Original Article

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The Correlation between Renal Color Doppler Indices and Pathological and Laboratory Parameters in Patients with Lupus Nephritis

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ABSTRACT

Background & Objective: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease affecting 20–50 per 100,000 people. This study aimed to assess the relationship between ultrasound indices and pathological and laboratory parameters in patients with lupus nephritis (LN).

Materials & Methods: This cross-sectional, descriptive-diagnostic study was conducted on 32 patients and 32 healthy individuals. Sonographic indices, renal biopsy results, and laboratory parameters were assessed. A Receiver Operating Characteristic (ROC) curve was used to predict sensitivity and specificity. P-value <0.05 was considered significant.

Results: The mean GFR and anti-dsDNA levels in patients were 77.4±30.2 ml/min/1.73m² and 2.8±4.4 IU/ml, respectively. Abnormal C3, abnormal C4, and positive aPL were observed in 17 (60.7%), 9 (32.1%), and 8 (28.5%) patients, respectively. In terms of biopsy classification, most patients were in class II (32.1%). The mean biopsy activity index (bxAI) and biopsy chronicity index (bxCI) were 12.11±7.8 and 4.39±3.60, respectively. There was no significant association between the resistive index (RI) and pathological or laboratory parameters (P>0.05). However, a significant association was found between peak systolic velocity (PSV) and end-diastolic velocity (EDV) with GFR, and a negative association between PSV and EDV with aPL and bxCI in patients with LN(P<0.05). The sensitivity and specificity of the anti-dsDNA test for detecting bxCI using a cut-off value of 0.245 were 84% and 96%, respectively (area under the ROC curve = 0.92).

Conclusion: This study found no association between RI and pathological or laboratory parameters. However, there was a negative association between PSV and EDV with the degree of chronic kidney damage in patients with LN. Anti-dsDNA appears to be a useful predictor of long-term renal outcomes in these patients.

Keywords: Laboratory Parameters, Lupus Nephritis, Pathological Parameters, Resistive Index, Ultrasonography

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease **(1-6)** affecting 20–50 per 100,000 people **(7)**. The risk of disease is higher among women, racial and ethnic minorities, and individuals with a

family history of SLE and other autoimmune diseases **(8)**. Although the precise etiology of SLE is unclear, genetic factors may interact with environmental exposures to influence susceptibility to developing SLE **(8)**. One of the most common manifestations of SLE is lupus nephritis, occurring in 40-75% of SLE patients **(9)**. Lupus nephritis is a significant predictor of poor outcomes in these patients. Additionally, patients with lupus nephritis have a 26-fold higher risk of mortality **(10)**.

Evaluating fibrosis and histopathological categorization of various types of lupus nephritis, as well as the degree of activity and chronicity are essential for determining an appropriate treatment strategy for these individuals **(11)**. Thus, early biopsy, i.e. the gold standard for diagnosing lupus nephritis, is recommended for patients with evidence of the condition, although it is associated with a range of side effects **(12)**.

Renal ultrasound is the first step in assessing the kidneys in various pathological conditions, including renal failure, arterial hypertension, and urinary abnormalities. Doppler analysis permits the acquisition of data on renal macro-abnormalities and changes in renal blood flow **(13)**.

Among the Doppler ultrasound indices – renal vein Doppler index, resistive index (RI), arterial peak systolic velocity (PSV), end-diastolic velocity (EDV), and pulsatility index (PI) –RI is routinely used as an indicator of intra-renal arterial resistance **(14)**. RI reflects peripheral resistance, arterial compliance, and pulsatility **(1)**. RI has clinical significance in predicting the renal chronicity index (CI), a key factor in determining renal outcomes **(15)**. Moreover, PSV refers to a valuable marker for determining the stage of chronic kidney disease **(16)**. The correlation between RI and PSV with renal function and histological damage scores has been revealed **(16)**. Furthermore, the relationship between renal RI, pathological findings, and laboratory parameters has been demonstrated **(1)**, though studies on the correlation between sonographic indices, laboratory parameters, and histopathological changes in the kidney are limited.

Since renal Doppler ultrasound can help identify patients more likely to experience improvement or deterioration in their renal condition **(17)** and there is no comprehensive study regarding the relationship between sonographic indices of the kidney and pathological and laboratory parameters in lupus nephritis, this study was aimed at assessing the correlation between renal color Doppler indices and pathological and laboratory parameters in LN.

Materials and Methods

This cross-sectional descriptive-diagnostic study was conducted on patients with LN (case group) and a control group (healthy individuals) in 2021.

Inclusion and Exclusion Criteria

Patients with LN referred to Shahid Sadoughi Hospital for biopsy were included in the study. Patients with transplanted kidneys, chronic kidney disease (CKD), renal artery stenosis, diabetes, hypertension, urinary tract strictures, heart failure, or those who had used non-steroidal anti-inflammatory drugs before the biopsy were excluded from the study.

Color Doppler Sonography

Prior to the renal biopsy, all patients diagnosed with LN based on laboratory results (proteinuria over 500 mg in 24 hours, proteinuria over 150 mg with hematuria, and proteinuria over 150 mg with dysmorphic red blood cells [d-RBC] and urinary casts) underwent color Doppler ultrasound of the upper, middle, and lower poles of the kidney. A 7 Hz and c-6-2 probe (HSV.A model) was used. Peak systolic velocity (PSV) and end-diastolic velocity (EDV) were defined as the absolute maximum value in systole and the absolute minimum value in diastole, respectively. Additionally, the resistive index (RI) ([PSV – EDV] / PSV) was calculated using electronic calipers and built-in software.

Renal Biopsy

An 18-gauge biopsy needle was inserted into the renal cortex under ultrasound guidance after local anesthesia. Renal biopsy specimens were assessed by an experienced pathologist and classified into 5 classes based on Ackerman's surgical pathology **(18)**. Additionally, the biopsy activity and chronicity index scores were evaluated based on predefined criteria.

Index of biopsy activity (bxAI) of lupus nephritis	Score
Glomerular karyorrhexis and fibrinoid necrosis	6
Cellular crescents	6
Wire loops and hyaline thrombi	3
Granulocyte infiltration of glomeruli	3
Glomerular mononuclear cellularity	3
Interstitial mononuclear cell infiltration	3
Index of biopsy chronicity (bxCI) of lupus nephritis	**Score**
Glomerular sclerosis	**3**
Fibrous crescents	**3**
Tubular atrophy	**3**
Interstitial fibrosis	**3**

1. Laboratory Analysis

Glomerular filtration rate (GFR) was assessed using the Modification of Diet in Renal Disease (MDRD) equation **(19)**. C3 and C4 were analyzed using the Alpha-Classic autoanalyzer (Aptec Kit, Belgium). The 24-hour proteinuria was measured by the Alpha-Classic autoanalyzer (Delta Darman Kit, Iran). Anti-dsDNA antibody and aPL were evaluated by ELISA method (Aeskulisa Kit, Germany). Serum and urine creatinine were measured by the Jaffe method (Pars Azmoon Kit, Iran). All measurements were performed according to the manufacturer's instructions.

2. Statistical Analysis

Data were entered into SPSS V19. The Spearman correlation coefficient was used for data analysis. An RI cut-off value of <0.7 was also considered to assess the relationship between sonographic indices and laboratory as well as pathological parameters ($P > 0.05$). A Receiver Operating Characteristic (ROC) curve was used to predict sensitivity and specificity. A p-value of <0.05 was considered statistically significant.

Results

The current study was conducted on 32 hospitalized patients [4 men (14.3%) and 28 women (85.7%)] during the COVID-19 pandemic and post-COVID-19 period. Four patients died due to COVID-19 complications. Additionally, 32 healthy individuals served as the control group. The mean age of patients was 31.3 ± 11.50 years, and the mean age of the healthy control group was 38.2 ± 15.17 years.The biopsy of renal tissues (class IV) is shown in Fig. 1. Fig. 2 shows renal color Doppler ultrasound results.The frequency distribution of patients based on normal and abnormal laboratory parameters revealed abnormal C3 levels (less than 90 mg/dL), abnormal C4 levels (less than 10 mg/dL), and positive aPL (antiphospholipid antibodies) in 17 (60.7%), 9 (32.1%), and 8 (28.5%) patients, respectively.The distribution of patients according to biopsy classification (bxclass) showed that 9 (32.1%) were in class II, 8 (28.6%) were in class III, 8 (28.6%) were in class IV, and 3 (10.7%) were in class V.Table 1 displays the mean values of variables in lupus nephritis (LN) patients and the control group. Table 2 shows the correlation between sonographic indices, laboratory, and pathological parameters. A significant association was observed between GFR and both PSV (peak systolic velocity) and EDV (end-diastolic velocity) ($p < 0.05$). Besides, a negative association was found between aPL and both PSV and EDV ($p < 0.05$). Furthermore, there was a negative

association between bxCI (biopsy chronicity index) and both PSV and EDV (p = 0.01) (see Table 2). Moreover, no significant correlation was found between RI (resistive index) and any pathological or laboratory parameters (p > 0.05). Even when RI was analyzed with a cut-off value of <0.7, no significant correlation was detected between RI and pathological or laboratory parameters (p > 0.05).In healthy individuals, the mean GFR was 83.81 ± 12.96 mL/min/1.73 m², C3 was 101.6 ± 25.99 mg/dL, C4 was 24.5 ± 7.9 mg/dL, and anti-dsDNA was 0.16 ± 0.05 IU/mL.Additionally, the sensitivity and specificity of the anti-dsDNA test to detect bxCI using a cut-off value of 0.245 were 84% and 96%, respectively (area under the ROC curve = 0.92). Figure. 3 shows this ROC curve.

Table 1. The mean variables in patients with LN and control group

	Sonographic indices	Mean ± SD	Minimum	Maximum
Case group	PSV	25.2±7.2	13.04	44.87
	EDV	9.9±3.7	5.44	23.70
	RI	0.59±0.05	0.48	0.73
	SD	2.5±0.33	1.93	3.67
Control group	PSV	28.3±6.48	17.83	47.83
	EDV	9.56±2.21	5.65	13.70
	RI	0.65±065	0.53	0.81
	SD	3.03±0.66	2.15	4.31
	GFR	83.8±12.96	51.2	122.3
	Creatinine	0.9±0.1	0.59	1.14
	C3	101.68±25.9	85.6	214
	C4	24.5±7.9	5.28	45.83
	Anti-dsDNA	0.16±0.05	0.1	0.2

Table 2. The correlation between sonographic indices with laboratory and pathological parameters in patients with LN

Laboratory parameters	Mean ± SD	PSV P-value (coefficient correlation)	EDV P-value (coefficient correlation)	RI P-value (coefficient correlation)	SD P-value (coefficient correlation)
GFR (mL/min/1.73m^2)	77.4±30.2	0.02 (0.4)	0.02 (0.4)	0.7 (-0.068)	0.47 (-0.1)
C3 (mg/dl)	71.8±46.1	0.5 (0.1)	0.5 (0.1)	0.9 (0.1)	0.7 (-0.05)
C4 (mg/dl)	17.01±12.26	0.7 (-0.07)	0.6 (-0.09)	0.67 (0.08)	0.86 (0.03)
Anti-dsDNA (IU/ml)	2.8±4.42	0.8 (0.03)	0.4 (0.1)	0.95 (-0.011)	0.8 (0.02)
aPL	……	0.03 (-0.4)	0.01 (-0.4)	0.78 (-0.5)	0.7 (-0.073)
24h-proteinuria	1413.6±1046.8	0.07 (0.36)	0.15 (0.2)	0.46 (0.15)	0.65 (0.09)
Pathological parameter					
Bx-class	…….	0.37 (0.17)	0.2 (0.2)	0.2 (-0.2)	0.17 (-0.2)
BxAI	12.11±7.8	0.2 (-0.2)	0.4 (-0.1)	0.2 (-0.2)	0.51(-0.1)
BxCI	4.39±3.6	0.01 (-0.4)	0.01 (-0.4)	0.3 (0.2)	0.1 (0.3)

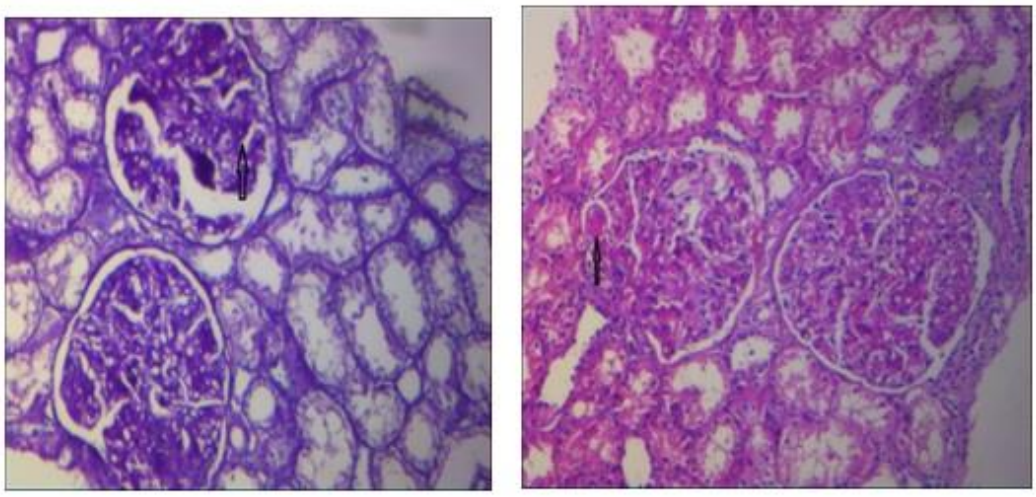

Figure 1. There is diffuse global endocapillary and extra capillary glomerulonephritis affecting the glomeruli included in the biopsy. There is marked thickening of the capillary walls that are called "wire loop" lesions (Fig 1a: left). In addition, the capillary lumina are occluded by the deposition of hyaline thrombi (Fig1b: right).

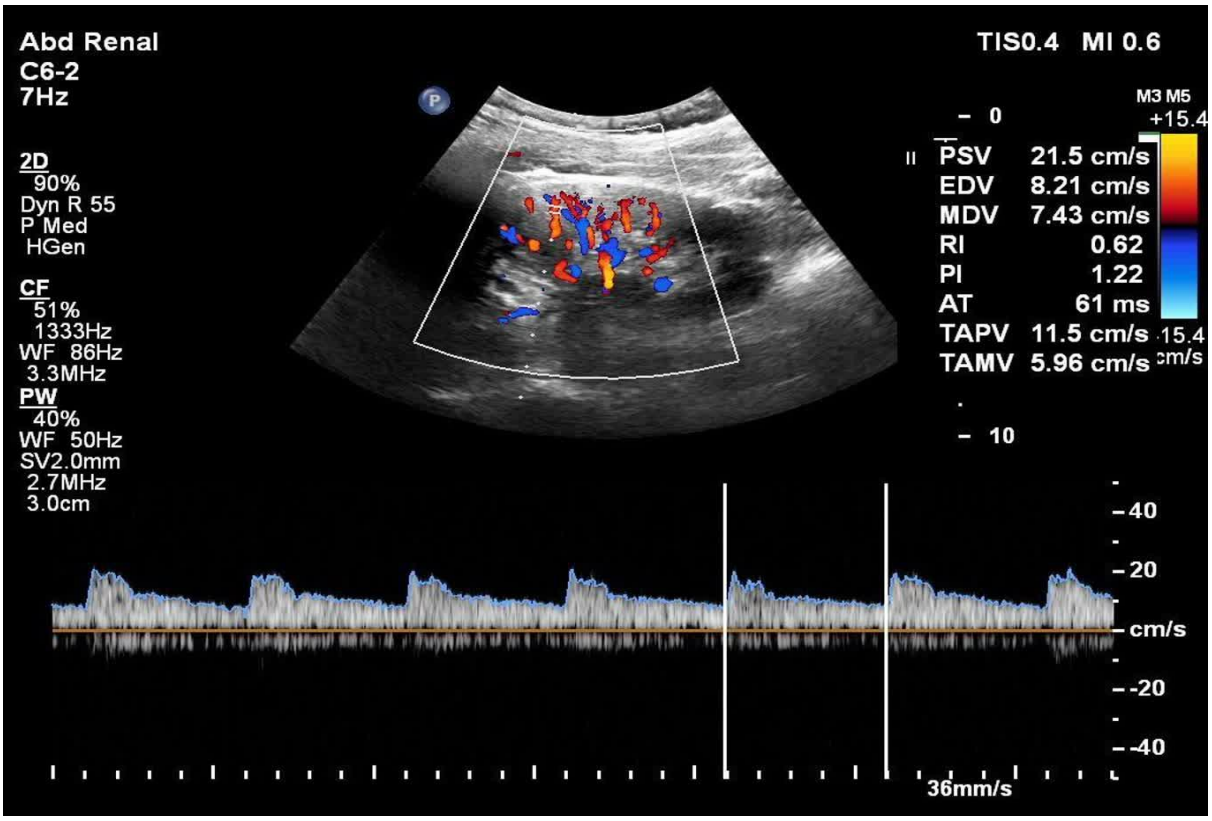

Figure 2. Renal Color Doppler ultrasound

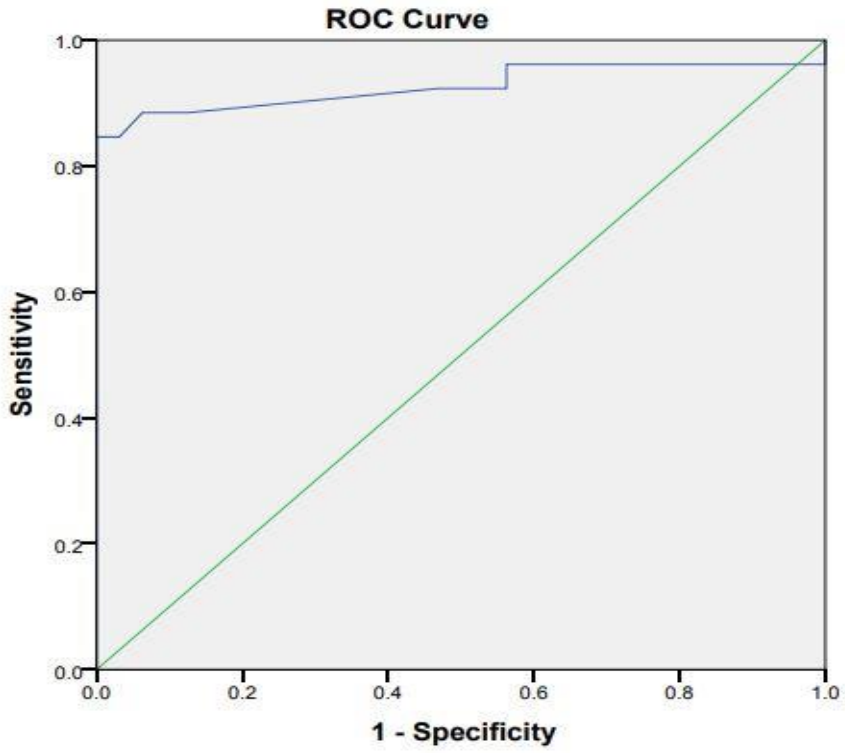

Figure 3. ROC curve of anti-dsDNA to predict BXCI

Discussion

Investigating the correlation between ultrasound indices (PSV, RI, SD, and EDV) and biopsy class (bxclass) demonstrated no significant correlation between bxclass and any of the ultrasound indices in the upper, middle, lower poles, or all poles of the kidney as one unit. Kasem et al. conducted a study on patients with LN and reported a significant relationship between bxclass and renal RI. According to their findings, RI can be used as a strong biomarker to predict renal bxclass **(20)**. The difference between the present study and Kasem's study may be attributed to the different distribution of patients in terms of renal bxclass. In our study, most patients (32.1%) were in class II, while in the study by Kasem et al., most patients were in classes III and IV, respectively **(20)**.

Additionally, in the current study, there was no significant correlation between bxAI (biopsy activity index) and ultrasound parameters (RI, SD, EDV, and PSV) in the upper, middle, lower, or all poles of the kidneys. However, investigating the relationship between bxCI (biopsy chronicity index) and ultrasound parameters revealed a negative relationship between bxCI and EDV in the upper and middle poles, and PSV in the upper pole. Furthermore, a negative relationship was observed between bxCI and both PSV and EDV (all poles as one unit). Platt et al. revealed that patients with elevated RI (> 0.70) had significantly higher bxCI **(17)**. Therefore, it seems that RI and the chronicity index are important indicators of adverse renal outcomes.

Wakil et al. evaluated renal RI in individuals with lupus nephritis and found a significant association between renal RI > 0.7 and higher bxCI **(15)**. Thus, the renal resistance index (RI) may play a crucial role in predicting the chronicity index of renal biopsy, serving as a key factor in determining renal outcomes. Moreover, it can be a useful and non-invasive procedure to assess the chronicity index in individuals with LN. They also revealed that an RI cut-off value of 0.7 was superior to an RI cut-off value of 0.65 for predicting renal bxCI **(15)**.

Since there was only one patient with RI > 0.7 in our study, it was impossible to divide patients into two groups based on the 0.7 cut-off value. Therefore, we experimentally set a cut-off value of 0.6 for RI, but no significant correlation was observed between RI and pathological or laboratory parameters. Elsamea et al. demonstrated that at an RI cut-off value of 0.57, renal RI had a higher activity index score than those with normal RI **(1)**. The differences between the studies may be due to different cut-off values and genetic factors. Another difference is the distribution of bxclass. Most of the patients in our study were in class II, while in the study by Elsamea et al., the majority were in class IV. Therefore, according to our study, it cannot be

concluded that RI is useful in predicting bxCI and bxAI, but PSV and EDV sonographic indices may be useful for predicting bxCI.

In the present study, the correlation between ultrasound indices and anti-dsDNA showed no significant correlation between any ultrasound indices (PSV, RI, SD, and EDV) in the upper, middle, and lower poles with anti-dsDNA. Furthermore, no correlation was observed between ultrasound indices (all poles as one unit) and anti-dsDNA. Elsamea et al. revealed that RI was significantly correlated with anti-dsDNA **(1)**. It seems that differences in disease severity may explain the discrepancies between the two studies.

Additionally, in the present study, the relationship between GFR and ultrasound indices in different poles showed a significant relationship between GFR and both PSV and EDV in the upper pole. Moreover, the relationship between GFR and ultrasound indices (all poles as one unit) showed significant correlations between both PSV and EDV and GFR. Chen et al. investigated the relationship between GFR and ultrasound indices in patients with LN, finding no significant relationship between GFR and PSV or EDV **(21)**. The difference between the two studies could be due to differences in the GFR levels of the patients. In the study by Chen et al., the mean GFR was 21.2 ± 5.9 **(21)**, whereas in our study, it was 77.4 ± 30.2.

Furthermore, in the present study, there was no significant correlation between ultrasound indices in any pole of the kidney and C3 or C4. Besides, no significant correlation was observed between ultrasound indices (all poles as one unit) and C3 or C4. Elsamea et al. assessed the relationship between RI and C3 levels but no significant relationship was observed **(1)**. These findings are consistent with our study.

A negative correlation was observed between aPL and PSV in the upper, middle, and lower poles, as well as EDV in the lower pole. Additionally, a negative relationship was demonstrated between aPL and both PSV and EDV (all poles as one unit). No comprehensive study was found regarding the relationship between aPL and sonographic indices or pathological findings. Moreover, we did not observe any relationship between 24-hour proteinuria and sonographic indices. Elsamea et al. demonstrated a significant correlation between RI and renal function, including 24-hour proteinuria **(1)**. The differences between the studies may be due to differences in the mean level of 24-hour proteinuria, and differences in bxclass may also contribute.

Conclusion

This study demonstrated no significant relationship between RI and pathological or laboratory parameters. However, a negative association was seen between PSV and EDV with the degree of chronic kidney damage. Furthermore, PSV and EDV had a positive correlation with GFR and a negative correlation with aPL. It also appears that anti-dsDNA could potentially be used to predict long-term renal outcomes in patients with LN.

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Authors' Contribution

SS designed the study, H.S and F.B conducted the study, AP.A, A.D, H.B wrote the study, R.H edited the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval and consent to participate

This study received approval from the Ethics Committee at Shahid Sadoughi University of Medical Sciences (IR.SSU.MEDICINE.REC.1400.118).

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