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Original Article

Clinical Implications of Pan-Immune-inflammatory Values in Patients with Hypertrophic Cardiomyopathy

Hipertrofik Kardiyomiyopatili Hastalarda Pan-İmmün-inflamatuar Değerlerin Klinik Etkileri

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ABSTRACT

Objective: Despite significant advances in understanding hypertrophic cardiomyopathy (HCM) in recent years, there is a need to improve risk stratification for patients at high risk of adverse outcomes. The relationship between inflammation and disease severity in HCM patients is known. Recently, a new inflammation parameter called the pan-immune inflammation value (PIV) has been introduced. However, the relationship between PIV and HCM has not yet been examined. Hence, we aim to investigate the effect of PIV on prognosis in a large series of HCM patients.

Methods: The study included 389 consecutive patients with HCM admitted to a tertiary care hospital between 2004 to 2021. The PIV for patients was calculated as: Neutrophil count x platelet count x monocyte count / lymphocyte count. The cohort was categorized into three groups according to PIV, and the association between these groups and long-term mortality was evaluated.

Results: Over an average follow-up period of 55.5±12.7 months, long-term mortality occurred in 47 out of 389 patients. Long-term mortality was recorded in 7 patients in tertile 1, 12 patients in tertile 2, and 28 patients in tertile 3. Multivariate regression analysis revealed that long-term all-cause mortality was 3.5 times higher in tertile 3 compared to tertile 1. The receiver-operating characteristic curve based on the PIV had 62% sensitivity and 65% specificity for long-term mortality.

Conclusions: High PIV levels may serve as a predictor of long-term mortality in patients with HCM. PIV could be a useful screening tool for identifying HCM patients at increased risk of adverse outcomes.

Keywords: Hypertrophic cardiomyopathy, pan-immune-inflammation value, systemic inflammatory markers, prognosis

ÖZ

Amaç: Son yıllarda hipertrofik kardiyomiyopati (HCM) konusunda önemli ilerlemeler kaydedilmiş olmasına rağmen, yüksek riskli hastalar için risk sınıflandırmasının iyileştirilmesine ihtiyaç vardır. HCM hastalarında inflamasyon ile hastalık şiddeti arasındaki ilişki bilinmektedir. Son zamanlarda, pan-immün inflamasyon değeri (PIV) adı verilen yeni bir inflamasyon parametresi tanıtılmıştır. Ancak, PIV ile HCM arasındaki ilişki henüz incelenmemiştir. Bu nedenle, geniş bir HCM hasta serisinde PIV'nin prognoz üzerindeki etkisini araştırmayı amaçlıyoruz.

Yöntemler: Çalışma, 2004 ile 2021 yılları arasında bir üçüncü basamak hastaneye kabul edilen ardışık 389 HCM hastasını içermektedir. Hastalar için PIV değeri şu şekilde hesaplandı: Nötrofil sayısı x trombosit sayısı x monosit sayısı / lenfosit sayısı. Kohort, PIV'ye göre üç gruba ayrıldı ve bu gruplar ile uzun dönem mortalite arasındaki ilişki değerlendirildi.

Bulgular: Ortalama 55,5±12,7 aylık bir takip süresi boyunca, 389 hastanın 47'sinde uzun dönem mortalite gözlendi. Uzun dönem mortalite, tertil 1'de 7 hastada, tertil 2'de 12 hastada ve tertil 3'te 28 hastada kaydedildi. Çok değişkenli regresyon analizi, tertil 3'te uzun dönem tüm nedenlere bağlı mortalitenin tertil 1'e göre 3,5 kat daha yüksek olduğunu ortaya koymuştur. PIV'ye dayalı alıcı çalışma karakteristiği eğrisi, uzun dönem mortalite için %62 duyarlılık ve %65 özgüllük göstermiştir.

Sonuçlar: Yüksek PIV seviyeleri, HCM hastalarında uzun dönem mortalitenin bir göstergesi olarak hizmet edebilir. PIV, HCM hastalarını olumsuz sonuçlar açısından artmış risk taşıyanlar olarak tanımlamak için yararlı bir tarama aracı olabilir.

Anahtar kelimeler: Hipertrofik kardiyomiyopati, pan-immün-inflamasyon değeri, sistemik inflamatuar belirteçler, prognoz

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disorder, occurring in approximately 1 in 500 individuals in the general population[1]. The primary pathological features of the myocardium in HCM include myocyte hypertrophy and disorganization, interstitial fibrosis, and small vessel disease[2,3]. The disease consists of a broad spectrum ranging from asymptomatic to severely limiting symptoms with adverse clinical outcomes including severe heart failure, malignant arrhythmias, and cardiac death[4-6]. In spite of substantial progress in understanding the etiology, diagnosis, and treatment of HCM in recent years, the condition and its related complications remain a significant healthcare burden[7,8]. Consequently, there is a need to assess the prognosis of HCM patients and improve risk stratification for those at high risk of adverse outcomes.

Recently, there has been increasing interest in evaluating the role of inflammation and oxidative stress in the pathogenesis and prognosis of HCM. Recently, the pan-immune inflammation value (PIV) has become a new, cost-effective, straightforward, and easily accessible marker based on inflammation and oxidative stress. PIV, initially considered an important prognostic marker in cancer patients[9]. However, the detailed relationship between HCM and PIV has not been extensively studied yet.

The purpose of this study was to examine the impact of PIV on the prognosis of a large cohort of HCM patients monitored at a tertiary care hospital.

MATERIALS and METHODS

We performed a retrospective analysis of 389 consecutive HCM patients who were monitored at our tertiary care center from 2004 to 2021. The clinical diagnosis of HCM is established through echocardiographic or cardiovascular magnetic resonance imaging, which shows a maximum end-diastolic wall thickness of ≥15 mm in any segment of the left ventricle (LV), provided there is no alternative cause for the hypertrophy[10]. Patients with left ventricular hypertrophy resulting from secondary causes, including hypertension, infiltrative diseases, and severe aortic stenosis, were excluded from the study. Additionally, to minimize bias, patients with a follow-up period of less than 5 years were excluded from the study.

Laboratory results including complete blood count, creatinine, urea, albumin, hormone levels, and glucose levels were assessed based on the first blood samples collected at admission. The MIND-RAY BC-6800 from China was utilized for automated blood cell count, while the ARCHITECT PLUS CI-4100 from the USA was employed for biochemical parameters. The PIV for patients was calculated as: neutrophil count (10^3/μL) x platelet count (10^3/μL) x monocyte count (10^3/μL) / lymphocyte count (10^3/μL). All patients received transthoracic echocardiography carried out by a cardiovascular imaging expert using the Vivid 7 system (GE Vingmed Ultrasound AS, Horten, Norway). The modified Simpson method was used to evaluate left ventricular ejection fraction. Maximum LV wall thickness was determined as the largest wall thickness measured in parasternal long and short axis views. The peak instantaneous LV outflow gradient was measured using continuous wave Doppler. LV outflow obstruction was defined as a gradient measurement of 30 mm Hg either at rest or during exercise[11]. The HCM risk-sudden cardiac risk model, was calculated according to the variables of the patients at the time of diagnosis[12]. The study population was categorized into tertiles 1, 2, and 3 based on the baseline PIVs tertiles. Clinical characteristics, risk profiles, echocardiographic measurements and laboratory parameters of the patients were assessed from follow-up visits, patient records, and the electronic database. The study examined the association between these three groups and their respective outcomes. The study was approved by Health Sciences University Hamidiye Scientific Research Ethics Committee (decision no: 28/17, date: 30.12.2022) and was conducted in full compliance with the Declaration of Helsinki.

The main objective of this study was to assess long-term all-cause mortality. The long-term survival status of each patient was determined through the National Death Notification System.

Statistical Analysis

The study population was grouped into tertiles in terms of PIV calculated at admission. The baseline characteristics, laboratory variables, and echocardiographic parameters were compared across the groups.

The assessment of normality was conducted using the Kolmogorov-Smirnov test. Quantitative variables with skewed distributions were shown as median (interquartile range), while continuous variables were compared using the Kruskal-Wallis test. Normally distributed variables are presented as mean±standard deviation, and an independent samples t-test was used for comparisons. Categorical variables were presented as numbers and percentages. Analyses of categorical variables were

performed by Pearson's chi-square test. Univariate and multivariate analyses, including Cox proportional hazards regression, were utilized to identify predictors of long-term mortality. Two Cox multivariable models were used: model 1, unadjusted; model 2, adjusted for age, gender, congestive heart failure, urea, albumin, glucose, total cholesterol and LV end-systolic diameter. The parameters used in model 2 were identified with a p-value<0.05 in multivariate Cox regression analysis. A two-tailed p-value of <0.05 was deemed statistically significant, and 95% confidence intervals were provided for all hazard ratios. Cut-off values for PIV and long-term mortality, demonstrating the highest sensitivity and specificity, were determined through non-parametric receiver-operating characteristics (ROC) curve analysis. Analyses were conducted using version 20.0 of the Statistical Package for the Social Sciences software (SPSS; IBM, Armonk, New York, USA).

RESULTS

During an average follow-up period of 55.5±12.7 months, 47 patients experienced long-term mortality. Non-ischemic heart failure was observed at a significantly higher in tertile 3 (p=0.089). Atrial fibrillation was observed in 30 patients in tertile 1, 39 patients in tertile 2, and 40 patients in tertile 3, with no significant difference detected among the groups (p=0.301). In tertile 2, there was a higher proportion of male patients (p=0.087). Table 1 summarized the basic clinical characteristics of the patients according to their PIV.

The mean PIV value was 256 (184-307) in tertile 1,490 (423-573) in tertile 2, and 1,001 (797-1309) in tertile 3 (p<0.001). While monocyte, neutrophil, and platelet counts were higher in tertile 3 compared to the other groups, lymphocyte values were lower. The tertile 3 had higher levels of glucose and total cholesterol compared to the other groups. LV end-systolic diameter was measured higher in tertile 3 compared to the other groups (p=0.049). The comparison of patients' echocardiographic parameters and laboratory variables according to the PIV is presented in Table 2.

Long-term mortality was observed in 7 patients in tertile 1, 12 patients in tertile 2, and 28 patients in tertile 3. After adjusting for all covariates using multivariate regression analysis, long-term all-cause mortality was determined to be 3.5 times greater in tertile 3 compared to tertile 1. Table 3 shows Cox-regression models for the incidence of long-term mortality based on PIV. ROC analysis indicated that a PIV cut-off level of 624 predicted long-term mortality with 62% sensitivity and 65% specificity (Figure 1).

Table 1. Baseline clinical characteristics of hypertrophic cardiomyopathy patients according to pan-immuno-inflammation value.

	Tertiles according to pan-immuno-inflammation value			
	Tertile 1 (n=130)	**Tertile 2 (n=130)**	**Tertile 3 (n=129)**	**p-value**
Age, years	61±14	60±14	58±14	0.179[a]
Gender, male, n (%)	76 (58.5)	93 (71.)	84 (65.1)	0.087[b]
Diabetes mellitus, %	25 (19.2)	17 (13.1)	21 (16.3)	0.401[b]
Diabetes mellitus with insulin dependent, %	5 (3.8)	1 (0.8)	3 (2.3)	0.256[b]
Hyperlipidemia, n (%)	19 (14.6)	11 (8.5)	22 (17.1)	0.111[b]
Hypertension, %	54 (41.5)	58 (44.6)	50 (38.8)	0.633[b]
Chronic obstructive pulmonary disease, %	4 (3.1)	7 (5.4)	8 (6.2)	0.480[b]
Cerebrovascular accident, %	5 (3.8)	7 (5.4)	5 (3.9)	0.786[b]
Atrial fibrillation, %	30 (23.1)	39 (30.0)	40 (31.0)	0.301[b]
Coronary artery disease, %	45 (34.6)	44 (33.8)	43 (33.3)	0.976[b]
Percutaneous coronary intervention, %	12 (9.2)	20 (15.4)	14 (10.9)	0.281[b]
Coronary artery bypass grafting, %	9 (6.9)	7 (5.4)	10 (7.8)	0.741[b]
Chronic kidney disease, %	8 (6.2)	12 (9.2)	11 (8.5)	0.631[b]
Congestive heart failure, ischemic, %	7 (5.4)	9 (6.9)	9 (7.0)	0.838[b]
Congestive heart failure, non-ischemic, %	8 (6.3)	11 (8.5)	18 (14.2)	0.089[b]

Continuous variables are reported as median and interquartile range, Nominal variables reported as frequency (%)

[a]: Independent sample t-test, [b]: Pearson's chi-square test

Table 2. Laboratory variables and echocardiographic parameters of hypertrophic cardiomyopathy patients according to pan-immuno-inflammation value.

	Tertiles according to pan-immuno-inflammation value			
	Tertile 1, (n=130)	**Tertile 2, (n=130)**	**Tertile 3, (n=129)**	**p-value**
Laboratory variables				
Hb (g/dL)	13.5 (12.5-14.9)	13.7 (12.0-15.1)	13.5 (11.5-15.0)	0.750[a]
Lymphocytes (10^3/μL)	2.4 (2.0-2.8)	2.0 (1.6-2.5)	1.4 (1.0-1.9)	<0.001[a]
Monocytes (10^3/μL)	0.45 (0.38-0.54)	0.54 (0.44-0.65)	0.69 (0.51-0.88)	<0.001[a]
Neutrophils (10^3/μL)	6.8 (5.9 –7.4)	7.7 (6.9-9.1)	9.0 (7.4-11.0)	<0.001[a]
Platelet count (10^3/μL)	208 (167-240)	231 (189-281)	260 (226-310)	<0.001[a]
PIV	256 (184-307)	490 (423-573)	1001 (797-1309)	<0.001[a]
Creatinine (mg/dL)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.918[a]
Urea (mg/dL)	25 (21-43)	24 (19-35)	25 (21-38)	0.083[a]
AST (U/L)	25 (20-42)	23 (19-35)	24 (18-36)	0.242[a]
ALT (U/L)	23 (17-39)	21 (15-30)	23 (17-34)	0.130[a]
TSH (mIU/L)	1.5 (1.1-2.3)	1.4 (0.9-1.9)	1.5 (1.0-2.3)	0.258[a]
Albumin (mg/dL)	4.2 (4.0-4.4)	4.1 (4.0-4.4)	4.1 (4.0-4.4)	0.095[a]
Glucose (mg/dL)	98 (93-108)	97 (91-112)	102 (93-125)	0.062[a]
HbA1c (%)	5.5 (5.4-5.9)	5.5 (5.4-5.7)	5.5 (5.4-6.0)	0.749[a]
Uric acid (mg/dL)	7.7 (7.0-9.8)	7.7 (6.8-9.5)	7.6 (6.8-9.8)	0.578[a]
Total cholesterol (mg/dL)	199 (169-222)	197 (160-217)	210 (176-225)	0.094[a]
LDL (mg/dL)	120 ± 35	117 ± 37	122 ± 37	0.346[b]
HDL (mg/dL)	38 (32-48)	39 (32-45)	38 (32-46)	0.787[a]
Triglycerides (mg/dL)	141 (100-198)	146 (89-202)	157 (113-212)	0.172[a]
Medical therapy				
Beta-blockers, %	111 (85.4)	111 (85.4)	114 (88.4)	0.721[c]
Echocardiography parameters				
Ejection fraction, %	60 (55-60)	60 (55-60)	60 (55-60)	0.835[a]
LVEDD, mm	46 (42-50)	46 (42-50)	46 (42-50)	0.998[a]
LVESD, mm	27 (23-30)	27 (23-30)	28 (24-31)	0.049[a]
Maximal wall thickness (mm)	18 (16-22)	18 (16-21)	18 (16-22)	0.906[a]
LV outflow gradient (mmHg)	25 (21-32)	27 (21-33)	30 (22-34)	0.292[a]
LA diameter (mm)	42 (36-49)	44 (37-50)	43 (38-49)	0.347[a]
Syncope, %	10 (7.7)	11 (8.5)	19 (14.7)	0.124[c]
Positive Family History (for SCD), %	7 (5.4)	8 (6.2)	13 (10.1)	0.293[c]
Non-sustained VT	8 (6.2)	6 (4.6)	8 (6.2)	0.820[c]
HCM Risk-SCD (%)	1.79 (1.21-2.43)	1.90 (1.27-2.79)	1.89 (1.30-2.95)	0.276[a]

Hb: Hemoglobin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDL: Low density lipoprotein, HDL: High density lipoprotein, TSH: Thyroid stimulating hormone, PIV: Pan-immune-inflammatory value, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, LV: Left ventricule, LA: Left atrium, VT: Ventricular tachycardia, SCD: Sudden cardiac death, HCM: Hypertrophic cardiomyopathy, [a]: Kruskal-Wallis test, [b]: Independent sample t-test, [c]: Pearson's chi-square test

Table 3. Cox-regression models for long-term mortality incidence by pan-immuno-inflammation value.			
	Tertiles according to pan-immuno-inflammation value		
	Tertile 1, (n=130)	**Tertile 2, (n=130)**	**Tertile 3, (n=129)**
Long-term mortality			
Number of patients	7	12	28
Case rate, %	5.4	9.2	21.7
Long-term mortality, HR (95% CI)			
Model 1: unadjusted	1[Reference]	1.8 (1.2-6.8)	4.8 (2.4-11.2)
Model 2: adjusted for all covariates[a]	1[Reference]	1.4 (0.8- 4.1)	3.5 (2.0-6.9)

Two Cox multivariable models were used: model 1, unadjusted; model 2, adjusted for age, gender, congestive heart failure, urea, albumin, glucose, total cholesterol and left ventricle end-systolic diameter. The parameters used in model 2 were identified with a p value<0.05 in multivariate Cox regression analysis

CI: Confidence interval, HR: Hazard ratio, [a]:Adjuested for age, gender, congestive heart failure, urea, albumin, glucose, total cholesterol and left ventricle end-systolic diameter

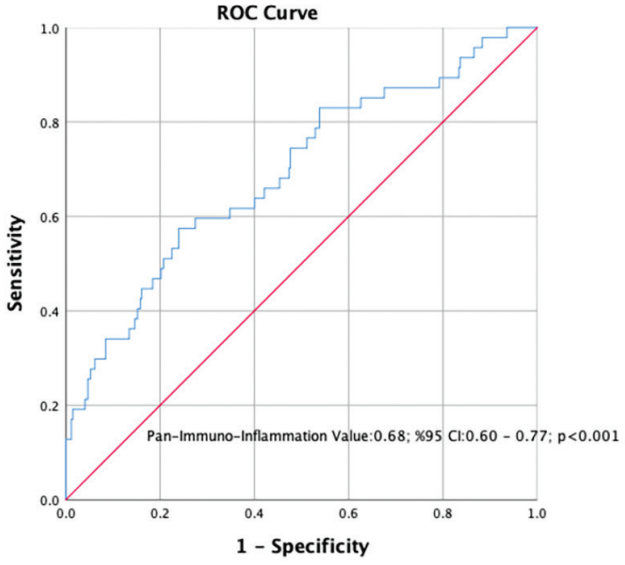

Figure 1. ROC curve analysis of pan-immuno-inflammation value to predict long-term mortality.

CI: Confidence interval, ROC: Receiver-operating characteristics

DISCUSSION

Our study demonstrated an association between PIV and adverse outcomes in patients with HCM. As far as we know this is the first study to investigate the potential role of PIV in predicting the prognosis of patients with HCM.

Inflammation is a recognized risk factor for the onset and progression of numerous cardiovascular diseases. Systemic inflammation has been shown to be associated with parameters of disease severity and particularly fibrosis in HCM patients[13]. The proposed mechanism suggests that sustained, low-grade myocardial inflammation triggers the invasion of inflammatory cells and fibroblasts, ultimately resulting in myocardial fibrosis[14,15]. It has been reported that oxidative stress levels are elevated in patients with HCM due to left ventricular pressure overload[16]. Moreover, myocardial fibrosis is a significant determinant of sudden cardiac death, heart failure, and ventricular tachyarrhythmia[17]. Since myocardial fibrosis is a key factor in malignant arrhythmias and systolic heart failure in HCM, modifying the inflammatory cascade may help prevent cardiac death by reducing myocardial fibrosis.

Several researches have identified interstitial inflammation, endocardial inflammation, and immunocyte infiltration as the primary histopathological characteristics of HCM[14,18]. Inflammatory parameters like TNF-α, MCP-1, and IL-6 are not typically accessible in routine clinical practice. Thus, there is a need for a clinically straightforward, cost-effective, and readily accessible method to evaluate inflammation and the resulting fibrosis. Parameters that can reflect inflammation and subsequent fibrosis may play a crucial role in the pathophysiology and prognosis of HCM. A recent study found that inflammation-indicating monocyte to high-density lipoprotein cholesterol ratio has a significant and independent prognostic value in HCM patients[19]. Additionally, the neutrophil-to-lymphocyte ratio has been identified as an independent risk factor for all-cause mortality in patients with HCM[20]. Lymphocyte to monocyte ratio predicts all-cause mortality in HCM patients[21]. Additionally, elevated levels of high-sensitivity C-reactive protein (CRP) have been found to substantially increase the risk of adverse outcomes, indicating the prognostic significance of this inflammatory marker[22].

The pan-immuno-inflammation value, which includes counts of neutrophils, platelets, monocytes, and lymphocytes, is an index used to assess the immune and inflammatory status of patients[23]. PIV has the potential to offer a more comprehensive reflection of inflammation compared to other immune indicators like the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio. Previous studies have indicated that PIV are linked to the prognosis of conditions such as myocardial infarction, hypertension and heart failure[24-26]. While the optimal cut-off value for PIV in patients with metastatic colorectal cancer is 390[23], another study evaluating frailty reported a cut-off value of 372, which is slightly lower than the value found in our study[27]. Another study evaluating the prognosis in ST-elevation myocardial infarction patients found the PIV cut-off value to be 622.71, which is close to the value identified in our study[28].

Considering that PIV reflects the inflammatory status of patients, it can be thought that high PIV values indicate high inflammatory processes in HCM patients. Elevated inflammatory markers have the potential to indirectly indicate the intensity of fibrosis, the severity of disease, and ultimately mortality risk in HCM patients. Given that PIV is a cost-effective and readily available marker with significant prognostic value for patients with HCM, it could assist in identifying high-risk individuals who need closer monitoring. Thus, PIV could be a potential screening tool to identify HCM patients who are at increased risk for adverse outcomes. PIV, which has already been shown in the literature to reflect inflammation status, is supported by our current study as a reliable inflammatory parameter. In addition, the fact that high inflammatory indicators, as we know from the literature, have prognostic value in HCM patients and that PIV shows similar results emphasizes the importance of inflammation in the course of HCM. Therefore, it is believed that the predictive significance of PIV in patients with HCM may be attributed to the presence of cardiac inflammation and fibrosis.

Our study has limitations that must be acknowledged. First, since our study is a single-center, observational, retrospective analysis involving a relatively small patient cohort, there may be potential biases. Consequently, the generalizability of the data is restricted. Second, unfortunately, cardiovascular magnetic resonance imaging was not conducted on all participants in the study. Third, commonly used markers of inflammation such as plasma CRP, procalcitonin, and erythrocyte sedimentation rate could not be assessed, thus their relationship with PIV is lacking. Forth, PIV levels were calculated only from blood samples collected during hospital admission.

CONCLUSION

This study demonstrated that high PIV levels have the potential to predict long-term mortality in patients with HCM. Thus, PIV could act as a useful screening tool for identifying HCM patients who are at increased risk of adverse outcomes.

Ethics

Ethics Committee Approval: The study was approved by Health Sciences University Hamidiye Scientific Research Ethics Committee (decision no: 28/17, date: 30.12.2022) and was conducted in full compliance with the Declaration of Helsinki.

Informed Consent: This study is retrospective.

Footnote

Author Contributions

Surgical and Medical Practices: S.D., H.K., Concept: L.P., M.I.H., Design: T.C., M.I.H., Data Collection and/or Processing: S.D., H.K., Analysis and/or Interpretation: T.C., T.Ci., Literature Search: L.P., H.K., Writing: L.P., A.C.Y., T.Ci, M.I.H.

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