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Evaluation of platelet-albumin-bilirubin (PALBI) and systemic immune-inflammation (SII) indices in acute intracerebral hemorrhage

Akut intraserebral hemorajide platelet-albumin-bilirubin ve sistemik immun inflamatuar indekslerin değerlendirilmesi

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ABSTRACT

Background: We aimed to evaluate systemic immune-inflammation (SII) and platelet-albumin-bilirubin indices (PALBI), which are new inflammatory markers, in intracerebral hemorrhage (ICH) patients and reveal the relationship of these values with the disease and their effect on the short-term prognosis of ICH.
Materials and Methods: Our retrospective study included 245 patients who were diagnosed with ICH and 250 healthy volunteers.
Results: Compared to healthy volunteers, ICH patients had lower PALBI ($p=0.028$) and higher SII values ($p<0.01$). Additionlly while SII rate were higher, PALBI rate were lower in patient group with poor prognosis and severe ICH according to mRS (modified Rankin scale) and NIHSS (National Institutes of Health Stroke Scale) both at admission and at the end of 30 days. 45 of 245 patients died within 30 days. Similarly, the SII value in the group who died was statistically significantly higher than the survived group ($p<0.01$), while PALBI value was lower ($p<0.01$). Multivariate logistic regression analysis revealed that SII and PALBI values at admission were independent predictors of mortality within 30 days after ICH. Receiver operating characteristic curves showed that 1098.12 for the SII value and -4.11 for the PALBI value were optimal cut-off values to predict 30-day mortality after ICH.
Conclusions: The SII and PALBI indices, checked in early period in ICH patients, are closely related to the severity and prognosis of ICH patients both in the acute period and at the end of 30 days. Furthermore, they can be used as independent predictive markers to estimate 30-day mortality after ICH.
Keywords: Acute intracerebral hemorrhage, Platelet-albumin-bilirubin index, Systemic immune-inflammation index, Inflammation, 30- day mortality

ÖZET

Amaç: Biz bu çalışmada intraserebral hemoraji (İSH) hastalarında yeni inflamatuar göstergeler olan sistemik immun-inflamatuar indeks (Sİİ) ile platelet-albumin-bilirübin indeksi (PALBİ) ölçmeyi ve bu değerlerin hastalıkla ilişkisi ile İSH'nin kısa dönem prognozu üzerindeki etkisini ortaya koymayı hedefledik.
Materyal ve Metod: Retrospektif çalışmamıza İSH tanısı almış 245 hasta ile 250 sağlıklı gönüllü dahil edildi.
Bulgular: Sağlıklı gönüllülerle karşılaştırıldığında, İSH hastaları daha düşük PALBİ ($p=0.028$) ve daha yüksek Sİİ değerlerine ($p<0.01$) sahipti. Ayrıca mRS (modifiye Rankin skalası) ve NIHSS (National Institutes of Health Stroke Scale)'ye göre hem yatışta hem de 30 gün sonunda prognozu kötü ve şiddetli İSH olan hasta grubunda Sİİ oranı daha yüksek iken, PALBİ oranı daha düşüktü. 245 İSH hastasının 45'i 30 gün içinde ex olmuştu. Benzer şekilde, exitus olan grupta Sİİ değeri, hayatta kalan gruba göre istatistiksel olarak anlamlı derecede yüksek ($p<0.01$), PALBİ değeri ise daha düşüktü ($p<0.01$). Çok değişkenli lojistik regresyon analizi, başvuru sırasındaki Sİİ ve PALBİ değerlerinin İSH'den sonraki 30 gün içinde mortalitenin bağımsız öngörücüleri olduğunu ortaya koydu. Alıcı çalışma karakteristik eğrileri, Sİİ değeri için 1098.12'nin ve PALBİ değeri için -4.11'in İSH sonrası 30 günlük mortaliteyi tahmin etmek için optimal eşik değerler olduğunu gösterdi.
Sonuç: İSH hastalarında erken dönemde bakılan Sİİ ve PALBİ indeksleri, İSH hastalarının hem akut dönemde hem de 30 günlük ciddiyeti ve prognozu ile yakından ilişkilidir. Ayrıca, İSH sonrası 30 günlük mortaliteyi tahmin etmek için bağımsız öngörücü belirteçler olarak da kullanılabilirler.
Anahtar Kelimeler: Akut intraserebral kanama, Platelet-albümin-bilirubin indeksi, Sistemik immün-inflamasyon indeksi, İnflamasyon, 30 günlük mortalite

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INTRODUCTION

Intracerebral hemorrhage (ICH), accounting for approximately 9% to 27% of all strokes, is associated with high mortality and morbidity rates (Johnson, 2019). Injury after ICH can be grouped under two headings as primary and secondary injuries. While the primary injury includes mechanical injury to the tissues due to hematoma that occurs within a few hours after ICH, secondary injury is triggered via the leakage of products in blood into the brain parenchyma (Shao, 2019). These blood products are thrombin, hemoglobin, iron, and unconjugated bilirubin, and they are toxic to tissues (Huang, 2002). Unconjugated bilirubin (UCB) occurs during heme catabolism and can be detected within 8 to 12 hours in hematoma in animal ICH models (Clark, 2008). UCB is considered as a poor antioxidant because of its ingenuity to remove reactive oxygen products. Additoinally in vitro studies have shown that UCB induces astrocytes and microglia to release of proinflammatory cytokines (Farrera, 1994; Gordo, 2006). Furthermore, studies have revealed that after ICH, UCB increases edema and perihematomal neutrophil infiltration (Fernandes, 2007). Increasing preclinical proof has determined that inflammation following ICH possesses a significant part in secondary injury and is associated with perihematomal edema (Zhou,2014). Moreover, clinical laboratory studies indicate that inflammation can be used to predict the prognosis of ICH. Increased peripheral leukocyte counts are frequently observed in ICH. It is also known that platelet counts are associated with the extent of edema, which is important in determining the prognosis of ICH (Volbers, 2018). Ratios such as neutrophil/lymphocyte, lymphocyte/monocyte, and platelet/lymphocyte are used to indicate inflammation. Numerous studies have shown that these ratios can be useful in predicting clinical prognosis after ICH by demonstrating inflammation (Lattanzi, 2009; Zhang, 2018; Qi, 2018).

The systemic immune-inflammatory index (SII), calculated according to the formula of peripheral platelet count X neutrophil count/lymphocyte count, was used to determine the prognosis in many cancer types, especially hepatocellular cancer (Hu, 2014). Studies have demonstrated that it is superior to conventional indicators in predicting major cardiovascular events (Yang, 2020). In addition, in the acute ischemic stroke study, it was revealed that high SII value is not relevant to stroke severity (Hou, 2020). Recent studies have shown the worth of SII for both short-term and long-term outcomes after ICH (Trifan, 2020; Li, 2021). It is known that low albumin values at admission are associated with poor prognosis in many critical diseases. Likewise, early hypoalbuminemia is a poor prognostic factor in both ischemic stroke and ICH (Kaustubh, 2016). Bilirubin value was also found to be an independent indicator in acute ischemic stroke (Thakkar, 2019). Therefore, it is thought that the platelet-albumin-bilirubin index (PALBI) value based on the platelet count, albumin and bilirubin values, which is calculated to evaluate hepatocellular cancer, can be used as a marker in acute ischemic stroke (Hou, 2020). However, there is no study yet on the PALBI value in ICH patients, in which both albumin and bilirubin levels and platelet count play a tremendous part in the prognosis.

Therefore, our goal in this work is to compare the values of SII and PALBI in ICH patients and healthy volunteers of similar age and gender and reveal the relationship of these values with the disease and their effect on the short-term prognosis of ICH.

MATERIALS AND METHODS

Determination of the patient and control groups:

This retrospectively designed work contained 245 patients over the age of 18 who applied to Sivas Cumhuriyet University Faculty of Medicine Neurology Department between 01.01.2010-01.09.2021, and were diagnosed with ICH by performing computerized brain tomography (CBT) or cranial magnetic resonance imaging (cMRI) within the first 24 hours of the onset of their complaints and whose hematoma area was measured, and platelet, lymphocyte, neutrophil counts, and albumin and bilirubin levels were determined in the first 24 hours. There was no gender restriction among the patients.

Patients diagnosed with secondary ICH due to aneurysm, vascular malformation or tumor, chronic heart, lung or kidney failure, connective tissue disease, hematological disease, malignancy, acute/chronic inflammatory or autoimmune disease, coagulopathy, or thyroid disorder, and patients with a history of infection in the last 2 weeks, use of immunosuppressant, anticoagulant or anti-inflammatory drugs, and acute coronary syndrome, acute cerebrovascular disease or surgery in the last 3 months were not included in our study.

In addition to the age and gender information of the patients, chronic diseases (a medical history of chronic obstructive pulmonary disease (COPD), arrhythmia, diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), cerebrovascular or cardiovascular disease) and regular medication (antihypertensive, anti-obstructive, antidiabetic, antilipidemic…) and substance (cigarette/alcohol) use were also evaluated.

The ICH volume was determined with the ABC/2 method (ellipsoid) (Sims, 2009). While the SII value was calculated according to the peripheral platelet count X neutrophil count/lymphocyte count formula, the formula 2.02 X $\log_{10}$ bilirubin - 0.37 X ($\log_{10}$ bilirubin) - 0.04 X albumin - 3.48X $\log_{10}$ p + 1.01 X ($\log_{10}$ P) was used for the PALBI value (Lu,2019).

The National Institutes of Health Stroke Scale (NIHSS), modified Rankin score (mRS) and Glasgow coma score (GCS) of the patients at their first admission were noted in the system. The NIHSS and mRS values of the patients who were hospitalized within 30 days were similarly obtained from the hospital system. The scores of some of the patients whose hospitalizations were terminated during this period were evaluated 1 month later when they came to the outpatient clinic controls. For a small number of patients, the 30-day NIHSS and mRS values were calculated retrospectively by calling the phone numbers of the relatives of the patients registered in the system. Patients with mRS value between 0 and 3 were considered to have good prognosis, while those with a value between 4 and 6 were considered to have poor prognosis. For the NIHSS, scores below 5 were accepted minor ICH, scores between 6 - 9 were accepted moderate ICH, and scores above 10 were accepted severe ICH.

The causes of death (herniation due to intracranial edema, hydrocephalus, mechanical ventilator-associated pneumonia, urinary tract infection) of the patients who died during their hospitalization were recorded.

Patients of similar age and gender with our patient group, who applied to the Neurology outpatient clinic with the complaint of headache or dizziness were retrospectively reviewed, and 250 healthy individuals without comorbidity and regular drug use were included in our control group.

The ethics committee approval of our work was received from the Ethics Committee of Sivas Cumhuriyet University Medicine Faculty (2021-11/09).

Assessment of biochemical and hematological parameters:

Data obtained from measurements of blood samples taken at rest from the left antecubital vein into dry (for biochemical analysis) and EDTA tubes (for hematological tests) within the first 24 hours of ICH were used. While complete blood counts were performed on a Mindray BC-6800 device with a Diagon kit, neutrophil, lymphocyte and platelet counts were obtained from these measurements. Biochemical analyses (glucose, C-reactive protein (CRP), creatinine, alanine aminotransferase (ALT), albumin, total and direct bilirubin, aspartate aminotransferase (AST), high-density lipoprotein (HDL), total cholesterol, triglyceride levels, low-density lipoprotein (LDL)) were performed by a fully automatic nephelometric method using the kits of the same trademark on a Beckman Coulter AU5800 device (Beckman Coulter Inc, Hialeah, Florida).

Statistical method:

The data of our study were defined through the SPSS 23.0 program. The Kolmogorov-Smirnov test was benefited to state the normalized data distribution. The chi-square test was utilized to evaluate the data obtained by count. If the data met the parametric conditions, two different groups were examined by the independent samples t-test and three independent groups were analyzed by one-way analysis of variance and the outcomes were given as mean ± standard deviation. When the data did not ensure the parametric requirements, the Mann-Whitney U test was benefited to evaluate two different groups, the Kruskal-Wallis test was selected for three different groups and the values were stated as median (interquartile range). Spearman correlation analysis was employed to evaluate the relationships between quantitative variables. Univariate logistic regression analysis was performed to identify the effect of each different laboratory indicators of inflammation (neutrophil, lymphocyte, platelet count, CRP, albumin value, and SII and PALBI indices) on mortality after ICH. Baseline properties with $0.05 > p$ was involved to the multivariate logistic regression analysis. Receiver operating characteristic (ROC) curves were benefited to test predictive markers for 30-day mortality after ICH and determine the optimal cut-off value at which total sensitivity and specificity were the highest. To this end, the highest Youden index was taken. The error level was approved as $0.05>p$.

RESULTS

Our study contained 245 patients with ICH who applied to our clinic within the first 24 hours of their complaints and 250 healthy volunteers with similar gender and age to the patient group. While the female patients in the patient group accounted for 68.8%, this rate was slightly lower, 64% in the control group ($p=0.27$). Mean value of age of the patient group was 67.2±6.4, it was 67.0±17.1 in the control group ($p=0.57$). While the both groups were compared in the way of hematological and biochemical parameters, UCB was high in the patient group ($p=0.04$), while LDL and total cholesterol values and neutrophil count were higher in the control group ($p=0.021$, $p=0.045$, $p=0.024$, respectively). While the SII rate was statistically high in the patient group, the PALBI rate was lower ($p<0.01$, $p=0.028$, respectively) (Table 1). When the relationship between SII and PALBI values and hematoma volume in the patient group was evaluated, no statistically significant relationship was found

between these values (r=0.25; p=0.13; r=-0.16; p=0.09, respectively).

Table1. The comprassion of the baseline demographic/ clinical characteristics and laboratory findings of patient and control groups.

	Patient Group(n=245)	Control Group(n=250)	X^2	p
Female, n(%)	168 (68.6%)	160 (64%)	0.01	0.27
Age (mean±SD)	67.2±3.21	67.0±3.15		0.57
GCS (median) (IR)	10 (6-14)	-		
CHRONIC DISEASES				
COPD Presence, n(%)	34 (13.9%)	-		
HT Presence, n(%)	184 (76.7%)	-		
DM Presence, n(%)	93 (38%)	-		
Hyperlipidemia Presence, n(%)	101 (41.2%)	-		
Cerebrovascular or Cardiovascular disease Presence, n(%)	40 (16.3%)	-		
Cardiac rhythm disorder Presence, n(%)	28 (11.4%)	-		
REGULAR MEDICATION				
Antihypertensive drug, n(%)	130 (53.1%)	-		
Antiobstructive drug, n(%)	30 (12.2%)	-		
Antidiabetic drug, n(%)	84 (34.3%)	-		
Antilipidemic drug, n(%)	50 (20.4%)	-		
HABITS				
Tobacco use, n(%)	121 (49.4%)	68(27.2%)	0.12	0.03
Alcohol use, n(%)	2 (1.2%)	1(0.04%)	0.14	0.04
ICH PARAMETERS				
Volume	20 (8-37)			
Intraventricular extension, n(%)	136 (55.5%)			
Deep location, n(%)	155 (63.3%)			
Lobar location, n(%)	53 (21.6%)			
BIOCHEMICAL ANALYSIS				
Glucose (mg/dL) (mean±SD)	145.9±32. 7	141.7±21.1		0.28
Creatine (mg/dL) (median) (IR)	0.72 (0.5–0.9)	0.73 (0.5-1.0)		0.36
CRP (mg/dL) (mean±SD)	5.6±0.5	4.3±0.9		0.06
AST (U/L) (median) (IR)	20 (10-21)	15 (9-17)		0.12
ALT (U/L) (median) (IR)	31 (9-33)	26 (8-28)		0.21
Albumin (g/L) (mean±SD)	36.1±3.3	45±1.8		0.08
Total bilirubin (mg/dL) (median) (IR)	0.48 (0.1-0.56)	0.42 (0.2-0.44)		0.27
Conjugated bilirubin (mg/dL) (median) (IR)	0.19 (0.0-0.2)	0.21 (0.0-0.3)		0.34
Unconjugated bilirubin (mg/dL) (median) (IR)	0.29 (0.12-0.44)	0.21 (0.11-0.30)		0.04
HDL (mg/dL) (median) (IR)	47 (33-72)	56 (44-81)		0.061
LDL (mg/dL) (mean±SD)	85.3±39.4	67.8±19.3		0.021
TotalChol (mg/dL) (mean±SD)	186.9±39. 3	134.7±21.1		0.045
Triglyceride (mg/dL) (median)(IR)	95 (40-100)	71 (45-75)		0.061
COMPLETE BLOOD COUNT VALUES				
Hb (g/dL) (mean±SD)	14.6±1.3	14.1±1.4		0.21
WBC (10^9/L) (median) (IR)	8.1 (4.8–11.1)	8.3 (4.9–11.4)		0.32
Monocyte (10^9/L) (mean±SD)	0.58±0.093	0.51±0.087		0.048
Neutrophil (10^9/L) (mean±SD)	4.93±1.26	3.22±1.11		0.024
Platelet(10^9/L) (median) (IR)	271 (155-290)	211 (150-220)		0.07
Lymphocyte (10^9/L) (median) (IR)	1.1 (0.8-2)	2.1 (1-2.2)		0.06
RATES				
SII (median) (IR)	1210.53 (393.90-1528.66)	321.533 (254.20-454.67)		<0.01
PALBI (median) (IR)	-3.89 (-5.08–-0.58)	-1.72 (-3.18–-0.32)		0.028

All values are presented mean±standard deviation (SD), median value (IR) or number (%). **Abbreviations:** GCS: Glaskow coma Score; COPD: Chronic obstructive pulmonary disease; HT: hypertension; DM: diabetes mellitus; ICH: Intracerebral hemorrhage; CRP: C- reactive protein HDL: high density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDL: low density lipoprotein; TotalChol: total cholesterol; WBC: white blood cell; SII: systemic immune-inflammatory index; PALBI: platelet-albumin-bilirubin index.

Then, the patient group were separated into 2 regarding to the mRS values at admission and 30 days later (0-3: good prognosis, 4-6: poor prognosis), and they were divided into 3 according to the NIHSS value at admission and 30 days later (scores of 5 and below: minor ICH, scores between 6 and 9: moderate ICH, scores above 10: severe ICH) (Table 2). The albumin value was higher (p=0.04), and the neutrophil count and SII rate were lower in the patient group (n=198) with good prognosis according to the mRS at admission (p=0.03, p=0.02, respectively). Likewise, albumin value was higher in the patient group with minor ICH (n=65) according to the NIHSS value at admission (p=0.03), the neutrophil count and SII rate were elevated in the severe ICH group (n=50) (p=0.04, p=0.04, respectively), and the PALBI value was found to be lower in this group (p=0.03). According to both mRS and NIHSS values at the end of 30 days, albumin and PALBI values in the poor prognosis (n=50) and severe ICH groups (n=54) were statistically significantly lower (p=0.04, p<0.01, p<0.01, p=0.02, respectively), while neutrophil count and SII rate were found to be higher (p= 0.02, p<0.01, p=0.03, p<0.01, respectively) (Table 2).

Table 2. The comparison of values in patient groups according to admission and 30-day mRS and NIHSS scores.

	Admission mRS			**Admission NIHSS**			
	Good prognosis(n=198)	**Poor prognosis(n=47)**	**p**	**Minor(n=65)**	**Moderate(n=130)**	**Severe(n=50)**	**p**
Albumin(g/L) (mean±SD)	37.2±3.3	35.8±2.8	0.04	41.0±2.8	36.8±2.4	32.6±2.2	0.03
Total bilirubin (mg/dL) (median)(IR)	0.47(0.1-0.54)	0.48(0.3-0.56)	0.28	0.46(0.1-0.56)	0.48(0.2-0.55)	0.47(0.1-0.55)	0.45
Neutrophil (10^9/L) (mean±SD)	4.68±1.08	5.13±1.24	0.03	4.71±1.11	4.88±1.12	5.18±1.08	0.04
Platelet(10^9/L) (median)(IR)	268(155-288)	275(175-290)	0.11	255(155-280)	273(160-282)	278(160-290)	0.07
Lymphocyte(10^9/L) (median)(IR)	1.2(1-2)	1.09(0.8-1.9)	0.56	1.1(1-2)	1.2(1-1.9)	0.9(0.8-1)	0.23
SII(median)(IR)	978.28(393.90-1228.36)	1250.13(493.82-1528.66)	0.02	1120.35(393.90-1212.66)	1210.25(398.50-1338.76)	1310.18(493.90-1528.66)	0.04
PALBI(median)(IR)	-3.78 (-4.72 – -0.58)	-3.99 (-5.08 – -0.69)	0.34	-2.99 (-4.14 – -0.58)	-3.89 (-4.98 – -0.78)	-4.95(-5.08–-0.92)	0.03
	30-day mRS			**30-day NIHSS**			
	Good prognosis(n=195)	**Poor prognosis(n=50)**	**p**	**Minor(n=85)**	**Moderate(n=106)**	**Severe(n=54)**	**p**
Albumin(g/L) (mean±SD)	37.1±3.1	35.7±1.8	0.04	42.0±2.2	35.2±2.1	31.6±2.3	<0.01
Total bilirubin (mg/dL) (median)(IR)	0.46(0.1-0.53)	0.48(0.4-0.56)	0.17	0.41(0.1-0.56)	0.47(0.2-0.56)	0.49(0.3-0.56)	0.57
Neutrophil (10^9/L) (mean±SD)	4.53±1.07	5.26±1.23	0.02	4.71±1.11	4.72±1.12	5.98±1.08	0.03
Platelet(10^9/L) (median)(IR)	265(155-288)	278(175-290)	0.04	265(158-278)	271(163-282)	278(188-290)	0.12
Lymphocyte(10^9/L)(median)(IR)	1.2(1-2)	1.19(1-1.9)	0.68	1.1(1-2)	1.2(1-1.9)	1.0(0.8-1.8)	0.21
SII(median)(IR)	956.18(393.90-1128.36)	1276.11(499.92-1528.66)	<0.01	998.25(393.90-1233.16)	1220.31(398.50-1335.23)	1450.18(593.90-1528.66)	<0.01
PALBI(median)(IR)	-2.18 (-4.72 – -0.58)	-4.39 (-5.08 – -1.96)	<0.01	-2.95 (-4.14 – -0.58)	-3.78 (-4.98 – -0.87)	-4.99(-5.08–-2.12)	0.02

All values are presented mean±standard deviation (SD) or median value (IR). **Abbreviations:** mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; SII: systemic immune-inflammatory index; PALBI: platelet-albumin-bilirubin index.

Forty-five of the 245 patients in the patient group were exitus within a month. Considering the causes of mortality, herniation due to intracranial edema (n=12 (26.7%)) was the first, hydrocephalus was the second (n=11 (24.4%)), mechanical ventilator-associated pneumonia was the third (n=10 (22.2%)), and urinary tract infection (n=9 (20%)) was the fourth. When the neutrophil, lymphocyte and platelet counts, albumin, bilirubin levels, PALBI and SII values of the patients who died and the patients who survived within 30 days were compared, the neutrophil count was statistically remarkably

elevated in the group who died, and the platelet count and albumin level were n found to be statistically significantly lower (p=0.02, p=0.04, p=0.03, respectively). Again, the SII value in the group who died was statistically significantly elevated than the group who survived (p<0.01), while the PALBI value was lower (p<0.01).

Table 3. Multivariate regression analysis of factors related to mortality within 30 days after ICH.

	Beta	SE	x2	P	OR, 95%CI
Age	0.009	0.011	0.660	0.417	1.009/0.988-1.030
Volume	1.113	0.986	1.273	0.259	3.042/0.440-21.01
Intraventricular extansion	0.011	0.013	0.649	0.420	1.011/0.985-1.523
Admission mRS	0.301	0.112	6.152	0.041	1.137/1.011-1.453
Admission GCS	-0.045	0.265	0.029	0.032	1.256/1.022-1.652
Albumin	0.128	0.543	0.471	0.428	1.009/0.988-1.030
Neutrophil Count	0.228	0.134	2.893	0.092	1.256/0.966-1.634
SII	1.84	0.41	6.320	0.001	8.253/2.84-14.04
PALBI	-0.63	0.18	1.882	0.001	1.98/1.32-2.69

Abbreviations: SE: standard error; OR: odd ratio; CI: confidence interval; mRS: modified Rankin Scale; GCS: Glaskow Coma Scale; SII: systemic immune-inflammation index; PALBI: platelet-albumin-bilirubin index.

Univariate logistic regression analysis was performed to establish the effect of each different inflammation indicators (neutrophil, lymphocyte, platelet count, CRP, albumin value and SII and PALBI indices) and clinical findings (hematoma volume, intraventricular spread, deep localization, lobar localization), and scores (NIHSS, mRS and GCS at admission, and NIHSS, mRS and GCS 30 days later) on mortality within 30 days after ICH. Baseline properties with 0.05>p were evaluated in multivariate logistic regression analysis. Multivariate logistic regression analysis illustrated that the mRS and GCS scores (OR:1.137, 95% CI=1.011–1.453, p=0.041; OR: 1.256, 95% CI=1.022–1.652, p= 0.032, respectively), and the SII and PALBI values (OR: 8.253, 95% CI=2.842–14.043, p=0.001; OR: 1.918, 95% CI=1.325–2.691, p=0.001, respectively) at admission were different predictors of mortality within 30 days after ICH (Table 3). Receiver operating characteristic (ROC) curves showed that 1098.12 (AUC:0.852, 95% CI:0.788-0.929, p=0.01) for the SII value and -4.11 (AUC:0.665, 95%CI: 0.557-0.773, p=0.04) for the PALBI value were optimal cut-off values with the corresponding maximum Youden index to predict 30-day mortality after ICH (Figure 1).

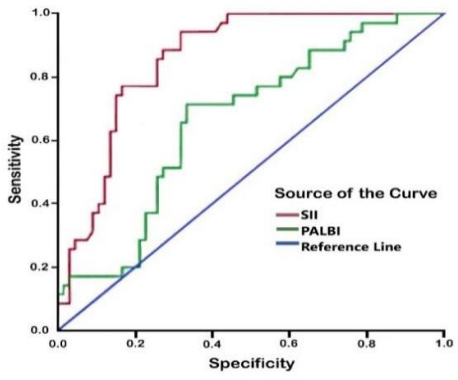

Figure 1. Receiver operating characteristic (ROC) curve analyses of the predictive power of SII (cut off value:1098.12, AUC:0.852, 95% CI:0.788-0.929, p=0.01) and PALBI (cut off value:-4.11, AUC:0.665, 95% CI: 0.557-0.773, p=0.04) for 30-day mortality after ICH. **Abbreviations:** SII: systemic immune-inflammatory index; PALBI: platelet-albumin- bilirubin index; AUC: area under the curve; CI: confidence interval; ICH: intracerebral hemorrhage.

DISCUSSION

In this study, we revealed that patients diagnosed with acute ICH had higher SII and lower PALBI indices compared to healthy control group. Moreover, while the SII value increased with the severity of ICH and worsening of the prognosis both in the acute period and after 30 days, the PALBI value decreased. Values above 1098.12 for the SII index and below -4.11 for the PALBI index were found to be independent predictors.

The reason for a close correlation between the SII rate consisting of neutrophil, lymphocyte, and platelet counts may be due to inflammatory changes that occur after ICH. Pathological investigations of ICH patients' brain determine that inflammation around the hematoma occurs as early as 5 hours after bleeding and does not disperse earlier than 3 days (Mackenzie, 1999). The hematoma occurring due to ICH induces the activation of complement and microglia, which increases especially tumor necrosis factor (TNF-α) and interleukin 1-b (IL-1b). Thus, the blood-brain barrier is disrupted, and edema occurs. Both the local proinflammatory environment and blood-brain barrier dysfunction increase the infiltration of peripheral leukocytes into the region that is related to secondary brain injury (Keep, 2012; Wang, 2010; Hua, 2000; Loftspring,2009). These inflammatory cells are detected 4 hours after ICH, peak around 2-3 days and begin to decline after 7 days (Wang, 2010). Animal studies have shown that after ICH, leukocytes in the brain are predominantly CD4+ lymphocytes of peripheral origin (Mracsko, 2014; Zhao, 2018). Early neutrophil infiltration after ICH is correlated with worse results, while sustained high neutrophil counts are related with possible milder neurological deficits via lactoferrin extrication and following iron sequestration (Sansing, 2011). The selective suppression of neutrophils in animal models of ICH led to a reduction in monocyte infiltration and functional improvement (Leira, 2004). After experimental ICH, lymphocytes were reached to peak during the four days, leading to increased neurological disruption, brain edema and be a detached indicator of death and morbidity (Sansing, 2003). In addition to leukocytes, increased early platelet levels evaluated 2-3 hours after admission probably contribute to the development of perihematomal edema by rising vascular permeability (Wagner, 2003). Usage of a combined inflammatory index such as the SII index might be more useful than using these values individually in evaluating the complex inflammatory response after ICH (Johnson, 2019). In support of this hypothesis, Trifan et al. found that the SII value measured in the early period in patients with spontaneous supratentorial ICH was an independent day, was closely related to the functional result in ICH patients lasting 90 days (Shao, 2019). In this work, elevated SII results were determined in the blood of the patient group on the 1st day compared to the control group. Similar to previous studies, the SII value was found to be higher in the poor prognosis and severe ICH group than in the good prognosis and minor ICH group. Based on our results, the SII value is an detached predictor of mortality within a month after ICH.

Within 24 hours of injury in ICH patients, activated membrane attack complexes break down the hematoma and extricate cytotoxic materials, containing free iron and heme (Keep, 2012; Loftspring, 2011). These cytotoxic substances are known to conduce to secondary brain injury after ICH (Wang, 2010; Hua, 2000). UCB, the product of heme catabolism, is hydrophobic, binds mainly to albumin. Low levels of UCB have a proinflammatory effect, and this effect decreases as the level rises (Gopal, 2010). While UCB can stimulate neutrophil collagenases' degranulation resulting in an increase in brain edema after ICH it was also shown that UCB causes the release of TNF-α and IL-1b from astrocytes and microglia, resulting in endothelial activation and extravasation of more leukocytes (Gordo, 2006; Fernandes, 2007). Albumin, which is the main component of plasma proteins, maintains microvascular permeability and oncotic pressure, preventing platelet aggregation. Hypoalbuminemia may occur due to liver or kidney dysfunction and nutritional deficiencies, or it may develop secondary to the presence of inflammatory cytokines or changes in their catabolism (Morotti, 2017). In a research carried out by Morotti et al., the correlation between low albumin levels and high 90-day mortality after ICH was revealed and explained by the effect of hypoalbuminemia on pneumonia and sepsis (Morotti, 2017). In another study conducted by Limaye et al., there was no correlation between hypoalbuminemia and mortality after ICH, and hypoalbuminemia was accepted as a modifiable factor with an effect on prognosis (Kaustubh, 2016). Adapted from the albumin-bilirubin (ALBI) rate and based on bilirubin, albumin and platelet counts, PALBI was used primarily in many types of cancer, including hepatocellular carcinoma (Johnson, 2015). It is thought that it may be a predictive marker with higher sensitivity and specificity in other inflammation models (Johnson, 2015). In a study conducted by Hou et al. on ischemic stroke patients, no correlation was found between the PALBI value and stroke severity due to insufficient consideration of the clinical severity of the parameters (Hou, 2020). Despite these works, there is no study yet conducted on ICH patients with the PALBI value based on bilirubin and albumin levels and platelet count, which have very important roles in determining both the acute and short-term prognosis for ICH, and our study is the first in this respect in the literature. Our work showed

that the PALBI rate obtained from the values measured in the first 24 hours of the onset of the disease was lower in ICH patients, while this value decreased further as the severity of ICH increased both in the acute period and at the end of the 30-day time-line. Also, our research revealed that the PALBI value was an independent predictor of ICH 30-day mortality development.
Unfortunately, the design of our study is retrospective, and the number of patients is relatively small due to its single-center nature. Therefore, causes of death and hematoma localization could not be performed. Moreover, only CRP values were used to evaluate inflammation, and other inflammatory markers (like IL-1b, TNF-α) could not be evaluated.

CONCLUSION

In conclusion, the SII and PALBI rates, which could be obtained with simple methods from the blood parameters routinely checked in the early period in ICH patients and therefore do not require additional costs, are closely related to the severity and prognosis of ICH patients both in the acute period and at the end of 30 days. Furthermore, both the SII and PALBI rates can be used as independent predictive markers to estimate 30-day mortality after ICH. To make further comments, there is a need for a more extensive, prospective, and multicenter study on this subject in the future.

It is also known that hypoalbuminemia is an indicator for detecting malnutrition but our patient group was not revised for malnutrition before they were included in the study.

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