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The use of ischemia modified albumin as a predictive and prognostic biomarker in patients with non-acetaminophen-induced acute liver failure

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Abstract

Aim: This study aimed to investigate to usability of ischemia modified albumin (IMA) and IMA/albumin ratio (IMAR) values in the follow-up of ALF patients. King College criteria (KCC) and Model for End-Stage Liver Disease (MELD) score are the most commonly used criteria in the follow-up of patients with acute liver failure (ALF). However, these criteria cannot always predict prognosis and the need for liver transplantation (LT).

Materials and Methods: IMA and IMAR values of 23 ALF patients and 43 healthy volunteers were measured. Then IMA and IMAR values were compared with KCC and MELD score to predict LT requirement and prognosis in ALF patients.

Results: IMA and IMAR values were significantly higher in ALF patients compared healthy volunteers (p=0.001, p=0.001; respectively). IMA and IMAR values predicted LT requirement in ALF patients such as KCC and MELD (≥30) score (p=0.006, p=0.04, p=0.001, p=0.03; respectively). IMA values were found to better than KCC in predicting mortality (p=0.008, p=0.02; respectively). MELD (≥30) score failed to predict mortality (p=0.44).

Conclusion: IMA and IMAR values can be used as diagnostic biomarkers in ALF patients. IMA is a better prognostic biomarker in the follow-up of ALF patients.

Introduction

Acute liver failure (ALF) is immediate and serious impairment of liver functions without any history of liver disease. The disease is usually accompanied by reversible hepatic encephalopathy (HE) and is associated with high mortality [1]. Liver transplantation (LT) is the definitive treatment for ALF patients who do not respond to medical treatment. In the course of ALF disease, while approximately one-third of patients listed for LT recover spontaneously, one-fifth of patients may be LT unnecessary [2]. Therefore, some prognostic criteria, such as King's College criteria (KCC), Clichy / Villejuif criteria, Model for End-Stage Liver Disease (MELD), Acute Physiology and Chronic Health Assessment (APACHE) II score, and Sequential Organ Failure Assessment (SOFA) are used in order to predict LT requirement and prognosis of patients with ALF [3-6]. However, even these prognostic criteria cannot always predict prognosis or determine candidacy for LT. Therefore, optimal treatment option and timing are still questioned.

Albumin is mainly a basic plasma protein synthesized by the liver. The amino-terminal end of the albumin molecule contains binding sites for metal ions such as cobalt and nickel. Under various conditions such as ischemia, hypoxia, and acidosis, binding capacity of the albumin for metals is reduced and a metabolic variant is formed. This new isoform of the albumin is called ischemic modified albumin (IMA), and its serum values can be measured [7]. The values of IMA do not change with age and sex. However, albumin values affect IMA values. A 1 g/dL change in albumin values results in a 2.6% change in IMA values [8]. A measurement method, such as IMAR value, has been pro-

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posed to eliminate the effect of albumin on IMA value [9]. IMAR value is calculated using the formula below: IMA value / serum albumin value (gr/dL). Serum IMA and IMAR values have been reported to be increased in various diseases including myocardial ischemia, acute stroke, muscle and intestinal ischemia [10]. In the literature, there are also studies reporting serum IMA and IMAR values in chronic liver diseases (CLD) with various etiologies [11-14]. In these studies, increased IMA and IMAR values in CLD have been found to be compatible with the degree of fibrosis of CLD, and correlated with MELD, international normalized ratio (INR) and bilirubin values. It has been shown that IMA and IMAR values can be used as biomarkers in the prognosis of CLD patients, and associated with morbidity and mortality in these patients.

In this study, we aimed to investigate whether IMA and IMAR values can be diagnostic biomarkers in the follow-up of ALF patients, and whether they can be predictive and prognostic criteria for LT indication and mortality.

Materials and Methods

This prospective cohort study was approved by the Local Ethics Committee (Inonu University Clinical Research Ethics Committee Approval No: 2017/117). Informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee. Twenty-three consecutive patients meeting ALF criteria (development of encephalopathy and impaired synthetic liver functions (INR >1.5 and elevated transaminases)) at time of admission in Inonu University Liver Transplantation Institute between January 2018 and January 2019 were included into study. Factor V levels were not measured in ALF patients during admission or during follow-up. In the follow-up of ALF patients, IMA samples were taken during the first day of admission. KCC, MELD scores and West Heaven stage were evaluated daily. The KCC and MELD scores at the time of the treatment decision were compared the IMA and IMAR values at the time of admission. According to KCC, LT decision was given for ALF patients as follows: PT >100 seconds or INR >6.5 or based on the presence of three of the following: (1) non-A, non-B hepatitis, drug-induced hepatitis; (2) serum bilirubin >17.4 mg/dL; (3) PT >50 seconds or INR >3.5; (4) patient age <10 or >40; or (5) time from jaundice to encephalopathy longer than 7 days [3]. MELD score was calculated according to United Network for Organ Sharing [5,15]. MELD score is a score derived from serum total bilirubin and creatinine, and INR. Pediatric end stage liver disease (PELD) score was evaluated only in the paediatric population. LT decision was given according to combination of KCC and MELD scores in ALF patients. ALF was subdivided as hyperacute (0-7 days), acute (8-28 days) and subacute (29-84 days) with respect to the interval between jaundice and HE [16]. HE is divided into four grades based on the severity of the symptoms, and the most commonly used staging system is West Haven Criteria: Stage 0: No change in consciousness, personality, intellectual function and behaviour [17]. Stage I: Hypersomnia, insomnia, euphoria or anxiety, shortening of the attention span, irritability. Stage II: Lethargy, orientation disorder, inappropriate behaviour, speech impairment, ataxia. Stage III: Somnolence, apparent confusion, response to persistent stimuli. Stage IV: Coma, lack of response to stimuli. Intracranial pressure was not measured in ALF patients. The following parameters were assessed to investigate the underlying cause, excluding that there was no previously known liver disease and predict the severity of the ALF: ALF phase, HE grade, IMA, IMA/albumin ratio (IMAR), total bilirubin (TBil), direct bilirubin (DBil), alanine transaminase (ALT), aspartate transaminase (AST), ammonia (NH3), lactate, arterial blood pH, international normalization rate (INR), urea, creatinine, electrolytes, albumin, copper (Cu), zinc (Zn), viral markers (HAV, HBV, HCV, HDV, HEV, CMV, EBV, HSV, HIV), antinuclear antibody, anti-neutrophil cytoplasmic antibody, antigliadin antibody, anti-smooth muscle antibody, cardiolipin, transglutaminase, radiological imaging (ultrasonography, computed tomography), MELD and PELD scores, complications and outcomes (alive, dead). The flowchart shows the clinical course of the 23 ALF patients during follow-up (Figure 1).

Study design and objectives

The study addressed the ultimate goal at three stages. In the first stage, we aimed to determine whether there was a difference in blood IMA and IMAR values between completely healthy people with ALF patients. Thus, we aimed to get an idea whether IMA and IMAR values can be diagnostic biomarkers in the diagnosis of ALF patients. Sample size was calculated using the data of the preliminary study for this stage of the study (Alpha =0.05, Power: 80%, minimum sample size for case / control groups: 21/42). The control group consisted of healthy volunteers scheduled for live donor hepatectomy in the preoperative period. Both groups were compared in terms of age, sex, albumin, IMA and IMAR values (Table 1). In the second stage of the study, we aimed to examine whether there were predictive IMA and IMAR values as to which ALF patients are candidates for LT and which patients should be followed with medical treatment. For this purpose, 23 ALF patients monitored according to KCC and MELD score were divided into two groups: ALF patients requiring LT (n=10) and those recovering medical treatment (n=13). For this purpose, cut-off values related to mortality were calculated for some variables with statistical significance using receiver operating characteristics (ROC) analysis in ALF patients (Table 2). Requiring LT and recovering medical treatment patients were compared for clinical and biochemical parameters using cut off values and Odds ratio (OR) was calculated for LT (Table 3). The sensitivity, specificity, accuracy, positive predictive values (PPV), negative predictive values (NPV), positive likelihood ratios (LR +) and negative likelihood ratios (LR-) of the IMA and IMAR values, MELD score and KCC for predicting LT requirement were determined (Table 4). In the third stage of the study, the relationship between IMA and IMAR values, KCC, and MELD scores with mortality were investigated (Table 5).

Ischemia modified albumin (IMA) and IMAR (IMA/albumin)

Complete blood count, coagulation tests and biochemical parameters from venous blood samples taken from healthy volunteers during hospitalization and from ALF patients were measured. For IMA measurements, the rest of the plasma was centrifuged for 10 minutes at 4000 rpm and then stored at -800 C. IMA values can be measured manually or automatically (ELISA kits). We were preferred automatically measure (ELISA kits). IMA values were measured using the albumin-cobalt binding test (ACB test) on the BioTek brand Synergy H1 model device (serial number: 1504022, BioTek, Winooski, USA) by colorimetric method. The principle of the method is as follows: 120 microlitre Reagent 1 was added to 35 microlitre patient's serum sample and after being gently shaken, the first absorption data was obtained at 470 nm wavelength within 30 seconds. Then 9 microlitre Reagent 2 was added to the mixture and after being gently shaken, was incubated for 10 minutes in room temperature and second absorption data were obtained at 470 nm wavelength. For IMA calculations (ΔAbs H_2O - ΔAbs Sample)/(ΔAbs H_2O-ΔAbs standard)*100 formula was used. IMA values were given in absorbance units (ABSU). The kit used for measurement was obtained from Real Assay Diagnostics (Gaziantep, Turkey). IMAR values were used in order to eliminate the effect of reduced albumin concentrations, commonly seen in patients with ALF, on serum IMA values.

Statistical analysis

Statistical analyses were performed using IBM SPSS v22.0 (Chicago, IL, USA) and MedCalc v18.11 (Ostend, Belgium) software programs. Continuous variables were expressed as mean ± SD and median (min-max). Categorical variables were reported as number and percent (%). Mann-Whitney U test was used to compare continuous variables and Fisher's exact tests were used to compare categorical variables. Receiver operating characteristics (ROC) analysis was performed to identify optimum cut-off values of continuous variables. Cut-off value for these variables were determined to obtain the most ideal sensitivity, specificity, PPV and NPV. P<.05 was accepted as statistically significant.

Results

Twenty-three ALF patients and 43 adult healthy volunteers were included in the study. Ten of the ALF patients were in the adult, 10 were in the children and three were in the adolescent age group. Eleven of the patients were cryptogenic ALF. Six patients had mushroom intoxication due to consumption of region-specific Heliz mushroom. There was no history of acetaminophen use in any ALF patient in our institution (Table 1). Twenty-two ALF patients were in hyperacute fulminant hepatitis stage ,and one ALF patient was in acute fulminant hepatitis stage. According to West Heaven stage, 13 of the patients with ALF were in stage I, four in stage II, three in stage III, and three in stage IV. Plasmapheresis treatment was given to eight patients in the LT group and three patients in the medical treatment group. Thirteen of the ALF patients recovered with medical treatment, and 10 of them required LT. Transplantation decision was made on median 0 (0-3) days. Living donor LT was performed in eight of the ALF patients (three adults, one adolescent, and four pediatric). Since no suitable donor was found, LT could not be performed in two ALF patients, and these patients died. One of the two patients who received transplantation died on

Table 1. Demographic characteristics of Acute Liver Failure patients and healthy volunteers (control group).

Parameters	ALF patients (n=23)	Control group (n=43)	p
Age	20.9 ± 20.1	27.8 ± 7.3	.052
Sex (M/F)	10/13	24/17	.73
Etiology			
Cryptogenic	11		
Mushroom intoxication	6		
Wilson's disease	2		
Autoimmune hepatitis*	1		
Hepatitis A virus	1		
HELLP syndrome	1		
Hepatitis B virus	1		
Albumin (gr/dL)	3.1 ± 0.5	4 ± 0.3	.001
Arterial pH	7.4 ± 0.1	-	na
IMA (ABSU)	210.0 ± 40.3	183.4 ± 19.9	.001
IMAR	69.9 ± 19.7	46.6 ± 5.9	.001

ALF: Acute liver failure, M: Male, F: Female, HELLP: Hemolysis, elevated liver enzymes, low platelet, SLE: Systemic lupus erythramatosus, pH: Power of hydrogen, IMA: Ischemia modified albumin, ABSU: Absorbance units, IMAR: IMA/albumin ratio, *: Secondary to depakine.

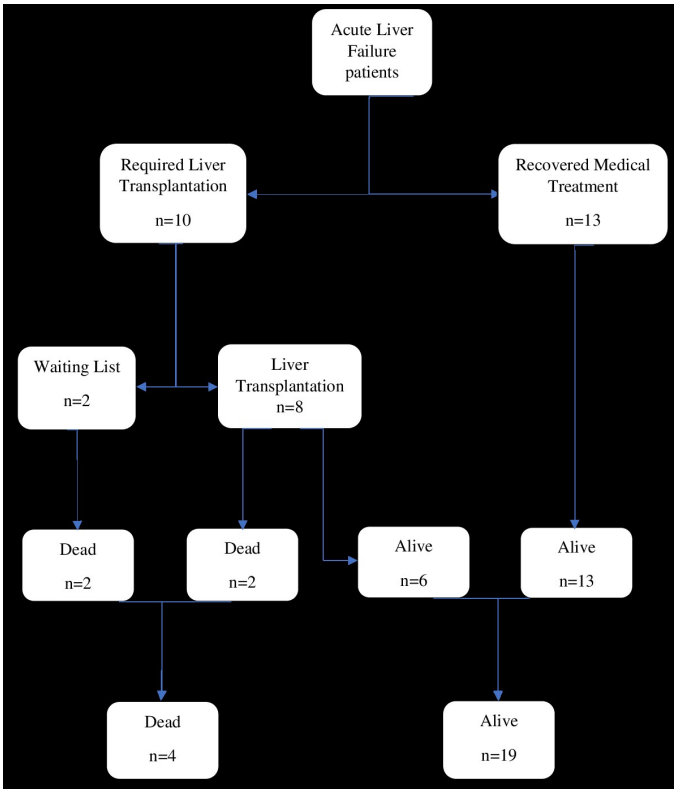

Figure 1. The clinical course of the 23 acute liver failure patients during follow-up.

Table 2. Calculation of cutoff values related to mortality for some quantitative variables using ROC curve analysis in Acute Liver Failure patients.

	Area	Std Error	Asymp Sig.	Cut-off values	Sensitivity (%)	Specificity (%)
IMA (ABSU)	0.855	0.081	.03	229.6	100	79
IMAR	0.855	0.095	.03	68.2	100	53
INR	0.789	0.097	.07	1.72	100	68
TBil (mg/dL)	0.804	0.102	.01	3.90	90	69
DBil (mg/dL)	0.785	0.105	.02	1.95	90	69
NH_3(µmol/L)	0.873	0.072	.003	222.5	80	77

IMA: Ischemia modified albumin, ABSU: Absorbance units, IMAR: IMA/Albumin ratio, INR: International normalization rate, TBil: Total bilirubin, DBil: Direct bilirubin, NH3: Ammonia.

the postoperative 22nd day of multiorgan dysfunction and the other because of hepatic vein thrombosis on the postoperative 2nd day. Pathology results were consistent with massive necrosis in all patients. Follow-up period was 9 (2-88) days for ALF patients and 12.5 (3-30) days for donor patients.

In the first stage of the study, 23 ALF patients and 43 healthy volunteers who underwent living-donor hepatectomy in the same time period were compared. There was no significant difference between the groups in terms of age and sex. IMA (p=0.001) and IMAR values (p=0.001) were found to be increased in ALF patients compared to healthy volunteers (Table 1). Cut-off values of the continuous variables with ROC analysis in ALF patients were calculated and listed as follows: IMA value (229.6), IMAR value (68.2), INR value (1.72), TBil value (3.9), DBil value (1.95), and NH3 value (222.5) (Table 2). Compared to patients who recovered by medical treatment, IMA value (p=0.006), IMAR value (p=0.04), INR value (p=0.001), TBil value (p=0.01), DBil value (p=0.01), NH3 value (p=0.01), HE grade (p=0.001), MELD score (≥30) (p=0.03), KCC (p=0.001), and mortality (p=0.02) were significantly higher in patients who required LT (Table 3). Sensitivity, specifity, PPV and NPV of IMA values, IMAR values, KCC and MELD score (≥30) used to predict the need for liver transplantation are shown in Table 4. In predicting mortality, while IMA values and KCC were successful, IMAR values and MELD score (≥30) failed (p=0.008, p=0.02, p=0.054, p=0.44; respectively, Table 5).

Discussion

About 8% of liver transplantations in Europe and the United States are performed for ALF [18,19]. In ALF, LT should be performed prior to the development of serious complications such as brain herniation, multiorgan system failure and sepsis. Unfortunately, there is only a very short window for LT, a procedure that needs to be performed at the optimal time, to avoid unnecessary transplants in patients who would spontaneously recover and to avoid transplantation in those who would not survive [20]. Therefore, some prognostic markers are used to differentiate patients who improved with medical treatment or need LT. KCC, MELD score, and Clichy / Villejuif criteria are the most commonly used criteria in the follow-up of ALF patients [3-5,15]. In one meta-analysis, the sensitivity of KCC has been found to be limited for patients with ALF [21]. In another a study, KCC has been found to more superior in the AALF subgroup compared to Non-acetominophen ALF subgroup [22]. Available prognostic scoring systems do not have a high predictive accuracy for death and survival without LT and therefore, it is not advisable to follow the guidelines completely [23].

This study is the first study to measure serum IMA and IMAR values in ALF patients. Study results showed that serum IMA and IMAR values were significantly higher in ALF patient compared to healthy volunteers. IMA and IMAR values predicted LT requirement in ALF patients, such as KCC and MELD (≥30) score. Sensitivity of IMA and IMAR values in predicting LT requirements were higher than KCC and MELD score (≥30) (70%, 80%, 30%, 30%; respectively, Table 4). Specifity of IMA values in predicting LT requirements were higher than KCC but lower than MELD score (≥30) (92%, 85%, 100%; respectively). Specifity of IMAR values in predicting LT requirements were lower than KCC and MELD score (≥30) (69%, 85%, 100%; respectively). While the sensitivity + specifity score of the IMA and IMAR values in predicting LT requirements was ≥140 (162, 149; respectively), the sensitivity + specifity score of KCC and MELD score (≥30) in predicting LT requirements was ˂140 (115, 130; respectively, Table 4). PPV of IMA and IMAR values in predicting LT requirements were higher than KCC but lower than MELD score (≥30) (88%, 67%, 60%, 100%; respectively). NPV of IMA and IMAR values in predicting LT requirements was higher than KCC and MELD score (≥30) (80%, 82%, 61%, 65%; respectively, Table 4). IMA values were found to better than KCC, IMAR values and MELD score (≥30) in predicting mortality. Sensitivity and NPV of IMA and KCC were found similar in predicting mortality (100.0%, 100.0%; respectively). Specifity and PPV of IMA values in predicting mortality were higher than KCC (79% vs 68%, 50% vs 40%; respectively). Sensitivity + specifity score of IMA values in predicting mortality was higher than KCC (179, 168; respectively).

O'Grady et al. have found that KCC has a sensitivity of 68% to 69% and specificity of 82% to 92% in the prognosis of ALF patients [3]. In a study of 91 patients with non-acetaminophen ALF (NAALF), sensitivity and specifity of KCC and MELD score (≥32 points) for mortality have been shown to be 79% to 88% and 71% to 71%, respectively [24]. In our study, sensitivity of IMA values in predicting LT requirement was found better than KCC

Table 3. Comparison of demographic, clinical and biochemical parameters of Acute Liver Failure patients who requiring liver transplantation and recovering with medical treatment.

Parameters	Requiring LT (n=10), (%)	Recovering MT (n=13), (%)	OR (95% C.I)	p
Age				.23
Mean ± SD	16 ± 21.3	24.5±19.3		
Median (Min-Max)	3.5 (1-59)	22 (1-62)		
Sex				.40
Male	3 (30.0)	7 (70.0)		
Female	7 (53.8)	6 (46.2)		
IMA (ABSU)			28 (2.4-323)	.006
<229.6	3 (20.0)	12 (80.0)		
≥229.6	7 (87.5)	1 (12.5)		
IMAR			9 (1.3-63)	.04
<68.2	2 (18.2)	9 (81.8)		
≥68.2	8 (66.7)	4 (33.3)		
INR				.001
<1.72	0 (0)	11 (100.0)		
≥1.72	10 (83.3)	2 (16.7)		
TBil (mg/dL)				.01
<3.9	1 (10.0)	9 (90.0)		
≥3.9	9 (69.2)	4 (30.8)		
DBil (mg/dL)				.01
<1.95	1 (7.7)	9 (92.3)		
≥1.95	9 (69.2)	4 (30.8)		
NH_3 (µmol/L)				.01
<222.5	2 (16.7)	10 (83.3)		
≥222.5	8 (72.7)	3 (27.3)		
HE Grade				.001
0-I	1 (7.7)	12 (92.3)		
II-IV	9 (90.0)	1 (10.0)		
MELD				.03
<30.0	7 (35.0)	13 (65.0)	NS	
≥30.0	3 (100.0)	0 (0)	NS	
King's College criteria				.001
Negative	0 (0)	13 (100.0)		
Positive	10 (100.0)	0 (0.0)		
ALT (IU/L)				.26
Mean ± SD	1667 ± 3240	1479 ± 1329		
Median (Min-Max)	289 (47-10213)	789 (20-3454)		
AST (IU/L)				.99
Mean ± SD	2655 ± 4819	1303 ± 1641		
Median (Min-Max)	343 (37-12227)	394 (42-4829)		
Outcome				.02
Alive	6 (31.6)	13 (68.4)		
Dead	4 (100.0)	0 (0)		

OR: Odds ratio, LT: Liver transplantation, MT: Medical treatment, C.I.: Confidence interval, SD: Standard deviation, Min: Minimum, Max: Maximum, IMA: Ischemia modified albumin, ABSU: Absorbance units, IMAR: IMA/Albumin ratio, INR: International normalization rate, TBil: Total bilirubin, DBil: direct bilirubin, NH3: ammonia, HE: Hepatic encephalopathy, MELD: Model for end-stage liver disease, ALT: Alanine transaminase, AST: Aspartate transaminase.

Table 4. Sensitivity, specificity, accuracy, positive and negative predictive values of four parameters used in predicting the need for Liver Transplantation for Acute Liver Failure patients.

Parameters	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	LR(+)	LR(-)
IMA (229.6)	70	92	83	88	80	8.8	0.33
IMAR (68.2)	80	69	74	67	82	2.6	0.29
MELD (30.0)	30	100	70	100	65	-	0.70
KCC	30	85	61	60	61	2.0	0.82

PPV: Positive predictive value, NPV: Negative predictive value, LR: Likelihood ratio, IMA: Ischemia modified albumin (ABSU), IMAR: IMA/Albumin ratio, MELD: Model for end-stage liver disease, KCC: King's College criteria.

Table 5. Relationship of IMA, IMAR, KCC, MELD scores with mortality in Acute Liver Failure patients.

Parameters		Mortality		p	Sensitivity (%)	Specifity (%)	Accuracy (%)	PPV (%)	NPV (%)	LR(+)	LR(-)
		Yes	No								
IMA (ABSU)				.008	100	79	83	50	100	4.76	0
	≥229.6	4	4								
	<229.6	0	15								
IMAR (ABSU)				.054	100	53	61	31	100	2.13	0
	≥68.2	4	9								
	<68.2	0	10								
MELD score				.44	25	89	78	33	85	2.27	0.84
	≥30	1	2								
	<30	3	17								
KCC				.02	100	68	74	40	100	3.13	0
	Positive	4	6								
	Negative	0	13								

PPV: Positive predictive value, NPV: Negative predictive value, LR: Likelihood ratio, IMA: Ischemia modified albumin, IMAR: IMA/Albumin ratio, ABSU: Absorbance units, MELD: Model for end-stage liver disease, KCC: King's College criteria.

and MELD score (≥30). Specifity of IMA values in predicting LT requirement was found better than KCC but worse than MELD score (≥30). Sensitivity and specifity of IMA values in predicting mortality were found better than KCC and MELD score (≥30). In studies with ALF patients, NPV and PPV of KCC were found 30-77% and 48-100%, NPV and PPV of MELD score (≥30) were found lowest 61% and 81% [25,26]. In other words, 23-70% of patients with low NPV, according to KCC criteria in ALF patients, either die or require LT, and 0-52% will live without LT [1]. Again, in ALF patients, 39% of the patients with low NPV, according to the MELD score, either die or require LT, and 19% will survive without LT. In our study, PPV of IMA and IMAR values in predicting LT requirement were found better than KCC and worse than MELD score (≥30), and NPV of IMA and IMAR values in predicting LT requirement were found better than KCC and MELD score (≥30). NPV of IMA values in predicting mortality was found better than MELD score (≥30), but it was found similar with KCC. PPV of IMA values in predicting mortality was found better than KCC and MELD score (≥30). In our study, IMA value more sensitively predicted the patients who would not need LT and would survive. The use of KCC, MELD and Clichy criteria only during patient admission might weaken the prognostic power of these systems [27]. Therefore; in KCC, MELD and Clichy / Villejuif criteria, patients are observed for 7-10 days for high predictive accuracy [28]. KCC uses 6 criteria for non-acetaminophen patients and 4 criteria for acetaminophen patients. Some criteria in KCC are as such: duration between jaundice and HE, history of acetaminophen or other drug use that may not be fully questioned. In Clichy / Villejuif criteria, factor V may not always be studied in all centres. Subjective, easy to use and remember, fast measurable, and the minimum number of criteria increases the strength of prognostic criteria. In our hospital, IMA result can be obtained in an average of three hours. In this study, we used single IMA and IMAR values at the time of admission for patients diagnosed with ALF. Since after IMA values increase rapidly, it decreases at the 6th hour and returns to normal at the 24th hour [7]. In ALF patients, a single IMA value at the time of admission predicted LT requirement, such as KCC and MELD score (≥30). A single IMA value at the time of admission predicted mortality better than KCC and MELD score (≥30). In our study, we showed that IMA and IMAR values can help predict mortality and LT requirement in ALF patients.

There are some limitations to our study. Our patient group was small and did not include acetaminophen-related ALF patients. Our patients consisted of both children and adults, and most patients were in the stage of hyperacute liver failure. Moreover, the number of patients with mor-

tality was low and this may lead to misinterpretation of the results.

Conclusion

The results of this study showed that IMA and IMAR values can be used as diagnostic, predictive and prognostic biomarkers for ALF patients. Randomized controlled trials are needed to assess the usability of IMA as a prognostic criterion in ALF patients.

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Data availability statement

Data derived from public domain resources.

Ethics approval

This prospective cohort study was approved by the local Ethics Committee (Inonu University Clinical Research Ethics CommitteeApproval No: 2017/117). All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Declaration of interest

The authors declares that they have no conflict of interest.

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