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ORIGINAL RESEARCH

Prognostic Value of Berden Histopathological Classification in Anca-Associated Vasculitis with Renal Involvement: A Single-Center Retrospective Cohort Study

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ABSTRACT

The kidneys are frequently affected by anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides, and this renal involvement is a significant determinant of the disease's prognosis. Certain demographic, laboratory, and histopathological findings are effective in predicting kidney and patient survival. The objective of this research was to evaluate both the prognostic utility of the Berden histopathological classification and the determinants of survival among patients with ANCA-associated vasculitis (AAV) and concurrent renal involvement, who were diagnosed at Bursa Uludağ University Hospital. This retrospective analysis comprised 47 cases of AAV identified from a cohort of 1954 patients who underwent renal biopsy at our institution between 1987 and 2017. The demographic, histopathological, and laboratory findings of the patients were examined. Glomerular findings in renal biopsies were evaluated to classify the histopathology and calculate the percentage of normal glomeruli. The prognostic value of these parameters for predicting first-year treatment responses (remission, end-stage renal disease, and death) was evaluated. Histopathological classification, the percentage of normal glomeruli, baseline creatinine, eGFR, proteinuria, and C-reactive protein (CRP) levels were all identified as significant predictors of first-year treatment response ($p = 0.046$, $p = 0.004$, $p = 0.026$, $p = 0.021$, $p = 0.039$, and $p = 0.016$, respectively). While the focal group showed the best prognosis, the sclerotic group had the worst. Factors associated with a poor prognosis included a low normal glomerular percentage in the kidney biopsy, low baseline eGFR, and high levels of baseline serum creatinine, CRP, and proteinuria. Histopathological biopsy findings, histopathological classification model, and certain laboratory markers are effective predictors of treatment response and prognosis in ANCA-associated glomerulonephritis.

Keywords: Anti-neutrophil cytoplasmic antibody. Glomerulonephritis. Histopathological classification. Vasculitis.

Böbrek Tutulumu Olan ANCA İlişkili Vaskülitte Berden Histopatolojik Sınıflandırmasının Prognostik Değeri: Tek merkezli Retrospektif Kohort Çalışması

ÖZET

Böbrekler sıklıkla anti-nötrofil sitoplazmik antikor (ANCA) ile ilişkili vaskülitlerden etkilenir ve bu böbrek tutulumu, hastalığın prognozunun önemli bir belirleyicisidir. Bazı demografik, laboratuvar ve histopatolojik bulgular böbrek ve hasta sağkalımını tahmin etmede etkilidir. Bu araştırmanın amacı, Bursa Uludağ Üniversitesi Hastanesi'nde ANCA ilişkili vaskülit (AAV) ve eş zamanlı böbrek tutulumu tanısı konulan hastalarda Berden histopatolojik sınıflandırmasının prognostik faydasını ve sağkalım belirleyicilerini değerlendirmektir. Bu retrospektif analiz, 1987 ile 2017 yılları arasında kurumumuzda böbrek biyopsisi yapılan 1954 hastadan oluşan bir kohorttan belirlenen 47 AAV vakasını kapsamaktadır. Hastaların demografik, histopatolojik ve laboratuvar bulguları incelendi. Böbrek biyopsilerindeki glomerüler bulgular, histopatolojiyi sınıflandırmak ve normal glomerül yüzdesini hesaplamak için değerlendirildi. Bu parametrelerin ilk yıl tedavi yanıtlarını (remisyon, son dönem böbrek hastalığı ve ölüm) tahmin etmedeki prognostik değeri değerlendirildi. Histopatolojik sınıflandırma, normal glomerül yüzdesi, başlangıç kreatinin, eGFR, proteinüri ve C-reaktif protein (CRP) düzeyleri, ilk yıl tedavi yanıtının önemli belirleyicileri olarak tanımlandı (sırasıyla $p = 0,046$, $p = 0,004$, $p = 0,026$, $p = 0,021$, $p = 0,039$ ve $p = 0,016$). Fokal grup en iyi prognozu gösterirken, sklerotik grup en kötü prognoza sahipti. Kötü prognozla ilişkili faktörler arasında böbrek biyopsisinde düşük normal glomerül yüzdesi, düşük eGFR değeri ve yüksek serum kreatinin, CRP ve proteinüri düzeyleri yer almaktadır. Histopatolojik biyopsi bulguları, histopatolojik sınıflandırma modeli ve bazı laboratuvar belirteçleri, ANCA ile ilişkili glomerülonefritte tedavi yanıtı ve prognozun etkili öngörücüleridir.

Anahtar Kelimeler: Anti-nötrofil sitoplazmik antikor. Glomerülonefrit. Histopatolojik sınıflandırma. Vaskülit.

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Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are multisystemic vasculitides characterized by necrotizing involvement of small vessels. The primary diseases within this group are granulomatous polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA)[1]. Renal involvement is frequent and constitutes a significant prognostic factor for the disease. Classically, this involvement in ANCA-associated vasculitis (AAV) manifests as rapidly progressive pauci-immune necrotizing and crescentic glomerulonephritis[2]. The most frequent clinical presentations of renal involvement include hematuria, proteinuria, and renal failure. Renal involvement occurs in approximately 90% of patients with MPA and 80% of those with GPA[3]. In AAV, kidney involvement is associated with poor outcomes, high morbidity, and increased mortality. Multiple determinants, including demographic characteristics, laboratory data, and histopathological findings, influence both patient and kidney survival. A histopathological classification model for ANCA-associated glomerulonephritis was developed by Berden et al.[4] This classification stratifies renal involvement into four subgroups according to the dominant glomerular pathology: focal (≥50% normal glomeruli), crescentic (≥50% crescent-shaped glomeruli), sclerotic (≥50% global sclerotic glomeruli), and mixed (<50% normal glomeruli, <50% crescent-shaped glomeruli, <50% global sclerotic glomeruli).

This study aimed to retrospectively evaluate the prognostic value of the Berden histopathological classification and the factors influencing survival in AAV with renal involvement.

Materials and Methods

A retrospective review was conducted of 101 patients, identified among 1,954 kidney biopsies performed at Bursa Uludağ University Hospital between 1987 and 2017, who were either pathologically diagnosed with crescentic necrotizing glomerulonephritis or clinically followed up with a diagnosis of AAV. Twenty patients whose data could not be accessed through the hospital information management system, and 34 patients without a kidney biopsy, were excluded. The final study cohort included 47 patients who underwent kidney biopsy and were either ANCA-positive or ANCA-negative but clinically diagnosed with MPA, GPA, or AAV. Patients whose subtype could not be precisely determined were classified as AAV.

Our study was planned and conducted in accordance with the principles outlined in the Declaration of Helsinki, patient rights regulations, and relevant ethical guidelines. Patients' ages, genders, types of diagnosis, ANCA serotypes, initial laboratory findings (serum creatinine, eGFR, albumin, C-reactive protein [CRP], sedimentation rate, immunoglobulin levels [IgG, IgA, IgM], complement C3 and C4, complete blood count parameters, 24-hour urine protein), histopathological findings obtained from kidney biopsy material (total, normal, global sclerotic, and crescentic glomerular counts and percentages), clinical and outcome parameters (lung involvement, need for plasmapheresis, serum creatinine levels in the first year, treatment responses, and survival times) were recorded. Clinical diagnoses were established according to the criteria outlined in the 2012 Chapel Hill Consensus Conference nomenclature for systemic vasculitis[1].

Renal biopsies were assessed using light microscopy and immunofluorescence. The histopathological classification was based on the model established by Berden et al.[4] Renal biopsies were classified as follows: sclerotic glomeruli ≥50% were classified as sclerotic, normal glomeruli ≥50% were classified as focal, crescentic glomeruli ≥50% were classified as crescentic, and normal glomeruli <50%, crescentic glomeruli <50%, and sclerotic glomeruli <50% were classified as mixed. In other studies, crescentic and mixed groups had similar prognoses. Due to the limited number of cases, the crescentic and mixed groups were considered together when examining the prognostic value of histopathological classification.

Cases were grouped according to diagnosis type (GPA, MPA, and AAV) and histopathological classification (focal, crescentic, sclerotic, and mixed). ANCA testing was performed using both indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA). First-year treatment responses (remission, end-stage renal disease [ESRD], and death) were considered as prognostic criteria. All cases were followed up for at least one year. Because the study was retrospective, informed consent was not obtained from the patients.

Statistical Analysis

Descriptive statistics were expressed as numbers and percentages for categorical variables, and as mean ± standard deviation or median for continuous variables. Group comparisons of categorical variables were performed using the Pearson Chi-square test. For non-normally distributed continuous variables, Mann-Whitney U and Kruskal-Wallis tests were utilized. Kaplan-Meier method and Log-rank test were used for survival analysis. Differences were considered statistically significant at a P value of <0.05. Statistical analysis was conducted using IBM SPSS Statistics 23.0 for Windows.

Results

The mean age of the patients was 51.4 ± 13.1 years. Of the patients, 36.2% (n = 17) were female and 63.8% (n = 30) were male. Of the patients, 36.2% (n = 17) were PR3-ANCA positive, 51.1% (n = 24) were MPO-ANCA positive, 12.8% (n =6) were ANCA negative, 42.6% (n = 20) were diagnosed with GPA, 48.9% (n = 30) with MPA, and 8.5% (n = 4) with AAV. According to the histopathological classification based on glomerular findings in the kidney biopsy materials, 14 of the 47 cases were focal, 13 were crescentic, 12 were sclerotic, and eight were mixed. The demographic information, diagnosis types, and ANCA serology results of the cases, classified according to general and histopathological classification, are presented in Table I.

Treatment responses in the first year were evaluated according to diagnosis type and ANCA serology, and no statistically significant differences were found (p = 0.213 and p = 0.10, respectively). The predictive effect of histopathological classification on the first-year prognosis was evaluated. A statistically significant difference was found among the focal, crescentic/mixed, and sclerotic groups (p = 0.046). Binary group comparisons: Remission and ESRD p-value=0.013. Remission and Death p-value=0.356. ESRD and Death p-value=0.553. The distribution of first-year treatment responses according to the types of diagnosis, ANCA serology, and histopathological classification of the cases is shown in Table II.

Normal glomerular percentages, eGFR, creatinine, CRP, and proteinuria levels were found to be statistically significant predictors of first-year treatment responses. (p = 0.004, p = 0.021, p = 0.026, p = 0.016, p = 0.039, respectively). There was no statistically significant association between baseline albumin, leukocyte count, hemoglobin, erythrocyte sedimentation rate, and positive hematuria levels and first-year treatment responses. Histopathological and laboratory findings, according to the first-year treatment responses, are presented in Table III.

There was no statistically significant association found between the presence of lung involvement and first-year treatment response (p = 0.862). Six patients required plasmapheresis. Furthermore, neither the types of diagnosis nor the histopathological classification showed a statistically significant correlation with the requirement for plasmapheresis.

Survival analysis

During the follow-up period, a total of 15 cases resulted in mortality. Cumulative mortality rates showed nine deaths by the end of the first year. The average survival duration for the deceased patients was 22.53 ± 40.14 months.

Of the 15 deceased patients, three were in the focal group, five in the crescentic group, four in the sclerotic group, and three were in the mixed group. The histopathological classification showed no statistically significant effect on survival, although the mean survival durations for the focal, crescentic, sclerotic, and mixed groups were 9.03 ± 3.02 months, 50 ± 28.62 months, 10.2 ± 5.31 months, and 6.77 ± 4.28 months, respectively (p = 0.642). (Figure 1)

Table I. Demographic information, types of diagnosis, and ANCA serology were classified according to general and histopathological classification

	Focal (n=14)	Crescentic (n=13)	Sclerotic (n=12)	Mixed (n=8)	TOTAL (n=47)
Age (years)	51.7 ± 12.8	48.2 ± 11.6	51.2 ± 17.5	56.5 ± 8.3	51.4 ± 13.1
Sex (M/F)	9/5	11/2	6/6	4/4	17/30
Diagnosis type, n (%)					
GPA	7 (50)	5 (38.5)	3 (25)	5 (62.5)	20 (42.6)
MPA	7 (50)	5 (38.5)	8 (66.7)	3 (37.5)	23 (48.9)
AAV	0 (0)	3 (27.7)	1 (8.3)	0 (0)	4 (8.5)
ANCA serology, n (%)					
PR3-ANCA	7 (50)	4 (30.8)	3 (25)	3 (37.5)	17 (36.2)
MPO-ANCA	7 (50)	5 (38.5)	7 (58.3)	5 (62.5)	24 (51.1)
ANCA negative	0 (0)	4 (30.8)	2 (16.7)	0 (0)	6 (12.8)

GPA, granulomatous polyangiitis; MPA, microscopic polyangiitis; AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3 ANCA; MPO-ANCA, myeloperoxidase ANCA

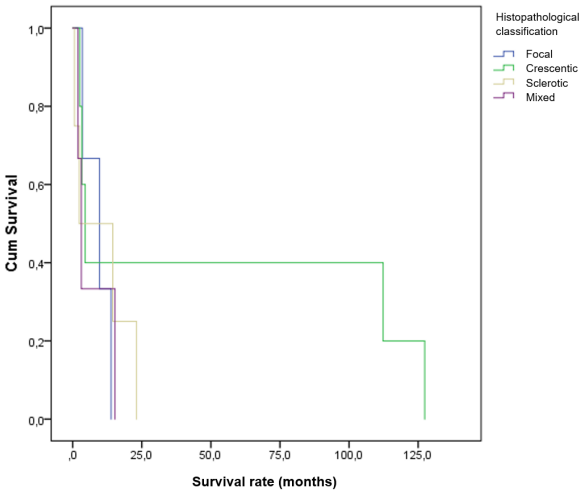

Figure 1:
Survival analysis graph according to the histopathological classification

While lung involvement was detected in 10 out of 15 deceased patients, it did not demonstrate a statistically significant impact on survival (p = 0.606). The mean survival duration was 21.24 ± 12.02 months in cases with lung involvement and 25.12 ± 21.8 months in cases without.

Table II. Distribution of first-year treatment responses according to case types, ANCA serology, and histopathological classifications

	Remission (n=20)	ESRD (n=18)	Death (n=9)	*p*
Types of diagnosis, n (%)				0,213
GPA	11 (55)	7 (35)	2 (10)	
MPA	9 (39.1)	8 (34.8)	6 (26.1)	
AAV	0 (0)	3 (75)	1 (25)	
ANCA serology, n (%)				0,1
PR3-ANCA	9 (52.9)	6 (35.3)	2 (11.8)	
MPO-ANCA	11 (45.8)	7 (29.2)	6 (25)	
ANCA negative	0 (0)	5 (83.3)	1 (16.7)	
Histopathological Classification, n (%)				**0,046**
Focal	10 (71.4)	2 (14.3)	2 (14.3)	
Crescentic + Mixed	8 (38.1)	8 (38.1)	5 (23.8)	
Sclerotic	2 (16.7)	8 (66.7)	2 (16.7)	

ESRD, end-stage renal disease; GPA, granulomatous polyangiitis; MPA, microscopic polyangiitis; AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; PR3-ANCA, proteinase-3 specific ANCA; MPO-ANCA, myeloperoxidase specific ANCA

Table III. Histopathological and laboratory findings based on first-year treatment responses

	Remission	ESRD	Death	*p*
Normal glomerular percentage (%)	48.65 (0-100) [a]	10.1 (0-76.9) [b]	33.3 (0-58.8) [ab]	**0.004**
Sclerotic glomerular percentage (%)	13.75 (0-77.6)	45.23 (0-100)	17.6 (0-56.3)	0.094
Creatinine (mg/dl)	2.7 (0.6-7) [a]	4.32 (0.92-10.7) [b]	2.25 (1.3-8.22) [ab]	**0.026**
eGFR (MDRD)	30 (6-117) [a]	16 (4-67) [b]	24 (7-61) [a]	**0.021**
Proteinuria (g/day)	1.41 (0.41-5.82) [a]	2.54 (1.36-6.83) [b]	2.07 (0.5-8.16) [ab]	**0.039**
Leukocytes (/µl)	13200 (7810-17200)	10700 (5320-20200)	11150 (5130-22800)	0.285
Hemoglobin (g/dl)	10.1 (7.84-12.4)	9.15 (8-17.1)	11 (8.5-14.6)	0.063
Platelets (/µl)	382 (233-527)	316 (104-665)	346 (116-561)	0.49
Albumin (g/dl)	3 (2.4-4.4)	3.05 (2.1-3.9)	2,9 (1.6-3.9)	0.877
Sedimentation rate (mm/hour)	53.5 (16-120)	41.5 (7-99)	63 (38-120)	0.214
CRP (mg/dl)	6.95 (0.5-25.4) [a]	3.56 (0.21-18.89) [b]	11.5 (2.27-21.1) [a]	**0.016**
IgG (mg/dl)	1050 (627-2060)	1585 (544-2520)	1530 (1070-2490)	0.598
IgA (mg/dl)	215 (109-599)	182 (106-303)	266 (192-312)	0.181
IgM (mg/dl)	71.95 (34.4-203)	101.3 (58-121)	109 (91.9-144)	0.084
Complement C3c (mg/dl)	139 (100-182)	114.5 (82.4-167)	146 (98.1-158)	0.531
Complement C4 (mg/dl)	31.2 (14-44.3)	30.3 (20.7-54.1)	18.4 (11.2-28.1)	0.154

ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CRP, C-reactive protein; Ig, immunoglobulin

There is no statistically significant difference between groups with the same letter in pairwise comparisons.

Discussion and Conclusion

In this single-center retrospective cohort study, both the Berden histopathological classification and certain baseline clinical and laboratory indicators were found to be predictive of short-term treatment response in AAV with renal involvement. When comparing classes, as expected, the focal group had the best prognosis, the sclerotic group had the worst prognosis, and the crescentic and mixed groups had an intermediate course. A decrease in the percentage of normal glomeruli in the biopsy material, along with higher creatinine, lower eGFR, higher proteinuria, and CRP levels at presentation, were associated with poor one-year outcomes. In contrast, clinical subtype (GPA/MPA/AAV), ANCA specificity, lung involvement, and plasmapheresis requirement did not appear to be discriminatory factors for one-year outcomes. Although no significant differentiation was found between classes in the survival analysis, given the sample size and follow-up duration, this may reflect statistical power limitations. Our findings demonstrate that Berden-based histopathological risk stratification -particularly the quantitative reporting of the normal glomerular percentage-provides valuable contributions to early clinical decision-making in real-world practice.

The mean age of patients in our study was similar to that reported by Ünlü et al in Turkey, but lower than that reported in other studies conducted abroad[5]. This finding may be related to environmental factors, sociocultural levels, and genetic factors.

The ANCA serotype distribution in our study showed a predominance of MPO-ANCA (51.1%), followed by PR3-ANCA (36.2%), with 12.8% of cases being ANCA-negative. When compared to a Turkish study by Ünlü et al. (40% MPO-ANCA, 39% PR3-ANCA, 18% ANCA-negative), our findings show a similar regional trend[5]. While MPO-ANCA predominance is noted in studies from China and Japan, other global literature suggests a similar distribution of MPO-ANCA and PR3-ANCA-positive cases[3,6–9].

Studies in the literature have previously demonstrated an association between prognosis and baseline creatinine and eGFR levels, as well as the percentage of normal glomeruli observed in the kidney biopsy[6,9–12]. Consistent with these studies, our study similarly showed a worse prognosis in patients presenting with high creatinine levels, low eGFR levels, and a low percentage of normal glomeruli.

The results are consistent with the study by Chang et al., which demonstrated higher proteinuria in the sclerotic group, correlating with a poor prognosis[6]. In our study, we likewise found a significant correlation between the amount of proteinuria and first-year treatment responses; high proteinuria levels were associated with poor prognosis. This association is considered an indirect indicator of damage to the glomerular architecture resulting from chronic inflammation.

A study by Crnogorac et al. previously found an association between CRP and both kidney and patient survival[12]. Consistent with this, our study also observed a significant correlation between CRP levels and first-year treatment responses. We propose that active necrotizing glomerular inflammation, reflected by the associated acute-phase response, may represent a stage of the disease more susceptible to immunosuppressive therapy. However, the inflammatory response in these patients must be carefully investigated, and infectious pathologies must be ruled out.

Varying data have been reported regarding the relationship between ANCA specificity and treatment response, prognosis, and risk of relapse. Andreiana et al. found that ANCA specificity did not affect treatment response or outcome[13]. A study by Córdova-Sánchez et al. reported similar remission, kidney, and patient survival rates between serological groups, but noted a higher relapse rate in PR3-ANCA vasculitis[14]. Quintana and Tanna showed that the prognosis was worse for cases with MPO-ANCA serology[15,16]. Furthermore, Shah et al. observed higher baseline renal function and interstitial fibrosis scores in ANCA-negative cases when comparing them with ANCA-positive cases. However, they found similar 1-year patient and renal survival rates in both groups[17]. Consistently, our study detected no significant effect of ANCA specificity on first-year treatment responses.

ANCA-GN renal morphology provides critical prognostic factors, where the percentage of normal glomeruli, the percentage of globally sclerotic glomeruli, and the amount of cellular crescents function as important histological markers of renal prognosis[4,18–20]. Berden et al. defined a histopathological classification model for ANCA-GN[4]. This study showed that the focal group had a relatively better prognosis, the crescentic group had a higher chance of renal function improvement despite initially having extremely active renal disease and severely reduced renal function, the mixed group had an intermediate prognosis, and the sclerotic group had the worst prognosis. Subsequent studies conducted across different populations generally confirmed that the focal group retained the best prognosis and the sclerotic group the worst. However, there is no consensus regarding the prognosis of the crescentic and mixed groups; some studies have found a better prognosis in the crescentic group, while others have found a better prognosis in the mixed group[3,5–9,11,13,15,16,21–26]. In our study, we similarly found the histopathological group with the best prognosis was the focal group, and the group with the worst prognosis was the sclerotic group. When the

crescentic and mixed groups were combined in our study, the prognosis of this resulting group was intermediate between the focal and sclerotic groups.

The study cases were distributed across the Berden classification as follows: 14 (30%) were in the focal group, 13 (28%) in the crescentic group, 12 (25%) in the sclerotic group, and 8 (17%) in the mixed group. Although the focal, crescentic, and mixed groups were found in similar percentages within our cohort, the focal group predominated. We note that the histopathological distribution of cases varies worldwide. While the distribution of groups is similar in Europe, Canada, India, and China, crescentic groups are more common, focal groups are more prevalent in Japan, and mixed groups are more common in the US and the UK. The higher prevalence of focal group cases in Japan is possibly linked to their practice of early biopsy intervention upon detecting urinary or renal function irregularities[3].

The findings should be interpreted with caution, considering the study's limitations. The single-center and retrospective design, the limited number of patients, and the variability in diagnosis and treatment approaches during the long follow-up period limit the generalizability of the results. Nevertheless, the study may provide an essential contribution in terms of revealing the prognostic value of the Berden histopathological classification in clinical decision-making processes using real-life data.

To better demonstrate the factors affecting prognosis and the importance of histopathological classification in the Turkish population, future studies should be conducted in multicenter settings and involve larger patient cohorts.

In conclusion, histopathological findings obtained from the kidney biopsy specimen, histopathological classification models, and certain laboratory parameters are effective in predicting both treatment response and overall prognosis in ANCA-associated glomerulonephritis.

Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Bursa Uludağ University Faculty of Medicine (Decision No. 2016-5/6, dated March 29, 2016).

Researcher Contribution Statement:
Idea and design: M.F.A., A.Y., A.O., M.G., K.D., A.E., B.A.V.; Data collection and processing: M.F.A., S.A., Y.A.; Analysis and interpretation of data: M.F.A., A.O., A.Y.; Writing of significant parts of the article: M.F.A., A.Y.
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