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Can routine biochemical tests be a short-term prognostic biomarker in patients operated for chronic subdural hematoma?

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ABSTRACT

Objectives: The effect of routine blood biochemistry parameters on the short-term prognosis of patients with chronic subdural hematoma (CSDH) has not been evaluated in literature before. In this study, it was aimed to establish markers for determination of short-term prognosis using data of patients who were operated for CSDH.

Methods: During admission to hospital, data of patients including age, sex, antiaggregan and/or anticoagulant drugs usage, comorbidity, Glasgow Coma Scale (GCS) and Glasgow Outcome Scale scores were evaluated. Location and thickness of CSDH were recorded using brain CT or MR images. Blood leukocyte, neutrophil, lymphocyte, eosinophil, basophil, platelet count results, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio results, activated prothrombin time and INR values, serum glucose, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, sodium, potassium, blood urea nitrogen and creatinine level values were also recorded. Patients were divided into two groups according to CSDH located "unilaterally (n=19)" and "bilaterally (n=12)". In addition, patients with unilateral CSDH were divided into two groups as CSDH located at the "right hemisphere (n=6)" and "left hemisphere (n=13)".

Results: It was concluded that short-term prognosis of patients with unilateral or bilateral CSDH was similar. Correlation analysis showed no correlation between short-term prognosis and demographic, clinical and laboratory findings. However, *Likelihood Ratio* test revealed that GCS score could be a biomarker in order to predict short-term prognosis of these patients, albeit weak (X^2=6.138, p=0.046).

Conclusion: It was thought that GCS scores could be effective in predicting short-term prognosis in patients with CSDH but routine biochemistry laboratory parameters could not predict short-term prognosis of these patients.

INTRODUCTION

Chronic subdural hematoma (CSDH) is characterized by the presence of fluid trapped in the capsule or membrane in the subdural space its annual incidence is 5-8.2 / 100000 and generally seen in patients older than 65 years. [1,2]

Keywords
biochemistry,
chronic subdural hematoma,
prognosis

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Several studies have reported that the cause of bleeding is often previous head trauma, brain atrophy, advanced age, alcohol abuse and anticoagulant use.[2,3] The rate of surgical treatment in CSDH patients is 2.7-33% and burr-hole drainage is the most commonly used surgical technique.[4] However, there is still some controversial in literature in deciding the short-term prognosis in CSDH patients. It has been suggested in some studies that midline shift thickness and volume of fluid accumulated in the subdural space may be prognostic markers.[5] In addition, it has been emphasized that the lower the modified Rankin Scale scores may make the prognosis worse.[6,7] It has been also demonstrated in studies in which CSDH cases were evaluated immunologically that interleukin-6 and "*Vascular Endothelial Growth Factor (VEGF)*" values measured in hematoma fluid were found to be higher than serum values.[8-10] However, to the best of our knowledge, there is no study in literature to demonstrate the effect of routine blood biochemical parameters on short-term prognosis of patients with CSDH.

Therefore, in this study, demographic, clinical and routine laboratory biochemistry results of patients operated for CSDH were investigated and markers were established to determine short-term prognosis.

Materials and Methods

Materials

This retrospective study was conducted after the approval of the "Local Ethics Committee for Clinical Trials".

The hospital records were scanned using "*The International Statistical Classification of Diseases and Related Health Problems* (ICD-10)" coding (I62: Intracerebral hemorrhage (non-traumatic), other hemorrhage) I62.1: Extradural hemorrhage (non-traumatic); I62.9: Intracranial hemorrhage (non-traumatic), undefined; S06.5: Traumatic subdural bleeding). Patients who were treated surgically (i.e. burr-hole evacuation) between January 2017 and June 2019 after the determination of the chronic subdural hematoma on brain computed tomography (CT) and / or magnetic resonance imaging (MRI) were included in this study.

Patients with intracranial mass, patients with acute and / or subacute subdural hematoma, patients whose CSDH was evacuated by craniectomy or patients whose CSDH was not treated surgically but followed-up were excluded from the study. The patients were also excluded from this study if data were incomplete, if they had another intracranial bleed secondary to the trauma (e.g., epidural hematoma, subarachnoid hemorrhage etc), if they had been incorrectly coded with ICD-10, did not have subdural hematoma, or were in the pediatric age group (<16 years)

Patients were divided into two groups according to the subdural hematoma located "unilaterally (n = 19)" or "bilaterally (n = 12)". In addition, patients with unilateral subdural hematoma were divided into two groups as subdural hematoma located at the "right hemisphere (n = 6)" and "left hemisphere (n = 13)".

Patients were also divided into two groups according to age (<70 years and <70 years) or gender (female = 6, male = 25).

Methods

During admission to hospital, age, sex, antiaggregan and anticoagulant drugs use, history of comorbidity, Glasgow Coma Scale (GCS) scores and Glasgow Outcome Scale (GOS) scores of the patients were recorded. The location and thickness of the chronic subdural hematoma were evaluated using by brain CT or MR images. Blood leukocyte, neutrophil, lymphocyte, platelet, eosinophil, basophil count results, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) results, activated prothrombin time and "*International Normalized Ratio*" (INR) values, serum glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), sodium (Na), potassium (K), blood urea nitrogen (BUN) and creatinine level values were recorded.

The scales used in this study are listed below:

- Glasgow Coma Scale (GCS): This scale is used to determine and simply define the consciousness level and neurological status of patients.[11] The scale consists of three subscales (eye findings, speech content, motor response) and is evaluated over 15 points. The higher the patient's score, the better the state of well-being.
- Glasgow Outcome Scale (GOS): It is evaluated over 5 points and is used to identify patients' current neurological levels, levels of help / care, and awareness at the time of discharge from hospital.[12] As the

scale score increases, the patient's level of well-being increases.

Surgical procedure

After sedation anesthesia, frontal and parietal skin incisions of approximately 3 cm were performed in the supine position. Subsequently, burr-holes were opened to the cranium using a drill (Midas Rex®, USA). First, the cross-shaped incision was made to the dura mater in the frontal localized burr-hole and after the chronic hematoma content started to discharge, then cross-shaped incision was made to the dura mater in the parietal localized burr-hole and the hematoma content was completely removed. Subdural space was then irrigated with saline solution using foley catheter and then suction drain was left to the frontal region from the parietal burr-hole and the galea and skin were sutured anatomically before the operation was terminated (Figure 1). In patients with bilateral CSDH, a similar procedure was performed on the other side (Figure 2).

Biochemical analysis

Biochemical data of the study were obtained from the analysis of patients' venous blood samples which were taken during their admission to the hospital. Serum glucose (reference range 74-109 mg / dL), CRP (reference range 0.15-5 mg / dL), ALT (reference range 5-41 u / L), AST (reference range 5-40 u / L), creatinine (reference range 0.84-1.24 mg / dL) and BUN (reference range 17-43 mg / dL) level values were measured of the "immunoturbidimetric method" and levels of serum sodium (reference range 136-146 mmol / L) and potassium (reference range 3.5-5.1 mmol / L) were determined by ion selective electrode (ISE) method using commercial kits (Roche) and an analyzer device (Roche Diagnostic COBAS c501). Blood leukocyte (reference range 4400-11300 uL), neutrophil (reference range 1,100-9600 uL), lymphocyte (reference range 500-6000 uL), eosinophil (reference range 0-1000 uL), basophil (reference range: 0-300 uL) and platelets (reference range 150000-500000 uL) count values were determined using an analyzer (Mindray BC-6800, Shenzen, China). Activated prothrombin time (reference range 24.0-39.2 minutes) and INR (0.8-1.2) values were measured using an analyzer (ACLTOP700, USA).

Statistical analysis

Mann-Whitney U test was used to compare the nonparametric data between the groups. *Independent Samples t* test was used to compare the parametric data between the groups ($p < 0.05$). Spearman's rho *Correlation* test was used to determine the relationship between the parameters ($p < 0.05$). *Likelihood Ratio* test was used to find the best parameter to predict the short-term prognosis of the patients ($p < 0.05$).

Results

A total of 31 patients (female = 6, male = 25) were included in this study. Demographic, clinical and laboratory findings of all patients are summarized in Table 1 and Figure 3.

At the end of the medical past history, it was found that 3 patients had coronary artery disease, 5 had essential hypertension, 4 had diabetes mellitus, 4 had chronic obstructive pulmonary disease, 3 had a history of cerebral stroke, and 1 had atrial fibrillation. Six of the patients were using antiaggregant and two of the patients were taking anticoagulant drugs, but activated prothrombin time and INR values were within normal limits. It was observed that new onset left hemiparesis was detected in 5 patients, new onset right hemiparesis in 5 patients, new onset dysphasia in 3 patients, and new onset stupor in 4 patients at their admission to the hospital. At the end of the correlation analysis of all parameters of all patients, there was found no correlation between short-term prognosis and demographic, clinical and laboratory findings. However, at the end of *Likelihood Ratio* test, it was seen that GCS scores could be a good parameter in predicting the short-term prognosis of patients with CSDH ($X^2 = 6.138$, $p = 0.046$).

When patients were divided into two groups according to unilateral or bilateral localization of chronic subdural hematoma, comorbidity was found to be higher in patients with unilateral CSDH ($X^2 = 4.288$, $p = 0.038$). In addition, the thickness of right-sided hematoma was higher in patients with bilateral CSDH ($Z = -4.169$, $p < 0.001$). Other demographic, clinical and laboratory data was not different between the groups (Table 2). At the end of the correlation analysis applied to the parameters of each group, no study parameter was found to be correlated with the patient's neurological status and post-treatment short-term prognosis.

In addition, when the patients with unilateral CSDH were divided into two groups according to the hematoma located on the right side hemisphere or the left side hemisphere, the GOS scores of the patients with right side hemisphere hematoma were found to be lower (Z = - 2.156, p = 0.031), while platelet count values were higher (t = 2.243, p = 0.040). However, there was no statistical difference between the groups in terms of other demographic findings and laboratory values (Table 3, Figure 2). At the end of the correlation analysis of the parameters belonging to each group, no study parameter was found to be correlated with the patient's neurological status or postoperative short-term prognosis. However, at the end of the *Likelihood Ratio* test, it was concluded that GCS score (X^2 = 12.079, p = 0.002) and PLR values (X^2 = 8.578, p = 0.014) could be a biomarker for predicting the short term prognosis of the patients with unilateral CSDH.

When the patients were divided into two groups according to age distribution and gender, the demographic, clinical and laboratory findings of the patients was not statistically different between the groups and it was observed at the end of the correlation test and *Likelihood Ratio* test that these parameters could not be a predictive biomarker in determining the short-term prognosis of these patients.

VARIABLE		Mean±SD/ Number (%)/ Median (min-max)
Age (year)		72.19±14.62
Gender	Female	6 (19.4)
	Male	25 (80.6)
Comorbidity	No	16 (51.6)
	Yes	15 (48.4)
Drug usage	No	23 (74.2)
	Yes	8 (25.8)
Convulsion	No	29 (93.5)
	Yes	2 (6.5)
Glasgow Coma Scale score		15 (8-15)
Glasgow Outcome Scale score		5 (1-5)
Right sided hematoma thickness (mm)		15.61±11.21
Left sided hematoma thickness (mm)		12.39±11.59
Leukocyte (uL)		8726.79±3517.66
Neutrophil (uL)		6686±3199.51
Lymphocyte (uL)		1460±739.55
Monocyte (uL)		495±257.46
Eosinophil (uL)		121±121.42
Basophil (uL)		57±86.75
Platelet (uL)		244035±88146.97
Neutrophil-lymhocyte ratio		5.79±4.04
Platelet-lymphocyte ratio		195.75±91.86
C-reactive protein (mg/dL)		
Glucose (mg/dL)		130.04±44.14
Blood urine nitrogen (mg/dL)		52.80±29.53
Creatinine (mg/dL)		1.13±0.89
Sodium (mmol/L)		134.93±17.25
Potassium (mmol/L)		4.36±0.86
Alanine aminotransferase (u/L)		12.28±3.80
Aspartate aminotransferase (u/L)		23.93±13.73
International Normalized Ratio (INR)		1.15±0.23
Activated protrombine time		28.29±11.91

Table 1. It shows the demographic data and blood biochemistry findings of the patients (SD: standard deviation, min: minimum, max: maximum).

VARIABLE		UNILATERAL HEMATOMA Mean±SD/ Number (%)/ Median (min-max)	BILATERAL HEMATOMA Mean±SD/ Number (%)/ Median (min-max)	t/X²/Z	p
Age (year)		74.32±15.12	68.83±13.75	1.017*	0.317
Gender	Female	4 (12.9%)	2 (6.5%)	0.091†	0.763
	Male	15 (48.4%)	10 (32.3%)		
Comorbidity	No	7 (22.6%)	9 (29.0%)	4.288†	**0.038**
	Yes	12 (38.7%)	3 (9.7%)		
Drug usage	No	14 (45. 2%)	9 (29.0%)	0.007†	0.935
	Yes	5 (16.1%)	3 (9.7%)		
Convulsion	No	18 (58.1%)	11 (35.5%)	0.115†	0.735
	Yes	1 (3.2%)	1 (3.2%)		
Glasgow Coma Scale score		15 (8-15)	15 (8-15)	-0.709‡	0.478
Glasgow Outcome Scale score		5 (1-5)	5 (4-5)	-0.983‡	0.326
Right sided hematoma thickness		6.84±10.77	21.17±6.25	-4.169*	**<0.001**
Left sided hematoma thickness		16.42±13.09	14.33±7.71	0.499*	0.622
Leukocyte (uL)		8532±3892.01	9027±3001.62	-0.358*	0.723
Neutrophil (uL)		6535±3302.91	6918±3176.02	-0.304*	0.764
Lymphocyte (uL)		1415±872.74	1530±499.34	-0.392*	0.698
Monocyte (uL)		469±296.07	534±189.44	-0.647*	0.523
Eosinophil (uL)		140±126.54	91±112.14	1.047*	0.305
Basophil (uL)		53±69.02	62±112.43	-0.266*	0.792
Platelet (uL)		240823±110146.06	249000±39020.51	-0.235*	0.816
Neutrophil-lymhocyte ratio		5.99±3.64	5.49±4.76	0.312*	0.758
Platelet-lymphocyte ratio		203.06±100.54	184.45±79.89	0.516*	0.610
C-reactive protein (mg/dL)		14.50 (2.00-65.00)	2.58 (1.14-71.00)	-1.791‡	0.073
Glucose (mg/dL)		138.75±50.03	116.50±30.84	1.191*	0.247
Blood urine nitrogen (mg/dL)		57.85±32.12	44.21±23.56	1.167*	0.254
Creatinine (mg/dL)		1.20±1.03	1.02±0.61	0.497*	0.623
Sodium (mmol/L)		133.09±21.38	138.06±5.47	-0.716*	0.481
Potassium (mmol/L)		4.34±1.01	4.39±0.57	-0.145*	0.886
Alanine aminotransferase (u/L)		12.46±4.29	12.03±3.18	0.269*	0.790
Aspartate aminotransferase (u/L)		26.90±16.25	19.47±7.44	1.347*	0.191
International Normalized Ratio		1.18±0.18	1.12±0.29	0.666*	0.512
Activated protrombine time		30.39±16.48	25.98±1.49	0.841*	0.397

Table 2. This table shows the results of the demographic, radiographic and biochemical analyses of the patients according to the subdural hematoma located "unilaterally" or "bilaterally" (t: t score, X2: chi-square, Z: Z score, SD: standard deviation, min: minimum, max: maximum).

VARIABLE		RIGHT SIDED HEMATOMA Mean±SD/ Number (%)/ Median (min-max)	LEFT SIDED HEMATOMA Mean±SD/ Number (%)/ Median (min-max)	t/X²/Z	p
Age (year)		81.17±9.60	71.15±16.44	1.374*	0.187
Gender	Female	0.0%	4 (21.1%)	2.338†	0.126
	Male	6 (31.6%)	9 (47.4%)		
Comorbidity	No	3 (15.8%)	4 (21.1%)	0.652†	0.419
	Yes	3 (15.8%)	9 (47.4%)		
Drug usage	No	4 (21.1%)	10 (52.6%)	0.223†	0.637
	Yes	2 (10.5%)	3 (15.8%)		
Convulsion	No	6 (31.6%)	12 (63.2%)	0.487†	0.485
	Yes	0 (0.0%)	1 (5.3%)		
Glasgow Coma Scale score		15 (8-15)	15 (9-15)	-0.203‡	0.839
Glasgow Outcome Scale score		4.50 (1-5)	5 (4-5)	-2.156‡	**0.031**
Hematoma thickness (mm)		21.67±5.68	24.00±7.75	-0.657*	0.520

Leukocyte (uL)	9916±4933.55	7955±3456.79	0.943*	0.361
Neutrophil (uL)	7372±4350.28	6187±2921.63	0.662*	0.518
Lymphocyte (uL)	1640±754.62	1322±931.92	0.672*	0.512
Monocyte (uL)	628±280.93	403±287.41	1.477*	0.160
Eosinophil (uL)	198±146.70	116±115.43	1.232*	0.237
Basophil (uL)	52±45.50	54±78.58	-0.062*	0.952
Platelet (uL)	323800±127609.56	206250±85391.21	2.243*	**0.040**
Neutrophil-lymhocyte ratio	5.27±2.37	6.29±4.12	-0.514*	0.615
Platelet-lymphocyte ratio	225.66±130.63	193.6±590.38	0.586*	0.567
C-reactive protein (mg/dL)	16.00 (5-65)	13.00 (2-53.14)	-0.570‡	0.569
Glucose (mg/dL)	154.31±77.67	132.52±38.13	0.723*	0.484
Blood urine nitrogen (mg/dL)	67.47±34.68	53.85±31.69	0.787*	0.444
Creatinine (mg/dL)	1.01±0.17	1.28±1.23	-0.486*	0.634
Sodium (mmol/L)	140.04±3.54	130.19±25.09	0.858*	0.404
Potassium (mmol/L)	4.77±0.48	4.16±1.13	1.155*	0.266
Alanine aminotransferase (u/L)	14.42±5.54	11.68±3.74	1.087*	0.299
Aspartate aminotransferase (u/L)	21.28±8.03	28.95±18.25	-0.798*	0.439
International normalized ratio	1.24±0.26	1.16±0.14	0.772*	0.455
Activated protrombine time	29.27±5.74	30.81±19.44	-0.132*	0.898

Table 3. This table shows the results of demographic, radiographic and biochemical analyses of the patients according to the subdural hematoma located "right hemisphere" or "left hemisphere" (t: t score, X2: chi-square, Z: Z score, SD: standard deviation, min: minimum, max: maximum).

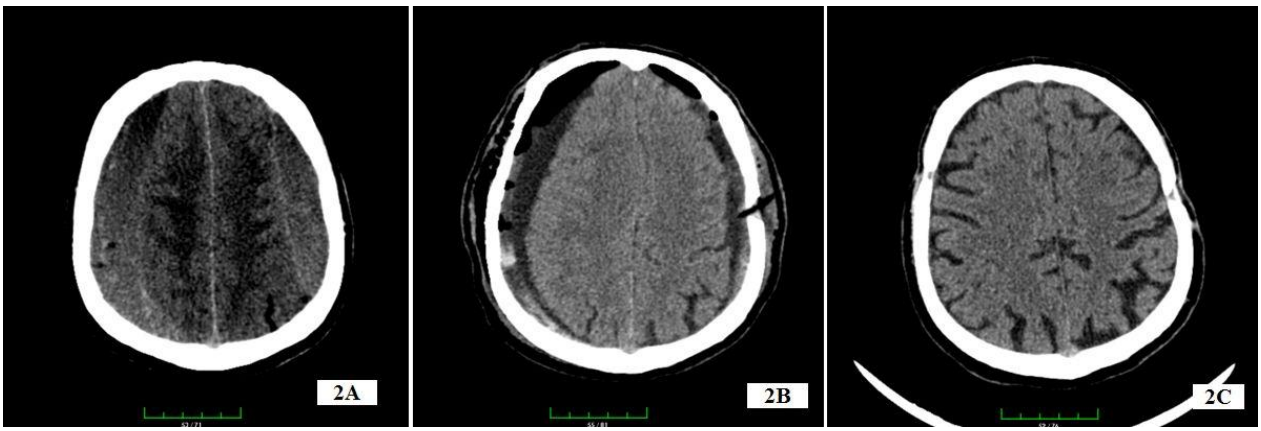
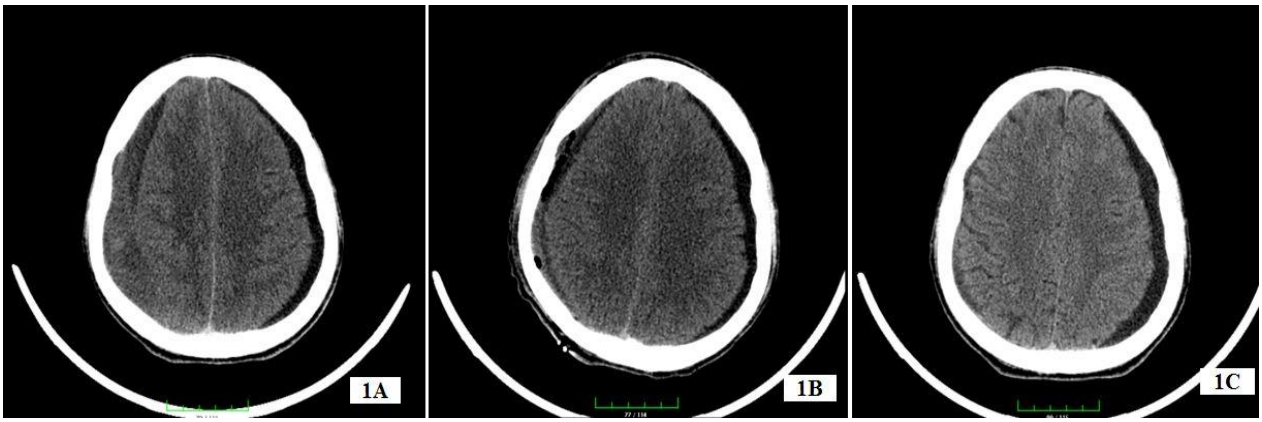


Figure 1. CT images of a patient with chronic subdural hematoma unilaterally; (1A) on admission to hospital; (1B) early postoperative image.

Figure 2. CT images of a patient with chronic subdural hematoma bilaterally; (2A) on admission to hospital, and (2B) early postoperative image and (2C) at discharge from the hospital.



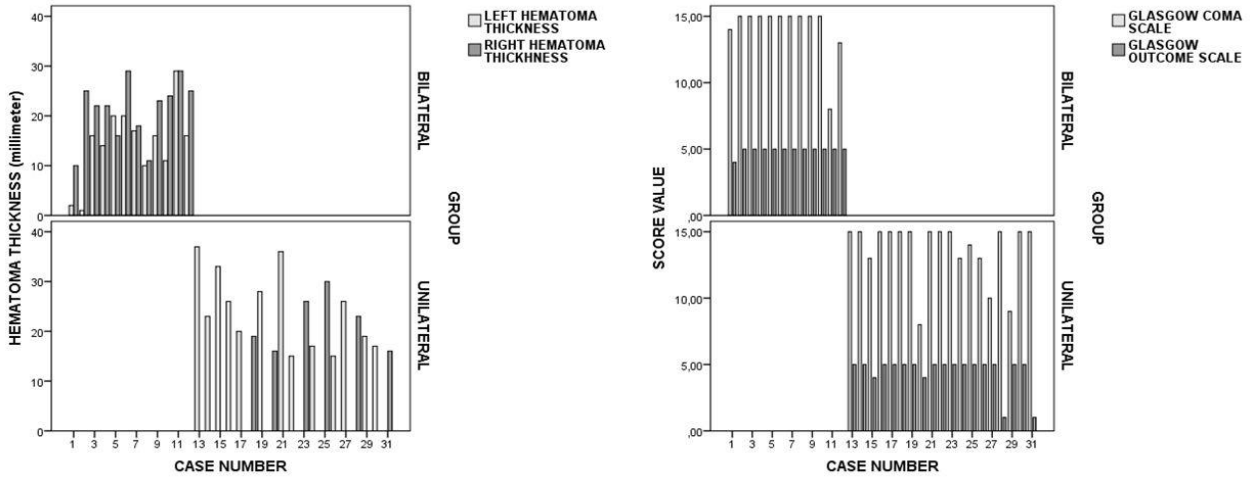


Figure 3. Graphics show the "Glasgow Coma Scale" and "Glasgow Outcome Scale" scores, chronic subdural hematoma thickness located at the left and right-side hemisphere of all patients.

Discussion

The aim of this study was to determine how its surgical treatment affected the short-term prognosis of the patient using their demographic, clinical and laboratory findings. For this purpose, GOS scores of patients included in the study were used to establish the short-term prognosis of these patients. Furthermore, in this study, it was aimed to determine short-term prognostic indicators in the patients with CSDH using simple, inexpensive and easily applicable blood biochemistry tests in almost every health institution.

It has been reported in the literature that the prognosis of the patient with intracranial hemorrhage who has a GCS score of 7 or less is worse.[13-15] In the studies conducted on this subject, the mean GOS score was found to be 1 point in cases with GCS score of 7 and below, while the GOS score was found in the range of 4-5 points in cases with GCS score above 7.[16-19] In addition, it has been shown that the advanced patient age and comorbidity such as vascular pathology, coagulation disorder and diabetes mellitus adversely affects the prognosis in patients with chronic subdural hematoma.[20] The most commonly preferred surgical treatment method in patients with chronic subdural hematoma is the burr-hole evacuation technique.[21-23] It has been reported that the mortality rate after surgical treatment is 10% in patients with CSDH, but in some studies, this rate can reach up to 32% and morbidity may occur in up to 20% of these patients.[23] In our study, it was found that the additional diseases detected in the study patients had no effect on the short-term prognosis but bilateral subdural hematoma was more common in patients with additional disease. In addition, it was found that anticoagulan and / or antiaggregant drug use did not affect short-term prognosis in these patients. With these findings it could be said that comorbidity and / or anticoagulan and / or antiaggregant drug use may not affect on the short term prognosis in surgically treated patients with CSDH. On the other hand, short-term prognosis was similar in patients with unilateral or bilateral CSDH.

Therefore, the presence of unilateral or bilateral CSDH had no effect on the short-term prognosis of these patients. However, in patients with unilateral CSDH, right-sided subdural hematoma was thought to adversely affect to the short-term prognosis. On the other hand, in our study, no significant correlation was found between the GCS scores of the patients at the time of hospital admission and GOS scores at the end of the treatment. In addition, no direct or indirect relationship was found between these GOS scores and other parameters including demographic or laboratory parameters. However, *Likelihood Ratio* test applied to the data of all patients revealed that the GCS scores of patients could be a parameter in predicting prognosis of these patients in the short-term period, albeit in a weak character.

As a matter of fact, 2 operated patients died in the hospital (mortality rate of 6.4%) despite the GCS score of 15/15 while 3 operated patients whose GCS scores were 8, 13, 14 were discharged from the hospital with the help of daily life (GOS score was 4, morbidity of 10.34%). Furthermore, all of the

remaining patients left the hospital with a GOS score of 5 regardless of GCS scores.

On the other hand, routine blood biochemistry results have been examined in studies conducted to determine the prognosis in patients with CSDH and it has been argued that hsCRP, albumin, prealbumin, INR elevations may be associated with poor prognosis but other routine blood biochemistry values have no effect on prognosis.[24] In our study, unfortunately, none of the simple routine blood biochemistry value had any effect on the short-term prognosis of the patients, postoperatively. However, it was concluded at the end of the *Likelihood Ratio* test that GCS scores and PLR values may be a biomarker in predicting the prognosis of these patients in the early postoperative period. As a matter of fact, two of the patients with unilateral subdural hematoma died postoperatively. One of these 2 patients had no additional disease and laboratory values were within normal limits. The other patient had chronic obstructive pulmonary disease and high leukocyte and lymphocyte count values. Both patients had no history of anticoagulant and / or antiaggregant drug use. Therefore, no parameter could be found to correlate the existing mortality with CSDH. In addition, GCS values were found to be similar in patients with CSDH which located on the right or left hemisphere and it did not show any statistical relationship with any study parameter. However, unilateral CSDH was thought to cause a relative increase in platelet count in patients and this could lead to an increase in PLR values. However, this increase in platelet count remained within the normal range of laboratory values.

Furthermore, GOS scores, platelet and lymphocyte count and PLR values were not different between groups and there was no direct or indirect relationship with the GOS scores and platelet and lymphocyte count and PLR values. Therefore these parameters could not be a biomarker in predicting the short-term prognosis of patients with CSDH.

Limitations

This study had some limitations. Firstly, the study was of a retrospective character and the number of patients included in the study was not sufficient because the patients' data was obtained from single health center. Secondly, patients with chronic subdural hematoma followed without performing surgery was not included in this study. Therefore, in this study, it could not be determined how chronic subdural hematoma itself affected the short-term prognosis of these patients. Thirdly, because ultra-structural methods such as histopathological and biochemical investigation of the hematoma and / or cerebrospinal fluid could not be included in this study, the effects of these investigation findings on short term prognosis could not be evaluated in this study. Finally, patients with chronic subdural hematoma evacuated by craniotomy were not included in the study. Therefore, the differentiation of the short term prognosis between the patients performed burr-hole evacuation and patients treated using craniotomy could not be discussed.

Conclusion

In conclusion, GCS values of patients with chronic subdural hematoma which were measured during the admission to the hospital could be weakly effective in predicting the short-term prognosis after surgical treatment of these patients. However, it was found that routine biochemical laboratory parameters were not successful in determining the short-term prognosis of these patients.

Conflict of interest and financial disclosure statements

The authors declare that they have no conflict of interest. There no any funding. They also declare that they have not engaged in any financial relationship with any company whose product might be affected by the research described or with any company that makes or markets a competing product.

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