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Lactate/Albumin Ratio as a Predictor of Mortality in Patients with Crimean-Congo Hemorrhagic Fever

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ABSTRACT

Objective: This study aimed to determine the relationship of lactate/albumin (L/A) ratio with prognosis and fatality in CCHF patients. **Materials and Methods:** A total of 260 patients diagnosed with CCHF between January 2019 and December 2022, 36 of whom were deceased and 224 of whom were alive, were retrospectively included in the study. The findings of survivor and non-survivor patients were compared. **Results:** There was no significant difference between the groups in terms of age and gender. While albumin, glucose and platelet levels were quite low in the patient group who died due to CCHF ($p<0.001$); White blood cells, urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, sodium, lactate, L/A ratio and high-sensitivity C-reactive protein in the blood were found to be significantly high ($p<0.05$). In the ROC analysis, the highest sensitivity and specificity were calculated as the L/A ratio. **Conclusion:** We found that the L/A ratio can be used as a tool to predict fatality in CCHF patients. In addition, the L/A ratio was more significant in predicting fatality than serum albumin and serum lactate levels alone.

Keywords: Emergency Department, Crimean-Congo Hemorrhagic Fever, Lactate/Albumin Ratio, Fatality.

Kırım-Kongo Kanamalı Ateşi Hastalarında Mortalitenin Belirleyicisi Olarak Laktat/Albumin Oranı

ÖZ

Amaç: Bu çalışma, KKH hastalarında laktat/albumin (L / A) oranının prognoz ve mortalite ile ilişkisini belirlemeyi amaçlamıştır. **Gereç ve Yöntem:** Ocak 2019 ile Aralık 2022 tarihleri arasında KKH tanısı almış, 36'sı mortalite, 224'ü canlı olmak üzere toplam 260 hasta retrospektif olarak çalışmaya dahil edildi. Sağ kalan ve sağ kalan olmayan hastaların bulguları karşılaştırıldı. **Bulgular:** Gruplar arasında yaş ve cinsiyet açısından anlamlı fark yoktu. KKKK nedeniyle ölen hasta grubunda albumin, glukoz ve trombosit düzeyleri oldukça düşük iken ($p<0,001$); Kanda beyaz kan hücreleri, üre nitrojen, kreatinin, alanin aminotransferaz, aspartat aminotransferaz, sodyum, laktat, L/A oranı ve yüksek duyarlılık C-reaktif protein anlamlı düzeyde yüksek bulundu ($p<0,05$). ROC analizinde en yüksek duyarlılık ve özgüllük L/A oranı olarak hesaplandı. **Sonuç:** L/A oranının KKKK hastalarında fataliteyi öngörmeye bir araç olarak kullanılabilirliğini bulduk. Ek olarak, L/A oranı, fataliteyi öngörmeye tek başına serum albumin ve serum laktat düzeylerine göre daha anlamlıydı.

Anahtar Kelimeler: Acil Servis, Kırım-Kongo Kanamalı Ateşi, Laktat/Albumin Oranı, Fatalite.

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INTRODUCTION

The Nairovirus (family Bunyaviridae) is a tick-borne virus that causes CCHF, a zoonotic viral illness. The disease's extensive range is related to the Hyalomma tick's global distribution, which serves as the vector for the spread of the virus. Infected animals usually exhibit preclinical symptoms of the disease, while humans die from it. Humans experience nonspecific febrile symptoms that progress to hemorrhagic shock. (Appannavar & Mishra, 2011; Fillâtreet, Revest, & Tattevin 2019) In our nation, the first prevalence was recorded in 2002. Examining the Ministry of Health's statistics reveals a discernible increase in CCHF notifications over that period. between 2002 and 2008, while there was a decrease in the number of cases and mortality between 2008 and 2017. Cases are observed in many regions of Türkiye. The majority of cases (95%) were detected between March and October (Binici et al., 2022). Humans can contract CCHF by coming into contact with the bodily fluids or tissues of an infected animal, primarily through hard-bodied Hyalomma ticks of the Ixodes family, especially Hyalomma marginatum, with a mortality rate of up to 30%. (Kazan & Sümer, 2019). Individuals in rural endemic areas engaged in animal husbandry are at the highest risk of infection. The incubation period of the virus is 1–13 days. The value of the viral load and the mode of transmission are effective in this regard. The incubation time has been determined to be 1-3 days after a tick bite, 3-6 days after contact with blood or body fluids, and 5-7 days for healthcare-associated disorders. Prolonged prothrombin time (PT), partial thromboplastin time (PTT), hyperbilirubinemia with high transaminases, leukopenia, and thrombocytopenia are among the laboratory abnormalities observed in the patients. (Hawman & Feldmann, 2018; Hawman et al., 2009). Viral RNA can be found using serology and reverse transcriptase polymerase chain reaction (RT-PCR) as diagnostic techniques. When predicting mortality in individuals with sepsis, the lactate/albumin (L/A) ratio is a more reliable diagnostic than lactate (Chebl et al. ,2021). Additionally, it has been demonstrated to be connected to mortality in individuals with moderate to severe traumatic brain injury. (Wang, He, Qu, Zhang, & Xu, 2022). Determining the risk of mortality quickly and effectively in CCHF disease is necessary for triage of the patient, blood product needs, and planning of follow-up strategies. Biomarkers are currently insufficient, though, to determine the mortality risk in CCHF patients. The L/A ratio does predict mortality in a large number of critically ill patients, however it is unclear if it

predicts critical disease in patients receiving continuous critical care units. Determining the predictive significance of lactate, albumin, and the L/A ratio in CCHF patients was the aim of this investigation.

MATERIALS AND METHODS

Study type

A descriptive, retrospective study was conducted using medical records of patients with CCHF who applied to Sivas Cumhuriyet University Emergency Department between January 2019 and December 2022.

Study group

Sivas Cumhuriyet University Hospital is a tertiary hospital located in Sivas, east of Central Anatolia. A search of the Sivas Cumhuriyet University Hospital Emergency Department database was conducted to identify CCHF presentations. Each CCHF patient identified from the initial screening then entered into a clinical database specifically designed for CCHF data acquisition. A total of 260 patients with CCHF were identified. Of the total 260 patients, 36 died and 224 survived.

Dependent and independent variables

While the independent variables of this research are age and gender, the dependent variable is mortality of the CCHF.

Procedures

The database included information about the 260 patient's demographics, complaints on admission, tick contact history, temperature, blood pressure, pulse rate, physical examination findings, complete blood count (CBC), blood biochemistry test, coagulation the panel, treatment, and post-treatment information and follow-up.

Statistical analysis

Based on data from SPSS Data 21.0 (SPSS Inc., Chicago, Illinois, USA), a statistical analysis was conducted. In terms of continuous statistics, mean±SD was used. During data processing, the independent t-test was employed to establish the importance of the variation between each of the averages; the Man-Whitney U test was used when the parametric test assumptions were not met; and the Shapiro-Wilk parametric test was used when the assumptions were satisfied. The appropriate cut-off settings for the L/A ratio were determined using a receiver operating characteristic curve (ROC) analysis. The error level $p < 0.05$ value was considered significant.

The inclusion criteria were; patients aged ≥ 18 years; and the emergency department's definitive diagnosis of CCHF by showing viral RNA with RT-PCR after laboratory examinations. Exclusion criteria: patients using drugs such as albuterol and metformin that

change serum lactate values, with liver disease, and patients whose data were not accessible were excluded from the study (Figure 1).

Ethical considerations

The study was approved by the local Ethical Committee of Sivas Cumhuriyet University (approval number and date: 2023-04/20, 19.04.2023).

RESULTS

Table 1 shows no significant differences in age and gender between the two groups. Tick-bite history,

mucosal hemorrhage, petechiae, ecchymosis, and somnolence were statistically higher in the non-survivor groups ($p < 0.001$ for all). While albumin, glucose and platelet levels were quite low in the patient group who died due to CCHF ($p < 0.001$); White blood cells, urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, sodium, lactate, L/A ratio and high-sensitivity C-reactive protein in the blood were found to be significantly high ($p < 0.05$).

Table 1. Demographic characteristics of the non-survivors vs. survivors.

Characteristics	Survivors (n=224, %)	Non-Survivors (n=36, %)	p
Age, year (Mean \pm SD)	53.01 \pm 16.8	54.94 \pm 16.9	0.574*
Gender			
Male	152 (67.8)	24 (66.6)	0.359**
Female	72 (32.2)	12 (33.7)	
Tick-bite history			
No	24 (10.8)	1 (2.8)	<0.001†
Yes	200 (89.2)	35 (97.2)	
Mucosal hemorrhage			
No	202 (90.1)	2 (5.6)	<0.001†
Yes	22 (9.9)	34 (94.4)	
Petechiae, ecchymosis			
No	185 (82.5)	4 (11.2)	<0.001†
Yes	39 (17.5)	32 (88.8)	
Somnolence			
No	220 (97.3)	8 (22.4)	<0.001†
Yes	4 (2.7)	28 (77.6)	

*:Student t test, **:Chi squared test, †: Fisher's exact test.

The ROC curve study revealed the resultant L/A ratio with a 94% sensitivity and 90% specificity. (Table2, Table 3, Figure 2, Figure 3).

Table 2. The mean values of blood parameters of the non-survivors vs. survivors.

Variables	Survivors (N= 224 mean \pm SD)	Non-Survivors (N= 36 mean \pm SD)	p*
White blood cell ($10^3/\mu\text{l}$)	3.57 \pm 2.72	7.21 \pm 4.58	<0.001
Hemoglobin (g/dL)	14.57 \pm 2.14	14.74 \pm 2.63	0.732
Platelet ($10^3/\mu\text{l}$)	81.97 \pm 45.32	38.40 \pm 33.53	<0.001
Glucose(mg/ dl)	122.32 \pm 43.16	84.75 \pm 15.10	<0.001
BUN(mg/dL)	28.98 \pm 17.19	44.01 \pm 25.90	0.003
Creatinine(mg/dL)	1.58 \pm 1.17	2.34 \pm 1.70	0.019
ALT (IU/L)	91.25 \pm 122.70	407.66 \pm 491.04	0.001
AST(IU/L)	173.98 \pm 184.48	1296 \pm 2377	0.008
Sodium(mEq/L)	134.69 \pm 3.55	136.95 \pm 3.51	0.002
Potassium(mEq/L)	4.20 \pm 0.57	4.19 \pm 0.82	0.957
Albumin(g/dL)	2.82 \pm 0.68	2.34 \pm 0.52	<0.001
Lactate(U/L)	1.61 \pm 0.90	3.58 \pm 4.76	0.001
Lactate/albumine ratio	0.49 \pm 0.19	3.03 \pm 2.32	<0.001
hs-CRP(mg/l)	35.96 \pm 40.73	65.40 \pm 42.37	0.001

*:Student t-test, BUN: Urea nitrogen in the blood, hs-CRP: high-sensitivity C-reactive protein, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase.

Table 3. Cut-off value, sensitivity, and specificity of Albumin, Lactate, and Lactate/ Albumin ratio for predicting mortality in crimean congo hemorrhagic fever.

	Albumin (g/dl)	Lactate (mmol/l)	Lactate/ Albumin ratio
Cut-off value	2.86	1.85	0.76
Sensitivity	0.80	0.80	0.94
Specificity	0.63	0.78	0.90
AUC (95% CI)*	0.731(0.641-0.822)	0.788(0.686-0.891)	0.983(964-1000)

*AUC, area under the curve; CI, confidence interval.

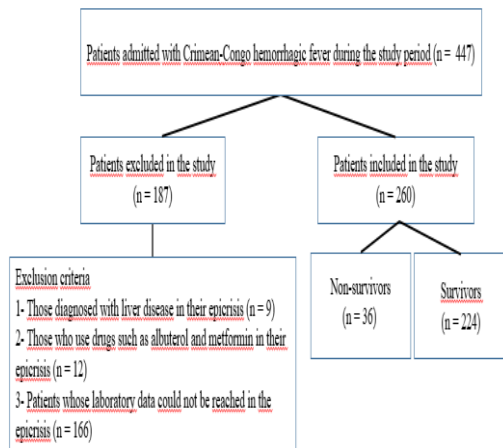


Figure 1. Flow chart of the patients admitted with Crimean–Congo hemorrhagic fever according to inclusion.

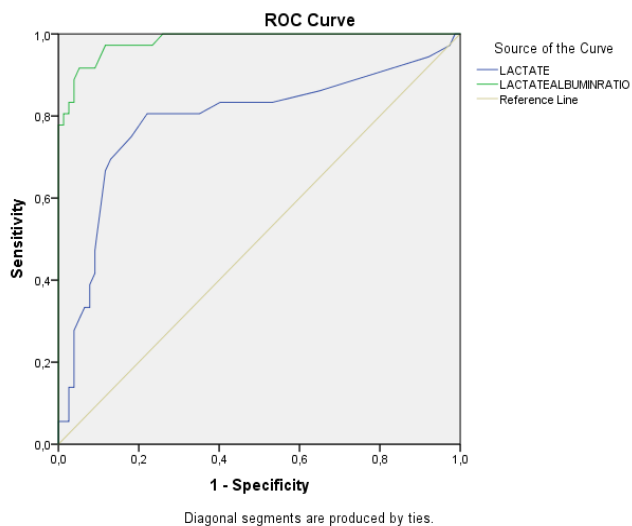


Figure 2. Cut-off value sensitivity, and specificity of the both Lactate, Lactate/albumin ratio for predicting mortality in crimean congo hemorrhagic fever.

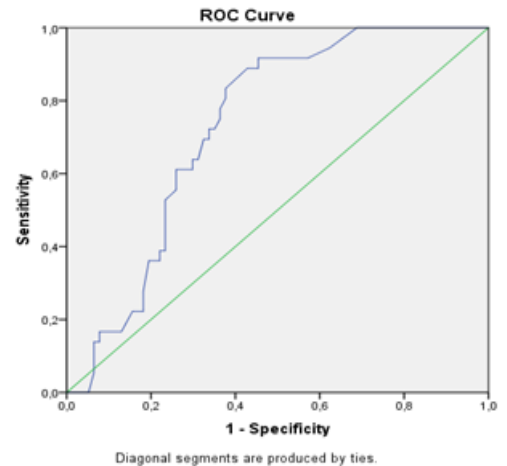


Figure 3. Cut-off value, sensitivity, and specificity of albumin for predicting mortality in Crimean-Congo hemorrhagic fever.

DISCUSSION

Our study results revealed that the L/A ratio was more significant in predicting fatality compared to serum lactate and albumin values in CCHF patients. There is no known definitive treatment for CCHF disease. Treatments are mostly provided in the form of supportive treatment. For the treatment of CHD patients, first of all, treatments with blood and blood products, antiviral therapies, and treatments aimed at preventing organ damage are performed. CCHF is a disease that can often lead to mortality. It is important to provide the necessary treatments and interventions in place and on time to reduce mortality.

Serum albumin is a negative acute-phase protein that decreases in response to inflammatory impulses and is an indicator of adverse clinical outcomes in critical diseases. In patients with impaired liver function, serum levels are also below normal due to decreased serum albumin synthesis (Shin et al., 2018). Among the laboratory changes that can be observed in the course of CCHF disease, it has been observed that there is a decrease in albumin and total protein (Gul Ozturk, Kisa, Kacmaz, & Yesilyurt, 2015; Öngürü & Bodur, 2012). In addition, endothelial damage is an expected condition in the pathogenesis of CCHF, and due to this, plasma and albumin pass into the

extracellular space and their serum levels decrease (Özmen & Parlak, 2020). Swanepoel et al. suggested that albumin levels were low in CCHF patients, resulting in mortality, which is similar to our study results (Swanepoel et al., 1989). The value of lactate in venous blood drawn once from patients suspected of having sepsis upon admission to the emergency room has been demonstrated in the literature to be a good prognostic biomarker for death and organ failure in critically ill patients as well as a dependable risk rating biomarker. (Mikkelsen et al., 2009; Shapiro et al., 2005; Trzeciak et al., 2007). Hyperlactatemia typically indicates tissue hypoperfusion in acute situations (Dellinger et al., 2012). Clinical research has demonstrated that tissue hypoxia, which is defined by supply-dependent oxygen consumption, is the cause of the rise in lactate levels observed in sepsis patients (Friedman, De Backer, Shahla, & Vincent, 1998). According to Filho et al., sepsis patients who die tend to have lower albumin levels and greater lactate levels (Filho et al., 2016). According to Kerget et al., individuals with severe congestive heart failure (CCHF) had a considerably greater lactate ratio than those with mild or moderate CCHF (Kerget, Kerget, & İba Yılmaz, 2021). The study's findings agreed with previous research in the field. For critically ill patients, the L/A ratio serves as the risk classification scale (Gharipour, Razavi, Gharipour, & Mukasa, 2020). Additionally, Wang et al. discovered that in patients with severe sepsis, a high L/A ratio indicated multiple organ failure and higher death (Wang, et al., 2015). According to Bou Chebl et al., baseline serum lactate was not a stronger predictor of in-hospital mortality in adult septic patients than the L/A ratio (Bou Chebl et al., 2020). According to Lu et al., patients experiencing acute respiratory failure may have an L/A ratio that is linked to death (Lu, Guo, Chen, & Zhang, 2021). According to Cakir et al., baseline serum lactate was not as predictive of in-hospital mortality in adult septic patients as the L/A ratio. When predicting clinical outcomes for sepsis patients in the critical care unit, the L/A ratio outperformed lactate or albumin alone (Cakir & Ozkocak Turan, 2021). According to Lau et al., the L/A ratio can be used to predict death in patients with necrotizing fasciitis since it indicates a better prognosis for in-hospital mortality in adult septic patients than baseline serum lactate (Lau, Hsiao, Fann, & Chang, 2021). Kokulu et al. found that the L/A ratio was a more accurate indicator of in-hospital mortality for adult septic patients than

baseline blood lactate. Compared to lactate or albumin levels alone, the L/A ratio plays a more important influence on predicting survival for patients receiving cardiopulmonary resuscitation after an out-of-hospital cardiac arrest. (Kokulu & Sert, 2021). In the emergency room, Lee et al. discovered that the L/A ratio was prognostically significant in predicting the development of acute renal damage owing to sepsis (Lee et al., 2019). Our study's findings were supported by this investigation

CONCLUSION

It was determined that the L/A ratio was a more statistically significant and independent predictor of fatality than serum lactate and albumin levels in CCHF patients. Since the L/A ratio is a widely available and moderately priced test in routine laboratory testing, it can help predict fatality in CCHF patients and have a positive impact on patients' evaluation, treatment, and follow-up procedures. However, prospective, multicenter studies involving many patients are needed to routinely use the L/A ratio in CCHF patients and to evaluate its relationship with the clinical situation fully.

There are some limitations in our work; this study's retrospective design, which includes a relatively small patient cohort from a single center and the retrospective acquisition of all data from the medical record database, is its main and most significant limitation.

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Conflict of Interest

The author declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Author Contributions

Plan, design: YKT, ŞÇ; **Material, methods and data collection:** YKT, ŞÇ; **Data analysis and comments:** YKT, ŞÇ; **Writing and corrections:** YKT, ŞÇ.

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Ethical considerations

The study was approved by the local Ethical Committee of Sivas Cumhuriyet University (approval number and date: 2023-04/20, 19.04.2023).

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