ORIGINAL ARTICLE

The role of C-reactive protein albumin ratio for predicting mortality in patients with Fournier's gangrene

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ABSTRACT

BACKGROUND: Fournier's gangrene (FG) is a rapidly progressing and life-threatening necrotizing fasciitis of the genital and perineal regions. To estimate the mortality rate associated with FG, Laor et al. developed the FG severity index (FGSI), an index with proven prognostic significance. On the other hand, the C-reactive protein (CRP)/albumin (CAR) ratio is a proven objective marker of inflammatory response. In light of the foregoing, the objective of this study is to assess the prognostic value of the CAR ratio in predicting mortality in patients with FG in comparison with FGSI.

METHODS: This retrospective study consisted of 58 patients who were operated on for FG between 2019 and 2022. Research data were obtained from electronic and paper patient files, surgery notes, clinical follow-up forms, anamnesis, intensive care forms, and laboratory test results obtained from the hospital automation system. The clinical course of each patient was reviewed based on these records. The relationships between patients' CAR ratios and their demographic and clinical characteristics, including age, gender, and comorbidities, whether ostomy was performed, length of hospital stay, growth in wound culture, isolated bacterial species, FGSI scores, and laboratory test results (hemoglobin, sodium, potassium, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, albumin, and CRP levels, white blood cell counts, hematocrit values, glucose-to-potassium, neutrophil-to-lymphocyte, platelet-to-lymphocyte, and lymphocyte-to-CRP ratios) and the prognostic power of CAR ratio in predicting the mortality associated with FG were investigated.

RESULTS: The mean age of the study group, 45 male and 13 female, was 57 (min. 17, max. 85) years. The most common predisposing factor was diabetes mellitus (DM), which was present in 32 (55.1%) patients. The most common symptoms at admission were erythema (89.6%), swelling/hardening (82.7%), pain (41.3%), fever (31%), and purulent discharge (37.9%). Of the 58 patients included in the study, six had died. The most common comorbidity, second to DM (55.1%), was cardiovascular disease (39.6%). The median ages of patients who had died and survived were 60 (min. 56, max. 85) and 56 (min. 18, max. 80) years, respectively. CAR ratio effectively differentiated FG patients who had survived from those who had died (area under the curve [AUC]: 0.907 [0.824–0.984]). The CAR ratio cutoff value of 2.8 effectively differentiated FG patients and FSGI scores who had survived from those who had died (AUC: 0.904 [0.823–0.992]).

CONCLUSION: The study findings demonstrated that the CAR ratio might serve as an effective biomarker in predicting the mortality associated with FG.

Keywords: Albumin; C-reactive protein; C-reactive protein albumin ratio; Fournier's gangrene.

INTRODUCTION

Fournier's gangrene (FG) is a rare disease characterized by rapidly progressing necrotizing fasciitis in the perianal and genitourinary regions.[1] FG was first described by Jean Alfred Fournier in 1883 as a rapidly progressive disease of unknown cause.[2] Given the rarity of FG patients, the data and experience on FG are limited. It is difficult to make a diagnosis of FG before necrosis or gangrene occurs. FG is a rapidly progressing disease.[3] Hence, the mortality rate associated with FG is re-

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Table 1. Demographic and clinical characteristics of FG patients by mortality status

	Patients who survived FG		Patients who died of FG		P value	
	Mean±SD/n (%)	Median	Mean±SD/n (%)	Median		
Age (years)	55.1±13.3	56.0	67.0±12.9	60.0	0.070	m
Gender						
Female	11 (21.2%)		2 (33.3%)		0.608	X2
Male	41 (78.8%)		4 (66.7%)			
Comorbidity						
(−)	15 (28.8%)		0 (0.0%)		0.323	X2
(+)	37 (71.2%)		6 (100.0%)			
BC						
(−)	26 (50.0%)		3 (50.0%)		1.000	X2
(+)	26 (50.0%)		3 (50.0%)			
LoS in Hospital (days)	30.7±16.2	29.0	23.7±24.8	14.0	0.201	m

FG: Fournier's gangrene; sd: Standard deviation; P: Probability statistic; LoS: Length of stay; BC: Blood Culture.

portedly around 40% despite aggressive treatment methods.[4] The overall mortality rate associated with FG reported in the literature ranges from 20% to 80%.[5] C-reactive protein (CRP) is one of the acute phase proteins released during the inflammation process.[6] Serum albumin is a negative acute phase reactant. The CRP/albumin ratio (CAR) has been shown to correlate with the severity of the infection[7] and to effectively predict prognosis and diagnosis as an inflammatory marker.[8] The incidence of FG is increasing, particularly in developed countries with an aging population and high morbidity due to metabolic diseases such as diabetes mellitus (DM). Therefore, it is critical to understand the risk factors, pathophysiology, and clinical course related to FG.[9] Laor et al. developed an scoring system which is defined in complex patients to identified risk factors. FSGI is a numerical score which includes temperatures, heart rate, respiration rate, sodium, potassium and creatinine levels, white blood count, hematocrit, and sodium bicarbonate levels.[10] In another study, Yilmazlar et al. defined Uludag FGSI (UFGSI) by adding age and sprawl area in a series of 80 patients. FGSI and UFGSI analysis systems, the most widely used to predict FG-related death, have high sensitivity and specificity with acceptable properties.[11]

MATERIALS AND METHODS

The study protocol was approved by the Local Clinical Research Ethics Committee (decision number: 21/16, decision date: November 24, 2022). The population of this retrospective study consisted of 58 patients who were operated on for FG at the clinic where this study was conducted between January 1, 2019, and September 1, 2022. There were no specific exclusion criteria. Research data were obtained from electronic and paper patient files, surgery notes, clinical follow-up forms, anamnesis of surgical indications, intensive care forms, and laboratory test results obtained from the hospital automation system. The clinical course of each patient was reviewed based on these records. The relationships between patients' CAR ratios and their demographic and clinical characteristics, including age, gender, comorbidities, whether ostomy was performed, length of hospital stay, growth in wound culture, isolated bacterial species, FGSI scores, and laboratory test results (hemoglobin [Hgb], sodium, potassium, bicarbonate, glucose, blood urea nitrogen [BUN], creatinine, albumin and CRP levels, white blood cell [WBC] count, and hematocrit, glucose-to-potassium ratio [GPR], neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], and lymphocyte-to-CRP ratio [LCR] values) and the prognostic power of CAR ratio in predicting the mortality associated with FG were investigated.

Statistical Analysis

The descriptive statistics obtained from the research data were expressed as mean and standard deviation, median and minimum-maximum, frequency, and percentage values. The normal distribution characteristics of the variables investigated within the scope of the study were analyzed with the Kolmogorov–Smirnov test. The Mann–Whitney U-test was used in the analysis of independent quantitative data. Pearson's Chi-squared test was used in the analysis of independent qualitative data, and Fisher's exact test was used in cases where the conditions required for Pearson's Chi-squared test were not met. Receiver operating characteristic curve analysis was used to assess the variables' impact levels and cutoff values. SPSS 28.0 (Statistical Product and Service Solutions for Windows, Version 27.0, IBM Corp., Armonk, NY, U.S., 2021) software package.

RESULTS

The distribution of patients' demographic and clinical characteristics of FG patients by their mortality status is shown in Table 1. A total of 58 patients, 45 (77.5%) male and 13 (22.5%) female, were evaluated within the scope of the study. The most common symptoms at admission were erythema (89.6%), swelling/hardening (82.7%), pain (41.3%), fever (31%), and purulent discharge (37.9%). Fifty-two pa-

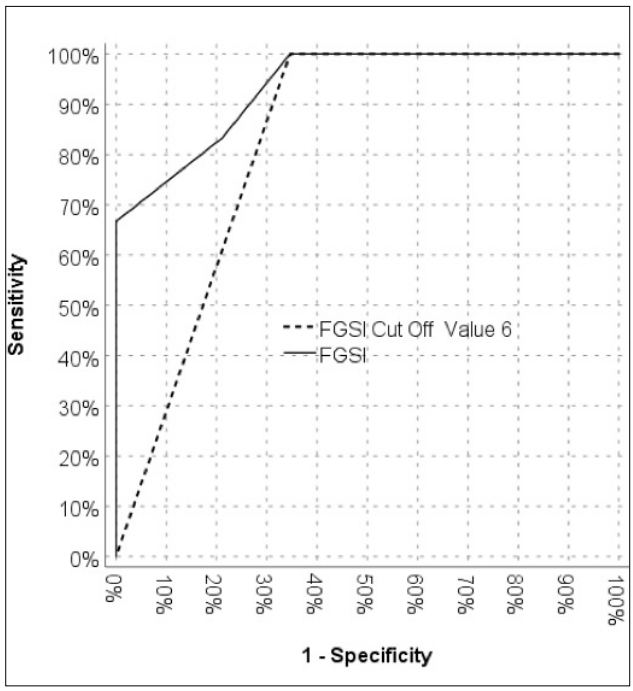

Figure 1. Cut off value FGSI.

tients had survived, whereas six had died. DM (55.1%) and cardiovascular diseases (39.6%) were the most common comorbidities. The median ages of patients who had died and survived were 60 (min. 56, max. 85) and 56 (min. 18, max. 80) years, respectively.

A significant efficacy of the FGSI value was observed in the differentiation of patients with and without EX (area under the curve [AUC] 0.936 [0.843–1,000]). FSGI efficiency of the FGSI 6 cutoff value was observed in the differentiation of patients with and without EX (AUC: 0.827 [0.712–0.942]). Sensitivity was 100%, positive prediction was 65.8%, specificity was 25.0%, and negative prediction was 100% (Table 2 and Fig.1).

CAR ratio effectively differentiated FG patients who had survived from those who had died (AUC: 0.907 [0.82–0.984]). The highest value of the sum of sensitivity and specificity was determined as the cutoff value and calculated according to Youden's index that is CAR ratio cutoff value of 2.8 effectively differentiated FG patients who had survived from those who had died with 100% sensitivity, 80.8% specificity, and 37.5% positive predictive and 100% negative predictive values (AUC: 0.904 [0.823–0.992]) (Table 3).

Table 2. Discriminatory Power of CAR Ratio in Distinguishing Survival Outcomes among FG Patients

	Curve area		% 95 GA			P
FGSI	0.936		0.843	-	1.000	0.001
FGSI Cut-off 6	0.827		0.712	-	0.942	0.009
	EX (-)	EX (+)				
FGSI						
≤2.8	34	0		Sensitive		100.0%
>2.8	18	6		Positive predictive		65.8%
				Specificity		25.0%
				Negative predictive		100.0%

ROC: Receiver operating characteristic; FSGI: Fournier's gangrene severity index.

Table 3. Efficacy of the FGSI Value in Patients with and without EX

	AUC		% 95 CI		P value
CAR	0.907	0.824	-	0.984	0.001
CAR cut-off value: 2.8	0.904	0.823	-	0.992	0.001
	Patients who survived FG	Patients who died of FG			
C/A					
≤2.8	42	0		Sensitivity	100.0%
>2.8	10	6		Positive Predictive Value	37.5%
				Specificity	80.8%
				Negative Predictive Value	100.0%

ROC Curve. AUC: Area under the curve; CI: Confidence interval; p: Probability statistic; CAR: C-reactive protein-to-albumin ratio; FG: Fournier's gangrene; ROC: Receiver operating characteristic.

Table 4. Comparison of Variables for Investigating Differences between Patient Groups Based on CAR Ratio

	Patients with CAR≤2.8		Patients with CAR>2.8		P value	
	Mean±sd/n (%)	Median	Mean±sd/n (%)	Median		
Age	56.1±12.8	56.0	57.1±16.0	58.5	0.938	m
Gender						
Female	9 (21.4%)		4 (25.0%)		0.771	X^2
Male	33 (78.6%)		12 (28.6%)			
Comorbidity						
(-)	13 (31.0%)		2 (4.8%)		0.151	X^2
(+)	29 (69.0%)		14 (33.3%)			
Kx (-)	21 (50.0%)		8 (19.0%)		1.000	X^2
(+)	21 (50.0%)		8 (19.0%)			
LoS in hospital	29.9±16.3	29.0	30.1±19.6	27.0	0.972	m
Ostomy						
(-)	40 (95.2%)		13 (31.0%)		0.123	X^2
(+)	2 (4.8%)		3 (7.1%)			
Flap (-)	20 (47.6%)		13 (31.0%)		0.021	X^2
(+)	22 (52.4%0		3 (7.1%)			
Peroperative VAC						
(-)	37 (88.1%)		9 (21.4%)		0.007	X^2
(+)	5 (11.9%)		7 (16.7%)			
FGSI	6.0±1.3	6.0	7.4±1.6	8.0	0.003	m
WBC	20.6±8.5	18.8	20.9±10.5	19.2	0.882	m
Hgb	11.9±2.1	12.2	11.1±2.3	12.0	0.305	m
CRP	257.5±112.9	251.0	300.5±170.9	323.0	0.178	m
Glucose	207.8±141.0	146.5	203.6±144.7	197.0	0.876	m
Potassium	4.1±0.6	4.1	3.8±0.7	4.0	0.166	m
BUN	25.6±14.6	21.0	40.3±17.8	39.0	0.002	m
Creatinine	1.3±0.5	1.2	2.2±1.8	1.6	0.040	m
ALT	32.0±26.3	20.0	26.5±16.8	22.0	0.938	m
AST	31.0±22.4	21.0	45.1±44.5	18.5	0.554	m
Albumin	29.3±4.2	30.0	25.4±5.8	28.0	0.011	m
GPR	51.1±33.9	37.7	54.2±37.3	47.9	0.585	m
NLR	15.5±11.1	12.9	22.1±17.9	21.6	0.164	m
PLR	229.6±92.5	222.5	321.2±232.0	262.3	0.313	m
CAR	1.0±0.7	0.9	6.9±5.1	5.2		
LCR	8.7±9.9	5.7	27.5±72.5	2.8	0.085	m

m: Mann-whitney u test, X^2: Pearson's Chi-squared test (Fisher's exact test). CAR: C-reactive protein-to-albumin ratio; sd: Standard deviation; P: Probability statistic; LoS: Length of stay; VAC: Vacuum-assisted closure, FGSI: Fournier's gangrene severity index; WBC: White blood cell; Hgb: Hemoglobin, CRP: C-reactive protein; BUN: Blood urea nitrogen; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GPR: Glucose-to-potassium ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LCR: Lymphocyte-to-CRP ratio.

Patients with a CAR ratio of ≤2.8 and >2.8 have not differed significantly in age and gender or comorbidities, growth in wound culture, length of stay in the hospital, and status of having an ostomy (P>0.05). On the other hand, the rate of patients with flap and perioperative vacuum-assisted closure was significantly higher in patients with a CAR ratio of >2.8 than in patients with a CAR ratio of ≤2.8 (P<0.021 and P=0.007, respectively). In addition, the mean FGSI score was significantly higher in patients with a CAR ratio of >2.8 than in patients with a CAR ratio of ≤2.8 (P=0.003). There was no significant difference between the patients with a CAR ratio of ≤2.8 and >2.8 in WBC, Hgb, CRP, glucose, potassium, alanine aminotransferase, aspartate aminotransferase, GPR, NLR, PLR and LCR values (P>0.05). The BUN, creatinine, and albumin values were significantly higher in patients with a CAR ratio of >2.8 than in patients with a CAR ratio of ≤2.8 [P=0.002, P=0.04, and P=0.011, respectively (Table 4)]. The mean FGSI score was significantly higher in patients with in-hospital mortality than in patients who survived (P<0.05).

DISCUSSION

The rate of mortality associated with FG can be as high as 65%.[12] This rate, which was reportedly around 80% in early studies, dropped below 40% with the incorporation of strong antibiotics into the relevant treatment regimens during the past 15 years.[13] FG is generally characterized by polymicrobial infections accompanied by urogenital, fecal, and skin flora, in which aerobic and anaerobic microorganisms coexist.[12] There are studies that reported an indeterminate relationship between age- and FG-induced mortality.[14,15] Given the better drainage of the perineal region with vaginal secretions in women, women are affected by FG much less than men.[16,17] The CAR ratio has been shown to correlate with the severity of the infection and to effectively predict prognosis and diagnosis as an inflammatory marker.[6-8] Hence, it has become a widely used marker in predicting the prognosis of a variety of diseases, from inflammatory processes such as sepsis and ulcerative colitis to malignancies such as hepatocellular carcinoma and pancreatic cancer.[18-20] Many studies investigated the predisposing factors that increase the risk for FG and FG-induced mortality.[12] According to these studies' findings, DM, found in approximately 30% of FG cases, seems to be the most common predisposing factor.[21,22] However, it is still a matter of debate whether DM is an independent risk factor for FG-induced mortality.[23-25] In a long-term multicenter study covering 17 years, a correlation, although not significant, was found between FG-induced mortality and comorbidities such as DM, coronary artery disease, and renal failure.[26] Sarofim et al. reported that the use of diverting ostomy due to FG is an indicator of poor outcomes.[27] Such prognostic factors vary from one study to another, yet male gender, presence of DM, spreading of gangrene beyond the perineum, delay in seeking medical consultation, delayed treatment, elective colostomy, and septic shock seem to be cited by most studies.[28-30] The emergence of all these predisposing factors has led to the need to demonstrate the effect of FG on mortality through the use of scoring systems in patients with various clinical presentations. Among these systems, the FGSI reportedly predicted survival from FG and FG-induced mortality by 78% and 75%, respectively.[12] In a study conducted with 80 patients, a modified version of FGSI, UFGSI, was developed by incorporating age and the extent of the spread of the disease into the parameters included in FGSI.[11] The findings of this study indicated that the CAR ratio was as powerful as FGSI and UFGSI in predicting FG-induced mortality. This study was conducted to evaluate whether the preoperative CRP/albumin ratio predicts death in FG. Based on our results, a simpler method, the CRP/albumin ratio, can be used to estimate mortality, as can FGSI. Described by Laor et al., the FGSI uses temperature, heart rate, respiratory rate, serum potassium and sodium, creatinine, bicarbonate levels, hematocrit, and white blood count to estimate mortality.[10]

Lim et al. have an example of a simple scoring system called FGSI that uses fewer parameters but are simplified without loss of sensitivity and specificity. If a reliable, simplified scoring system that is easier to calculate for clinicians can be developed, the likelihood of clinical use increases.[3]

We believe that the findings of this article support that the CRP/albumin ratio can offer improved predictions for clinical outcomes such as FGSI.

CONCLUSION

This study, which featured 58 FG patients, is among the largest series conducted on FG patients to date. This study was conducted to evaluate whether the pre-operative CRP/albumin ratio predicts death in FG. Based on our results, a simpler method, the CRP/albumin ratio, can be used to predict mortality, like FGSI. The study findings indicated that the CAR ratio effectively predicted the FG-induced mortality with 100% sensitivity, 80.8% specificity, and 37.5% positive predictive and 100% negative predictive values. However, both scoring systems are quite complex. Due to this complexity, their clinical use is impractical. Therefore, there is a need for simpler and more practical scoring systems in clinical practice Future studies need to be designed with a more appropriate sample size and detailed factors. As a cost-effective biomarker that can be checked rapidly in every health institution, the CAR ratio can facilitate the work of surgeons in their attempt to treat FG patients despite the treatment, the mortality rate of FG is still high. FGSI is still a good scoring system for prognostic measurement, but its use in practice is complex. Alternatively, the CRP/albumin ratio can be simply measured and easily administered. Therefore, we recommend using the CRP/albumin ratio to determine the severity of FG.

Ethics Committee Approval: This study was approved by the Antalya Training and Research Hospital Ethics Committee (Date: 24.11.2022, Decision No: 21/16).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: H.Ö.; Design: H.Ö.; Supervision: H.Ö.; Resource: H.Ö.; Materials: H.Ö.; Data collection and/or processing: Y.U.; Analysis and/or interpretation: H.Ö.; Literature search: H.Ö., Y.U.; Writing: H.Ö., Y.U.; Critical review: H.Ö.

Conflict of Interest: None declared.

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ORİJİNAL ÇALIŞMA - *ÖZ*

Fournier gangreni hastalarında mortaliteyi öngörmede c-reaktif protein albumin oranının rolü

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AMAÇ: Fournier kangreni genital ve perineal bölgelerin hızla ilerleyen ve hayatı tehdit eden nekrotizan fasiitidir. Fournier kangreni ile ilişkili ölüm oranını tahmin etmek için Laor ve ark. Kanıtlanmış prognostik önemi olan bir indeks olan Fournier's Gangrene Severity Index'i (FGSI) geliştirdi.C-reaktif protein/albümin (CAR) inflamatuar bir belirteç olup, birçok çalışmada prognoz ve tanı üzerinde belirleyici etkiye sahip olduğu bildirilmişti. Çalışmamız Fournier Gangrenli hastalarda mortaliteyi öngörmede CAR oranının prognostik değerini belirlemeyi amaçlamaktadır.

GEREÇ VE YÖNTEM: Bu retrospektif çalışma, 2019-2022 yılları arasında Fournier gangreni nedeniyle opere edilen 58 hastayı içermektedir. Araştırma verileri, hastane otomasyon sisteminden alınan elektronik ve kağıt hasta dosyaları, ameliyat notları, klinik takip formları, anamnez, yoğun bakım formları ve laboratuvar test sonuçlarından elde edildi. Hastaların CAR oranları ile yaş, cinsiyet, komorbiditeler, ostomi yapılıp yapılmadığı, hastanede kalış süresi, yara kültüründe üreme, izole edilen bakteri türleri, FGSI skorları ve laboratuvar test sonuçları CAR oranının Fournier kangreni ile ilişkili mortaliteyi öngörmedeki prognostik rolü araştırıldı.

BULGULAR: Çalışmada 45 erkek ve 13 kadın olan çalışma grubunun yaş ortalaması 57 (min.17, maks. 85) idi. En sık predispozan faktör 32 (%55.1) diabetes mellitus idi. Başvuru sırasında en sık görülen semptomlar eritem (%89.6), şişlik/sertleşme (%82.7), ağrı (%41.3), ateş (%31) ve cerahat içeren akıntı (%37.9) idi. Çalışmaya dahil edilen 58 hastada mortalite görüldü. Diabetes mellitustan (%55.1) sonra en sık görülen komorbidite kardiyovasküler hastalıktı (%39.6). Ex olan ve olmayan hastaların medyan yaşları sırasıyla 60 (min. 56, maks. 85) ve 56 (min. 18, maks. 80) idi. CAR oranı, mortal olmayan grupta Fournier kangren hastalarını ölenlerden etkili bir şekilde ayırt etti. 2.8'lik CAR oranı kesme değeri, hayatta kalan Fournier kangren hastalarını ölenlerden etkili bir şekilde ayırdı.

SONUÇ: Çalışma bulguları, CAR oranının Fournier kangreni ile ilişkili mortaliteyi tahmin etmede etkili bir biyobelirteç olarak hizmet edebileceğini göstermiştir.

Anahtar sözcükler: Albumin; C reaktif protein albumin oranı; C reaktif protein; fournier gangreni.

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