ORIGINAL ARTICLE

Investigation of the effects of clinical parameters on mortality in patients with necrotizing fasciitis

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ABSTRACT

BACKGROUND: Necrotizing fasciitis is a rapidly progressing, potentially fatal soft-tissue infection that spreads through the fascia. Due to the late onset of diagnostic signs during the disease's advanced stage and its rapid progression, it can be challenging to make a prompt diagnosis. However, with a rapid and accurate diagnosis, the progression of the disease can be halted through appropriate early surgical intervention. Even with correct and timely treatment, the mortality rate for necrotizing fasciitis is higher compared to other soft-tissue infections. This study aims to investigate the effects of clinical parameters in patients with necrotizing fasciitis on mortality.

METHODS: The study included 37 patients with a necrotizing fasciitis diagnosis between 2009 and 2018. Demographic characteristics of the patients (age, gender, comorbid conditions), duration from diabetes diagnosis if present, blood glucose level at the time of diagnosis, microorganisms isolated from wound cultures, presence of positive blood cultures, administered antibiotic therapy, laboratory risk indicator for necrotizing fasciitis (LRINEC) score at presentation, number and types of surgical procedures performed, length of hospital stay, and mortality rates were retrospectively recorded. Statistical analysis of dependent and independent variables was conducted using t-tests, Mann-Whitney U test, Chi-square test, and Fisher's exact test.

RESULTS: Age was found to be an average of 70 in the mortality group, and it is significantly higher compared to the non-mortality group. A high LRINEC score, the presence of comorbidity, and a positive blood culture were also found to be significant in the mortality group. The low number of surgical procedures performed is significantly lower in the mortality group.

CONCLUSION: This study highlights the conditions associated with high mortality in patients with necrotizing fasciitis, which is a treatable disease through timely and accurate diagnosis followed by appropriate antibiotic therapy and surgical intervention. It emphasizes the importance of updating the approach for high-risk group patients and aims to provide information that will help lower the threshold for diagnosing necrotizing fasciitis.

Keywords: Acute progressive soft-tissue infection; necrotizing fasciitis; soft-tissue infection.

INTRODUCTION

Necrotizing fasciitis is a soft-tissue infection characterized by necrosis of the skin, subcutaneous fat tissue, fascia, and muscles. It is less commonly seen compared to other soft-tissue infections. It frequently affects the lower extremities, followed by the perineal and genital regions. It is usually associated with skin infections, surgical trauma, animal and insect bites, catheters, and injection procedures. The condition presents with erythema, increased warmth, and pain in the early stages, similar to other soft-tissue infections (Fig. 1). However, it rapidly progresses within hours, leading to a life-threatening clinical picture. Without surgical intervention, it follows a lethal course, and the basis of surgical treatment is incision, drainage, and removal of necrotic tissues. In instances where limb viability or function cannot be restored, amputa-

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Figure 1. Late presentation of necrotizing fasciitis of the foot with skin necrosis and erythema

tion may also be considered. The gold standard for diagnosis is clinical examination, and the findings leading to a diagnosis include pain disproportionate to the wound size, presence of crepitus in the skin, development of skin anesthesia, presence of skin necrosis, and severe necrotic odor. Early diagnosis and prompt implementation of effective treatment are among the most important variables in reducing mortality in cases of necrotizing fasciitis.[1]

Early recognition of necrotizing fasciitis, which has a rapid progression and a high mortality rate in the absence of surgical intervention, is critical. In this regard, the search for repeatable, objective, rapid, and effective diagnostic methods that can be used before interventional procedures continues. The definitive diagnosis can only be made through surgical incision and drainage in line with the clinical picture. Based on this situation, Wong et al. developed a scoring system called the "Laboratory Risk Indicator for Necrotizing Fasciitis" (LRINEC) by using laboratory parameters to support the diagnosis.[2] In this scoring system, hemoglobin value, white blood cell count, serum C-reactive protein value, serum creatinine value, serum sodium value, and blood glucose value of patients suspected of having necrotizing fasciitis are scored according to the results. Scores of 6 and above have a 92% positive predictive value and a 96% negative predictive value, according to the criteria. Due to the high mortality rates in the natural course of necrotizing fasciitis, research in the literature has focused on investigating parameters associated with mortality. In this study, retrospective data of patients diagnosed with necrotizing fasciitis were reviewed, and clinical parameters that could be associated with high mortality were investigated. The main aim of the study is to identify clinical parameters associated with high mortality in fasciitis cases. Thus, when encountering patients with these parameters, it is aimed to raise reasonable suspicion in clinicians and to predict high-mortality fasciitis cases in advance.

MATERIALS AND METHODS

Ethical approval was obtained from the Istanbul University-Cerrahpasa Ethical Committee for Non-Intervational Clinic Research (ID: 2023/99). A total of 37 patients who were clinically diagnosed with necrotizing fasciitis and underwent major surgery after the initial evaluation and assessment in our emergency department between 2009 and 2018 were included in the study. Demographic characteristics of the patients (age, gender, comorbid conditions), duration since diabetes diagnosis if applicable, blood glucose level at the time of diagnosis, microorganism isolated from wound culture, presence of positive blood culture, administered antibiotic therapy, LRINEC score at presentation, number and types of surgical procedures performed, length of hospital stay, and mortality rates were recorded retrospectively. Descriptive statistics such as mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used for data analysis. The distribution of variables was assessed using the Kolmogorov-Smirnov test. Independent sample t-tests and Mann-Whitney U tests were used for the analysis

Figure 2. Infection of the heel region, incisions were needed to make proximally to the calf and distally to the plantar region, patient eventually required below-knee amputation

Figure 3. Aggressive debridement of the fascia/tendon and ligaments, all the potential fascias needed to be incised and drained

Table 1. Number and percentage of evaluated criteria of the patients

Age	Min-Max	Median	Mean±	Percentage
	32–98	55	57.11±15.04	
Sex				
Female			11	30.6
Male			25	69.4
Duration of DM (year)	1-28	9	11.38±7.85	
Hospitalization time	1-95	23.5	26.97±18.98	
LRINEC score	2-10	6.5	6.64±2.14	
DM				
(−)			20	55.6
(+)			16	44.4
Blood sugar regulation				
(−)			23	63.9
(+)			13	36.1
Comorbidity				
(−)			9	25
(+)			17	75
No. of operation				
I			19	52.8
II			12	33.3
III			3	8.3
IV			1	2.8
V			1	2.8
Culture positivity				
(−)			8	22.2
(+)			28	77.8
Hemoculture positivity				
(−)			26	72.2
(+)			10	27.8
Imaging				
(−)			25	69.4
(+)			11	30.6
Mortality				
(−)			27	75
(+)			9	25

LRINEC: Laboratory risk indicator for necrotizing fasciitis.

of quantitative independent variables. The chi-square test and Fisher's exact test were used for the analysis of qualitative independent variables when the conditions of the chi-square test were not met. SPSS 22.0 software was used for the analyses, and a $P<0.05$ was considered statistically significant.

Surgical Technique

In the study, the infection stemmed from and spread to the lower extremities in 28 patients, the perineum in 7 patients, and the genital area in 2 patients. All patients with lower extremity involvement had necrotizing fasciitis progressing from distal to proximal. The initial site of involvement was the forefoot in 16 patients, the midfoot in 8 patients, and the heel and back of the foot in 4 patients. In surgeries performed on the lower extremities, a skin incision that would provide access to the entire affected fascia was preferred. The incisions were planned to reach all involved fasciae, parallel to the extremity, with enough length and similar to the previously described

fasciotomy incisions whenever possible. If necrosis was present in the skin, the necrotic skin was included in the debridement, and the debridement was extended as needed after reaching the infected cavity (Fig. 2). Drainage was achieved by opening the affected foot, crural, or thigh fasciae. Aggressive debridement of poorly vascularized and necrotic-looking fascia, tendon, septum, and similar structures was done to open all necessary spaces surgically for wound management [(Fig. 3). Another important finding indicating the debridement of necrotic tissues is the gradual decrease and disappearance of the intense preoperative necrotic odor. After achieving hemostasis, a decision regarding the wound care method needs to be made. Proper follow-up of the open wound, prevention of drying, and prevention of secondary necrosis due to desiccation are critical. It is also important to stimulate wound healing and prevent the accumulation of wound discharge by placing squeezed gauze soaked in normal saline in all pockets. If the infection is localized to an extremity, applying a splint in an anatomically appropriate position is necessary to preserve function and prevent joint contracture due to extended immobilization. After the initial surgery, a sterile, moist, absorbent dressing was applied, and an orthosis was used in patients with extremity involvement.

RESULTS

There were 25 male patients and 11 female patients. The average age was 57. Out of the patients, 9 died due to complications, with 4 being female and 5 being male. A total of 16 patients were diagnosed with diabetes. Among the patients, 23 had blood sugar levels below 200 mg/dL at the time of admission, while 13 had levels above this value. There were 9 patients with comorbidities. The most common comorbidity was diabetes, followed by hypertension, coronary heart disease, and malignancy in decreasing order. In total, 19 patients have undergone surgery. Among the remaining patients, 12 had two surgeries, 3 had three surgeries, and the last two had four or more surgeries. Bacterial growth was detected in 28 sets of specimens taken during the surgeries, with Methicillin-Resistant Staphylococcus aureus (MRSA) being the most common in 11 patients and Escherichia coli in 17 patients. Blood culture positivity was seen in 10 patients. Demographic information is summarized in Table 1. Among the evaluated parameters, advanced age, number of surgeries, length of hospital stay, blood culture positivity, and a high LRINEC score at admission were found to have a statistically significant relationship with increased mortality. Advanced age and blood culture positivity were identified as independent factors affecting mortality. The average age of patients in the mortality group was 69.8, significantly higher than that of the non-mortality group (53) (P=0.002). The average length of hospital stay in the mortality group (11.1) was significantly lower than that in the non-mortality group (32.3) (P=0.000). The average LRINEC score in the mortality group (8.3) was significantly higher than that in the non-mortality group (6.1) (P=0.005). The comorbidity rate was significantly higher in the mortality group (P=0.046). The average number of surgeries in the mortality group was significantly lower than that in the non-mortality group (P=0.004). The rate of blood culture positivity was also significantly higher in the mortality group (P=0.003). There were no significant differences in gender distribution, presence and duration of diabetes, blood sugar regulation (200 mg/dL), or bacterial growth rate in wound cultures between the mortality and non-mortality groups. The results are summarized in Table 2.

DISCUSSION

TNecrotizing fasciitis is a well-known condition since the Hippocratic era.[3] Classic surgical methods such as extensive debridement and the opening of dead spaces are still used today. Once the clinical picture is established, making a diagnosis and applying the appropriate treatment are relatively straightforward. However, early recognition of necrotizing fasciitis in the early stages is challenging due to overlapping clinical features. Early diagnosis and recognition of necrotizing fasciitis before the obvious skin signs and applying appropriate surgical treatment in the localized stage reduce mortality rates. Wong et al. demonstrated in their study that the main determinant of mortality was the delay in surgery within the first 24 h, and the delay increased mortality by nine times.[4] The rapid progression of infection through the fascia from the initial site of infection with increasing bacterial load will lead to sepsis and deterioration of health as it ascends to the torso, and it can be the primary factor for this. This can be explained by the presence of better vascularized muscle tissues in the proximal tissues of the extremities and the increased likelihood of bacterial translocation leading to sepsis due to local bacterial suppuration in these regions.

In the surgical drainage of necrotizing fasciitis, it is important to prefer previously well-described fasciotomy incisions in the extremities to preserve the lymphatic drainage of the extremity while simultaneously allowing access to the involved fascia beneath the incision site. However, the presence of existing skin necrosis may require unconventional incisions. When adequate exposure to the whole fascia cannot be achieved after the removal of necrotic skin, new incisions should be made or existing incisions should be extended, considering the circulation of the subsequent skin flaps. The choice of incision should be evaluated carefully to prevent disruption of skin circulation and preserve the cutaneous perforators wherever and whenever possible. Furthermore, standard fasciotomy incisions are theoretically advantageous for primary closure after the infection cools off or have a more straightforward reconstructive path to closure, such as skin grafting or simple rotation flaps during wound closure. Another point to consider in surgery is aggressive control of bleeding to avoid causing secondary burns to the tissues. A majority of tissue beds may have impaired vascularization due to underlying diseases and existing pathology, but at the same time, bleeding disorders caused by sepsis may lead to

Table 2. Mortality related results

	Mean± Percentage	Mortality (-)	Median	Mean± Percentage	Mortality (+)	Median	P-value
Age	52.9±14.3		53	69.78±9.38		73	0.002[t]
Sex							
Female	7	25.9		4	44.4		0.296x^2
Male	20	74.1		5	55.6		
Duration of DM (year)	11±8		9	14±8.49		14	0.524[m]
Hospitalization time	32.3±18.4		27	11.11±9.93		9	0.000[m]
LRINEC score	6.1±2		6	8.33±1.5		8	0.005[m]
DM							
(−)	13	48.1		7	77.8		0.121x^2
(+)	14	51.9		2	22.2		
Blood sugar regulation							
(−)	15	55.6		8	88.9		0.071x^2
(+)	12	44.4		1	11.1		
Comorbidity							
(−)	9	33.3		0	0		0.046x^2
(+)	18	66.7		9	100		
No. of operation							
I	10	37		9	100		0.004x^2
II	12	44.4		0	0		
III	3	11.1		0	0		
IV	1	3.7		0	0		
VI	3.7		0	0			
Culture positiviy							
(−)	8	29.6		0	0		0.064x^2
(+)	19	70.4		9	100		
Hemoculture positivity							
(−)	23	85.2		3	33.3		0.003 x2
(+)	4	14.8		6	66.7		
Imaging							
(−)	17	63		8	88.9		0.144x^2
(+)	10	37		1	11.1		

[t]: t-test, [m]: Mann-Whitney u test; x^2: Chi-square test (Fischer's test): LRINEC: Laboratory risk indicator for necrotizing fasciitis.

difficulty controlling the oozing of blood. Aggressive efforts in hemostasis in these poorly vascularized tissues with compromised blood supply may result in progressive necrosis, and it should be prevented as a rule of thumb. It should also be kept in mind that tissues are diversely circulated in the manner of vascularization level. Hence, poorly vascularized tissues such as tendon, septum, and joint capsule should be debrided more aggressively because if left undebrided, these tissues will not heal and progressively go into necrosis.

Early recognition of necrotizing fasciitis is possible only through proper evaluation of the patient with a suspicious mind and the identification of predisposing conditions that may validate this suspicion. The clinical presentation of necrotizing fasciitis initially resembles simple cellulitis, starting with cardinal signs of inflammation such as erythema, increased warmth, and pain. Rapidly progressing infection and local suppuration due to tissue necrosis occur in tissues with poor vascularity, such as fascia and subcutaneous fat. The condition progresses rapidly in the presence of factors such as insufficient blood delivery to the area or underlying immune deficiency-causing diseases, with poorly controlled diabetes being a prime example of such conditions. As the infection

spreads proximally, the likelihood of sepsis also increases.[5] The presence of crepitus on examination is an important finding that strongly indicates suppuration. Crepitus can also be a sign of bacterial agents that cause gas formation, such as C. perfringens. Most of this clinical picture predominantly progresses subcutaneously and "away from the eyes" up until the later stages, and delays in diagnosis can occur due to the preconceived notion that necrotizing fasciitis equals a graphic presentation with skin necrosis and ulceration. The most important message that learned the hard way is that when skin findings occur, it means condition, has already progressed to the level of systemic diseases, and sepsis is almost always present. Therefore, the aim for the primary physician should be to recognize the subtle findings in the initial stage before late-stage findings such as skin necrosis and ulceration occur. The time between the localized limited stage and the progressive septic stage will surely increase the amount of tissue that needs to be discarded, leading to both direct morbidity due to the loss of extensive tissue volume and increased mortality due to the resulting prolonged clinical course.

Studies have been conducted on the significance of laboratory parameters in early diagnosis due to misleading clinical examination findings. The LRINEC score, described by Wong, supports the diagnosis of necrotizing fasciitis when it is 6 or higher, and higher scores have been shown to be associated with mortality. In this scoring system, parameters such as CRP, sodium, creatinine, leukocyte count, and hemoglobin, which reflect infection and the body's response to infection, are evaluated. In our study, consistent with the literature, LRINEC scores of 6 or higher were found in 27 patients. The mean LRINEC score in the mortality group was 8.33, while in the non-mortality group it was 6.1, which is statistically significant (P=0.005).

Despite advancements in diagnosis and treatment, necrotizing fasciitis cases with delayed diagnosis can still be observed, and they are also associated with higher mortality rates. Exploring and identifying parameters related to mortality is crucial in determining high-risk patients, especially during time periods outside of regular working hours, in order to make sound triage decisions such as operating room prioritization and intensive care unit bed allocation. An age-related parameter known to be closely associated with mortality is advanced age. Elderly patients constitute a group with significantly higher mortality rates, as shown in studies by Arif et al. for ages 45 and above and by Elliot et al. for ages 60 and above.[6,7] In our study, the mean age in the mortality group was 70, while in the non-mortality group, it was 52. This may be attributed to the presence of comorbidities that increase in frequency with advancing age and the fact that clinical findings are often milder in elderly patients. Clinical and laboratory parameters indicating the body's response to infection can be concealed in elderly patients, leading to a delayed diagnosis. Moreover, prominent complaints related to the active comorbidities of the patients can mask vague signs of infection or make them manifest in different ways (fatigue, malaise, loss of appetite, increased sleepiness, etc.).

The positivity of blood cultures is associated with mortality as an indicator of septic conditions.[8] The pathogens grown in blood cultures generally correspond to the bacteria grown in wound cultures. With the development of antibiotic resistance, more virulent and potent strains have emerged. The most commonly grown pathogen in wound cultures is traditionally Group A Streptococcus pyogenes.[9] Recent studies have shown that multidrug-resistant pathogens are increasingly detected in wound cultures.[10] In our study, MRSA and E. coli were frequently isolated as poly-microbial pathogens. The development of resistant strains and the transformation of the wound environment from a single pathogen to a polymicrobial form have become important determinants of mortality.[11] The presence of resistant strains in cases that ended in mortality can be explained by the need for hospitalization and the infection caused by hospital-acquired flora. In some fast progressing cases, bacteria may not be detected in blood cultures, although they were cultured at the site of the wound. This can be attributed to the use of antibiotic therapy prior to blood culture collection.

Previously, the duration of time from infection onset to mortality has been investigated in the literature. Mortality rates of 45% within the first 10 days (as reported by Rouse et al.) and 60% within the first 7 days (as reported by Stone and Martin) have been referred in the literature.[12,13] Consistent with the literature, mortality was frequently observed in the early stages of our study as well. We believe that the fact that only one operation could be performed in the mortality group is due to the loss of patients due to fast-progressing disease, and patients didn't survive to undergo a second operation. Therefore, it is crucial to establish this logical relationship to avoid drawing incorrect conclusions from the statistical analysis of this study. Early patient loss in the mortality group may be associated with delayed presentation, rapidly progressing sepsis, and disrupted homeostasis due to existing comorbidities.

Diabetes is one of the most common comorbidities associated with soft-tissue infections.[14] The presence of diabetes can transform the clinical picture into necrotizing fasciitis by weakening the immune system, impairing wound healing, and leading to specific conditions such as diabetic foot infections. Although diabetes was found to be the most common comorbidity in our study, its relationship with mortality was determined to be insignificant. Blood sugar regulation is generally impaired in diabetic patients with an infected condition. However, in our study, it was observed that having a blood sugar level above 200 mg/dL at the time of admission in patients diagnosed with necrotizing fasciitis did not have any statistical significance for mortality.

In our study, the presence of colorectal carcinoma was found to be the most common comorbidity among the mortality

Figure 4. Wound related to the perineal and thigh related necrotizing fasciitis, patient had colorectal carcinoma resection a month ago presented with horseshoe pattern involving both thighs and perineum.

group. In malignancy patients, even in the absence of chemotherapy, general immune deficiency and susceptibility to opportunistic infections can be observed, especially in patients with non-solid tumors. Among the observed cases of necrotizing fasciitis associated with colorectal carcinoma in our patient group, three stemmed from the perineal region. In operated patients, especially those who have undergone rectal interventions, the anatomical barriers of the region are weakened, which accelerates the progression of an infection towards the central parts of the body. In operated patients, there is also a regional immune response disorder due to impaired lymphatic drainage in the area. Perineal surgery due to colorectal carcinoma, in addition to immunosuppression associated with malignancy and its treatment and the easy transmission of contaminated feces due to impaired continence, may be associated with the development and mortality course of necrotizing fasciitis (Fig. 4).

CONCLUSION

Necrotizing fasciitis is a soft-tissue infection that can result in death within hours if left untreated. It is important to accurately evaluate the clinical parameters of patients with necrotizing fasciitis at the time of admission and during follow-up. Barring a late diagnosis, mortality can be reduced through early and adequate surgical treatment, followed by appropriate antibiotic therapy and wound closure. Despite effective and prompt treatments, the course of necrotizing fasciitis can still be fatal, especially in elderly individuals with underlying diseases. But identifying parameters with a high risk of mortality can provide an opportunity to take proactive measures in the clinical management of patients that may surely increase the chance of survival and get away with life-altering morbidities.

Ethics Committee Approval: This study was approved by the University of Health Sciences Istanbul University Ethics Committee (Date: 07.06.2023, Decision No: 2023/99).

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ORİJİNAL ÇALIŞMA - *ÖZ*

Nekrotizan fasiitli hastalarda klinik parametrelerin mortalite üzerine etkilerinin araştırılması

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AMAÇ: Nekrotizan fasiit, fasyalar üzerinden hızla ilerleyen ölümcül olabilen bir yumuşak doku enfeksiyonudur. Tanı koyduracak inspeksiyon bulgularının hastalığın geç döneminde oluşması ve hızlı seyri nedeniyle hızlı tanı koymak zor olabilir. Hızlı ve doğru tanı konulması sonrasında erken dönemde yapılacak uygun cerrahi müdahale ile hastalığın ilerleyişi durdurulabilir. Doğru ve zamanında tedaviyle bile mortalite diğer yumuşak doku enfeksiyonlarından çok daha sık görülür. Bu çalışmada nekrotizan fasiitli hastalardaki klinik parametrelerin mortalite üzerine olan etkileri araştırılacaktır.
GEREÇ VE YÖNTEM: Çalışmaya 2009-2018 yılları arasında nekrotizan fasiit tanısı almış 37 hasta dahil edilmiştir. Hastalara ait demografik özellikler (yaş, cinsiyet, komorbid durumlar), eğer diyabet tanısı varsa tanı aldığından itibaren geçen süre, tanı aldığı andaki kan şekeri düzeyi, yaradan kültür ile izole edilen mikroorganizma, hemokültür pozitifliği olup olmaması, uygulanan antibiyoterapi, başvuru anındaki LRINEC skoru, geçirilen cerrahi işlem sayısı ve şekilleri, hastanede kalış süresi ve mortalite oranları retrospektif olarak kaydedilmiştir. Bağımlı ve bağımsız değişkenlerin istatistiksel incelemesi t-testi, Mann-Whitney U, ki-kare ve Fisher'ın kesinlik testi ile yapılmıştır.
BULGULAR: Yaş, mortalite grubunda ortalama 70 olarak bulunmuş olup mortalite olmayan gruba göre anlamlı olarak yüksektir. Yüksek LRINEC skoru, komorbidite varlığı, Hemokültür pozitifliği de mortalite ile ilişkili olarak anlamlı bulunmuştur. Geçirilen cerrahi işlem sayısının azlığı mortalite grubunda anlamlı olarak daha düşüktür.
SONUÇ: Zamanında ve doğru tanı sonucu uygulanan uygun antibiyoterapi ve cerrahi işlem ile tedavi edilebilen bir hastalık olan nekrotizan fasiitli hastalarda yüksek mortalite ile ilişkili durumları ortaya koyan bu çalışma, yüksek riskli grup hastalara yaklaşımı güncellemek için önem arz etmekte ve nekrotizan fasiit tanısını koyma eşiğini düşük tutmaya fayda sağlayacak bir bilgi sunmayı amaçlamaktadır.

Anahtar sözcükler: Akut ilerleyici yumuşak doku enfeksiyonu; nekrotizan fasiit; yumuşak doku enfeksiyonu.

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