ORIGINAL ARTICLE

REVISITING THE VALUE OF HAEMATOLOGICAL AND BIOCHEMICAL MARKERS AND THE RATIOS IN PATIENTS WITH CORONARY ARTERY DISEASE

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ABSTRACT

The aim: To investigate haematological and biochemical parameters and their potential for grading the severity of coronary artery lesions to predict the course atherosclerosis.

Materials and methods: The study is based on data obtained from a prospective analysis of 131 patients at the age of 51 to 82 years old from January to December 2019, whose complaints could indicate the coronary artery disease. All patients underwent a comprehensive clinical, laboratory and instrumental examination.

Results: The ratios of haematological and biochemical parameters significantly correlated with Syntax Score I. Some indexes did not confirm significant correlations with the severity of coronary artery disease. NT-proBNP, as a biochemical parameter, was the highest in patients with multi-vessel coronary artery disease and it had a moderate positive correlation with Syntax Score I ($r = 0.428$, $p = 0.0001$).

Conclusions: This study shows that ordinary indexes can be useful for assessment in daily practice for difficult patients. NTproBNP as an indicator requires further study as an additional marker for assessing the state of the cardiovascular system and can influence the choice of treatment.

KEY WORDS: ischemic heart disease (CHD), NT-proBNP, SYNTAX Score

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INTRODUCTION

Annually, cardiovascular disease (CVD) causes 3.9 million deaths in Europe and more than 1.8 million deaths in the European Union. Currently, CVD mortality is decreasing somewhat in most European countries, including Central and Eastern European countries that had shown substantial rises until the beginning of the 21st century [1]. Atherosclerosis is one of the main causes of CVD.

Pathophysiological mechanisms of atherosclerosis are still not well understood. Atherosclerosis is associated with inflammatory processes of the vascular wall. In the initial stage of atherosclerotic plaque formation, the vascular wall becomes permeable to both low-density lipoproteins (LDL) and leukocytes, namely neutrophils and monocytes, from the circulating blood [2]. Monocytes will differentiate into macrophages absorbing LDL, forming foam cells which subsequently will develop to lipid spots. Given the involvement of peripheral blood elements in the formation of atherosclerotic plaques, the investigation of haematological indices including lymphocyte-to-monocyte ratio [3, 4], platelet-to-lymphocyte ratio [5,6,7], neutrophil-to-lymphocyte ratio [8,9] and systemic immune-inflammatory index [10,11] is in active use.

Further, the progression of atherosclerosis is associated with elevated LDL-concentrations leading to higher risk of cardiovascular events . Cohen et al. demonstrated higher acute coronary event rates in individuals with PCSK9 mutations and low plasma LDL [12].

The imbalance of the lipid components has a significant impact on the development of atherosclerotic lesions and the progression of atherosclerosis. For example, the negative effect of reduced high-density lipoproteins (HDL) and elevated triglycerides has been proven [13]. The ratios of various fractions of lipid metabolism are also useful for predicting cardiovascular events.

THE AIM

The present study focuses on the value of haematological and biochemical parameters and their potential for grading the severity of coronary artery lesions to predict the course atherosclerosis.

MATERIALS AND METHODS

At the Ukrainian Children's Cardiac Center (Kyiv, Ukraine) 131 patients whose complaints were highly suggestive for coronary heart disease (CHD) were enrolled throughout 2019. Patients with connective tissue disease, hormone replacement therapy, severe valvular heart disease, hyper-

Table I. Patient's characteristics

Parameter	Group I (n= 30)	Group II (n= 35)	Group III (n= 66)	p-value
Age, years	60.53 ± 1.77	64.31 ± 1.62	63.0 ± 1.14	0.39
Male,%	30%	68.6%	78.8%	0.0001
BMI, kg/m2	31.74 ± 1.09	29.76 ± 0.77	30.71 ± 0.62	0.432
History of heart attack, n (%)	0	10 (28.6%)	33 (50%)	0.0001
History of stroke, n (%)	3 (10%)	5 (14.3%)	12 (18.2%)	0.576
Chronic Kidney Disease, n (%)	6 (20%)	7 (20%)	13 (19.7%)	0.999
Alcohol, n (%)	0	1 (2.9%)	5 (7.6%)	0.219
Smoking, n (%)	7 (23.3%)	11 (31.4%)	23 (34.8%)	0.529
Atrial fibrillation, n (%)	5 (16.7%)	5 (14.3%)	4 (6.1%)	0.215
COPD, n (%)	7 (23.3%)	1 (2.9%)	9 (13.6%)	0.049
Family history, n (%)	16 (53.3%)	16 (45.7%)	27 (40.9%)	0.523
Thyroid disease, n (%)	10 (33.3%)	8 (22.9%)	10 (15.2%)	0.127
Diabetes mellitus / impaired tolerance, n (%)	4 (13.3%)	7 (20%)	20 (30.3%)	0.388
Arterial hypertension, n (%)	30 (100%)	35 (100%)	66 (100%)	1.0
NYHA I, n (%)	-	9 (25.7%)	13 (19.7%)	0.49
NYHA II, n (%)	-	18 (51.4%)	37 (56.1%)	0.68
NYHA III, n (%)	-	8 (22.9%)	16 (24.2%)	0.87
Statins, n (%)	13 (43.3%)	25 (71.4%)	57 (86.4%)	0.0001
β-blockers, n (%)	17 (56.7%)	17 (48.6%)	49 (74.2%)	0.03
RAAS inhibitors, n (%)	16 (53.3%)	23 (65.7%)	52 (78.8%)	0.04
Calcium antagonists, n (%)	8 (26.7%)	10 (28,6)	19 (28.8%)	0.98
Syntax score I	-	5 (0;10)	27.75 (18; 38)	0.007

BMI – Body Mass Index, COPD - chronic obstructive pulmonary disease, NYHA - heart failure class according to the New York Association of Cardiologists, RAAS - renin-angiotensin-aldosterone system.

trophic cardiomyopathy, and pregnancy were excluded. The study was conducted in accordance with the World Medical Association's Code of Ethics (Declaration of Helsinki) and was approved by the Center Review Board. All subjects provided written informed consent.

Based on the findings of coronary angiography, the patients were divided into group I – control group without CHD (n=30), group II – single-vessel CHD or non-stenotic coronary atherosclerosis (n=35) or group III – multi-vessel CHD (n=66).

All groups were comparable with respect to age, body mass index (BMI) and comorbidities (Tab.I). However, the control group consisted of a higher number of females and a higher percentage of patients with chronic obstructive pulmonary disease. Between group II and III no statistically significant differences were observed for NYHA class.

All patients underwent clinical examination and laboratory testing. Venous blood samples were taken from each subject, and were subsequently centrifuged prior to testing. Blood count analyses (leucocyte- [WBC], neutrophil-, lymphocyte-, monocyte-, red blood- [RBC] and platelet count [PLT]) as well as hemoglobin [Hb] and haematocrit measurements were performed using an ABX Pentra 60 C+ hematology analyzer («HORIBA ABX» – Montpellier, France). For complete blood count and ESR analyses, venous blood samples were taken from each patient and were collected in blood tubes containing ethylenediaminetetraacetic acid or citrate. Biochemical analyseis (total protein, C-reactive protein [CRP], fasting blood glucose, alanine aminotransaminase [ALT], aspartate aminotransferase [AST], blood urea, creatinine, total bilirubin, calcium [Ca], potassium [K], sodium [Na], fasting triglyceride [TG], total cholesterol [TC], low density lipoprotein- cholesterol [LDL-C], and high density lipoprotein-cholesterol [HDL-C]) were performed using an AU 480 chemistry analyzer (Beckman Coulter – Brea, California, United States). All tests were performed according to the manufacturers' instructions. The level of the N-terminal fragment of the brain natriuretic peptide precursor (NT-proBNP) was analyzed with enzyme-linked fluorescence assay by automatic miniVIDAS® (bioMerieux – Craponne, France). Samples for coagulation tests which included prothrombin index (PTI) and international normalization ratio were investigated by Thrombotimer 4 (Behnk Elektronik – Norderstedt, Germany).

Statistical analyses were performed using Excel 2010 and SPSS Statistics 20.0. Both, parametric and non-parametric (Shapiro-Wilk test) data were presented as mean values with

Table II. Biochemical parameters

Parameter	Group I (n= 30)	Group II (n= 35)	Group III (n= 66)	p-value
Haemoglobin, g/L	139.5 (127.0; 152.0)	148.0 (133.0;157.5)	150.5 (142.0;158.0)	0.06
RBC,1012/L	4.65 (4.20; 5.00)	4.80 (4.35; 5.00)	4.90 (4.70; 5.10)	0.09
ESR, mm/h	9.5 (4.0; 19.0)	11.0 (7.0; 16.5)	12.0 (7.0; 22.0)	0.69
Haematocrit, %	42.0 (39.0; 46.0)	45.0 (40.0; 47.0)	46.0 (43.0; 47.0)	0.07
PLT, 109/L	225.5 (196.0; 266.0)	232.0 (197.5; 266.0)	237.5 (192.0; 285.0)	0.53
WBC, 109/L	5.7 (4.9; 6.8)	6.9 (5.8; 7.6)	7.2 (6.3; 7.9)	0.007
Neutrophils, 109/L	3.34 (2.35; 4.09)	3.95 (3.35; 5.21)	4.20 (3.47; 5.03)	0.003
Lymphocytes, 109/L	1.91 (1.37; 2.21)	1.73 (1.42; 2.20)	2.0 (1.61; 2.58)	0.11
Monocytes, 109/L	0.48 (0.28; 0.60)	0.51 (0.39; 0.71)	0.53 (0.42; 0.65)	0.12
Total protein, g /L	73.25 (70.30; 78.90)	72.90 (70.80; 75.60)	73.20 (70.20; 76.00)	0.587
Glucose, mmol / L	6.0 (5.2; 7.3)	5.8 (5.5; 6.5)	6.2 (5.6; 7.5)	0.212
Urea, mmol /L	6.0 (5.3; 7.3)	5.7 (5.3; 6.9)	6.2 (5.2; 7.8)	0.647
Creatinine, μmol /L	94.55 (82.30; 104.90)	95.30 (83.00; 105.05)	106.35 (96.10; 122.10)	0.001
GFR by MDRD, mL/min /1.73 m2	63.00 (52.00; 73.00)	68.00 (60.50; 77.00)	60.50 (52.00; 71.00)	0.204
Total bilirubin, μmol/L	14.15 (11.80; 19.40)	14.20 (12.25; 21.15)	12.85 (11.50; 17.20)	0.268
ALT, U/L	21.85 (16.40; 35.70)	22.80 (17.95; 32.35)	27.40 (18.40; 42.10)	0.225
AST, U/L	19.85 (16.70; 23.90)	21.20 (18.20; 26.25)	23.10 (18.10; 31.40)	0.132
NT-proBNP, pg/mL	99.00 (42.70; 135.10)	121.60 (71.65; 201.50)	299.35 (96.60; 578.00)	0.0001
CRP, mg /L	3.95 (2.30; 6.70)	2.80 (1.81; 7.00)	4.30 (2.00; 10.10)	0.397
K+, mmol/L	4.20 (4.00; 4.60)	4.20 (4.05; 4.60)	4.30 (4.00; 4.60)	0.808
Na+, mmol/L	141.00 (139.00; 142.00)	140.00 (138.00; 142.00)	140.00 (138.00; 143.00)	0.421
Ca2+, mmol/L	1.23 (1.19; 1.25)	1.21 (1.20; 1.26)	1.24 (1.20; 1.28)	0.188
PTI, %	85.00 (78.00; 93.00)	85.00 (76.00; 94.50)	82.00 (75.00; 90.00)	0.206
INR	1.10 (1.05; 1.15)	1.10 (1.04; 1.18)	1.13 (1.07; 1.18)	0.157

Data are represented as mean values - M ± m and median with 25th and 75th percentiles - Me (25–75%). RBC – red blood count, ESR - erythrocyte sedimentation rate, WBC - leukocyte count, PLT - platelet count, GFR by MDRD - glomerular filtration rate according to the MDRD equation, ALT - alanine aminotransferase, AST - aspartate aminotransferase, NT-proBNP - N-terminal pro–B-type natriuretic peptide, CRP - C-reactive protein, K – potassium, Na - sodium, Ca - calcium, PTI - prothrombin index, INR - International Normalized Ratio.

Table III. Lipidogram

Parameter	Group I (n= 30)	Group II (n= 35)	Group III (n= 66)	p-value
Cholesterol, mmol/L	5.00 (4.50; 5.80)	4.30 (3.45; 5.20)	4.15 (3.50; 5.00)	0.008
Triglycerides, mmol/L	1.14 (0.74; 1.69)	1.10 (0.78; 1.29)	1.36 (1.05; 2.04)	0.002
HDL, mmol/L	1.17 (1.12; 1.46)	1.08 (0.96; 1.27)	1.02 (0.86; 1.14)	0.0001
LDL, mmol/L	3.26 (2.41; 3.75)	2.58 (1.97; 3.34)	2.49 (1.92; 3.23)	0.014
Non-HDL, mmol/L	3.73 (3.24; 4.45)	3.27 (2.45; 4.00)	3.15 (2.46; 3.92)	0.029
HDL / Cholesterol	4.02 (3.53; 4.57)	3.82 (3.22; 4.53)	4.18 (3.33; 5.00)	0.241
TG / HDL	0.92 (0.59; 1.53)	0.92 (0.61; 1.26)	1.48 (1.00; 2.08)	0.0001
LDL / HDL	2.54 (1.97; 3.14)	2.26 (1.84; 2.90)	2.44 (1.85; 3.13)	0.417
Non-HDL / HDL	3.02 (2.53; 3.57)	2.82 (2.22; 3.53)	3.18 (2.33; 4.00)	0.241

Data are represented as mean values - M ± m and median with 25th and 75th percentiles - Me (25–75%).

Table IV. Hematological and biochemical indices

Parameter	Group I (n= 30)	Group II (n= 35)	Group III (n= 66)	p-value
Monocyte-to-HDL (10*9 / mmol /L)	0.34 (0.20; 0.51)	0.44 (0.32; 0.70)	0.55 (0.39; 0.71)	0.002
Neutrophil-to-HDL (10*9 / mmol /L)	2.66 (1.89; 3.30)	3.39 (2.70; 4.80)	4.30 (3.36; 5.03)	0.0001
Lymphocyte-to-HDL (10*9// mmol / L)	1.45 (1.1; 1.93)	1.67 (1.30; 2.15)	1.97 (1.52; 2.85)	0.002
Lymphocyte-to-monocyte (10*9)	4.27 (2.80; 6.67)	3.63 (2.79; 4.86)	4.15 (2.73; 5.25)	0.176
Platelets-to- lymphocytes (10*9)	116.58 (92.03; 153.52)	129.42 (100.29; 176.26)	120.29 (92.11; 158.41)	0.552
Neutrophil-to- lymphocytes (10*9)	1.65 (1.44; 2.48)	2.07 (1.66; 3.19)	2.02 (1.50; 2.72)	0.131
SII	369.54 (243.28; 627.43)	450.95 (358.96; 777.90)	369.12 (502.03; 645.65)	0.077

SII - systemic immuno-inflammation index

standard deviation (M ± m) and as median with 25th and 75th percentiles (Me (25–75%)). Pearson χ^2 and Kraskel-Wallis tests were used to assess significance between two independent samples. Spearman and Pearson's correlation coefficient were used for ratio assessment. Statistical significance was considered with a two-sided p-value < 0.05.

RESULTS

Haematology test panel showed no differences for haemoglobin, erythrocytes, erythrocyte sedimentation rate (ESR), haematocrit, platelets, lymphocyte and monocyte levels between all groups (Tab.II). In contrast, significant differences were observed for leukocyte (p = 0.007) and neutrophil (p = 0.003) levels with the highest rates in group III. Medians of these values were within normal ranges in all groups. Biochemical blood assay revealed a significantly higher level of creatinine in group III, but glomerular filtration rate (GFR) by MDRD did not differ significantly between the groups (p = 0.204, Tab.II).

The NT-proBNP level was significantly higher in group III (median: 299.35 pg/mL (96.60; 578.00), p = 0.0001; reference value: <125 pg/mL) [14]. NT-proBNP levels correlate with the patients' prognosis and is recommend for patients with acute or chronic heart failure to verify the diagnosis. Ce Zhang et al. studied NT-proBNP as an

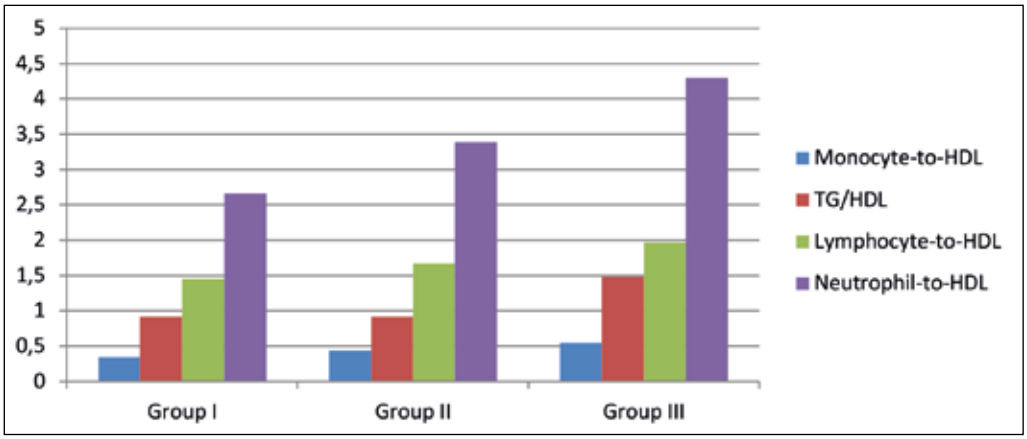

Fig 1. Shows the ratios that were significantly correlated with the degree of CHD according to Syntax Score I.

additional biomarker for risk stratification and therapeutic decision-making in patients with three-vessel lesions [15]. The results of our study demonstrated a moderate positive correlation with Syntax Score I (r = 0.428, p = 0.0001, Tab.II).

The lipidograms were significantly different between all groups. Group III had the lowest total cholesterol, probably due to statin intake because group III showed the highest percentage of patients receiving statins (86.4%).

Triglyceride levels were in line with the recommended standards of the ESC Guidelines: <1.7 mmol /L [16]. Highest triglyceride levels were observed in group III: 1.36 (1.05; 2.04) mmol /L whereas group II showed the lowest levels: 1.10 (0.78; 1.29) mmol /L.

The highest level of HDL-C was found in controls: 1.17 (1.12; 1.46) mmol /L, the lowest in group III: 1.02 (0.86; 1.14) mmol /L. LDL-C was increased in all groups. The highest level was observed in group I: 3.26 (2.41; 3.75) mmol /L exceeding the recommended limits, although all patients were classified as low risk patients [15]. In high risk patients with multi-vessel CHD (group III) a LDL-C target of <1.4 mmol/L is recommended [15]. Although 86% of patients in group III were on statins, the median of 2.49 (1.92; 3.23) mmol/L indicates an underestimation of the cardiovascular risk with probably insufficient statin dose.

Non-HDL values were not within target ranges, either: groups I: 3.73 (3.24; 4.45) mmol/L, groups II: 3.27 (2.45; 4.00) mmol/L and groups III: 3.15 (2.46; 3.92) mmol/L.

While evaluating the ratios of various lipid fractions, a significant difference was only seen in TG-to-HDL ratios (p = 0.0001). In group III, this ratio was more than 1.5 times higher than in groups I and II and there was a moderate positive correlation with Syntax Score S scores (r = 0.306, p = 0.0001, median 1.48 (1.00; 2.08); Tab.III).

High-density lipoproteins are used to calculate indices with haematological parameters, such as the number of lymphocytes, monocytes and neutrophils. These indices are classified as markers of inflammatory processes. Mehmet Serkan Cetin at al. reported that a higher monocyte-to-HDL ratio is a negative predictor for the development of acute coronary syndrome (ACS) and the severity of CHD [17]. In comparison to neutrophil-to-lymphocyte ratio and C-reactive protein, monocyte-to-HDL ratio might be superior predicting the severity of CHD in patients with ACS who underwent percutaneous coronary interventions [18]. According to the present data, monocyte-to-HDL ratio was significantly higher in patients with multi-vessel CHD (p = 0.002) and showed a moderate positive correlation with Syntax Score I (r = 0.301, p = 0.0001; Tab.IV).

Furthermore, neutrophil-to-HDL and lymphocyte-to-HDL ratios were significantly higher in group III (p = 0.0001 and p = 0.002, respectively) being consistent with the data reported by Jia-Bao Huang et al., who demonstrated that this ratio might be a useful predictor of long-term clinical outcomes in the elderlies with acute myocardial infarction [19].

DISCUSSION

1. The level of triglycerides was significantly higher in group III (p = 0.002), but in all groups the value was <1.7 mmol /l. The level of high-density lipoprotein (HDL) was the highest in the control group (p = 0.0001). Non-HDL was the lowest in group III, but its level in all groups was not target (p = 0.029).

One of the reasons for this is the non-appointment of statin therapy in patients with high and very high risk. Thus, März W. et al.- [20] notes that in a cohort of patients (more than 42,000 patients) the percentage of hypolipidemic therapy remains quite low at 35%. All patients had proven atherosclerotic lesions and risk factors such as diabetes. Achieving LDL targets had low ranges (from 26.9% to 46.7%). One more reason for not enough reduction is the choice of insufficient dose or medication. According to STELLAR Trial [21], rosuvastatin outperformed other drugs significantly and the percentage of achievement of target values for LDL ranged from 82 to 89%. On the other hand, LDL reduction by 50% is the option as a goal, not only to achieve absolute numbers; an individualized approach should remain a priority for the cardiologist.

2. The ratios of haematological and biochemical parameters that significantly correlated with Syntax Score I were as follows: monocyte-to-HDL (r = 0.400, p = 0.0001) and TG-to-HDL (r = 0.306, p = 0.0001), lymphocyte-to-HDL (r = 0.336, p = 0.0001), and neutrophil-to-HDL (r = 0.400, p = 0.0001). The results of monocyte-to-HDL coincide with

the data of Akboga MK. et al [22] who notes that this index is associated with a more significant coronary lesion by the number of points on the SYNTAX scale, namely ≥23.

Li Y. et al. [23] demonstrated that elevated TG-to-HDL index is one of the potential indicators of stent stenosis after PCI. In our work it is shown that this index positively correlates with the degree of damage on the SYNTAX score. It should be noted that the increased level of triglycerides, as a component of this index, plays an important role in the progression of atherosclerosis [24].

The lymphocyte-to-HDL and neutrophil-to-HDL indices are not widely described in the literature. These markers are studied in metabolic syndrome in some articles [25]. In our work, it has been shown for the first time that both markers have a moderate positive correlation with the degree of coronary artery disease, namely the quantitative characteristic in points on the SYNTAX score. These markers need further investigation.

The given data testify to indisputable expediency of the use of indices in the practice of the doctor. These parameters to calculate are simple and can be useful for risk estimation by a Heart team for decision-making.

3. NT-proBNP levels were the highest in patients with multi-vessel coronary artery disease, and they had a moderate positive correlation with Syntax Score I ($r = 0.428$, $p = 0.0001$). Recently, there has been growing evidence for decision-making on intervention (CABG, PCI) that requires a quantitative assessment of the presence and extent of hemodynamic stress and manifestations of heart failure. NT-proBNP concentration is used for this purpose [26].

The increased concentration of this marker may provide additional prognostic information for adverse effects, including death, myocardial infarction, and stroke [27]. There is an assumption that at a normal level of NT-proBNP even insignificant increase is an indicator for the necessity to give preference to PCI. At the same time, CABG is recommended when this marker increases significantly[15]. It can be beneficial as an additional parameter for patients with coronary artery disease and may influence a choice of treatment (PCI, CABG).

4. There was no significant difference in lymphocyte-to-monocyte, platelet-to-lymphocyte, neutrophil-to-lymphocyte ratio, or systemic immuno-inflammation index between the groups. The above values did not correlate with the degree of coronary artery disease on the Syntax Score Scale, either. Therefore, these markers need further study to address their prognostic value.

CONCLUSIONS

This study shows ordinary indexes can be useful for assessment in daily practice for difficult patients, but our investigation did not show the significance of some of them such as lymphocyte-to-monocyte, platelet-to-lymphocyte, neutrophil-to-lymphocyte ratio, or systemic immuno-inflammation index.

Further research is useful and undeniable for NTproBNP as an independent marker of more significant coronary vessels lesions. It can be used as a predictor of not only more significant vascular lesion but also assessment for treatment after PCI and CABG.

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