.0646
Level of urine protein, -/+/++/+++	81/32/28/5	1/8/18/18	61.1805	□0.0001
Level of urine occult blood, -/+/++/+++	14/39/58/35	1/5/10/29	21.6862	□0.0001

*, Fisher's exact test

Table 2
Univariate analysis of the factors associated with quantitative data in HSPN patients with and without crescent formation

Variables	Grade I-II n = 146	Grade III-V n = 45	P
C-reactive protein, mg/l	3.6629 ± 8.0603	6.5598 ± 11.712	0.0307*
White blood cell count,×10^9/l	10.029 ± 4.0135	11.723 ± 3.8933	0.0135
Lymphocyte, %	28.412 ± 12.924	24.107 ± 13.352	0.0540
Platelet count, ×10^9/l	309.17 ± 88.675	343.07 ± 82.524	0.0239
Complement component 3, g/l	1.1476 ± 0.1881	1.2171 ± 0.1938	0.0330
Complement component 4, g/l	0.2555 ± 0.0857	0.2822 ± 0.0875	0.0707
Immunoglobulin A, g/l	2.2246 ± 0.8366	2.3653 ± 0.8168	0.3237
Immunoglobulin G, g/l	9.601 ± 2.495	9.1013 ± 2.3659	0.2371
Immunoglobulin M, g/l	1.181 ± 0.5038	1.2353 ± 0.5734	0.5425
Total cholesterol, mmol/l	4.2461 ± 1.2149	5.1396 ± 1.5511	<0.0001
Triglyceride, mmol/l	1.2288 ± 0.7094	1.6627 ± 0.9239	0.0006*
Serum uric acid, mmol/l	267.91 ± 83.918	266.55 ± 78.065	0.9232
Blood urea nitrogen, mmol/l	4.4997 ± 1.2614	4.6858 ± 1.4228	0.4031
Serum creatinine, mmol/l	39.261 ± 10.863	38.998 ± 8.1706	0.7791*
CD4+/CD8+, %	1.1854 ± 0.3808	1.1422 ± 0.4351	0.5220
CD3+, %	67.1528 ± 10.3439	66.1283 ± 9.3301	0.5504
CD3 + CD4+, %	32.488 ± 7.649	31.087 ± 8.6809	0.3005
CD3 + CD8+, %	28.1910 ± 6.1454	28.9500 ± 6.2194	0.4680
CD19 + CD23+, %	9.0250 ± 3.8344	8.6178 ± 3.6392	0.5300
Mycoplasma IgG, AU/l	68.3077 ± 65.7568	71.9142 ± 73.0422	0.7652
Mycoplasma IgM, COL	1.0552 ± 0.8047	1.0084 ± 0.6630	0.7329
Anti-streptolysin O, IU/ml	161.0 ± 264.4	150.0 ± 141.8	0.1712*
24 h urinary microalbumin, mg	269.2 ± 293.6	565.7 ± 330.4	<0.0001
24 h urinary total protein, mg	542.32 ± 821.84	1799.5 ± 1778.9	<0.0001

*, The variance of the two samples is uneven, and the nonparametric rank sum test is used.

Variables	Grade I-II n = 146	Grade III-V n = 45	P
Urinary RBC count, /UL	94.49 ± 233.54	630.65 ± 1505.9	<0.0001*
Urinary WBC count, /UL	20.255 ± 63.389	80.811 ± 132.25	<0.0001*
N-acetylglucosaminidase, U/L	26.003 ± 16.885	34.677 ± 33.282	0.0310*
α1-Microglobulin, U/L	7.359 ± 4.9073	9.333 ± 5.0892	0.0204
β2-Microglobulin, U/L	0.3357 ± 0.4068	0.3231 ± 0.1824	0.5001*
Urinary transferrin, mg/l	24.014 ± 34.348	75.179 ± 42.057	<0.0001*
Urinary microalbumin/creatinine, mg/mg	0.2835 ± 0.2725	0.7933 ± 0.5126	<0.0001*
Prothrombin time, s	12.698 ± 1.2648	12.293 ± 1.3303	0.0659
D-dimer, μg/l	928.71 ± 1645.2	1177.3 ± 1941.1	0.4177
Fibrinogen, g/l	2.5638 ± 0.7827	2.7704 ± 0.9135	0.1394
Antithrombin III, %	110.97 ± 17.292	109.79 ± 22.1	0.7695*
Thrombin time, s	17.732 ± 1.72	17.704 ± 1.9175	0.9275
Activated partial thrombin time, s	32.706 ± 7.7257	30.46 ± 8.4283	0.0975
Weight, kg	32.762 ± 12.69	34.611 ± 14.598	0.4110

*, The variance of the two samples is uneven, and the nonparametric rank sum test is used.

After multivariate logistic regression analysis, urinary WBC count (OR = 3.300; 95% CI; 1.119–9.739; P = 0.0306) and urinary ACR (OR = 25.053; 95% CI, 1.354–463.708; P = 0.0305) were found to be independent risk factors for glomerular crescentic renal damage (Table 3). The area under the ROC (AUC) of urinary WBC and ACR were 0.753 and 0.698, respectively (Fig. 1), with the Hosmer and Lemeshow goodness-of-fit test (P = 0.0669, P > 0.05).

Table 3
Logistic analysis of the risk factors in HSPN patients with crescent formation

Variable	OR (95% CI)	P value
Abdominal pain	2.119(0.770–5.833)	0.1459
Recurrence of skin rash ≥ 3times	2.050(0.339–12.385)	0.4341
C-reactive protein	0.990(0.241–4.069)	0.9890
White blood cell count	1.288(0.423–3.922)	0.6561
Platelet count	1.153(0.359–3.698)	0.8113
Complement 3	13.666(0.205-912.816)	0.2225
Total cholesterol	1.530(0.523–4.479)	0.4377
Triglyceride	1.920(0.567–6.501)	0.2943
24 h urinary microalbumin	> 999.999(< 0.001->999.999)	0.9520
24 h urinary total protein	< 0.001(< 0.001->999.999)	0.9374
Urinary RBC count	6.577(0.646–66.966)	0.1116
Urinary WBC count	3.300(1.119–9.739)	0.0306
N-acetylglucosaminidase	1.799(0.147–21.969)	0.6456
α1-Microglobulin	1.856(0.556–6.196)	0.3149
Urine transferrin	1.086(0.054–21.903)	0.9572
Level of urine occult blood	1.749(0.040-76.622)	0.7720
Level of urine protein	> 999.999(< 0.001->999.999)	0.9400
Urine microalbumin/creatinine	25.053(1.354-463.708)	0.0305

Discussion

In this retrospective study, risk factors were determined between pediatric patients with HSPN who had or did not have renal crescent formation (ISKDC grade ≥ III versus ISKDC grade < III). Multivariate logistic analysis showed that urinary WBC and urinary ACR were independent risk factors for crescent formation. To the best of our knowledge, these risk factors have not previously been identified in relation to pediatric HSPN.

Proteinuria denotes severe renal injury, and proteinuria at the time of symptom onset was associated with poor prognosis [8, 17]. This is consistent with our study, where multiple proteinuria indicators of renal function were associated with crescent formation, based on our univariate analysis. However, based on logistic regression analysis, only urinary ACR was found to be independent risk factor for predicting

crescentic glomerulonephritis (ISKDC grades III–V). ACR is a sensitive indicator of glomerular damage with high specificity [18]. Significant elevation in 24-hour urinary protein levels and urinary protein/creatinine ratio were found in ISKDC grades IIb, IIIa, and IIIb HSPN patients compared to ISKDC grade I and IIa subjects (the area under the ROC curve was 0.767 and 0.731, respectively), suggesting that 24-hour urinary protein levels and urinary protein/creatinine ratio may predict the pathological classification of HSPN [19], supporting the view that the severity of clinical manifestations in HSPN is related to the formation of crescents [10]. Other studies employed log-term follow-up to assess renal outcome in children with HSPN. Twenty-four hour proteinuria was associated with poor prognosis [17]. Additionally, multivariate analysis showed that patients with poor prognosis had a higher urinary albumin/creatinine ratio after 17 years of follow-up [8].

Increased urinary WBCs are an indicator of renal injury. Urinary WBCs positively correlated with complement C3 in HSPN subjects, suggesting that that the complement system is involved in promoting renal injury [19]. Complement-leukocyte-dependent interactions cause glomerular damage. Indeed, data indicate that in HSP subjects, WBCs may incite renal vasculitis [20]. In children with HSP, increased peripheral blood leukocyte and neutrophil counts were risk factors for small vessel injury and kidney involvement [21]. Analysis of HSPN patient samples and renal biopsies from animals with experimental HSPN found that WBCs participated in crescent formation [7]. WBC count, CRP, and humoral immune complement C3 levels were identified risk factors for crescentic nephritis in this study. Additionally, cytokine-driven neutrophilia was associated with epithelial cell proliferation and fibrosis in Bowman's space [7].

Of further novelty, we found that abdominal pain and recurrence of skin rash more than three times were possible risk factors for the formation of HSPN crescents. Again, to the best of our knowledge, such associations have not been reported previously. Other studies noted that abdominal pain and persistent purpura (> 1 month) were risk factors for pediatric HSPN [22]; purpura relapses more than four times predicted a poor prognosis of HSPN [23]. Repeated rashes in the setting of HSPN may indicate increased inflammation/neutrophilia and vasculitis.

Hematuria is one of the initial renal manifestations of HSPN [14]. Urinary red blood cell count and urinary occult blood were possible risk factors in our study. The published data in this regard is mixed. For example, a meta-analysis showed that hematuria and mild proteinuria with hematuria were associated with better prognosis [11]. In contrast, patients with isolated hematuria or mild albuminuria at the onset of the disease had adverse consequences [24]. These conflicting reports may be due to different treatment schemes. For example, the current strategy for HSPN treatment is mostly based on the KDIGO guidelines [15], but some experts have pointed out that the current treatment schemes for HSPN are insufficient if only the KDIGO guidelines are followed, especially for mild types of HSPN [25].

Finally, few studies have shown that platelets are involved in the process of renal injury [26]. We found that platelet count, total cholesterol, and triglyceride levels were likely risk factors for crescent formation

in pediatric HSPN. All of these related indexes need to be further clarified in terms of their role in the pathogenesis and the prognosis of HSP and HSPN.

There are limitations to our study. First, the sample size studied was small. Second, further detailed classification the pathological characteristics of the glomerular crescent (cellular, cellular-fibrous, and fibrous crescent) was not completed. This is important as it may affect the accuracy of the results. In addition, our study did not assess the risk of variables in relation to other pathologic changes such as mesangial cell proliferation, intracapillary hyperplasia, glomerulosclerosis, and tubular atrophy/interstitial fibrosis, all of which are reported findings in HSPN. Lastly, tissue assessment was not complemented with a control group of pediatric patients with renal disease. Thus, it is not clear if the pathologic lesions and risk factor associations are limited only to HSPN.

Conclusions

Results presented herein find that, in pediatric HSPN, increased urinary WBCs and/or urinary ACR are risk factors for worse renal pathology. In the setting of HSPN, such laboratory findings may warrant increased treatment intervention by specialists to limit renal damage.

Abbreviations

HSPN: Henoch-Schönlein purpura nephritis; ISKDC:International Study of Kidney Disease in Children; WBC:white blood cell; ACR:microalbumin/creatinine ratio; HSP:Henoch-Schönlein purpura; KDIGO:Kidney Disease Improving Global Outcomes; CRP:C-reactive protein; RBC:red blood cell; OR:odds ratios; CI:confidence intervals; ROC:the receiver operating characteristic curve; NAG:N-acetylglucosaminidase; TRU:urinary transferrin; AUC:The area under the ROC;

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Children’s Hospital of Soochow University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

YRS made a contribution to the concept and design, acquisition, analysis of data and drafted the article. WLG, MS and XZL made a contribution of concept, design, analysis and interpretation of data, and critically revised the overall content of the manuscript. QL, XMZ made a contribution of acquisition, analysis and critically revised the article. All authors read and approved the final manuscript.

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Figures

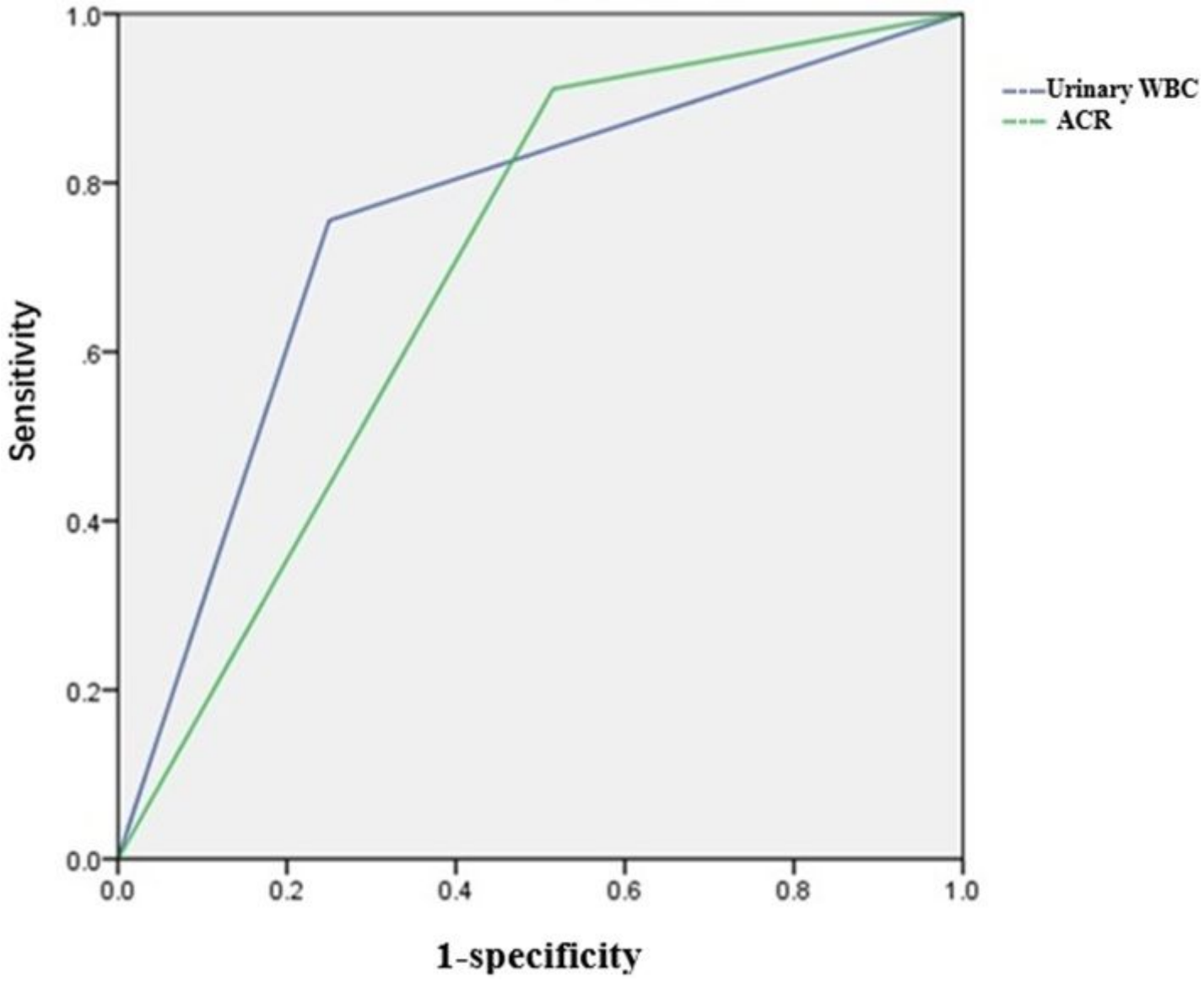

Figure 1

ROC curve to evaluate the diagnostic efficiency of the model [(AUC)of urinary WBC and ACR were 0.753 and 0.698 respectively]