J Turgut Ozal Med Cent
DOI: 10.5455/jtomc.2016.12.135 2017;24(3):310-5

Original Article

Ischemia modified albumin levels and its association with clinical follow-up in acute renal failure

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Abstract

Aim: In cases with acute ischemia, albumin's binding capacity for transition metals decreases and the resulting albumin is defined as ischemia modified albumin (IMA). In this study, we aimed to investigate the relationship between IMA and clinical follow-up in patients with acute renal failure (ARF).

Material and Methods: Levels of IMA were measured in 51(23 male, 28 female) patients with ARF. Venous blood samples were drawn from patients for biochemical tests and put in plain tubes containing the gel.

Results: Mean age of male and female patients was 65.39±15.28 and 70.11±15.25, respectively. The IMA levels in 25.5% of the patients were within the normal range (<400 ABSU), while the IMA levels were higher (>400 ABSU) in 75.5% of the patients. The survival rates of patients in IMA <400 ABSU group for 12 and 24 months were 66.7% and for 30 and 32 months it was 33.3%; while the survival rates of patients in IMA ≥400 ABSU group for 12 months were 85.8%, for 24 months were 61.3%, and for 30 and 32 months were 30.6%. No significant difference was determined among survival rates of IMA groups (p=0.719).

Conclusion: The comparison between the groups having normal or higher IMA values did not show any significant differences in terms of survival. However, in our study the proportion of patients who needed dialysis during treatment were significantly higher in higher IMA group(IMA≥400 ABSU). Therefore, we believe that higher IMA levels may indicate a necessity for dialysis in patients with ARF.

Keywords: Acute Renal Failure; Ischemia Modified Albumin; Acute Kidney Injury.

INTRODUCTION

Acute Renal Failure (ARF) is a common clinical syndrome increasing mortality. It is caused by various etiologic factors, but they may potentially be prevented or treated. ARF covers a broad spectrum ranging from minor changes in renal function indexes to conditions necessitating renal replacement therapy (RRT). Despite all the restrictions and new developments, ARF is still diagnosed based on the increase in serum creatinine levels and the decrease in the amount of urine (1).

ARF is a condition associated with ischemia (3). In the last 20 years, the frequency of ARF in hospitalized patients had increased (2). In recent years, various biomarkers have been discovered with a goal of: (i) further improving the detection of ARF; (ii) early diagnosis before kidney damage spreads and becomes permanent; (iii) differentiation between different types of ARF; and (iv) better identification of the prognosis of ARF. In the recent decade, it was determined that the structure of serum albumin changes in ischemic conditions, and this discovery facilitated the identification of a new serum marker for ischemia. The amino-terminus of albumin is a binding site for transition metals such as cobalt, copper, and nickel (4). Conditions such as hypoxia, acidosis, free radical damage, and disruption of membranes that occur during ischemia reduce the binding capacity of albumin's N-terminus region to the transition metals (5,6).

This modified albumin structure is called ischemia modified albumin (IMA) and the changes in the albumin molecule can be measured calorimetrically by adding a known amount of cobalt into the patient's serum. The IMA test is a measurement of albumin's cobalt binding capacity and involves spectrophotometric measurement of unbound cobalt. The formation of this new albumin molecule that lost its cobalt binding capacity is one of the earliest markers of ischemia. Based on this principle, we aimed to investigate the relationship between the IMA

Received: 26.12.2017 **Accepted:** 27.06.2017
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levels and the prognosis in patients diagnosed with ARF in this study.

MATERIALS and METHODS

A total of 51 patients admitted to Izmir Tepecik Training and Research Hospital between March 2014 and October 2014 were diagnosed with acute renal failure (ARF) and followed prospectively. Hospitalization or outpatient follow-up protocol numbers were obtained and all patients without a history of chronic renal failure were included in the study. Patients under the age of 18 years, patients whose ARF etiology was a postrenal situation, patients that did not continue their follow-up visits, and patients that had preexisting chronic renal failure were excluded from the study. Age, gender, comorbid diseases, vital signs, urine volume, sodium, potassium, urea, creatinine, hemoglobin, leukocyte, neutrophil, lymphocyte, albumin, and blood gas values were recorded for all patients. Reference limits of the laboratory were accepted when classifying these parameters as lower or higher than normal limits. In the recent decade, new criteria such as Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) and Acute Kidney Injury Network (AKIN) was established to bring the standard of ARF definition and classification (7-10).

Our patients were diagnosed according to these classification criteria. We did not stratify our patients according to the severity of the renal failure. We did not classify the specific etiologic factors causing ARF. Some patients underwent to hemodialysis treatment according to the clinical and/or laboratory findings compelling the patients to renal replacement therapy. Classical indications for hemodialysis such as hyperkalemia, severe metabolic acidosis, hypervolemia, anuria were accepted as hemodialysis indications for our patients. IMA levels of the patients were measured at the time of hospital admission. The serum IMA levels were measured with albumin cobalt binding test by using venous blood samples drawn into plain biochemical tubes containing a gel. The IMA measurement in serum samples was done by the method described by Bar-Or et al., where the albumin's binding to reduced cobalt was measured based on a rapid colorimetric test. This test measures ischemia-induced reduction in the binding capacity of albumin's amino terminus towards metals such as cobalt, nickel, and lead. It is known that a very small amount of cobalt binds to albumin in ischemic conditions (4,11). In the aforementioned test 50 microliters of 0.1% cobalt chloride was added to 20 microliters to serum. The sample was gently agitated to ensure the binding and incubated for 10 minutes. Fifty microliters of dithiothreitol (DTT) was added as a dying material. After 2-minute incubation the reaction was stopped by the addition of 1 ml of saline. The control sample was prepared by using distilled water. The absorbance values of all samples were measured at 450 nm by using a spectrophotometer. Results were obtained in absorbance units (ABSU). In this method, values above 0.40 absorbance units were considered positive for ischemia (low cobalt binding capacity).

OpenSTAT software for Windows was used for statistical analysis. The descriptive statistics were defined as numbers and percentages for categorical variables and as mean, standard deviation, median, minimum, and maximum for numeric variables. In dual independent group comparisons, the t-test was used when the normal distribution assumption was met for the numerical variables, and the Mann-Whitney U test was used when the normal distribution assumption was not met. On the other hand, for pairwise comparison of categorical variables the chi-square tests was used when the conditions for chi-square test were satisfied, and if those conditions were not satisfied, the Monte Carlo Simulation was used for multiple group comparisons and Fisher's exact test statistic was used for pairwise comparison. Meanwhile, in correlation analyses to determine the relationship between numeric values, the Pearson's test statistic was used when the assumption of a normal distribution was met and Spearman's rho test statistic was used when that assumption was not met. The Kaplan-Meier survival analysis was used for survival analyses and Log Rank test statistic was used for comparison of survival rates. Backward LR method and Cox regression analysis were used in determining the risk factors affecting survival. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study included a total of 51 patients with mean age of 67.98 ± 15.25 years: 23 men with mean age of 65.39 ± 15.28 years and 28 women with mean age of 70.11 ± 15.25 years. Laboratory findings of the patients were shown in Table 1.

In 25.5% of the patients, the IMA levels were detected as normal (< 400 ABSU), while the IMA levels were higher (> 400 ABSU) in 75.5% of patients. During the follow-up, hemodialysis was performed for 76.5% of patients. Forty patients fully recovered and were discharged. A total of 3 patients were diagnosed with chronic kidney disease and 2 of those were entered to permanent hemodialysis program. Eight patients died during the treatment period (Table 2).

A statistically significant difference was found between the IMA groups in terms of the amount of urine ($p = 0.008$). In the IMA ≥ 400 ABSU group, the number of patients with lower urine output (0-400 mL/day) and the presence of the complaints about decreased urine were significantly higher, while the presence of diarrhea were significantly lower compared to IMA<400 ABSU group ($p=0.006$, $p=0.001$, $p=0.008$; respectively). Compared to IMA < 400 ABSU group, there were significantly more patients with hypocarbia in the IMA≥400 ABSU group ($p = 0.013$). Moreover, the number of patients requiring dialysis during treatment was significantly higher in IMA ≥400 ABSU group in comparison to IMA<400 ABSU group ($p = 0.023$) (Table 3).

We did not detect any significant associations between IMA and factors such as age, blood pressure and laboratory tests, dialysis sessions and length of hospital stay. Potassium and creatinine levels and number of patients having IMA ≥ 400 ABSU were significantly higher, while the hemoglobin levels were significantly lower in the patient group having dialysis treatment. The urine output levels were significantly higher in patients that died compared to the patients that survived (p = 0.044).

The survival rates of patients in IMA < 400 ABSU group for 12 and 24 months were 66.7% and for 30 and 32 months it was 33.3%; while the survival rates of patients in IMA ≥ 400 ABSU group for 12 months were 85.8%, for 24 months were 61.3%, and for 30 and 32 months were 30.6%. No significant difference between IMA groups was determined in terms of survival rates (p = 0.719) (Table 4).

Table 1. Laboratory Findings of the Patients

(n=51)			mean±SD (median)
Na			137,39±9,24 (136)
	Low	19 (37,3)	
	Normal	24 (47,1)	
	High	8 (15,7)	
K			4,58±1,11 (4,5)
	Low	7 (13,7)	
	Normal	30 (58,8)	
	High	14 (27,5)	
Urea			130,53±65,11 (126)
	Low	1 (2,0)	
	Normal	1 (2,0)	
	High	49 (96,1)	
Creatinine			3,84±3,12 (2,7)
	High	51 (100,0)	
Hemoglobin			11,79±2,69 (12)
	Low	32 (62,7)	
	Normal	18 (35,3)	
	High	1 (2,0)	
Neutrophil			8935,1±6504,99 (8260)
	Low	1 (2,7)	
	Normal	20 (54,1)	
	High	16 (43,2)	
Lymphocyte			1245,22±699,4 (1000)
	Low	5 (9,8)	
	Normal	45 (88,2)	
	High	1 (2,0)	
Leukocyte			11009,57±6779,21 (9900)
	Low	3 (5,9)	
	Normal	25 (49,0)	
	High	23 (45,1)	
Albumin			3,35±0,58 (3,4)
	Low	21 (41,2)	
	Normal	30 (58,8)	
IMA			543,20±188,14 (567)
IMA	<400	13 (25,5)	
	≥400	38 (74,5)	

Table 2. The patients' requirement for dialysis, dialysis sessions, post-treatment outcomes, renal ultrasonography (USG) results and hospitalization times during the treatment

(n=51)		n (%)
Requirement for dialysis during	No	39 (76.5)
	Yes	12 (23.5)
Post-treatment outcome	Recovery	40 (78.4)
	Permanent dialysis	2 (3.9)
	Death	8 (15.7)
	Chronic renal failure remained	1 (2.0)
Renal USG	Normal kidneys	41 (80.4)
	Normal size, increased echo	9 (17.6)
	Small and increased echo	1 (2.0)
		mean±SD(median)
Dialysis sessions		3.25±1.87 (3)
Hospitalization time (days)		9.22±7.42 (7)

Table 3. The clinical outcome and requirement for dialysis based on IMA levels

		IMA Group		p
		<400 ABSU (N=13)	≥400 ABSU (N=38)	
Requirement for dialysis during treatment period	No	13 (100.0)	26 (68.4)	0.023
(n (%))	Yes	0 (0.0)	12 (31.6)	
Post-treatment outcome	Recovery	11 (84.6)	32 (84.2)	1.000
(n (%))	Death	2 (15.4)	6 (15.8)	

Table 4. The cumulative survival rates by time of IMA groups

		Cumulative Survival Rates by Time		
	Time	**Estimate**	**Standard Error**	**p**
IMA <400	12 month	0.667	0.272	
	24 month	0.667		
	30 month	0.333	0.272	
	32 month	0.333		0.719
IMA ≥400	12 month	0.858	0.083	
	24 month	0.613	0.158	
	30 month	0.306	0.231	
	32 month	0.306		

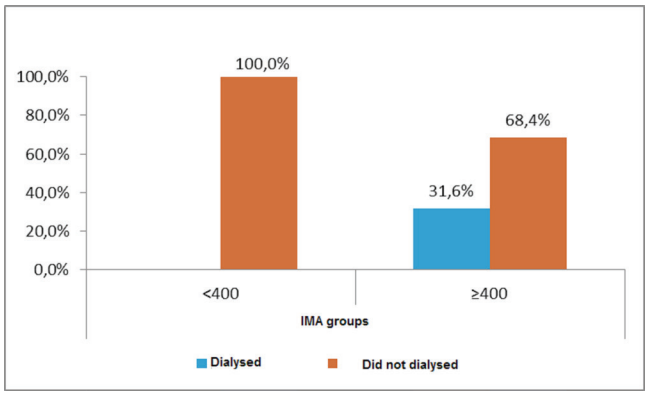

Figure 1. Requirement for dialysis and IMA levels

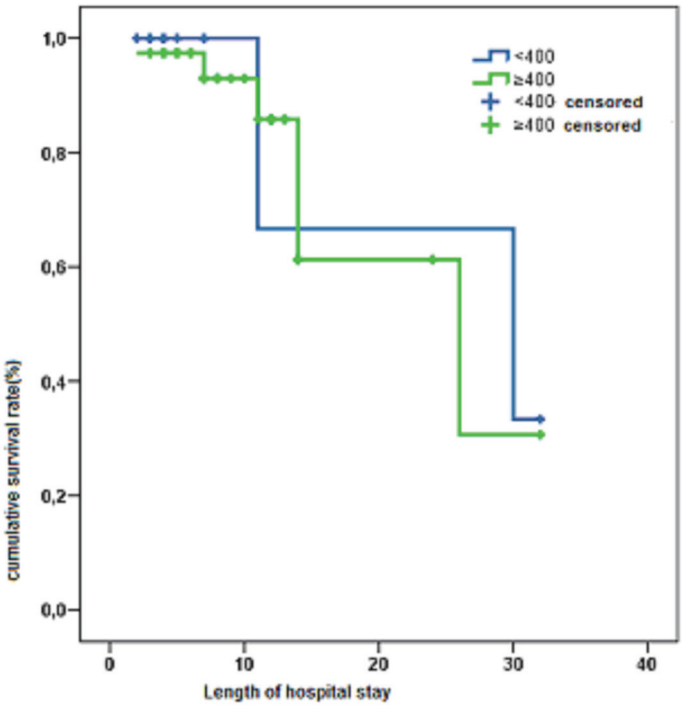

Figure 2. Survival rates of IMA groups

Factors affecting the risk factors for dialysis such as gender, age, lack of appetite, potassium, urine, creatinine and hemoglobin (gender, age and comparison variables whose p-value are 0.100) were used in the univariate

analysis model to determine the requirement for dialysis and in this analysis the creatinine was determined as risk factor while hemoglobin was determined as a protective factor.

In a model created to determine whether higher IMA was a risk factor having any effect on survival or not, presence of higher IMA (≥400) was not significant as a risk factor.

DISCUSSION

ARF can be described as a sudden decline in kidney function that manifests itself with changes in serum biochemistry and urine output. Prerenal azotemia is the most common cause of ARF and constitutes 40-55% of all cases (12,13). The effective arterial volume is defined as a sufficient quantity of arterial blood supplied to vital organs (13). The development of ARF is one of the factors responsible for the direct increase in mortality. Therefore, due to its significant impact on mortality, an early detection of ARF and taking timely necessary preventive and therapeutic measures is very important.

In recent years, ischemia modified albumin (IMA) has been studied in various clinical conditions such as acute coronary syndrome, diabetic nephropathy, diabetic complications, epilepsy, acute stroke, and cerebrovascular events. In some studies, the IMA had been investigated as a prognostic marker, while in other studies as an indicator of complications. Moreover, in several studies the IMA levels have been investigated as an oxidative stress index in the context of its relationship with other inflammatory parameters. In a study conducted by Turkmen et al., the IMA levels of renal transplant patients and patients undergoing hemodialysis and peritoneal dialysis were shown to be correlated with inflammatory parameters such as hs-CRP, carotid intima-media thickness, pentraxin-3 (PTX-3), and neutrophil / lymphocyte ratio (14). Guided by the available data from studies conducted until now, we also investigated IMA levels in patients diagnosed with ARF and clinically followed-up patients in order to examine the relationship between IMA levels and prognosis of the disease in our study.

In our study, IMA levels were normal (< 400 ABSU) in 25.5% of patients and high (> 400 ABSU) in 75.5% of the patients. No significant relationships were determined between IMA levels and factors such as gender, mean age, mean blood pressure, and pulse rate at the time of admission to the hospital. Complaints of patients with high levels of IMA were found to be generally similar to those of patients with normal IMA. Since the diagnosis of ARF can be made based on the AKIN criteria (based on the creatinine value or urine output), according to our data the IMA values were determined to be higher in patients with ARF. This finding indicates that the factors that cause ARF can elicit ischemia-reperfusion injury and thus oxidative stress.

In a study conducted by Turedi et al., the IMA levels of 94 patients diagnosed with end stage renal disease were compared to control group (n=30). The IMA levels of patients with end-stage renal disease were determined at pre-hemodialysis (pre-HD) and post-HD periods. The pre-HD and post-HD IMA levels in these patients were significantly greater compared to IMA values of the control group (15). In our study, 23.5% of the patients required hemodialysis during the clinical follow-up. We did not measure the IMA levels before and after the hemodialysis. Carrega and colleagues suggested that hemodialysis did not have any significant impact on the IMA levels (16).

In our study, we detected negative correlation between the hemoglobin levels and IMA levels, but this correlation was not statistically significant. In Turedi et al.'s study, the IMA levels of post-HD low hemoglobin (Hb <10) group were determined to be higher compared to the other groups (14). In contrast to other studies conducted with chronic kidney disease patients, we investigated the significance of measuring IMA levels at the time of admission to the hospital in predicting the prognosis of the disease in patients diagnosed with AKI in our study.

In our study, the proportion of patients that required dialysis during the treatment was significantly higher in patients with high levels of IMA ($p = 0.023$). Many studies have been conducted to investigate the predictive value of IMA levels on mortality and prognosis based on the different clinical situations. Yucel et al. reported that the IMA levels were associated with early mortality after cardiopulmonary resuscitation (CPR) (17).

Moreover, Consueqra-Sanchez et al. have demonstrated that IMA levels measured at the time of admission can be used as an independent predictor of short-term and long-term mortality in patients presenting with a typical chest pain supporting the acute coronary syndrome (18). Our findings suggesting that IMA levels did not predict the survival could be explained by several other factors could also affect survival in patients with renal failure.

Serum IMA levels can be measured by using a rapid spectrophotometric method (19). In some cancers, infections, end-stage renal disease, liver disease, and brain ischemia, the serum IMA levels increase and constitute a limitation for IMA test (20, 21). Specific physiopathological factors resulting with ARF may also affect IMA levels itself; for example, ischemic acute tubular necrosis it may be proposed that IMA levels could be increased to higher levels in comparison to other causes of ARF.

CONCLUSION

There was no statistically significant difference between the group with normal IMA levels and the group with high IMA levels in terms of survival. According to the data we obtained by regression analysis, the IMA was not determined as an independent predictor of patient survival. To to the best of our knowledge, there are no clinical studies in the literature that investigated the relationship between the IMA levels and prognosis of ARF.

According to findings from our study, high IMA levels can be used as a predictor of requirement for hemodialysis in patients admitted with ARF symptoms, but it was not identified as an independent predictor affecting survival.

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