Received: 04 Sep 2023 | **Accepted:** 02 Oct 2023 **Genel Tıp Derg. Volume** 33/**Issue** 5 (October), 608-613
DOI: 10.54005/geneltip.1354789

ORIGINAL ARTICLE

Assessing the Diagnostic Value of the Red Blood Cell Distribution-To-Platelet Ratio in Acute Leg Embolism Requiring Emergent Surgical Intervention

Acil Cerrahi Müdahale Gerektiren Akut Bacak Embolisinde Kırmızı Kan Hücresi Dağılımı-Trombosit Oranının Tanısal Değerinin Değerlendirilmesi

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How to cite ?

Çiçek Ö. F. , Atalay A. , Çelik R. , Özdil M. , Boncuk F. , Ünlü A. , Babadağ N. N. , Ayyıldız Ş. A. , Salehi F. , Coşkuner E. , Yıldırım E. , Ceylan Z. Assessing the Diagnostic Value of the Red Blood Cell Distribution-To-Platelet Ratio in Acute Leg Embolism Requiring Emergent Surgical Intervention. Genel Tıp Dergisi. 608-613.

ABSTRACT

Background: The objective of this study was to evaluate the significance of the red blood cell distribution-to-platelet ratio (RPR) as a diagnostic indicator, derived from the initial hemogram measurements of patients who underwent emergent surgical treatment for acute leg embolism, by comparing it to a control group of healthy individuals.
Methods: The study included 48 patients who underwent femoral embolectomy for acute lower limb ischemia, while an additional 49 individuals were enrolled as a control group. Demographic, clinical, and laboratory data were compared between the two groups. Using the receiver operating characteristic curve to determine the RPR cutoff value, the area under the curve, sensitivity, and specificity were calculated.
Results: The age and gender distribution of both groups were comparable. The admission RPR values of patients who underwent surgery for acute embolism were statistically higher compared to healthy individuals (0.0677 (IQR: 0.0547-0.0803) vs. 0.0504 (IQR: 0.0441-0.0572), p<0.001). The area under the curve for acute extremity embolism was determined as 0.832, and the RPR cut-off value of 0.566 was found to predict acute extremity embolism with a sensitivity of 72.9% and a specificity of 73.5% (p<0.001).
Conclusion: Our findings provide preliminary evidence that RPR can be used as a novel diagnostic indicator for acute leg embolism. Rather than being used diagnostically alone, it is thought that a comprehensive evaluation of this ratio, when combined with the patient's medical history and other clinical findings, has the potential to expedite the diagnostic process, particularly in healthcare settings with limited access to imaging resources.

Keywords: acute leg ischemia, hemogram, platelet, red blood cell distribution.

ÖZ

Amaç: Bu çalışmanın amacı, akut bacak embolisi nedeniyle acil cerrahi tedavi uygulanan hastaların başvuru hemogram ölçümlerinden elde edilen kırmızı kan hücresi dağılımı-trombosit oranının (RPR) tanısal bir gösterge olarak önemini, sağlıklı bireylerden oluşan bir kontrol grubuyla karşılaştırarak değerlendirmektir.
Yöntemler: Çalışmaya akut alt ekstremite iskemisi nedeniyle femoral embolektomi yapılan 48 hasta dahil edilirken, 49 kişi de kontrol grubu olarak kaydedilmiştir. Demografik, klinik ve laboratuvar verileri iki grup arasında karşılaştırılmıştır. RPR kesme değerini belirlemek için receiver operating characteristic eğrisi kullanılarak eğri altında kalan alan, duyarlılık ve özgüllük hesaplanmıştır.
Bulgular: Her iki grubun yaş ve cinsiyet dağılımı benzerdi. Akut emboli nedeniyle ameliyat edilen hastaların başvuru RPR değerleri sağlıklı bireylere kıyasla istatistiksel olarak daha yüksekti (0,0677 (IQR: 0,0547-0,0803) vs. 0,0504 (IQR: 0,0441-0,0572), p<0,001). Akut ekstremite embolisi için eğri altında kalan alan 0,832 olarak belirlenmiş ve 0,566 RPR kesim değerinin akut ekstremite embolisini %72,9 duyarlılık ve %73,5 özgüllükle öngördüğü bulunmuştur (p<0,001).
Sonuç: Bulgularımız, RPR'nin akut bacak embolisi için yeni bir tanısal gösterge olarak kullanılabileceğine dair ön kanıtlar sunmaktadır. Bu oranın tek başına tanısal olarak kullanılmasından ziyade, hastanın tıbbi geçmişi ve diğer klinik bulgularla birleştirildiğinde kapsamlı bir değerlendirmesinin, özellikle görüntüleme kaynaklarına sınırlı erişimi olan sağlık hizmeti ortamlarında tanısal süreci hızlandırma potansiyeline sahip olduğu düşünülmektedir.

Anahtar Kelimeler: akut bacak iskemisi, hemogram, kırmızı kan hücresi dağılımı, trombosit.

Introduction

Acute limb ischemia is a pathological condition that occurs suddenly and requires immediate intervention. Acute embolism refers to the blockage of a distant vessel by an embolus that originates from another part of the body. The primary origin frequently documented for emboli in the lower extremities is the cardiac region, contributing to 55 to 87 percent of occurrences (1,2). Around 70-80% of emboli are situated within the extremities, exhibiting a prevalence five times greater in the lower limbs (3). Acute arterial embolism and thrombosis are the most common causes, while vascular trauma and aortic dissection can also lead to this condition. Clinical symptoms include the classic "6 Ps": pallor, pulselessness, pain, paresthesia, paralysis, and poikilothermia. Diagnosis is directly related to pain and dysfunction of the extremity. Arterial embolism begins suddenly and rapidly deteriorates. Differential diagnosis should include deep vein thrombosis, chronic peripheral arterial disease, soft tissue injuries, and neurological conditions. Early diagnosis of the disease can prevent

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - iThenticate
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Selcuk University School of Medicine
Genel Tıp Dergisi | e-ISSN: 2602-3741
https://dergipark.org.tr/tr/pub/geneltip

limb loss. Otherwise, delayed intervention in embolic conditions can result in amputation and death (4).

The substantial diagnostic, prognostic, and therapeutic clinical associations in the ratios derived from parameters within the complete blood count have been demonstrated. The neutrophil-to-lymphocyte ratio, for instance, has been identified as an important marker for inflammation, and its relationship with numerous conditions such as cardiovascular disease has been established (5). Red cell distribution width (RDW) is a parameter in the complete blood count that indicates the variation in the size of red blood cells. It is taken into consideration in the diagnosis and treatment of anemia, thalassemia, and cardiovascular disorders (6). Platelet (PLT) count, on the other hand, reflects the level of platelets in the blood and plays a critical role in the diagnosis and treatment of many diseases. The ratio of RDW to PLT, an index readily accessible in routine practice and calculable with ease, is emerging as a novel indicator reflective of the severity of inflammation (7).

Preexisting data substantiates the pivotal involvement of inflammatory mechanisms in various cardiovascular disorders associated with thrombotic events and across all stages of the atherosclerotic continuum, spanning from endothelial impairment to the development of atherothrombotic phenomena (8). The interaction between inflammatory markers and thromboembolic events has attracted considerable interest and has been the subject of inquiry by a multitude of researchers. However, according to our comprehensive literature review, the predictive value of the RDW/PLT ratio has not been previously examined in the diagnosis of acute lower extremity embolism. In this study, we aimed to assess the predictive value of the RDW/PLT ratio (RPR) as a diagnostic marker, obtained from the initial hemogram values of patients admitted to the emergency department with acute leg embolism and treated surgically, by comparing it with healthy individuals.

Materials and Methods

Between January 2017 and December 2022, patients who presented with acute lower limb ischemia and underwent emergency surgical procedures were included in the study. Within this retrospective study, pertinent demographic data of patients, their underlying medical conditions, routine blood parameters, and procedural particulars were extracted from the institutional database. As part of the diagnosis and treatment, a complete blood count (CBC) test was routinely conducted upon admission of all patients. The calculation of the RPR was executed following the methodology outlined by Chen et al. (9). The RPR is determined as the quotient of RDW (%) divided by platelet count (109/L). The control group consisted of individuals who did not exhibit any acute health issues and had sought hospital attendance for a routine check-up. The study included 48 patients who had femoral embolectomy for acute lower limb ischemia and 49 individuals as a control group. All participants were ≥18 years old. Patients with delayed limb ischemia, active infection, hematological disease, and hepatic disease were excluded. The study protocol was approved by the Local Ethics Committee of the Selçuk University Faculty of Medicine (approval number: 2023/141 and approval date: 14.03.2023). The study was conducted in accordance with the principles delineated in the Declaration of Helsinki. Following a comprehensive patient history assessment and meticulous physical examination, all patients underwent evaluation via arterial Doppler ultrasound and/or computerized tomographic angiography (CTA). A surgical procedure was decided upon after an in-depth evaluation of all relevant details. Following that, the related risks were explained to the patient, resulting in the obtaining of their informed consent was obtained.

Surgical procedure

All operations were performed under local or general anesthesia. The groin was explored through a vertical incision, and common, superficial, and profunda femoral arteries were encircled with loops and controlled. Intravenous heparinization was performed with 5,000 units of standard heparin, with the activated clotting time (ACT) kept above 200 seconds. Arterial clamps were applied, and a transverse arteriotomy was performed. Subsequently, proximal and distal embolectomy was meticulously performed using suitably sized Fogarty catheters. The procedure was repeated until complete clearance of thromboembolic material was accomplished and finalized when adequate proximal flow and observable distal backflow were attained. The arteriotomy was repaired, restoring the blood flow. The surgical procedure was completed when a normal intraoperative pulse evaluation was confirmed.

Statistical Analyses

The data was analyzed with the SPSS version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA) software, and the distribution analysis of the data was performed using the Shapiro-Wilk test. Categorical variables were presented as numbers and percentages while continuous variables were presented as mean ± standard deviation if normally distributed or as median (interquartile range) if not normally distributed. An independent sample t-test or Mann-Whitney U test was used to compare continuous variables between independent groups, and chi-square test was used for categorical variables. A p-value less than 0.05 was considered statistically significant. A receiver operating characteristic (ROC) curve was plotted to demonstrate the relationship between the RDW/PLT ratio and acute embolism. The area under the curve (AUC), sensitivity, and specificity were calculated by determining the cutoff value for RDW/PLT using the ROC curve.

Results

The demographic information of the patients is provided in Table 1. In the statistical evaluation, both groups were similar in terms of age and gender distribution (p=0.181 and p=1.000, respectively). When comparing the acute embolism group and the control group in terms of the occurrence of diabetes mellitus, they were found statistically similar (p=0.068). In terms of hypertension, a statistically significant increase was detected in the acute embolism group when compared to the control group (p=0.025). When comparing both groups in terms of COPD, chronic kidney disease, active smoking and malignancy, no statistically significant difference was observed (p=0.111, p=0.059, p=0.524, and p=0.056, respectively). When comparing the embolism and control groups in terms of atrial fibrillation, it was determined that atrial fibrillation was statistically significantly more common in the acute embolism group (p=0.001).

The admission laboratory values of the acute embolism and control groups are presented in Table 2. When comparing the acute embolism and control groups in terms of blood parameters, the glucose value of the acute embolism group was statistically significantly higher compared to the control group (p=0.002). When comparing the creatinine values of the two groups, the acute embolism group had a higher creatinine value (p=0.003). In terms of hemoglobin value, the acute embolism group had a statistically significantly lower value compared to the control group (p=0.013). However, there was no statistically significant difference between the two groups in terms of hematocrit value (p=0.121). When comparing the WBC value, the acute embolism group had a higher WBC value compared to the control group, and this difference was statistically significant (p=0.001). The acute embolism group had statistically significantly higher values than the control group when the platelet and RDW values were compared (p<0.001 for both). The admission RDW/PLT values of patients who underwent surgery for acute embolism were statistically higher compared to healthy individuals (0.0677 (IQR: 0.0547-0.0803) vs. 0.0504 (IQR: 0.0441-0.0572), p<0.001) (Figure 1).

The operative and postoperative data of patients underwent femoral embolectomy are presented in Table 3. Color Doppler ultrasound was used for diagnosis in 16.7% of the patients, CTA in 68.8% of the patients, and a combination of CTA and Doppler ultrasound in 14.6% of the patients. Right femoral embolectomy was performed in 56.3% of the patients, left femoral embolectomy in 41.7% of the patients, and bilateral femoral embolectomy in 2.1% of the patients. Amputation was observed in 2.1% of the patients, and early-term mortality (within the first 30 days after surgery) was observed in 8.3% of the patients.

To determine the relationship between the RDW/PLT value and acute lower extremity embolism requiring surgery, a ROC curve was drawn (Figure 2). The AUC for acute extremity embolism was determined as 0.832 (95% confidence interval: 0.749-0.915). When the cut-off value of 0.566 was taken for the RDW/PLT value at admission, it was found to predict acute extremity embolism with a sensitivity of 72.9% and a specificity of 73.5% (p<0.001).

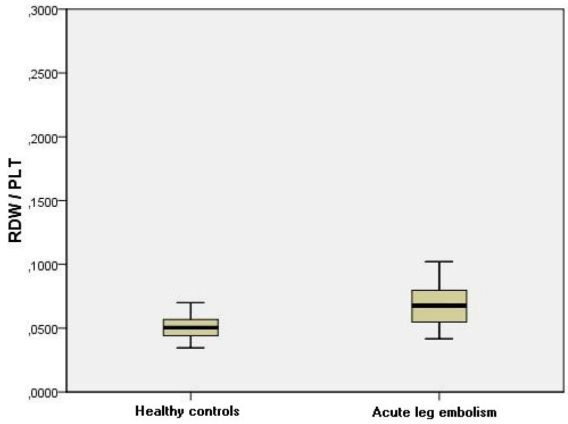

Figure 1: Admission RDW/PLT values of the control group and patients operated on for acute embolism (p<0.001).

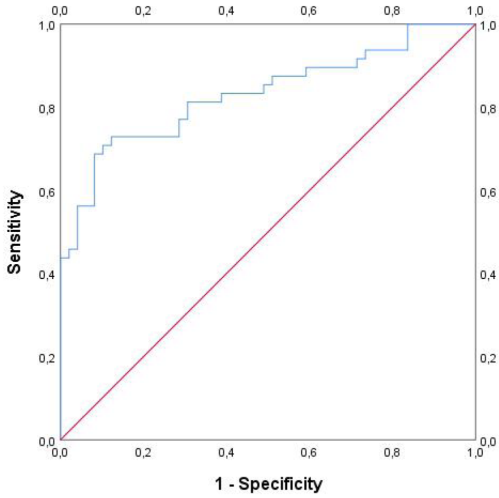

Figure 2: ROC curve illustrating the relationship between RDW/PLT value and acute embolism.

Table 1. Demographic data of the acute embolism and control groups

	Acute embolism group (n=48)	Control group (n=49)	p value
Age (years)	64.19±12.57	61.47±6.07	0.181
Male gender [n (%)]	22 (45.8)	23 (46.9)	1.000
Female gender [n (%)]	26 (54.2)	26 (53.1)	
Diabetes mellitus [n (%)]	10 (20.8)	3 (6.1)	0.068
Hypertension [n (%)]	16 (33.3)	6 (12.2)	0.025
Chronic obstructive pulmonary disease [n (%)]	5 (10.4)	1 (2)	0.111
Chronic kidney disease [n (%)]	6 (12.5)	1 (2)	0.059
Active smoking [n (%)]	6 (12.5)	4 (8.2)	0.524
Malignancy [n (%)]	4 (8.3)	-	0.056
Atrial fibrillation [n (%)]	12 (25)	-	0.001

Table 2. Laboratory values of the acute embolism and control groups

	Acute embolism group (n=48)	Control group (n=49)	p value
Glucose (mg/dL)	126.5 (105.25-173.25)	105 (97-124)	0.002
Creatinine (mg/dL)	0.96 (0.775-1.087)	0.78 (0.675-0.935)	0.003
Hemoglobin (g/dL)	13.36±2.3	14.4±1.59	0.013
Hematocrit (%)	41.6 (34.65-45.8)	42.7 (39.1-45.5)	0.121
White blood cell (K/uL)	9.65 (7.63-12.61)	7.97 (6.44-9.09)	0.001
Platelet (K/uL)	228.04±66.47	271.2±45.61	<0.001
RDW (%)	14.7 (13.425-16.65)	13.1 (12.65-13.9)	<0.001
RPR	0.0677 (0.0547-0.0803)	0.0504 (0.0441-0.0572)	<0.001

RDW: Red blood cell distribution; RPR: Red blood cell distribution-to-platelet ratio

Table 3: Operative and postoperative data of patients underwent femoral embolectomy

	Number	Percentage
Diagnostic Method		
Color Doppler USG	8	16.7
CTA	33	68.8
Color Doppler USG and CTA	7	14.6
Femoral embolectomy side		
Right	27	56.3
Left	20	41.7
Bilateral	1	2.1
Amputation	1	2.1
Mortality	4	8.3

CTA: Computed tomographic angiography; USG: Ultrasonography

Discussion

This study assessed the relationship between RPR and acute lower extremity embolism for the first time. To examine the diagnostic role of RPR, we compared patients with acute lower extremity embolism who underwent emergency surgery to healthy individuals as a control group. The primary outcomes of this study are outlined as follows: 1) The admission RPR of patients who underwent surgery for acute lower extremity embolism was statistically higher compared to healthy individuals; 2) The ROC analysis demonstrated that the optimal threshold for the RPR to predict acute lower extremity embolism was determined to be 0.566.

The occurrence of acute leg embolism is a significant vascular emergency, leading to the development of ischemia in the leg due to a sudden occlusion. If left untreated, acute leg embolism can result in the loss of a limb or perhaps death (4). Surgical intervention should be considered for all patients presenting with acute limb ischemia. In the past, elderly individuals were not thought to be surgical candidates, but a recent study by Kubat et al. (10) has demonstrated that older patients have comparable outcomes, indicating that age is not a limitation to surgery. Hence, timely diagnosis and intervention hold the utmost significance. While the assessment of acute limb ischemia typically relies on patient history and physical examination, a comprehensive diagnosis necessitates the use of modern radiological imaging techniques. The diagnosis of this clinical condition, which requires immediate intervention, poses significant challenges in rural hospitals lacking access to radiologic imaging. Consequently, patients may experience delays in the diagnostic process. Hence, the idea that the diagnosis or confirmation of acute leg embolism can be facilitated by an easily available laboratory test such as a complete blood count, has consistently attracted research interest. This study was conducted to address the existing research gap and the absence of prior studies on this particular topic in the literature. While relying solely on this basic ratio for diagnosis is challenging, we argue that it could serve as a supplementary tool when considered alongside the patient's clinical findings.

RDW is a measure of the variation in red blood cell size and shape. RDW has been shown to be associated with inflammation, oxidative stress, endothelial dysfunction, and thrombosis (6,11,12). RDW has been reported to be elevated in various cardiovascular diseases such as coronary artery disease, heart failure, stroke, and pulmonary embolism (11,12). PLT count is a measure of the number of platelets in the blood. Platelets are involved in hemostasis and thrombosis, and their activation and aggregation can contribute to vascular occlusion and ischemia (13). Previous studies have indicated a decrease in platelet count in thromboembolic conditions; for instance, Cil et al. (14) observed a statistically significant reduction in mean platelet count among patients with deep vein thrombosis when compared to healthy controls. Furthermore, the initiation of the coagulation cascade results in the formation of blood clots within the small blood vessels and, in severe cases, disseminated intravascular coagulation, leading to a decrease in the number of platelets (15). The RDW/PLT ratio is a novel index that offers a comprehensive understanding of both RDW and PLT parameters concurrently, surpassing their individual analyses. Consequently, RPR was a more potent combination of two important parameters that had been shown to accurately predict the diagnosis and prognosis of numerous diseases. This is supported by research by Xi et al. (16), who found that when evaluating hemophagocytic lymphohistiocytosis, RPR exhibited a higher diagnostic value than RDW. In the context of all of this, previous research has demonstrated that RPR has been suggested as a potential diagnostic and prognostic biomarker for a range of diseases, including liver cirrhosis, acute pancreatitis, acute kidney injury, rheumatoid arthritis, and sepsis (7, 9, 17-19). The association between these various diseases and RPR likely possesses a multifaceted underlying mechanism, wherein inflammation assumes a pivotal role.

It is known that inflammation and thrombosis have a close association. The stimulation of coagulation has been recognized as a significant constituent of the inflammatory process. There is a wide range of inflammatory cytokines that have the capacity to induce the destruction of vascular endothelial cells, leading to the migration of leukocytes towards tissues. This process subsequently promotes platelet adhesion and aggregation. Prior research has indicated that there is an elevation in inflammatory markers during thromboembolic events, potentially occurring either prior to or subsequent to the event (20). In our study, we observed a notable elevation in RPR levels among individuals diagnosed with acute leg embolism in comparison to a control group of healthy individuals. This association is thought to primarily arise from inflammatory processes, considering it may also involve additional sophisticated mechanisms. In fact, previous studies demonstrated that the RPR is a novel indicator of inflammation severity (21). The measurement of RPR exhibits an extent of prognostic and diagnostic significance in relation to inflammatory conditions, and its calculation is quite simple. Although RPR was initially identified as a novel measure and a much stronger predictor of substantial fibrosis (9), it is now known that it also reveals the degree of inflammation. The precise mechanism underlying the increase in RPR levels in patients with acute limb ischemia in comparison to those who are healthy remains unclear; nonetheless, it is speculated to be associated with inflammatory processes.

Our results show that RPR with a cutoff value of 0.566 can significantly differentiate a healthy individual and acute leg embolism (AUC=0.832). An examination of prior research indicates that this parameter exhibits considerable variability. Liu et al. (7) identified a specific threshold value of 0.109 for the RPR, which can be utilized as a predictive indicator for 28-day mortality for patients diagnosed with sepsis. However, Qui L et al. (21) established a cut-off point of 0.197 for the RPR in order to predict mortality on the third day in patients with severe burn injury. In contrast, Jiang et al. (22) determined a cutoff value of 7.66 for RPR in the prediction of early neurological impairment following thrombolysis. In another study, ROC curve analysis of RPR revealed that 4.2 was the optimal cutoff value for predicting no reflow phenomenon in patients undergoing primary percutaneous coronary intervention with ST segment elevation myocardial infarction (23). The observed disparity in the cut-off point for RPR among the studies can be attributed to the inclusion of various patient populations, heterogeneity, and variations in sample sizes among the studies.

The limitations of our study should be acknowledged. First, our study was retrospective and comprised a modest sample size. Second, because these patients were emergent cases, we could not be able to measure other potential confounding factors, such as iron or vitamin B12 deficiency. In addition, high-sensitivity C-reactive protein is not routinely evaluated in patients undergoing femoral embolectomy in our department; therefore, this test was absent from the comparison of inflammatory status between the groups. Lastly, we did not evaluate the prognostic value of RPR in patients with acute limb embolism, which may be an intriguing area for future study.

In conclusion, our study represents the initial evidence suggesting that RPR serves as a novel diagnostic indicator for acute leg embolism. A complete blood count is a frequently utilized laboratory test in medical practice due to its widespread availability and cost-effectiveness. Hence, the RPR, which is derived from a routine test ¬¬– complete blood count –, can be readily calculated and is an inexpensive parameter. It is considered that the comprehensive evaluation of this ratio, in conjunction with the patient's medical history and other clinical findings, has the potential to expedite the diagnostic process, particularly in healthcare settings with limited access to imaging resources, rather than being used diagnostically alone.

Ethical Approval

The study protocol was approved by the Local Ethics Committee of the Selçuk University Faculty of Medicine (approval number: 2023/141 and approval date: 14.03.2023).

Conflict of Interest

The authors declare no conflict of interest.

Funding

The authors received no financial support for the research and/or authorship of this article.

Acknowledgment

We express our gratitude to Assoc. Prof. Fikret Akyürek from the Department of Biochemistry for his sincere help.

Statement

This study was presented as a poster within the scope of our Faculty's Evidence-Based Medicine Board of Class II students in the 2022-2023 academic year and was awarded first prize by the jury.

Authors' Contributions

Conception: AA, RÇ, Materials: NNB, ŞAA, FS, ZC, Data Collection and/or Processing: MÖ, EC, Analysis and/ or Interpretation: ÖFÇ, Literature Review: AÜ, FB, EY, Writer: ÖFÇ, AA, RÇ, MÖ, FB, AÜ, NNB, ŞAA, FS, EC, EY, ZC, Critical Review: ÖFÇ

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