ORIGINAL ARTICLE

The correlation between hemostatic blood parameters and sepsis in patients with gunshot wounds referred to a training and research hospital

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ABSTRACT

BACKGROUND: War injuries are different among the causes of trauma compared to cases in normal life. Patients with multi-trauma due to war injury are prone to develop infective complications such as sepsis or septic shock. Septic complications are one of the leading causes of late death in multi-trauma patients. Prompt, appropriate, and effective management of sepsis has been shown to prevent multiorgan dysfunction and improve mortality and clinical outcomes. However, there is no ideal biomarker to predict sepsis. The aim of this study was to determine whether there is a correlation between hemostatic blood parameters and sepsis in patients with gunshot wounds (GSW).

METHODS: This descriptive study was conducted as a retrospective analysis of patients who were referred to the adult emergency department of a training and research hospital between October 1, 2016, and December 31, 2017, with a diagnosis of GSW and who developed sepsis (n=56) and did not develop sepsis (n=56) during follow-up. Demographic data such as age, sex, and blood parameters obtained from the hospital information system in the emergency department were recorded for each case. The statistical difference in hemostatic blood parameters between the two groups with and without sepsis was evaluated with Statistical Package for the Social Sciences 20.0 program.

RESULTS: The mean age of the patients was 26.9±6.67. All of the patients were male. Of the patients who developed sepsis, 57% (n=32) were injured with improvised explosive devices (IEDs), 30% (n=17) were injured with firearms and when the anatomical injury sites were analyzed, 64% (n=36) had multiple injuries. In patients who did not develop sepsis, 48% (n=27) had IED, 43% (n=24) had GSW and 48% (n=27) had multiple injuries and 32% (n=18) had extremity injuries. Among the hemostatic blood parameters, platelet count (PLT), PTZ, INR, and Ca values showed a statistically significant difference between patients with and without sepsis, and when analyzed with the receiver operating characteristics curve, PTZ and INR showed the best diagnostic performance compared to the tested values.

CONCLUSION: Increased PTZ and INR values and decreased Ca and PLT values in patients with GSW may alert clinicians to sepsis and direct them to initiate or change antibiotic therapy.

Keywords: Blood parameters; gunshot wound; hemostatic; sepsis.

INTRODUCTION

Trauma is an important problem that causes morbidity and mortality in the whole population, especially in young adults.[1] Trauma patients account for 40% of all patients admitted to the emergency department in the USA and are reported as the primary cause of death in the 0–44 age group with 59%.[2,3] In Türkiye, trauma is the primary cause of death in the 0–40 age group.[4] Gunshot wounds (GSW) is one of the

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most important traumas affecting mortality and morbidity.[5] In the emergency department, trauma patients with serious GSW should be evaluated for airway obstruction, tension pneumothorax, massive internal and external bleeding, open pneumothorax, flail chest, cardiac tamponade, and sepsis and should be intervened rapidly.[6,7]

Sepsis is a life-threatening organ failure caused by the systemic manifestation of infection in the body and an inappropriate response to infection. Although there is insufficient data on sepsis rates in Türkiye, sepsis causes more than six million deaths worldwide every year. Specialists emphasize the need for rapid detection and treatment to reduce the number of deaths.[8-10] Despite the application of optimal treatments, the mortality rate of septic shock is approximately 70%.[11] Extensive tissue damage and contamination in GSW predispose patients to infection.[12] Infection and subsequent development of sepsis in these patients are highly fatal. Predicting the onset of sepsis and thus providing early treatment can prevent the development of sepsis in patients and reduce mortality. There is no gold standard test for the diagnosis and prognosis of sepsis and biomarkers such as procalcitonin test (PCT) and C-reactive protein (CRP) levels are used.[13,14] However, more rapid, reliable, and cost-effective biomarkers are needed. Therefore, the aim of this study was to determine whether there is a correlation between hemostatic blood parameters and sepsis status in patients with GSW.

MATERIALS AND METHODS

This study is a retrospective descriptive study in which the correlation between the hemostatic blood parameters at the time of admission and the sepsis status that developed in the follow-up of patients referred to the Adult Emergency Department of Biruni University between October 1, 2016, and December 31, 2017, with the diagnosis of GSW was examined.

In patients who were referred to the emergency department within the specified period and who were over the age of 18, the records created by entering the International classification of diseases10 Y22-Y25 GSW diagnosis codes into the hospital electronic record system, the examination files in the emergency department and the hospitalization files of the patients who were hospitalized and followed up were scanned. In total, data from 216 patients were obtained. Of these patients, 114 were excluded from the study due to missing files and data in the clinics or computers. The study included 56 patients who were diagnosed with sepsis on arrival to the emergency department or during clinical follow-up and 56 patients who were not diagnosed with sepsis.

Whole blood, PCT, CRP, and sedimentation values obtained from the patients when they came to the emergency department were obtained from the hospital record system. Whole blood parameters were analyzed in the biochemistry laboratory with Symex brand XN-1000 model and Beckman Coulter brand UniCel DxH800 models, CRP parameter was analyzed with Beckman Coulter brand AU 480 and Au 680 models, sedimentation parameter was analyzed with Berchun brand SDM-60 model and Sistan Diagnosis and Treatment Systems LTD. STI. brand ESR-120 model and PCT parameter were analyzed with the Getein Biotech Inc brand Getein 1600 model. white blood cell (WBC), RBC, Hgb, Htc, neutrophil, and lymphocyte values were analyzed as non-hemostatic blood parameters. NLR, which is the number of neutrophils divided by the number of lymphocytes, was also included in the evaluation. The platelet count (PLT), PDW values, and PLR obtained by dividing PLT by lymphocyte count, serum Ca, and PTZ-INR values were analyzed as hemostatic blood parameters. Ca parameter was analyzed in the biochemistry laboratory using Beckman Coulter brand AU 480 and Au 680 models, PTZ-INR parameters were analyzed using Trinity Biotech brand Amax-200 model and Sysmex brand CS2500 models.

Patient data obtained within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences for Windows 20.0 package program (IBM Corporation, Armonk, NY, USA). Frequency and percentage for discrete data, mean ± standard deviation, median (median), minimum, and maximum for continuous data were given as descriptive values. The Kolmogorov–Smirnov test was applied to evaluate whether the continuous variables fit the normal distribution. Mann–Whitney U-test and independent sample t-test were used to compare the differences between the groups. The diagnostic decision-making properties of PLT, Ca, PTZ, and INR values in predicting sepsis positivity were analyzed by receiver operating characteristics (ROC) curve analysis. These values were also tested for their success in predicting sepsis positivity using logistic regression analysis. $P < 0.05$ value was accepted as significant.

RESULTS

All 112 patients in the study were male. The mean age of the individuals was 27.0±6.6 years and the oldest group was between the ages of 18 and 24 years (42%, n=47). When the patients who developed sepsis (n=56) were examined, it was found that 57% (n=32) were injured by improvised explosive device (IED), followed by GSW with a rate of 30% (n=17). When the anatomical injury sites were examined, it was found that 64% (n=36) had multiple injuries. When the type of injury and anatomical injury site were examined together, it was observed that 48% (n=27) of the patients had multiple injuries due to IED.

It was found that 48% (n=27) of the patients who did not develop sepsis were injured by IED and 43% (n=24) by GSW. When the anatomical injury sites were examined, it was found that 48% (n=27) had multiple injuries and 32% (n=18) had extremity injuries. When the type of injury and anatomi-

Table 1. Descriptive statistical results for laboratory values and evaluation criteria

Variables	Average	Median	Standard Deviation	Minimum	Maximum
PLT (×103 Cϵ)	206.9	184.5	128.284	39.0	752.0
PDW (%)	11.7	11.5	2.298	8.0	20.6
NLR (%)	10.0	7.7	8.025	1.1	40.5
PLR (%)	170.1	139.2	105.935	28.3	659.6
PCT (ng/mL)	11.5	1.5	21.952	0.0	100.0
Ca (mg/dL)	8.1	8.2	0.839	5.4	9.7
WBC (×103 Cϵ)	12.6	10.9	5.518	3.1	38.1
RBC (×106 /µL)	4.1	4.0	0.911	2.4	6.9
HGB (g/dl)	11.8	11.6	2.592	6.9	20.3
HTC (%)	34.3	33.7	7.343	20.8	55.8
NEU (%)	10.2	8.8	5.327	2.3	33.7
LYM (%)	1.4	1.2	0.772	0.4	4.1
PTZ (sn)	17.9	17.5	2.806	13.0	27.7
INR	1.6	1.4	1.443	0.958	16.4
CRP (mg/L)	95.9	89.5	73.757	0.4	219.6
Sedimentation	42.3	33.0	32.502	2.0	115.0
Age (year)	26.9	25.0	6.676	19.0	64.0
Dispatch time (days)	2.7	1.0	3.223	1.0	21.0
Glasgow coma scale	11.4	14.0	3.976	3.0	15.0
Respiratory rate	23.1	23.5	6.580	15.0	40.0
Systolic blood pressure (mmHg)	103.0	100.0	28.704	47.0	148.0
Diastolic blood pressure (mmHg)	55.7	52.0	19.773	23.0	90.0

PLT: Platelet count, PCT: Procalcitonin test, CRP: C-reactive protein, WBC: White blood cell

cal injury site were examined together, it was found that 27% (n=15) of the patients had multiple injuries due to IED and 18% (n=10) had extremity injuries due to GSW.

Table 1 shows the descriptive statistical results of the participants' laboratory values and evaluation criteria (Table 1).

Age, dispatch duration, GCS, and vital signs of individuals based on sepsis status were examined (Table 2). Accordingly, while there was no significant difference between the groups in age and dispatch duration (P>0.05), there was a statistically significant difference in respiratory rate and systolic and diastolic blood pressures (P<0.05).

It was found that there was a statistically significant difference between the groups in laboratory parameters except for WBC and neutrophil scores (Table 3) and in PLT, Ca, PTZ, and INR scores among hemostatic blood parameters (Table 4) (P<0.05).

When Table 5 is examined, the "area under the curve (AUC)" value shows the AUC for the relevant parameter. An AUC value of 0.5 is considered the worst case and indicates that the performance of the test is poor.[15] When the table values are examined, it is observed that PTZ and INR values are above the cutoff point of 0.6 and are more successful markers for sepsis positivity than other parameters (Fig. 1).

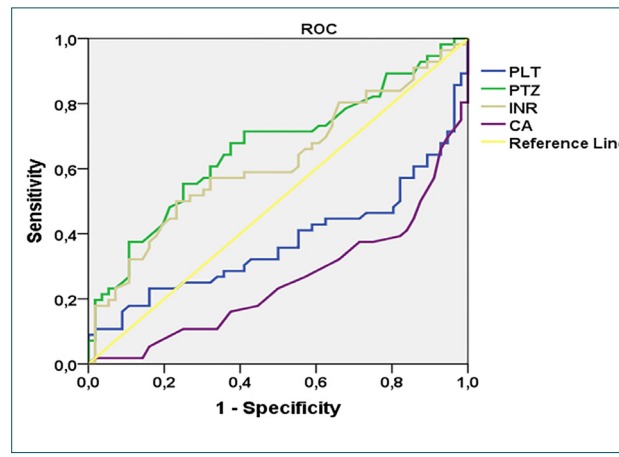

Figure 1. Receiver operating characteristics curves of laboratory values of individuals

Table 2. Evaluation of age, dispatch duration, GCS, and vital signs of individuals based on sepsis status

Variables	Median		P*
	Sepsis positive (n=56)	Sepsis negative (n=56)	
Age (year)	26.0	24.5	0.387
Dispatch time (days)	1.0	1.5	0.522
GCS	7.5	15.0	0.000
Systolic blood pressure (mmHg)	77.5	130.5	0.000
Diastolic blood pressure (mmHg)	37.0	74.5	0.000
Respiratory Rate	28.0	16.5	0.000

*Mann–Whitney U-test

Table 3. Evaluation of laboratory parameters of individuals based on sepsis status

Variables	Median		P*
	Sepsis positive (n=56)	Sepsis negative (n=56)	
WBC (×103 Cϵ)	11.9	10.7	0.140*
RBC (×106 /µL)	3.70	4.41	0.000**
HGB (g/dl)	10.83	12.89	0.000**
HTC (%)	31.44	37.17	0.000**
Neutrophil	9.6	7.6	0.046*
Lymphocyte	1.1	1.4	0.158*
NLR (%)	9.1	5.7	0.036*
CRP (mg/L)	146.4	42.8	0.000*
PCT (ng/mL)	7.2	0.5	0.000*
Sedimentation	52.0	18.5	0.000*

*Mann–Whitney U-test **Independent Sample T-test. CRP: C-reactive protein; PCT: Procalcitonin test; WBC: White blood cell

Table 4. Evaluation of hemostatic blood parameters of individuals based on sepsis status

Variables	Median		P*
	Sepsis positive (n=56)	Sepsis negative (n=56)	
PLT (×103 Cϵ)	142.0	201.5	0.022
PLR (%)	140.9	135.9	0.633
PDW (%)	11.5	11.4	0.188
Ca (mg/dL)	7.7	8.5	0.000
PTZ (sn)	18.4	16.7	0.003
INR	1.5	1.3	0.029

*Mann–Whitney U-test. PLT: Platelet count

Table 5. ROC curves of laboratory values of individuals

Laboratory values	PLT (×103 Cϵ)	PTZ	INR	Ca (mg/dL)
AUC	0.374	0.663	0.620	0.257
SE	0.055	0.052	0.053	0.047
P-value	0.022*	0.003*	0.029*	0.000*
The confidence interval of 95%				
Lower limit	0.267	0.561	0.515	0.166
Upper limit	0.481	0.764	0.725	0.348
Limit value	184.50	17.50	1.40	8.30
Sensitivity (%)	41.1	64.3	55.4	32.1
Specificity (%)	41.1	64.3	67.9	33.9

*P<0.05. PLT: Platelet count; ROC: Receiver operating characteristics;, AUC: Area under the curve.

Table 6. Logistic regression comparison of sepsis positivity based on hemostatic blood parameters

Risk factor	OR (95% CI)	P
PLT (×103 Cϵ)	1.003 (1.000–1.007)	0.070
PTZ	1.874 (1.012–3.470)	0.046*
INR	0.010 (0.000–4.354)	0.138*
Ca (mg/dL)	0.237 (0.115–0.488)	0.000*

*P<0.05. PLT: Platelet count

Table 6 shows the results of the logistic regression analysis performed to investigate the values affecting the sepsis positivity of individuals. Hosmer-Lemeshow test was used for the fit of the model and since P=0.372 > 0.05, the model was accepted to be compatible. As a result of the test, since P<0.05 for PTZ, INR, and Ca values, these parameters were determined to be significant in terms of sepsis positivity. A one-unit change in PTZ value affects sepsis positivity 1. 8 times, a one-unit change in INR value 0.01 times, and a one-unit change in Ca value 0.2 times.

DISCUSSION

In developed countries, trauma is the most common cause of death in people younger than age 44, and multi-traumas frequently occur due to traffic accidents.[16] In Türkiye, the frequency of traumas related to GSW has increased due to terrorist incidents that have been ongoing for nearly 40 years.[17] Patients with multi-trauma in GSW are prone to develop infective complications such as sepsis, severe sepsis, or septic shock.[18] Septic complications are one of the leading causes of death after 1 week in multi-trauma patients.[19] Early diagnosis is necessary for the effective and appropriate use of antibiotics in sepsis. It has been reported that each 1-h delay in antibiotic administration after the development of hypotension in septic patients increases mortality by 7.6%.[20] The use of a biomarker is important for the early differentiation of the septic or non-septic course of patients. The ideal biomarker should have high sensitivity, specificity, and reliability, be easy to test, give rapid results and be cost-effective.[21] Considering the fact that whole blood and coagulation parameters are inexpensive, easy, and fast, in this study, we examined the correlation between sepsis status and hemostatic blood parameters by comparing the sepsis group with the non-sepsis group in patients with GSW.

Trauma is more common in young people and is associated with factors such as age, sex, and geographical region. In a study on trauma patients, Regnier et al. reported that 71.5% of the patients were male and 28.5% were female; Jo et al. reported that 69.2% were male and 30.8% were female; Odom et al. reported that 67.2% were male and 32.8% were female and found that the female to male ratios were similar.[22-24] Regarding sex in sepsis cases, Nguyen et al. reported 51%, Kim et al. reported 55.5%, and Singer et al. reported 54% of sepsis cases as male.[25-27] In studies conducted in Türkiye, Gursoy et al. reported 51% of the patients with sepsis as male, and Sonmez et al. reported 60.5% as male.[11,28] In our study, 112 patients participated and all of them were male. We believe that this is because the cases included in our study consisted of soldiers and police officers working in operational units.

Although many biomarkers can be used to diagnose sepsis, none of them have sufficient sensitivity or specificity to be used alone in clinical practice.[29] Despite the fact that PCT and CRP are the most commonly used biomarkers in this context, their effectiveness in differentiating sepsis from other inflammatory conditions or in determining prognosis is limited.[30] In our study, PCT and CRP results of patients who developed sepsis were statistically significantly higher than those without sepsis. In a similar study conducted on trauma patients, a significant increase in blood PCT levels was reported in patients who developed sepsis after trauma.[30] In studies by O'Connor et al. and Egger et al., no significant

relationship was found between PCT levels and sepsis.[31,32] Hensler et al. reported that PCT levels predicted multiorgan dysfunction but failed to predict sepsis.[33] Some previous studies show that CRP levels cannot predict specific septic complications in trauma patients.[34,35]

In a study by Francois et al., it was thought that thrombocytopenia may have developed due to hemophagocytosis in patients with sepsis.[36] In their retrospective study, Aydemir et al. found that thrombocytopenia occurred in 151 of 214 sepsis patients during intensive care unit hospitalization and that there was a relationship between thrombocytopenia and mortality in the 1st days of follow-up.[37] Similarly, in a study conducted by Vanderschueren et al. on patients hospitalized in the intensive care unit due to sepsis, it was found that mortality was higher in patients with a PLT of 150.000 or less and in patients with more than a 50% decrease in PLT during intensive care unit follow-up. It was found that there was a relationship between PLT and mortality in sepsis patients and it was statistically more significant when compared with other factors affecting mortality.[38] Similarly, in our study, the PLT values of patients with sepsis were statistically significantly lower than those without sepsis.

Approximately 28% of patients with multi-trauma have developed dysfunction in coagulation processes by the time they reach the emergency department.[39] This is usually due to the dilution of blood by IV fluids used during resuscitation. Coagulopathy increases mortality by 3.5–5 times, and the combination of this condition with hypothermia and acidosis is called the triad of death.[40] Simmons et al. first described the relationship between bleeding and coagulopathy and morbidity during the Vietnam conflict.[41] In the late 1970s, prothrombin, partial thromboplastin, and bleeding time were found to be associated with prolonged coagulopathy in patients receiving massive transfusion.[42] Rossaint et al. stated that INR, aPTT, fibrinogen level, and platelet values should be measured routinely.[43] In our study, we found a statistically significant difference in PTZ and INR values. Furthermore, when hemostatic blood parameters were analyzed by the ROC curve, we found that PTZ and INR values were more successful markers for sepsis positivity than other parameters. Furthermore, when hemostatic blood parameters were analyzed by logistic regression analysis, it was observed that a one-unit change in PTZ value affected sepsis positivity 1.8 times, and a one-unit change in INR value affected sepsis positivity 0.01 times.

Hypocalcemia is common in patients with sepsis, major trauma, or pancreatitis. It has been found to be associated with mortality and to have prognostic value in critically ill patients.[44] Inadequate secretion or inhibitory effect of parathyroid hormone, decreased Vitamin D3 production, and both intracellular and extracellular calcium accumulation have been suggested to be involved in the pathogenesis of hypocalcemia.[45] Vivien et al. reported a progressive increase in mortality with decreasing Ca levels in patients with multi-trauma. Hypocalcemia has been found to be associated with mortality with low GCS score and large transfusion amount received after hospital arrival.[46] In our study, similar to previous studies, a statistically significant difference was found in Ca values between the two groups. Furthermore, when hemostatic blood parameters were analyzed by logistic regression analysis, it was observed that a one-unit change in Ca value affected sepsis positivity 2 times.

The limitations of the study are that the study was retrospective and single-centered and all participants were male.

Conclusion

As a result, we found statistically significant differences in PLT, PTZ, INR, and Ca values between patients with and without sepsis. When we analyzed the hemostatic blood parameters by ROC curve, PTZ, and INR showed the best diagnostic performance among the tested values. According to the logistic regression analysis we applied, it was observed that a one-unit change in PTZ value affects sepsis positivity 1.8 times, a one-unit change in INR value 0.01 times, and a one-unit change in Ca value 0.2 times. Based on the data obtained in our study, increased PTZ and INR values and decreased Ca and PLT values in patients with GSW may alert clinicians to sepsis and direct them to initiate or change antibiotic therapy. These four biomarkers are fast, cheap, and easy to detect. Considering all these, it may be useful to routinely study whole blood, PTZ, INR, and Ca values when encountering cases of GSW. However, we believe that prospective studies should be performed in larger patient groups.

Ethics Committee Approval: This study was approved by the University of Health Sciences Clinical Research Ethics Committee (Date: 06.02.2018, Decision No: 46418926

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: D.C., M.E.; Design: D.C., M.E.; Supervision: M.E.; Fundings: D.C., M.E.; Materials: D.C., M.E.; Data: D.C., M.E.; Analysis: D.C.; Literature search: D.C.; Writing: D.C., M.E; Critical revision: D.C., M.E.

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ORİJİNAL ÇALIŞMA - *ÖZ*

Ateşli silah yaralanması nedeniyle bir eğitim ve araştırma hastanesine sevk edilen yaralıların hemostatik kan parametreleri ile sepsis tabloları arasındaki korelasyon

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AMAÇ: Travma nedenleri arasında harp yaralanmaları normal yaşamdaki olgulara göre farklıdır. Harp yaralanmasına bağlı multitravma hastaları sepsis veya septik şok gibi enfektif komplikasyonlar geliştirmeye yatkındır. Septik komplikasyonlar, multitravma hastalarında geç ölümlerin önde gelen nedenlerinden biridir. Sepsisin hızlı, uygun ve etkili yönetiminin multiorgan disfonksiyonunu önleyebileceği, mortaliteyi ve klinik sonuçları iyileştirebileceği gösterilmiştir. Ancak, sepsisi öngörebilecek ideal bir biyomarker bulunmamaktadır. Bu çalışmada, ateşli silah yaralanması (ASY) olan hastaların hemostatik kan parametreleri ile sepsis tablosu arasında korelasyon olup olmadığının belirlenmesi amaçlandı.

GEREÇ VE YÖNTEM: Tanımlayıcı nitelikteki bu çalışma, bir eğitim ve araştırma hastanesinin erişkin acil servisine 01.10.2016 ve 31.12.2017 tarihleri arasında ASY tanısı ile sevk edilen ve takiplerinde sepsis gelişen (n=56) ve gelişmeyen (n=56) olguların retrospektif olarak incelenmesi şeklinde yapıldı. Her olgunun yaş, cinsiyet gibi demografik verileri ile hastane bilgi sisteminden acil serviste alınan kan parametreleri alınarak kayıt edildi. Sepsis gelişen ve gelişmeyen iki grup arasında hemostatik kan parametreleri açısından istatistiksel olarak fark olup olmadığı SPSS 20.0 ile değerlendirildi.

BULGULAR: Hastaların yaş ortalaması 26.9±6.67 idi. Hastaların tamamı erkekti. Sepsis gelişen hastaların %57'sinin (n=32) el yapımı patlayıcı (EYP) ile %30'unun (n=17) ateşli silahla yaralandığı ve anatomik olarak yaralanma bölgelerine bakıldığında %64'ünde (n=36) çoklu yaralanma olduğu tespit edildi. Sepsis gelişmeyen hastaların ise %48'inde (n=27) EYP, %43'ünde (n=24) ASY olduğu ve anatomik bölge olarak %48'inde (n=27) çoklu yaralanma, %32'sinde (n=18) ekstremite yaralanması olduğu bulunmuştur. Hemostatik kan parametrelerinden PLT, PTZ, INR ve Ca değerlerinde sepsis gelişen ve gelişmeyen olgular arasında istatistiksel olarak anlamlı fark saptanmış ve ROC eğrisi ile incelendiğinde ise PTZ ve INR, test edilen değerler arasında en iyi tanı performansını göstermiştir.

TARTIŞMA: ASY olan hastalarda PTZ, INR değerlerinde artış ile Ca ve PLT değerlerinde azalma olması klinisyenleri sepsis açısından uyarabilir ve antibiyotik tedavisini başlatmaya veya değiştirmeye yönlendirebilir.

Anahtar sözcükler: Ateşli silah yaralanması; hemostatik; kan parametreleri; sepsis.

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