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Research Article

Hypoalbuminemia – prognostic factor for the short-term evolution of patients with unstable angina

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Abstract. Introduction. Hypoalbuminemia is considered to be a negative prognostic factor for cardiovascular disease which favours the occurrence of myocardial infarction, heart failure, atrial fibrillation, and stroke. Objective. The aim was to establish if there is a relationship between the serum albumin level in patients with unstable angina (UA) and their short-term evolution. Method and materials. We enrolled 40 patients with UA, who were admitted to the Cardiology Department of the County Emergency Hospital in Cluj-Napoca. They were diagnosed with UA in accordance with the European Society of Cardiology guidelines. We considered the evolution to be unfavourable if the patient developed recurrent angina pectoris, signs of heart failure or arrhythmias. The serum albumin level was measured at time of admission. We also studied the presence of traditional cardiovascular risk factors in the study group. Results. Patients with UA and a serum albumin level below 3.4 g/dl on admission (Se-62.5%, Sp-68.7%, 20 patients) more frequently had an unfavourable short-term evolution. These patients more frequently presented arrhytmias (p=0.045, AUC=0.684, 95% CI (0.496;0.872), Exp(B)=0.217) and left ventricular systolic dysfunction (ejection fraction < 50%) (p=0.009, AUC=0.746, 95% CI (0.586;0.985), Exp(B)=0.144) and recurrent angina pectoris (p=0.042, AUC=0.691, 95% CI (0.528;0.855), Exp(B)=0.193). We did not find a correlation between serum albumin levels and other traditional cardiovascular risk factors: age (p=0.107), sex (p=0.215), smoking (p=0.760), diabetes mellitus (p=0.454), LDL cholesterol (p=0.154), body mass index (p=0.793), and hypertension (p=0.138). Conclusion. A low serum albumin level on hospital admission is a negative prognostic factor for the short-term evolution of patients with UA.

Key Words: unstable angina, serum albumin level, prognostic factor

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Introduction

The evolution of patients with unstable angina is hardly predictable, thus the identification of new markers in order to achieve a better risk stratification in the case of these patients is of utmost importance.

Albumin is a non-glycosylated, hydrosoluble, hepatically synthesized protein with a low molecular weight, which represents approximately 60% of the total plasmatic proteins. It has a three-dimensional structure, with three bonding domains (I-III), each one being subdivided into 2 subdomains (A and B). Each subdomain has a different bonding affinity (subdomain IIA represents the bonding site for warfarin, and subdomain IIIA – for indoles and benzodiazepines) (Aquues 2018).

Hypoalbuminemia is considered to be an independent, negative prognostic factor for many cardiovascular diseases, even after the adjustment of the traditional risk factors, and it is associated with the occurrence of myocardial infarction, heart failure, atrial fibrillation, and stroke (Aquues 2018).

Albumin is synthesised in the liver. A low albumin concentration is the result of either low synthesis, an increase in catabolism, extravascular distribution, or exogenous loss. An inadequate nutritional supply and systemic inflammation both affect albumin synthesis. Certain conditions such as chronic lung diseases, neoplasic diseases, and chronic renal failure may lead to an increase in albumin catabolism. The plasma albumin concentration in patients with heart failure may be decreased by haemodilution. Direct exogenous albumin loss is frequently observed in patients with nephrotic syndrome (Chien et al 2017). In acute coronary syndromes, such as unstable angina, reduced albumin concentration could be the result of inflammatory conditions or inadequate alimentary intake. Albumin is a negative-phase protein whose concentration decreases by 20% in response to inflammation. The mechanism is not very clear,

but it is hypothesised that during an inflammatory response liver uses amino acids to synthesize positive-phase proteins rather than albumin, thus the albumin serum concentrations decrease. (Gabay et al 1999). Nutritional status and nutritional intake of proteins and carbohydrates influence the serum albumin concentrations. In physiological states the albumin concentrations are controlled by several processes such as absolute rate of albumin synthesis, fractional catabolic rate or albumin distribution. When malnutrition is associated to inflammation low concentrations of albumin are found in acute coronary syndromes (Hartopo et al 2015).

The aim of the present study was to determine if there is a relationship between the serum albumin level and the short-term evolution of patients with unstable angina, and whether the serum albumin value is correlated with other traditional cardiovascular risk factors.

Method and materials

The present prospective, analytical, and observational study included 40 subjects with unstable angina who were hospitalized in the Cardiology Department of the Cluj County Clinical Emergency Hospital in Cluj-Napoca during one year (1st October 2017 - 1st October 2018). The inclusion criteria in this study was a diagnosis of unstable angina established in accordance with the current criteria of the European Cardiology Society Guidelines (Roffi et al, 2015): retrosternal pain with characteristic angina (de novo, aggravated by effort, occurring at an early stage after percutaneous or surgical myocardial revascularization), the presence of electrocardiographic changes, and the absence of a myocardial enzymatic reaction (CK, CK-MB, troponin). Patients with any ECG or biological proof of ST elevated acute myocardial infarction (STEMI): ST elevation >1 mm in two or more consecutive limb leads or >2 mm in two or more precordial leads and TroponinI <0.6 ng/ml were excluded. Patients who presented with pathologies that may influence the studied biochemical markers were excluded: neoplasia – either current or in their history (which had been treated surgically, or by radio- and/or chemotherapy); acute focal infections (over the previous 6 months) or chronic focal infections, collagen diseases (with or without immunosuppressive treatment), treatment with non-steroidal anti-inflammatory drugs or cortisone, surgical interventions over the past 6 months, myocardial infarction in their history, or currently developed NYHA > II class heart failure, a history of rhythm and conduction disorders, a history of revascularization procedures (angioplasty, bypass), hepatic cirrhosis, enteropathy or malabsorption syndromes, nephrotic syndrome, severe renal failure (creatinine clearance < 15 mL/kg/m^2), and lack of compliance.

All patients included in the study gave their written consent regarding their participation, and the presented study was approved by the ethics commission of the Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca.

We observed the presence of cardiovascular risk factors: age (females > 55 years of age, males > 45 years of age), sex (male), smoking, obesity, dyslipidaemia (LDL cholesterol > 100 mg/dl, HDL cholesterol < 40 mg/dl in males and < 50 mg/dl in females, triglycerides > 150 mg/dl), hypertension, diabetes mellitus, and a history of pathological heredo-collateral and personal ischemic cardiovascular disease. For biological investigation purposes, blood was collected via venous puncture, under sterile conditions and with minimal venous compression. Troponin was determined on admission to hospital, within 8-12 hours from admission, and in case of angina reoccurrence.

Biological dosing was performed with the aid of the KONELAB 30 I analyser, and the normal serum level were considered as follows: serum albumin (3.5-5 g/dl), blood sugar (70-100 mg/dl), HDL cholesterol (>40 mg/dl in males and >50 mg/dl in females), LDL cholesterol > 100 mg/dl. The level of serum troponin was determined by chemiluminescence-Immulite, and the patients who showed an increase > 0.2 ng/ml were excluded from the study. The serum albumin level was determined on admission to hospital.

The patients underwent an ECG on admission, 6 hours later, within the first 24 hours and later, in the course of their hospitalization period in angina pectoris crises, to evaluate the occurrence of new ischemic changes as compared to the ones they had on admission. The following ECG changes were considered as diagnosis criteria for unstable angina: ST depression ≥0.05 mV in two or more contiguous leads, ST depression combined with transient ST elevation (not fulfilling the STEMI criteria mentioned above), T-wave inversion (Roffi et al 2015). The ST and/or T variability on different ECG was considered an important diagnosis criteria for unstable angina. The occurrence of rhythm disturbances were considered positive in case of: premature ventricular beats (PVB) more than 2 on ECG, atrial fibrillation and atrial flutter, atrioventricular block grade II, left bundle branch block (LBBB) or right bundle branch block (RBBB).

Echocardiography was used to track the dimensions of the left ventricle and its systolic and diastolic function, the presence of wall motion abnormalities, significant valvulopathies (valvular stenosis or failure), and a pericardial collection. The left ventricular ejection fraction was calculated using Simpson's rule (Zoran et al 2015), in which normal adult levels were considered to be 52-78%. All parameters were calculated as the arithmetic mean of 3 determinations, in the case of patients experiencing atrial fibrillation (Popescu et al 2011). The echocardiography was performed by means of the AGILENT SONOS 4500 mobile ultrasound system using a transthoracic echocardiography probe, sector transducer S4 2133OA.

According to the recommendations of the current European Cardiology Society guidelines, all patients were assessed by coronary angiography, which provided information on the extent and severity of the coronary disease coronary stenosis. Significant coronary artery disease was define as stenosis >50% in main trunk and > 70% in the other coronary vessels (Roffi et al. 2015).

Throughout the hospitalization, frequent angina recurrence (more than 2 episodes of angina), cardiac failure clinical signs (more than 2 symptoms from Framingham score) in an acute ischemic context, and rhythm and conduction disorders were noted as unfavourable evolution.

The statistical analysis was conducted in SPSS 24 (IBM). The variables were assessed via descriptive and inferential statistical methods; the standard deviation and the mean were assessed for the quantitative data, and the frequency and percentage for the qualitative data. Of the descriptive statistical methods, frequency tables and dispersion indices were used. The assessment of the statistical significance of the differences between variables

was done via the Chi-Square test (qualitative data), via parametric (Student's t-test) or non-parametric tests (Mann-Whitney U test) (for the quantitative data, depending on the shape of their distribution). In order to assess the influence of the serum albumin level on the evolution of patients with unstable angina, we analysed the data using the ROC curve method, in which we calculated the area under the curve and the standard error margins. We considered a threshold of 5% to be of significance. The aim of the ROC analysis is to identify the optimum threshold value for the differentiation of a positive result from a negative one. The parametric statistical methods (the values of the diagnostic test follow the normal distribution) or the non-parametric statistical methods (no assumption is made on the distribution of the diagnostic test values) are used for the ROC analysis and for obtaining the AUC (area under the curve) values. The method is used to assess a diagnostic test or to compare two different diagnostic methods, both of which are applied to each patient. We performed a regression analysis in order to test if there are other factors that predict the recurrent angina. As the predicted variable is binary, a logistic binary regression analysis was performed in order to see if: serum albumin level, LDL cholesterol, obesity, hypertension, diabetes mellitus, smoking, age, sex, cardio-vascular pathological personal history, the presence of coronary lesions on coronary angiographic exploration can be used as predictor factors for recurrent angina. Iteratively the least significant variables were eliminated from the model. The only significant predictor for this sample was serum albumin level. The resulting model is a significantly better at predicting the dependent variable as resulting from the omnibus test of model coefficients ($\chi2(1)=6.490$, $p=0.011$) and the Hosmer and Lemeshow Test ($\chi2(8)=6.490$, $p=0.117$).

Results

The main clinical, electrocardiographic, echocardiographic, bio-humoral, and therapeutic characteristics of patients with unstable angina are shown in Table 1.

The average age of the subjects taken into study was 60±10.68 years most of whom were males (60%). Males were predominant in the 40-60 age group, while females, in the >80 age group. The distribution by gender was equal in the 60-70 and 70-80 age groups.

Over 50% of patients showed an important number of cardiovascular risk factors, the most frequent were obesity (67.5%) and hypertension (55%).

No significant correlation was found between the serum albumin levels and the traditional cardiovascular risk factors studied (Table 2).

Ischemia was highlighted in the case of all patients either by the electrocardiographic changes (50% ST segment depression, 55% variable ST-T changes, 60% negative T waves), or by the echocardiographic changes (in 52% of cases hypokinesia, akinesia, dyskinesia; 60% stage I diastolic dysfunction; 42% systolic dysfunction).

During the hospitalization period, 33% of patients showed rhythm disorders (10 patients - PVB, 5 patients - atrial fibrillation, 1 patient- atrial flutter) and no conduction disorders were registered (no patients with LBBB or RBBB were identified).

In 55% of these patients, the angiographic examination highlighted significant coronary lesions. The serum albumin level

Table 1. Baseline characteristics. The main clinical, bio-humoral, ECG, and echocardiographic characteristics of patients included in the study

Patient characteristics	n=40 Number (%)
Risk factors	
Age	60±10.68
Male sex	24 (60)
Hypertension	22(55)
Diabetes mellitus	12(30)
Obesity	27 (40)
Smoking	10 (25)
Dyslipidemia	18 (45)
ECG changes	
ST segment depression	20 (50)
ST-T changes	22 (55)
T-wave inversion	24 (60)
Rhythm and/or conduction disorders	13 (33)
Echocardiography	
LVEF* <50%	17 (42)
LVEF (mean±SD)	46.46±5.12
Segmental kinetics disorders	21 (53)
Diastolic dysfunction	24 (60)
Biochemical	
Fasting plasma glucose (mg/dl)	115.05±16
Cholesterol (mg/dl)	205.50±20
HDL(mg/dl)	46.52±20
LDL(mg/dl)	115.17±6
Triglycerides(mg/dl)	194.05±21
Creatinine (mg/dl)	0.98±0.1
Medication prior to inclusion into study	
ACE Inhibitor**	22 (55)
Beta blocker	24 (60)
Nitrates	10 (25)
Aspirin	30 (75)
Statin	28 (70)

Table 2. The correlation between serum albumin level and the main cardiovascular risk factors

Risk factors	Serum albumin level
Age	p=0.107
Sex	p=0.213
Hypertension	p=0.138
Diabetes mellitus	p=0.454
Smoking	p=0.760
LDL cholesterol	p=0.154
Obesity	p=0.793

was not correlated with the severity of the coronary lesions highlighted by coronarography (p=0.766).

During hospitalization, 40% of the patients had an unfavourable evolution, which manifested itself through frequent angina recurrence, rhythm and/or conduction disorders, or clinical signs of heart failure.

A serum albumin level of <3.4 mg/dl on admission to hospital allows to distinguish the patients who run the risk of having an unfavourable short-term evolution. Moreover, its decrease by one will determine a rise in the risk of recurrent angina by 0.193 (p=0.042, AUC=0.691, 95% CI (0.528;0.855), Exp(B)=0.193, cut-off =3,44 mg/dl, Se=62,5%, Sp=68,7 %) (Fig. 1), a rise in the risk of occurrence of rhythm/conduction disorders by 0.217 (p=0.045, AUC 0.684, 95% CI (0.496;0.872), Exp(B)=0.217, cut-off=3,44mg/dl, Se=69,2 %, Sp=59,6%) (Fig. 2), and a rise in the risk of developing left ventricular systolic dysfunction by 0.144 (p=0.009, AUC=0.746, 95% CI (0.586;0.985), Exp(B)=0.144,cut-off=3,44mg/dl, Se=76,5%, Sp=70%) (Fig. 3).

Discussion

Fig. 1. ROC curve analysis for the capacity of serum albumin to predict the recurrent angina in patients with unstable angina

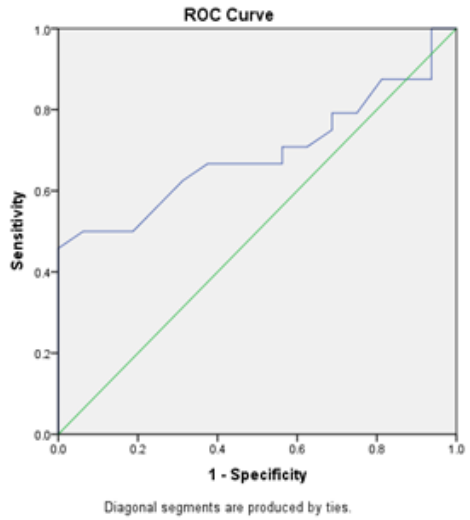


Fig. 2. The capacity of albuminemia to predict the occurrence of rhythm and/or conduction disorders in patients with unstable angina

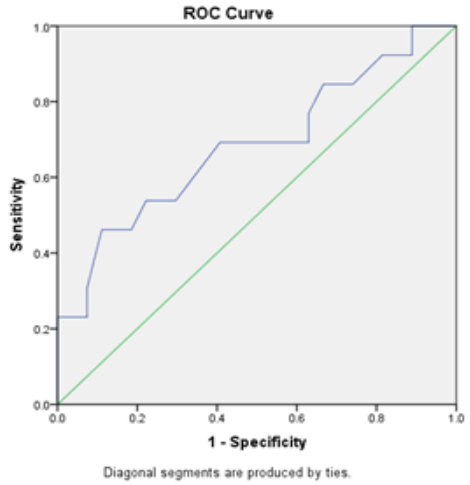
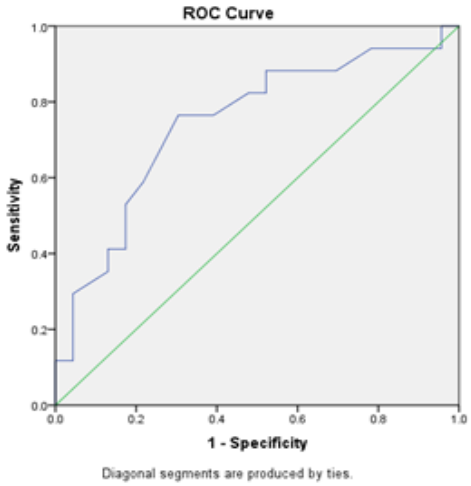


Fig. 3. The connection between the serum albumin level and the presence of left ventricular systolic dysfunction in patients with unstable angina



In our study, the presence of hypoalbuminemia < 3.4 mg/dl on admission to hospital was predictive for unfavourable evolution defined as the occurrence of rhythm and/or conduction disorders, and/or heart failure and recurrent angina during the hospitalization period, with a Se of 65,2% and a Sp of 75 % .

Previous studies have shown that hypoalbuminemia was associated with a rise in in-hospital mortality and an increase in the risk of developing cardiac failure in patients with ACS (acute coronary syndrome) (Aquues et al 2018). Moreover, hypoalbuminemia represented an independent negative prognostic factor for the long-term post percutaneous myocardial revascularization evolution in these patients, with a dose-dependent relationship between albuminaemia levels and the prognostic (Chien et al 2018; Kimura et al 2017).

In our study, more than 50% of patients with unstable angina did not show any significant coronary changes. There was no statistically significant correlation between the serum albumin level and the severity of coronary stenosis. Unstable angina originates from non-occlusive, vulnerable atherosclerotic plaque (Cioni et al 2018). The inflammation and the endothelial dysfunction cause the erosion or rupture of the atherosclerotic plaque and favours the generation of intravascular thrombosis (Manning et al 2018). The evolution of patients with unstable angina is unpredictable because it is associated with ischemic recurrences and a 5% in-hospital mortality rate. The use of GRACE (Global Registry of Acute Coronary Events) and TIMI (Thrombolysis In Myocardial Infarction) scores helps identify high-risk patients, influencing the supervision and treatment-related decisions in the case of these patients, especially the decisions related to early myocardial revascularization (Cioni et al 2018; Khandelwal et al 2015).

These scores can not always accurately predict the short- and long-term prognostic for patients with unstable angina. As a result, attempts continue to be made to identify certain new parameters which may help improve the capacity of these scores to predict the evolution of patients with unstable angina.

The atherosclerotic process is determined by a series of exogenous risk factors (smoking, sedentariness, diet, socio-economic status, etc.) and endogenous risk factors: endothelial dysfunction,

pro-inflammatory status, pro-thrombotic status, and dyslipidaemia (Xia et al 2017), which are included in the TIMI score. Although part of the traditional risk factors are to be found in the TIMI and GRACE scores, the said scores can neither predict the occurrence of severe occlusive coronary disease, nor can they predict the extent and severity of the coronary disease. Serum albumin, through its properties, is involved in these pathogenic stages and thus its level could constitute a prognostic factor in the case of unstable angina patients.

Serum albumin has proven to have the capacity to predict the prognostic of patients with a cardiovascular pathology. Numerous studies have provided information referring to the mechanisms through which it can favourably influence the atherosclerotic process: an antioxidant effect (bonding the free radicals with oxygen, which are substances that play an important role in atherosclerosis pathology), an anti-thrombotic activity (through the bonding of nitric oxide), an anti-inflammatory effect (through the inhibition of pro-inflammatory cytokine synthesis), the improvement of the endothelial dysfunction (by supporting the efflux of cholesterol from the endothelial cells), and the bonding of homocysteine (an amino acid with an important role in atherosclerosis) (Xia et al 2017; Savulescu-Fiedler et al 2015; Babu et al 2013).

As a result of these properties, a decrease in the serum albumin level has negative consequences throughout the entire body and is associated with a short- and long-term high mortality risk, while the normalization of albuminemia levels on discharge from hospital was associated with a better prognostic as compared to patients who had low albuminemia when discharged from hospital (Xia et al 2017; Cioni et al 2018).

The distribution by sex and age was in accordance with the data provided by the literature, unstable angina is more frequent in middle - aged male patients (Mathews et al 2018).

The echocardiographic examination highlighted a low LVEF in 42% in patients. In our study this parameter was a negative prognostic factor in patients with unstable angina, also Perelshtein Brezinov O et al showed that patients with low LVEF at admission had an unfavourable evolution.

The results obtained were in accordance with the data provided by the literature that subjects with low serum albumin levels had a less favourable evolution defined as the occurrence of rhythm and/or conduction disorders, and/or heart failure clinical signs and recurrent angina during the hospitalization period as compared to patients whose serum albumin levels were within normal limits. We could hypothesised that in the presence of hypoalbuminemia myocardial edema develops aggravating myocardial dysfunction and generating electric instability (Aquues et al 2018).

Another mechanism which could explain the unfavourable evolution of patients with hypoalbuminemia is the anti-inflammatory effect of albumin: the low levels of serum albumin are associated with an increase of inflammation markers, with the aggravation and progression of atherosclerotic lesions and their instability in the case of ACS patients (Aquues et al 2018).

Another important role played by serum albumin is its antioxidant effect, high oxygen free radical levels being associated with an unfavourable prognostic in ACS patients. Oxidative stress plays an important role in atherogenesis, heart failure, atrial fibrillation, and stroke. And last but not least, serum albumin inhibits platelet activation and aggregation, inhibits endothelial cell apoptosis, hinders vasospasm, and improves blood rheology (Xia et al 2017; Gabriela Fanali et al 2012).

All these mechanisms explain why patients with hypoalbuminemia, both in the study group as well as in a variety of other specialty studies that have been conducted, have a negative prognostic.

Some limitations of the present study should be mentioned. First of all, this was a cross-sectional study with a single measurement of serum albumin level. Thus, the study does not benefit from the inherent variability in time of the tested biomarker introduced by other unknown variables or linear trends. On the other hand, we have to acknowledge that the number of participants was relatively small because of the multiple exclusion criteria and they were under therapy, which could not be interrupted for ethical reasons. Larger clinical trials are needed for the validation of the predictive capacity of serum albumin levels in clinical practice

Conclusion

Hypoalbuminemia may be considered a negative prognostic factor for the short-term evolution of patients with unstable angina.

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