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Original Article

The Value of Serum Albumin for Prediction of In-Hospital Complications in Patients with Acute Myocardial Infarction

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Abstract *- Introduction: Despite significant advancements in medical care, ischemic heart disease, notably acute myocardial infarction, remains the leading cause of morbidity and mortality worldwide; given the complexity of the atherosclerosis process, the severity of the associated pathologies, it is crucial to explore new prognostic factors that may have an impact on the course of this disease. Previous studies have shown that serum albumin is a powerful prognostic factor in various other conditions. Objective: to study the relationship between low serum albumin and the occurrence of complications in patients with acute myocardial infarction during hospitalization. Methods: the study included 93 patients with acute myocardial infarction with or without ST-segment elevation who attended Tishreen University Hospital in Lattakia, Syria, during the period from June 2022 to June 2023, and was divided into two groups: hypoalbuminemia group 36 patients (albumin <3.5 g/dl) and normal albumin group 57 (albumin ≥ 3.5 g/dl). Results: complications were more prevalent in the hypoalbuminemia group, 61.1%, compared to 26.3% in the normal albumin group, with a statistically significant difference (P-value: 0.001). Specifically, there was a higher incidence of mortality (P-value:0.03), acute heart failure (P-value:0.002) and cardiogenic shock (P-value:0.003) in the hypoalbuminemia group. Conclusions: Low serum albumin levels in patients with acute myocardial infarction (STEMI or NSTEMI) have significant predictive value for complications during hospitalization, particularly death, acute heart failure, and cardiogenic shock.*

Keywords *- Acute myocardial infarction, Complications, Hypoalbuminemia, Mortality, STEMI.*

1. Introduction

Albumin is a protein that constitutes about 60% of serum proteins.[1] It consists of 585 amino acids. [2] low albumin levels have many causes, for example:

1- leakage of albumin from the vessels into the interstitial space due to increased vascular permeability following the production of cytokines leading to a decrease in albumin levels. Like what happens in the case of critical illnesses such as sepsis and other infections, significant surgical stress, and inflammation, that's why albumin is considered a negative acute phase reactant; the serum albumin concentration will decrease early during these conditions, the altered distribution in this situation involves damage of the endothelial barrier in the lining of the vessels, which causes capillary leakage and protein loss, inflammatory factors and fluids into the interstitial space.[3] Also, patients suffering from burns have increased vascular permeability, leading to albumin leakage from within the vessels into the extravascular spaces.[4]. 2-Decreased production of albumin: hypoalbuminemia can be a sign of cirrhosis and other liver diseases.[5] 3- Nutritional Deficiency.[5].4-Increased Loss of Albumin (Renal causes) Hypoalbuminemia can be found in patients with nephrotic syndrome. [5] and end-stage renal disease (ESRD). [6] - (Gut Loss) Like the case of protein-losing enteropathy (PLE) in Crohn's disease, for example. [7] (PLE) can also be found in cardiac disease, cancers and infections.[5]

Albumin functions: albumin plays several essential roles in maintaining homeostasis: Such as keeping the colloidal osmotic pressure (COP), albumin contributes around 80% of the normal COP in plasma, about 25 mmHg.[8] Albumin transports many substances, such as ions, drugs, lipids, vitamins, and others. [9] Maintaining microvascular integrity: Albumin may have a role in limiting the leakage from capillary beds during stress-induced increases in capillary permeability. This may be due to its strong negative charge, which causes repulsion with the rest of the negatively charged molecules in the membrane, or because of its large size, which occupies space in the lumen. [10] Albumin also plays a role in maintaining vascular expansion by protecting (NO) Nitric Oxide from rapid decomposition [11]. Antioxidant function.[12] plus it is also proposed to have a heparin-like activity.[13]

Several studies have recently confirmed the role of albumin deficiency as a prognostic factor in many diseases, such as chronic renal failure [13], heart failure [14], Cancers [15], and more recently, Covid-19 [16]. Many others studied

its effect on long-term adverse events in patients with chronic coronary syndromes. Still, the picture was less clear regarding the impact that hypoalbuminemia has on the occurrence of complications in patients with AMI during hospitalization, especially when we know that acute infarction is an inflammatory process [17], during which many cytokines are secreted, such as IL-6, IL-1, TNF Which subsequently induce the acute-phase response [18], which causes the albumin level to drop.

Therefore, we conducted our study to clarify this relationship, which will help better understand the pathological mechanism of infarction and more accurately identify high-risk patients.

2. Patients and Methods

This study was designed as an analytical cohort Study (Prospective)**;** the initial sample consisted of 93 patients with AMI diagnosed based on ECG, ultrasound and biomarks features with ages > 18, who attended the Tishreen University Hospital in Lattakia, Syria, and the onset of active angina chest pain occurred less than 24 hours before the sighting during the period from June 2022 to June 2023. Exclusion criteria included:

1. Patients with advanced renal failure or dialysis patients.
2. Chest pain patients from the NSTACS group for whom cardiac biomarks analysis was not performed, so we could not differentiate between NSTEMI or UA.
3. Patients whose albumin withdrawal was delayed for more than 24 hours.
4. Patients who do not meet the study criteria.

2.1. Examination Methods

A detailed history was taken for all patients subject to the study, including medical history and cardiac risk factors (age, sex, smoking, diabetes, blood pressure, and history of ischemic heart disease (IHD). The patients were divided according to albumin value into Patients with hypoalbuminemia <3.5 g/dl - Patients with normal ≥ 3.5 g/dl. And they were also classified according to the type of the AMI into two groups (STEMI or NSTEMI), STEMI is defined as descriptive angina chest pain that lasts more than 20 minutes, and the ECG shows ST junction elevation measured at the J point with at least two contiguous ≥ 1 mm on all leads except V2 and V3, which require an elevation ≥ 2.5 mm in males under 40 years of age. ≥ 2mm in males aged 40 and above and ≥ 1.5mm in women. And an elevation ≥ 0.5 mm on leads v7-v8-v9 With ST depression in the leads V1-V2-V3.[19].

NSTEMI is defined as descriptive angina chest pain with elevated cardiac biomarks without ECG changes that meet the criteria for STEMI. The GRACE SCORE was calculated for all patients

2.1.1. Laboratory Testing

Intravenous tests were performed for all patients at admission, including) ALBUMIN ,WBC, HGB, CRP CKMB, CREA, GLU) .

2.1.2. In-Hospital Complications

One of the following**:**

1 death, 2-malignant arrhythmia, 3-acute heart failure, 4-cardiogenic shock, 5-reinfarction.

Acute Heart Failure (*AHF)*

AHF is defined according to the (AHA) (American Heart Association) as gradual or rapid change in heart failure (HF) signs and symptoms resulting in a need for urgent therapy. These symptoms are primarily the result of severe pulmonary congestion due to elevated left ventricular (LV) filling pressures (with or without low cardiac output) [20] and were diagnosed based on clinical signs or symptoms of pulmonary congestion in a physical examination and CXR, (dyspnea breathlessness, fatigue, orthopnea, cough, tachypnea, tachycardia, 3rd/4th heart sound, rales, intolerance of the supine position), plus the use of intravenous loop diuretics or the use of inotropic agents .

Cardiogenic shock was diagnosed based on a systolic blood pressure ≤ 90 mm Hg for ≥ 30 minutes or support (inotropic agents, vasopressor agents) to maintain systolic blood pressure ≤ 90 mm Hg and urine output ≤ 30 mL/hr. or cool extremities and based on Echo findings.

Malignant arrhythmias were diagnosed based on ECG findings and include ventricular tachycardia (VT) or ventricular fibrillation (VF), Atrioventricular blocks (AV BLOCKS), specifically (Mobitz type II block and complete heart block Third-degree AV block

Recurrent MI or reinfarction was defined as the recurrence of clinical signs and symptoms of ischemia in patients with previously diagnosed MI, with accompanying electrocardiographic changes and raised serum biomarker levels consistent with myocardial necrosis

2.2. Ethical Consideration

All patients were provided complete and clear informed consent after discussing the study. The Declaration of Helsinki performed this study.

2.3. Statistical Analysis

Our study's Statistical assessment was performed using IBM Statistical Package for Social Sciences (SPSS) for Windows, version 20, manufactured by IBM Corp., located in Armonk, N.Y., USA, and summarized as frequencies and proportions. P<0.05 value was accepted to be statistically significant. The results were indicated in average ±SD and percentage (%). One-way ANOVA was used for comparing groups. The independent-sample t-test was used for comparing the two groups, and the t-test was used for variables.

3. Results

The study collective included 93 patients (62.4% males, 37.6% females); the patients' ages ranged from 43 -89 years, with a mean age of 58.6±11.7 years. Patients with hypoalbuminemia 36 **(**38.7%), patients with normal

albumin value 57 (61.3%), 66 (71%) were diagnosed with STEMI and 27 (29%) NSTEMI.

There was no difference between the hypoalbuminemia group and the normal albuminemia group concerning gender and smoking. Still, the average age of patients in the hypoalbuminemia group was higher (63.66±15.2) with a statistically significant difference (p-value 0.001) than in the normal albumin group (55.42±7.3). (see table 1).

When studying the differences in distribution between the two groups according to medical history, we observed statistically significant differences regarding the incidence of hypertension and diabetes mellitus (but not for history of ischemia), which were higher in the group of patients with low albumin values, (p-value 0.04 – 0.0001) respectively. (see table 1)

There were statistically significant differences concerning the type of infarction, 83.3% of the group of patients with albumin values less than 3.5 were of the STEMI type p-value (0.03), as well as the average values of ejection fraction EF, which were lower in that group 44.62±11 compare to 51.35±11.9 (p-value 0.001) (see table 1). Also noticed that Grace Score values were significantly higher in the hypoalbuminemia group (135.8±33.1) compared with (112.05±24.2) (p-value 0.001). (see Table 1), there weren't any statistically significant differences between the two study groups regarding all therapeutic procedures performed on patients (see Table 1). Regarding the differences in the mean values of laboratory parameters, All the ratios were higher in the group of hypoalbuminemia patients, except for haemoglobin, which was lower in them.

Still, the differences were statistically significant concerning HGB (12.07±2.1) compared to (12.98±2.1) (p-value 0.04), CRP (30.19±27.5) compared to (19.27±22.6) (p-value 0.04), and CREA (1.34±0.6) compared to (1.20±0.7)) (p-value 0.04) but were not present concerning GLU, CKMB, WBC. (see table 2). The rate of complications as a whole was higher in patients with hypoalbuminemia (61.1%) compared to (26.3%) (p-value 0.001), especially the rate of death (22.2%) compared to (7%) (p-value 0.03), acute heart failure (44.4%) compared to (15.8%) (p-value 0.002), and cardiogenic shock (33.3%) compared to (8.8%) (p-value 0.003). At the same time, the difference between the two groups was not statistically significant about malignant arrhythmias and reinfarction (see Table 3).

Table 1. Characteristics of study subjects according to serum albumin

Variables	Subjects with Alb<3.5 n (36) Mean ± SD	Subjects with Alb≥3.5 n (57) Mean ± SD	P-value
Male n%	19(52.8%)	39(68.4%)	0.1
Female n%	17 (47.2%)	18 (31.6%)	0.1
Smoking n%	21(58.3%)	33(57.9%)	0.9
Age	63.66±15.2	55.42±7.3	0.001
HTN n%	19(52.8%)	21(36.8%)	0.04
DM n%	21(58.3%)	12(21.1%)	0.0001
IHD n%	9(25%)	21(36.8%)	0.2
Type of infarction STEMI n% NSTEMI n%	30(83.3%) 6(16.7%)	36(63.2%) 21(36.8%)	0.03
EF	44.62±11.	51.35±11.9	0.001
Grace Score	135.8±33.1	112.05±24.2	0.001
Treatment n%			
PCI	2(5.6%)	6(10.5%)	0.8
Thrombolysis Success Failure	20(55.6%) 7(19.4%)	33(57.9%) 7(12.3%)	0.4
Medical treatment	7(19.4%)	11(19.3%)	0.2

HTN: hypertension, DM: diabetes mellitus, IHD: ischemic heart disease, STEMI: ST-Segment Elevation Myocardial Infarction, NSTEMI: Non-ST-elevation myocardial infarction, EF: ejection fraction, PCI: Percutaneous coronary intervention.

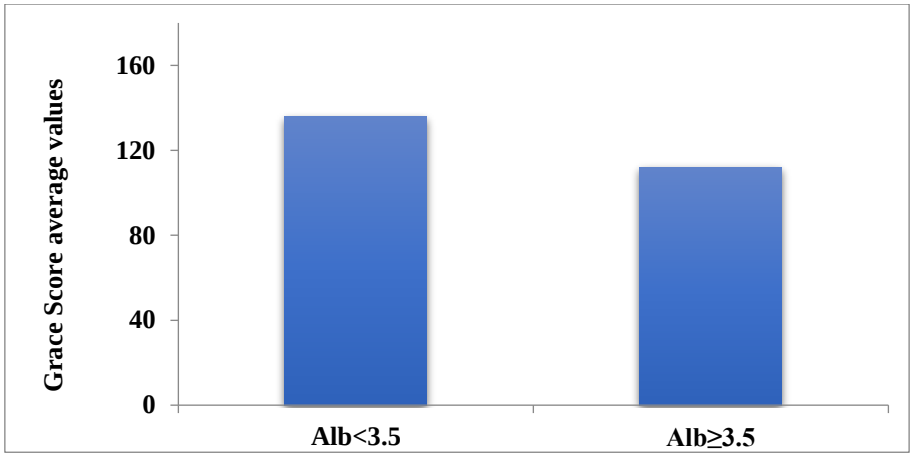

Fig. 1 The average values of the Grace Score between the two groups of myocardial infarction patients were classified according to the value of albumin admitted to tishreen university hospital in latakia, syria, during the study period

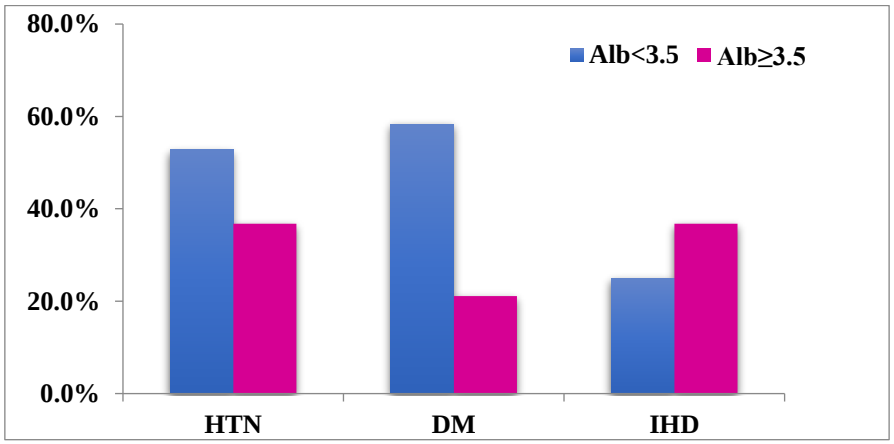

Fig. 2 The distribution of medical history between the two groups of myocardial infarction patients was classified according to the value of albumin admitted to tishreen university hospital in lattakia, syria, during the study period

Table 2. Differences in the mean values of laboratory parameters between the two groups of myocardial infarction patients classified according to the albumin value

Laboratory parameters	Subjects with Alb<3.5 n (36) Mean ± SD	Subjects with Alb≥3.5 n (57) Mean ± SD	p-value
GLU	161.2±73.4	150.21±64.5	0.09
HGB	12.07±2.1	12.98±2.1	0.04
WBCs	11.93±4.4	11.28±3.6	0.4
CRP	30.19±27.5	19.27±22.6	0.04
Crea	1.34±0.6	1.20±0.7	0.03
CKMB	107.16±106.2	98.40±80.3	0.6

GLU: glucose. HGB. Hemoglobin. WBCs: white blood cells. CRP: C-reactive protein, CREA: creatinine, CKMB: creatine kinase-myocardial band.

Table 3. Distribution differences according to the occurrence of complications between the two study groups according to the albumin value

Type of complication	Subjects with Alb<3.5 n (36) Mean ± SD	Subjects with Alb≥3.5 n (57) Mean ± SD	p-value
AHF	16(44.4%)	9(15.8%)	0.002
Cardiogenic shock	12(33.3%)	5(8.8%)	0.003
Arrhythmia	8(22.2%)	9(15.8%)	0.4
Reinfarction	3(8.3%)	3(5.3%)	0.5
Death	8(22.2%)	4(7%)	0.03
Total complications	22(61.1%)	15(26.3%)	0.001

AHF: acute heart failure.

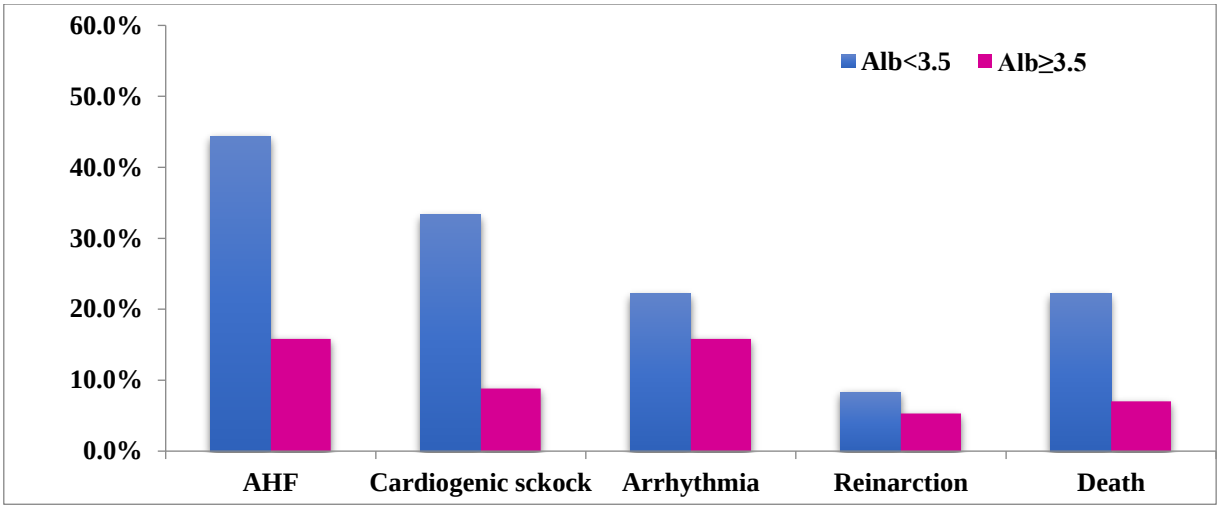

Fig. 3 Distribution according to the development of complications between the two groups of myocardial infarction patients classified according to the value of albumin admitted to tishreen university hospital in lattakia, syria, during the study period

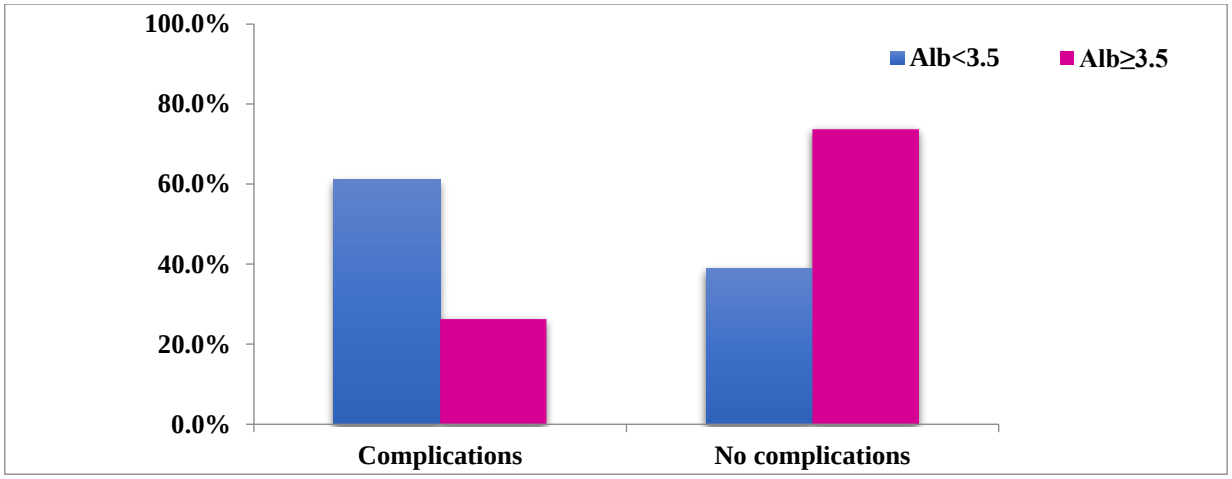

Fig. 4 Distribution differences according to the incidence of total complications between the two groups of myocardial infarction patients classified according to the value of albumin admitted to tishreen university hospital in lattakia, syria, during the study period

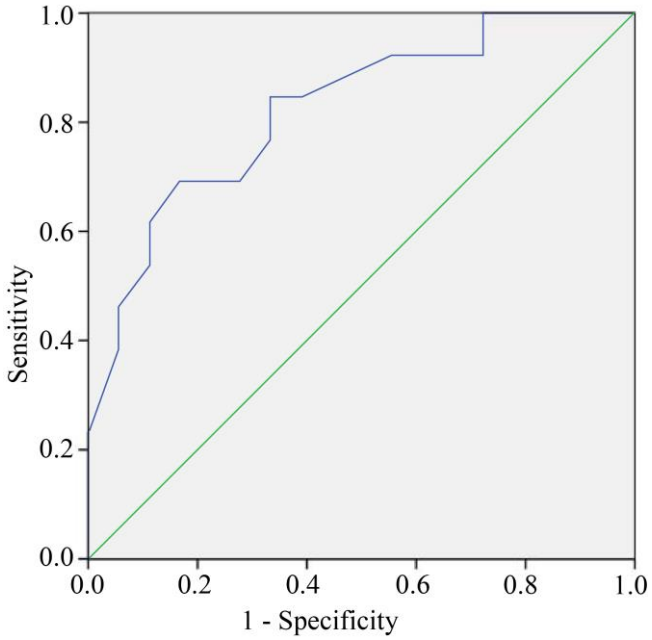

Fig. 5 Roc Curve for predicting complications in myocardial infarction patients classified according to the albumin value admitted to Tishreen University Hospital in Lattakia during the study period: CUT-OFF VALUE=3. 39 AUC=0.82[0.74-0.91] Sensitivity = 76.9 [68-83] Specificity=66.7[55 - 79] Cut off=3.39

4. Discussion

This study showed that hypoalbuminemia in patients with acute infarction is a prognostic factor for the occurrence of complications and deaths. We noted that there were statistically significant differences regarding the occurrence of complications between the two study groups, which were higher in the hypoalbuminemia group, reaching 61.1% versus 26.3%. In the normal albumin group, the p-value (0.001) This is consistent with the results of the Indonesian study conducted by Anggoro Budi Hartopo in 2008-2009, which included 83 patients and demonstrated that hypoalbuminemia upon admission is a prognostic factor for the occurrence of adverse outcomes in patients with acute coronary syndrome during hospitalization (p=0.04) [21]. It is well known that atherosclerosis is a Progressive inflammatory event triggered by injury to the endothelial tissue.

The onset of atherosclerosis is characterized by infiltration of low-density lipoprotein (LDL) into the arterial intima, which undergoes oxidation. Subsequently, leukocytes (mainly monocytes and lymphocytes), recruited with the help of adhesion molecules expressed by inflamed endothelium, penetrate the intima and produce a variety of inflammatory cytokines and chemokines. [22] The results reached in the study can be explained through the data obtained and considering the knowledge of the properties and functions of albumin.

The determining factor for the endothelial dysfunction seen in atherosclerosis is the lack of endothelium-dependent vasodilation, which is mediated by Nitric oxide gas (NO) derived from the endothelial cells themselves, a defect in the production or activity of NO is the main mechanism for endothelial dysfunction that contributes to atherosclerosis. [23] Albumin is the most important source of sulfhydryl groups in the circulation [24]. Nitric oxide (NO) binds to these sulfhydryl groups to form a stable S-nitrosothiol group, thus protecting it from fast degradation. From this, it is suggested that hypoalbuminemia impairs the vasodilatory response to nitric oxide (NO).[11] [25] albumin also binds and mobilizes polyunsaturated fatty acids (PUFAs) from the liver and other tissues, thus promoting the formation of biologically active cell-protective lipids - lipoxins, resolvins and protectins, which are a series of molecules derived from polyunsaturated fatty acids (PUFAs). These play important anti-inflammatory roles, as they prevent the production of prostaglandins that cause inflammation, free radicals, and cytokines.

Lipoxins, resolvins, and protectins also reduce the infiltration of white blood cells, inhibit inflammation, prevent apoptosis caused by oxidative stress, and inhibit the expression of cox-2 enzymes. Which causes inflammation and production of tumour necrosis factor-alpha (TNFα). Which contributed to reducing the severity of the inflammatory event and promoting healing. [26] [27] In addition, albumin play important role in inhibiting platelet aggregation [28] and has antithrombotic effect due to its similarity in structure to heparin, as heparin contains negatively charged groups that bind with positively charged groups on the antithrombin III molecule, and thus exerts its antithrombotic effect by inhibiting factor X. [29] All of this information demonstrates the important role that hypoalbuminemia plays in the development of atherosclerosis. Not only that but albumin can also be considered as an indicator for assessing the severity of injury in acute myocardial infarction. It has been shown that serum albumin routinely decreases in most inflammatory diseases studied, so albumin has been described as a negative acute phase reactant.[30] In the acute phase of MI, the inflammatory process accelerates significantly, leading to a temporary decrease in albumin levels [31]. Various cells in the atherosclerotic lesion (endothelial cells, smooth muscle cells, macrophages, etc.) produce proinflammatory markers such as cytokines including IL-6), pentraxin-3, MMPs, oxidized LDL, LOX-1, and microRNAs. And others), and these factors are released into the circulation at different stages of atherosclerosis, especially when infarction occurs, [32] which exacerbates the infarction on the one hand and hypoalbuminemia on the other hand. This also indicates an inverse relationship between albumin and CRP. The CRP values in patients with albumin deficiency were higher with a statistically significant difference than in the group with normal albumin, 30.19±27.5 in patients with albumin deficiency compared to 19.27±22.6 in patients with normal albumin. (P-VALUE 0.04).

When looking at the results of complications, the mortality rate was higher in the hypoalbuminemia group, 22.2%, compared to 7% in patients in the normal albumin group, with a statistically significant difference. (P-VALUE = 0.03), and this reflects the severity of the disease in the albumin deficiency group. This is what most international studies have found, such as a study in the state of Minnesota in the USA, which proved that there is a relationship between hypoalbuminemia and mortality among cardiac intensive care unit patients (p-value <0.001). [33] Also, the results of this study were identical to the results of a Chinese meta-analysis, included several studies on the association of hypoalbuminemia and mortality in patients with acute coronary syndrome, and found that ACS patients with hypoalbuminemia had a three-fold risk of in-hospital mortality. [34] Considering the complications, the incidence of acute heart failure was higher in patients with albumin deficiency, 16 (44.4%) compared to 9 (15.8%) in patients with normal albumin (P-VALUE = 0.002).

The explanation for this is based on the fact that according to Starling's law, hydrostatic pressure pushes fluids from the intravascular to the interstitial space, which is opposed by the colloid-osmotic pressure, of which albumin plays the major role, an imbalance of Starling's pressures produced by low serum albumin leads to net extravasation of fluid to the interstitial space, when this happens, pulmonary edema will develop, [35] Thus, low serum albumin (LSA) facilitates the occurrence of peripheral edema and pulmonary congestion even at relatively lower left atrial pressures, making it an aggravating factor in heart failure. [36] These results were

consistent with the results of the Mexican study by Hector and colleagues (2017), who studied the association of serum albumin value at admission with the occurrence of new-onset heart failure and mortality during hospitalization in patients with ACS, The study included 7,192 patients who were divided into four groups according to albumin levels (G1: ≤3.50 g/dl; G2: 3.51 to 3.80 g/dl; G3: 3.81 to 4.08 g/dl; and G4: >4.08 g/dl) and found out that the rate for both new-onset heart failure (37.7%- 20.2%- 14.7%- and 11.4% for G1, G2, G3, and G4, respectively; p <0.0001) and mortality (9.8%-3.4%-2.0%-and 1.7% for G1, G2, G3, and G4, respectively; p <0.0001) were higher among patients with low serum albumin.[37] There was no significant difference between the two groups in terms of gender and smoking, The study showed that patients with hypoalbuminemia were older, as the average age of patients in the hypoalbuminemia group was (63.66±15.2), while the average age of patients with normal albumin was (55.42±7.3) This may be explained by the abundance of chronic and inflammatory diseases and the lack of nutritional intake in the elderly. the study showed that the percentage of patients with a history of high blood pressure was higher in patients with low albumin (52.8%) than in patients with normal albumin (36.8%).

This may be due to the anti-inflammatory and antioxidant properties of albumin., Its regulatory role in many different physiological processes and hypo albuminemia is linked to the severity of the systemic inflammatory response, vascular endothelial cell injury, and the development of chronic vascular diseases [38] [39]. This makes albumin deficiency a risk factor for the occurrence of hypertension. For patients with DM, the percentage of patients with hypoalbuminemia who had a history of diabetes was 21 (58.3%) compared to 12 (21.1%) for patients with normal albumin. A P-Value 0.0001 can be justified with a statistically significant difference, as previous studies found that insulin stimulates albumin synthesis. Diabetic patients have a deficiency in albumin synthesis, which improves with insulin injections [40]. In addition, in a previous American study that included 15,800 patients, the average albumin concentration was 0.04 to 0.12 g/L lower in diabetic patients. [41] High blood pressure and diabetes also play a causative role in causing various systemic diseases, which contributes to causing albumin deficiency in the long term.

This gives another explanation for the increase in the percentage of patients with high blood pressure and diabetes in the hypoalbuminemia group in this study. There was also a correlation between hypoalbuminemia and the presence of anaemia, as the average haemoglobin values in patients with hypoalbuminemia were 12.07±2.1 compared to 12.98±2.1 in those with normal albumin, with a statistically significant difference, P-value 0.04. This relationship is explained by the fact that hypoalbuminemia is associated with increased inflammation, as we mentioned previously, which contributes to the development of inflammatory anaemia. This relationship is important because of the prevalence of hypoalbuminemia and anaemia in hospitalized patients in general [42], in addition to the fact that both are considered indicators of malnutrition. When comparing the average values of the Grace Score in the two study groups, it was revealed that there was a significant inverse relationship between albumin and the Grace Score, as the values were 135.8±33.1 in patients with hypoalbuminemia compared to 112.05±24.2 in those with normal albumin, (P-VALUE 0.001), and this is explained as among the eight Grace Score variables are age, creatinine, and Killip class,[43] When analyzing the results of our study, we found that the average age of patients in the albumin deficiency group is greater than that of the normal albumin group, the average creatinine value is higher, and the incidence of acute heart failure and cardiogenic shock is higher, which raises the Killip class value, [44] and thus raises the Grace Score value in these patients.

5. Conclusion

- Hypoalbuminemia is not uncommon finding in patients with acute myocardial infarction
- Low serum albumin plays an essential predictive role in the occurrence of complications, especially death, acute heart failure, and cardiogenic shock during the hospitalization period in patients with AMI.
- Hypoalbuminemia is associated with higher Grace Score values in patients with acute infarction.
- Patients with hypoalbuminemia are older and have a higher rate of high blood pressure and diabetes.
- Hypoalbuminemia is associated with higher CRP and creatinine values and lower HGB values.

6. Recommendations

- We suggest that acute infarction patients with low serum albumin should be considered high-risk and monitored more carefully.
- We recommend adding albumin analysis to routine tests, especially for patients with AMI.
- Conducting subsequent studies with a larger sample size
- Conducting future studies on the relationship between albumin and long-term complications in patients with AMI.
- Conducting experimental studies to determine the benefit of treating hypoalbuminemia to improve prognosis in patients with AMI during hospitalization or in the long term.

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