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RESEARCH ARTICLE

Four Determinative Factors in Fournier's Gangrene Mortality

Fournier Gangreni Mortalitesinde Belirleyici Dört Faktör

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ABSTRACT

Aim: We aimed to more accurately predict mortality in Fournier's gangrene (FG) by investigating factors affecting mortality such as age, extent of infection, presence of accompanying comorbidities, the intensive care unit (ICU) length of stay (LOS).

Method: Routinely recorded data of 37 FG patients treated between February 2012-May 2018 were retrospectively evaluated. The patients were divided in two groups as the deceased group (DG) (n=10) and surviving group (SG) (n=27) and compared in terms of sex, age score (AS), dissemination score (DS), Uludağ Fournier's gangrene severity index (UFGSI) score, Fournier gangrene severity index (FGSI) score, serum urea levels, presence of diabetes and obesity, presence of comorbidities other than diabetes and obesity (COTDO), presence of diversion colostomy, number of days of vacuum-assisted closure treatment, hospital LOS, ICU LOS, and species of isolated bacteria. Associations between mortality and factors such as age, DS, COTDO, and ICU LOS were investigated in all cases.

Results: There was a significant difference between the two groups in terms of AS. DS was significantly higher in the DG than in SG. All of the patients in the DG had COTDO, while only 13 of the patients in the SG had these comorbidities, and the difference between the two groups was statistically significant. ICU LOS was significantly higher in the MG. In reciever operator characteristics curve analysis, UFGSI and FGSI had 93% specificity and 90% and 70% sensitivity, respectively. In logistic regression analysis, age, DS, COTDO, and ICU LOS were independent predictive factors associated with mortality.

Conclusion: Age, DS, COTDO, and ICU LOS showed significant differences between deceased and surviving patients, and emerged as independent predictive factors associated with mortality. As a result, these factors have been shown to be determinative factors in FG mortality.

Keywords: Fournier's gangrene, mortality, vacuum-assisted closure

ÖZ

Amaç: Fournier gangreninde (FG) mortaliteyi etkileyen yaş, enfeksiyonun yaygınlığı, eşlik eden yandaş hastalıkların varlığı, yoğun bakım gün sayısı (YBGS) faktörlerini araştırarak, mortalite öngörüsünü doğru şekilde önceden belirlemektir.

Yöntem: Şubat 2012-Mayıs 2018 arasındaki 37 FG hastasının prospektif kaydedilen verileri retrospektif değerlendirildi. Mortal (grup 1=10 hasta) ve sağkalan grup (grup 2=27 hasta) olarak iki gruba ayrılan hastalar cinsiyet, yaş skoru (YS), enfeksiyonun yayılım skoru (EYS), Uludağ Fournier gangreni şiddet indeksi (UFGSI) ve Fournier gangreni şiddet indeksi (FGSI) skorları, serum üre düzeyleri, enfeksiyon kaynağı, diyabet, obezite, diyabet ve obezite dışında yandaş hastalık (DODYH) varlığı, saptırıcı stomanın varlığı, vakum yardımlı kapama tedavisi gün sayısı, hastanede kalma gün sayısı, YBGS ve izole edilen bakteri tipleri açısından karşılaştırıldı. Tüm olguların tedavileri sırasında, mortaliteye belirgin etkilerini gözlemlediğimiz yaş, EYS, DODYH varlığı ve YBGS faktörlerinin mortalite üzerindeki etkileri incelendi.

Bulgular: YS bakımından da iki grup arasında anlamlı fark bulundu. EYS grup 1'de grup 2'den anlamlı olarak daha yüksekti. Grup 1'deki hastaların tamamında ve grup 2'dekilerin 13'ünde DODYH vardı ve iki grup arasında anlamlı fark bulduk. YBGS grup 1 hastalarda anlamlı olarak yüksekti. Alıcı işletim karakteristiği analizinde, UFGSI'nin ≥9 eşik değer için %90 duyarlılık ve %93 özgüllüğe, FGSI'nin ≥7 eşik değer için %70 duyarlılık ve %93 özgüllüğe sahip olduğunu saptadık. Lojistik regresyon analizinde, yaş, EYS, DODYH varlığı ve YBGS faktörlerinin mortaliteyle ilgili bağımsız öngörü faktörleri olduğunu bulduk.

Sonuç: Yaş, EYS, DODYH varlığı ve YBGS faktörlerinin gruplar arasında ileri derecede anlamlı farklar göstermesi ve bu faktörlerin mortaliteyle ilgili bağımsız öngörü faktörleri olması, FG'de mortalite öngörülebilirliği konusunda bu faktörlerin belirleyici olduğunu göstermektedir.

Anahtar Kelimeler: Fournier gangreni, mortalite, vakum yardımlı kapama

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Introduction

Fournier's gangrene (FG) is a suppurative bacterial infection of the anorectal, perineal, and genitourinary regions associated with high mortality and morbidity rates. It is a form of synergistic necrotizing fasciitis that causes thrombosis in subcutaneous vessels and results in gangrene in the overlying skin.[1,2,3] Delays in diagnosis and treatment increase mortality; therefore, symptoms should not be overlooked. The condition requires urgent and aggressive surgical debridement. The disease is named after Jean Alfred Fournier, a Parisian dermatologist and venereologist who presented the first case description in 1883.[1,2,4] Diabetes is the most common predisposing factor and is present in 20-70% of cases.[2,5] Chronic alcoholism is the second most common factor (25-50%). With all predisposing factors, immune resistance is impaired due to reduced cellular immunity.[1] Although FG can occur at all ages, its prevalence increases over the age of 50 years.[3,4] It is considered a disease of poverty.[1] Urogenital and anorectal infections and trauma are important in its etiology.[5] In addition to aggressive surgical debridement with effective antibiotic therapy, the basis of treatment is closing the open wounds created by debridement with skin flaps or grafts, using vacuum-assisted closure (VAC) systems to accelerating the formation of granulation tissue. Although a consensus has been reached regarding treatment of FG, the factors that determine mortality remain a subject of debate. In articles on this topic, each study group suggests different factors influencing mortality. Despite current advances in treatment, the mortality rate ranges between 3% and 45%.[1]

The aim of our study was to facilitate the accurate prediction of mortality by investigating factors that affect mortality in FG, including age, extent of infection, comorbidities, and length of stay (LOS) in intensive care. Our hypothesis was that age over 60 years, high dissemination score (DS), presence of comorbidities, and extended LOS in intensive care would increase the expected rate of mortality in patients with FG.

Materials and Methods

Ethical approval was obtained from the İstanbul Okmeydanı Training and Research Hospital Ethics Committee. Routinely recorded data from the medical files of 37 patients treated for FG between February 2012-May 2018 at the General Surgery Clinic of Okmeydanı Training and Research Hospital were retrospectively examined. Data pertaining to the 37 cases were evaluated in terms of age, sex, presence of obesity and comorbidities, etiology of infection, FG severity index (FGSI) score, Uludağ FGSI (UFGSI) score, need for stoma surgery, duration of VAC therapy, hospital LOS, intensive care LOS, mortality, and morbidity to identify factors that affect mortality in FG.

We attempted to establish more accurate prediction of mortality by particularly focusing on four factors we observed in our surgical practice to be closely associated with mortality in the cases examined in this study. Age and extent of infection are factors which have been highlighted in most previous studies and are accepted as directly associated with mortality. In terms of comorbidities, we observed diabetes and obesity in the majority of patients. Besides diabetes and obesity, we also observed greater mortality among patients with diseases such as heart failure, chronic obstructive pulmonary disease, hypertension, and various malignancies. We found it more suitable to evaluate intensive care LOS and presence of comorbidities other than diabetes and obesity (COTDO) for comorbidities.

All patients were diagnosed based on physical examination findings. For all patients, oral intake was discontinued at time of presentation to the emergency department and intravenous fluid and antibiotic treatment were initiated. At the same time, our surgical team began operative preparations major surgery. The purpose of surgical debridement is to remove all necrotic tissues, halt dissemination, and reduce systemic toxicity.[1] Surgical debridement was performed until perfused tissue was reached. Reinspections were done at 24- to 48-hour intervals to determine when repeat debridement was necessary, and continued until the infection was well controlled. Fecal diversion was done when necessary to protect the debrided area from contagion. Although there is no general consensus on colostomy, it is recommended in the presence of extensive sphincter damage or large perineal wounds.[5] The decision to conduct colostomy was made during the second debridement, when the sphincters could be better evaluated and the inflammation had substantially decreased.

Aggressive surgical debridement resulted in large tissue defects in all patients. Wound care is a key component of FG treatment due to the large tissue defects. VAC therapy has gained prominence in recent years and made significant contributions to this extremely difficult phase of the disease by accelerating wound healing with minimal skin defects.[6] All of our patients underwent VAC therapy after the completion of surgical debridement. VAC dressings were changed at intervals of 3 or 4 days. The final step in the treatment of all patients is closure of the large wound defects following the formation of granulation tissue induced by VAC therapy. In some patients, wound closure was possible with delayed primary suturing or V-Y local advancement flaps. However, split-thickness skin grafts were the most commonly used and preferred method for extensive wounds.

A total of 37 FG patients (21 males and 16 females) over the age of 30 were included in our study. Patients who underwent only VAC therapy after aggressive surgical debridement met

the inclusion criteria. Patients who were not treated with VAC after surgical debridement were excluded. These were patients with small, localized regions of involvement which were closed with cutaneous and subcutaneous primary suturing after at least two surgical debridements.

There is no reliable tool to estimate the severity of FG, but scoring systems can be used. An ideal scoring system should provide clear and effective information about the patient and also identify high complication and mortality rates.[7] Laor et al.[8] recommended the FGSI, which they created by adapting the acute physiological and chronic health evaluation (APACHE II) score for FG prognosis. They showed that the FGSI score can predict mortality rate with 75% accuracy and survival rate with 78% accuracy. The FGSI, which has attracted considerable attention in the literature, is a valid and effective scale commonly used in many studies to determine clinical outcomes of the disease. Yılmazlar et al.[9] have proposed a new scoring system by adding an age score (AS) and the DS to the FGSI. The most important feature of this scoring system, called the UFGSI, is the dissemination score.

The patients in our study were divided into the deceased (group 1, n=10) and surviving (group 2, n=27) groups. Patients in these groups were compared in terms of sex; AS, DS, UFGSI, and FGSI scores; serum urea levels; source of infection; presence of diabetes, obesity, and COTDO; the presence of a diversion stoma; VAC therapy duration, hospital LOS, and intensive care LOS; and species of bacteria isolated from culture. In addition, we evaluated associations between mortality and AS, DS, presence of COTDO, and intensive care LOS, which we observed clinically to have significant impact on mortality in our patients.

Statistical Analysis

Statistical analyses were done in SPSS for Windows version 15.0. The results were evaluated using a Mann-Whitney U test, chi-square test, receiver operating characteristic (ROC) curve analysis, and regression analysis. Differences were considered statistically significant at $p<0.05$.

Results

The mortality rate was 27% (10 patients).There was a significant sex difference between the groups (Table 1). Eight of the deceased patients were female. The mean age of the patients in our study group was 58.10±14.15 years. The mean age of the patients in group 1 (72.40±13.49) was significantly higher than that of the patients in group 2 (52.81±10.32) (Table 2). We noted a significant difference between the two groups in terms of AS, which is one of the parameters of the UFGSI (p=0.003) (Table 3). The DS, another of the UFGSI parameters, was also significantly higher in group 1 compared to group 2 (Table 3). The UFGSI and FGSI scores of the patients in group 1 were significantly higher than those of group 2 (Figures 1 and 2). Heart and respiratory rates, which are UFGSI and FGSI parameters, were significantly higher in group 1 compared to group 2, while hematocrit values were significantly lower in group 1 than in group 2 ($p<0.05$) (Table 2).

When we separately compared the groups' scores for each index, there were significant differences between the groups in body temperature, heart rate, respiratory rate, and serum potassium and bicarbonate levels ($p<0.05$) (Table 3). There was no significant difference between the groups in prevalence of diabetes mellitus (DM) or obesity (Table 1).

Table 1. Characteristics of the groups and factors associated with mortality

	Group 1 (deceased)	Group 2 (surviving)	p
Sex			
Female	8	8	**0.006***
Male	2	19	
Infection source			
Urogenital	7	15	0.42
Anorectal	3	12	
Diabetes mellitus			
(+)	8	25	0.27
(-)	2	2	
Comorbid disease (other than diabetes and obesity)			
(+)	10	13	**0.004***
(-)	0	14	
Obesity			
(+)	4	10	0.86
(-)	6	17	
Bacterial isolate			
(-)	3	10	
Escherichia coli	4	9	0.90
Other	3	8	
Diverting colostomy			
(+)	0	5	0.14
(-)	10	22	

All of the patients in group 1 and 13 of the patients in group 2 had COTDO (p=0.004) (Table 1). Intensive care LOS was significantly higher in group 1 patients (p=0.0001) (Table 2). All of the patients in group 1 stayed in the intensive care unit for 21.6±12.88 days, while 12 of the patients in group 2 stayed in the intensive care unit for 4.41±9.07 days.

Bacterial growth was observed in the wound cultures of 24 patients (64.8%). Bacteria were isolated from the cultures of 7 group 1 patients and 17 group 2 patients. The most common bacterium was *Escherichia coli*, which was isolated in 13 cases (35%). Other bacteria such as *Acinetobacter, Streptococcus, Staphylococcus aureus, Pseudomonas,* and *Klebsiella* were isolated in the wound cultures of 11 patients (29.7%). No significant difference was found between groups in terms of bacterial growth in cultures (Table 1).

In ROC analysis, the UFGSI had a sensitivity of 90% and a specificity of 93% at a threshold value of ≥9. The FGSI had 70% sensitivity and 93% specificity with a threshold of ≥7. The ROC curves are presented in Figure 3.

Table 2. Comparison of parameter means between groups and statistical significance of the differences

	Group 1** (deceased)	Group 2** (surviving)	p
Age (years)	72.4±13.49	52.81±10.32	0.0001*
Body temperature (°C)	37.75±1.01	37.25±0.60	0.139
Heart rate (/min)	101±14.88	90.22±8.79	0.034*
Respiratory rate (/min)	27±4.73	23.03±1.69	0.037*
Serum potassium (mmol/L)	3.64±0.91	4.16±0.80	0.072
Serum sodium (mmol/L)	136.4±4.92	137.18±4.56	0.801
Serum creatinine (mg/100 mL)	1.02±0.71	1.24±0.72	0.229
Hematocrit (%)	31.12±4.19	37.28±6.36	0.009*
Leukocyte count (x1000/mm^3)	21.13±4.47	19.38±5.25	0.353
Serum bicarbonate, venous (mmol/L)	22.58±6.43	22.92±4.15	0.169
VAC treatment duration (days)	32.3±14.5	28.92±18.27	0.489
Hospital length of stay (days)	38.5±17.29	41.04±21.14	0.602
ICU length of stay (days)	21.6±12.88	4.41±9.07	0.0001*

VAC: Vacuum-assisted closure, ICU: Intensive care unit
**Mean ± standard deviation

Table 3. Distribution of Fournier's gangrene severity index and Uludağ Fournier's gangrene severity index scores of the groups

	Group 1 (deceased)	Group 2 (surviving)	p
Body temperature score			
0	5	24	**0.011***
1	5	3	
Heart rate score			
0	6	25	**0.017***
2	4	2	
Respiratory rate score			
0	6	26	**0.004***
1	4	1	
Serum potassium score			
0	2	16	**0.016***
1	6	11	
2	2	0	
Serum sodium score			
0	9	24	0.923
2	1	3	
Serum creatinine score			
0	5	15	0.81
2	4	10	
3	1	1	
4	0	1	
Hematocrit score			
0	7	23	0.336
1	0	1	
2	3	3	
Leukocyte score			
0	1	6	0.617
1	3	9	
2	6	12	
Serum bicarbonate score			
0	2	19	**0.039***
1	1	1	
2	6	6	
3	1	0	
4	0	1	
Dissemination score			
Urogenital or anorectal: 1	3	23	**0.002***
Confined to the pelvic area: 2	2	0	
Extending beyond the pelvic area: 6	5	4	
Age score			
<60:0	2	20	**0.003***
≥60:1	8	7	

The sensitivity, specificity, odds ratios, and positive and negative predictive values for both scoring systems are shown in Table 4. Logistic regression analysis showed that age, DS, presence of COTDO, and intensive care LOS were independent predictive factors associated with mortality (Table 5). In addition, we found that female sex, heart rate, respiratory rate, and hematocrit value were also independent predictive factors associated with mortality.

Discussion

Prediction of mortality in FG continues to be a controversial topic. While 8 of the 16 females in our study died, only 2 of the 21 males died (Table 1). Comparison of the deceased and surviving groups confirmed that female sex was associated with higher mortality risk and was an independent predictive factor. As in our study, it has also been argued in some previous studies that female sex is a risk factor for mortality.[10,11]

Age is an important issue that has consistently emerged as a factor influencing mortality in many studies conducted to date.[7,9,12,13] We also found significant differences between the groups for patients above and below the age of 60 years (Tables 2 and 3). In addition, our analysis showed that age was an independent predictive factor for mortality.

The second noteworthy finding of our study was that DS was significantly higher in group 1 patients compared to group 2 patients (Tables 3 and 5). In line with the studies reported by Yılmazlar et al.[9,14], we found a significant correlation between DS and mortality and determined that it is an independent predictive factor.

Table 4. Uludağ Fournier's gangrene severity index and Fournier's gangrene severity index results with threshold values

	Threshold value 95% CI	Sensitivity	Specificity	Odds ratio	PPV	NPV
UFGSI	≥9*	90%	93%	34.86%	71%	85%
FGSI	≥7*	70%	93%	25.13%	66.6%	81.4%

CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, UFGSI: Uludağ Fournier's gangrene severity index, FGSI: Fournier's gangrene severity index

Table 5. Distribution of age, extent of infection score, presence of comorbidities other than diabetes and obesity, and intensive care length of stay in the groups

	Group 1 (deceased)	Group 2 (surviving)	p
Age (years)			
	72.4±13.49**	52.81±10.32**	**0.0001***
Age score			
<60:0	2	20	**0.003***
>60:1	8	7	
Comorbidity (other than diabetes and obesity)			
(+)	10	13	**0.004***
(-)	0	14	
Dissemination score			
Urogenital or anorectal: 1	3	23	
Confined to the pelvic area: 2	2	0	**0.002***
Extending beyond the pelvic area: 6	5	4	
ICU length of stay (days)			
	21.6±12.88**	4.41±9.07**	**0.0001***

**Mean ± standard deviation, ICU: Intensive care unit

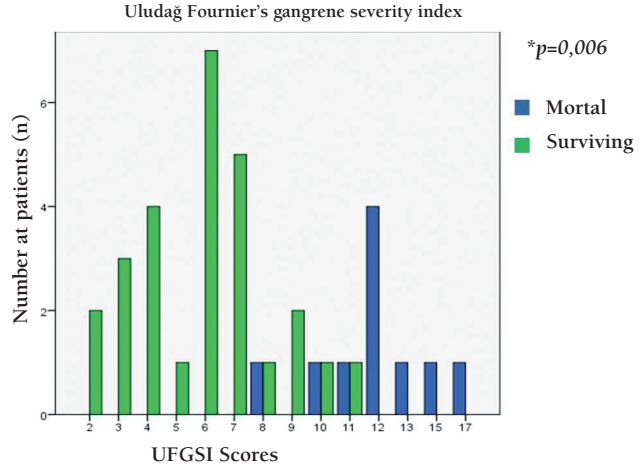

Figure 1. Distribution of patients according to UFGSI
UFGSI: Uludağ Fournier's gangrene severity index

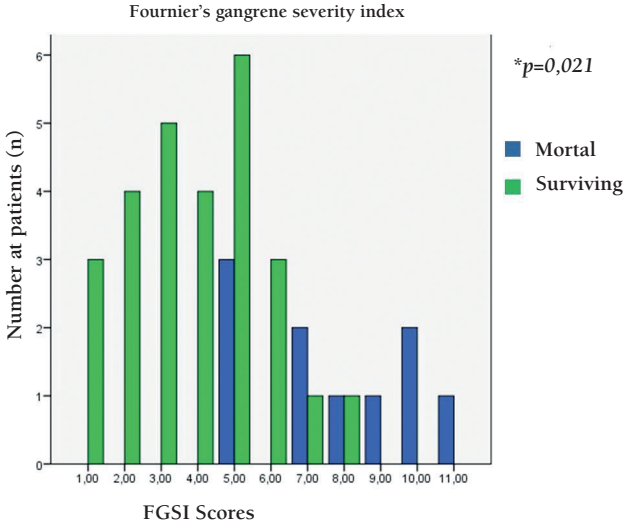

Figure 2. Distribution of patients according to FGSI
FGSI: Fournier's gangrene severity index

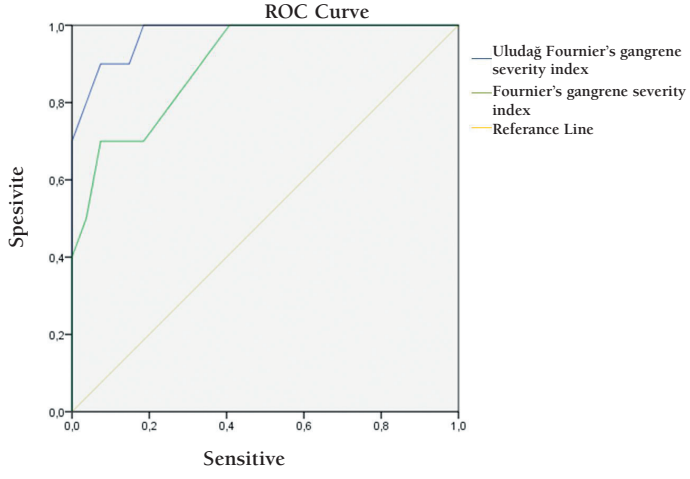

Figure 3. ROC curves for the Fournier's gangrene severity index and Uludağ Fournier's gangrene severity index
ROC: Receiver operating characteristic

Many previous studies have investigated the role of comorbid diseases in mortality. DM, which is considered one of the factors affecting FG, was present in 33 patients (89%) in our study (Table 1). However, we were unable to detect a correlation between DM and mortality in this study. Although the prevalence of DM was also high in other studies, DM alone does not impact mortality.[7,9,12] In our study, we found that although the presence of DM and obesity alone were not associated with mortality, comorbidities such as malignancies, heart failure, and respiratory failure had a significant effect on mortality (Table 1 and 5). The presence of COTDO was found to be an independent predictive factor for mortality.

In this study, hospital LOS did not differ significantly between the groups, but intensive care LOS was significantly longer in the deceased group (Table 2 and 5). Intensive care LOS was also observed to be an independent predictive factor for mortality. We did not encounter this result in other publications. This result is also among the most remarkable findings of our study.

Although the UFGSI and FGSI, which are the most widely used methods for predicting mortality due to FG, have shown acceptably high sensitivity and specificity, both scoring systems are quite complex. Due to this complexity, their implementation is not practical in the clinical setting. We believe that simpler and more practical scoring systems are needed. As mortality is a nearly inevitable outcome in patients with the four salient factors in our study, it may be possible to reduce mortality rates by minimizing intensive care LOS, which is a modifiable risk factor. With early diagnosis and extensive surgical debridement, DS can also be reduced by rapidly localizing infection to restricted areas, thus preventing mortality. The other significant factors in our study, age and comorbidities, are nonmodifiable host-related factors.

In our study, scores in the FGSI and UFGSI, which are scoring systems that predict mortality in patients with FG, were associated with mortality. Both scoring systems were found have 93% specificity (Table 4). Sensitivity was 90% for the UFGSI and 70% for the FGSI. Yılmazlar et al.[9] reported 94% sensitivity and 81% specificity for the UFGSI. Our results are similar to those reported by Yılmazlar et al.[9] Roghmann et al.[7] reported 85% sensitivity and 67% specificity for the UFGSI. In the aforementioned two studies, sensitivity and specificity for the FGSI were 65%-100% and 88-67%, respectively. In another study by Yılmazlar et al.[14], no patient with an UFGSI score ≥9 survived in a series of 120 patients. They reported threshold values of 9 and 7 for the UFGSI and FGSI, respectively. In the present study, we also used UFGSI and FGSI score thresholds of 9 and 7, respectively (Table 4).

In our study, 9 of the 13 patients with UFGSI scores ≥9 died, while only 1 of the 24 patients with scores of <9 died (Figure 1). Seven of the 9 patients with FGSI scores ≥7 died, while 3 of the 28 patients with scores <7 died (Figure 2). Although Yilmazlar et al.[9] reported no survival for patients with UFGSI scores ≥9 in their series of 120 patients, in our study there were 4 survivors among our patients with UFGSI scores ≥9 (Figure 1). There were also 2 survivors among patients with FGSI scores ≥7. Although these patients had scores above the threshold values and were at high risk of mortality, rapid and extensive debridement and effective treatment resulted in some survivors.

The most common bacterial species encountered in our study was *E. coli* (Table 1).[7,15] However, positive cultures and the bacterial species isolated were not associated with mortality.

We never recommend fecal diversion unless the patient has extensive sphincter damage or large perineal wounds. VAC therapy enables less frequent dressing changes, causes less pain, and has similar costs compared to traditional wound dressings in the treatment of FG patients. Using this method, the area of debridement can be kept clean, can heal quickly, and the need for fecal diversion and repeated debridement can be reduced.

Limitations of our study are its retrospective nature and the low number of patients. There are no large patient series pertaining to FG in the literature. The fact that we have a homogeneous patient population managed with the same treatment strategy is a strength of our study.

In conclusion, there are issues that remain to be clarified regarding the prediction of mortality in FG. Simple and practical scoring systems can assist clinicians in terms of modifiable factors that can reduce mortality rates. This study demonstrated very significant differences between deceased and surviving patients in DS, presence of COTDO, and intensive care LOS, and showed that these factors were independent predictive factors associated with mortality. Our findings suggest that these factors can serve as predictive indicators of mortality in FG. All of the predictions set forth in our study hypothesis were investigated and all were confirmed. In order for our findings to gain general acceptance in the literature, further research is needed to investigate the mortality predictive factors proposed here in a larger series of FG cases.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul Okmeydanı Training and Research Hospital Ethics Committee (Approval no: 05.06.2018/925).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.E., B.G., M.Y., S.H., D.Ö.K., Concept: S.E., S.K., Design: S.E., Data Collection or Processing: S.E., S.K., Analysis or Interpretation: S.E., S.K., Literature Search: : S.E., Writing: S.E.

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