

Fournier's Gangrene: Evaluation of Patient Outcomes Using Clinical Data and Prognostic Biomarkers

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ABSTRACT

Objective: To find out the outcomes of Fournier's gangrene (FG) patients using clinical data and prognostic biomarkers based on the current literature.

Study Design: Descriptive study.

Place and Duration of the Study: Department of General Surgery, University of Health Sciences, Gulhane Training and Research Hospital, Ankara, Turkey, from January 2018, to January 2022.

Methodology: Patients who were diagnosed with and treated for FG were included in the study. Patients younger than 18 years of age, those with missing hospital records and postoperative follow-up data, those with benign diseases related to the perianal or anal region, and those with other malignant diseases were excluded from the study. Patients' demographic, clinical, and laboratory data, including the calculated systemic immune-inflammation index (SII) and pan-immune-inflammation values (PIV) were obtained retrospectively from the medical records. Variables were analysed using SPSS statistics software, version 25.0. The value of $p < 0.05$ was considered statistically significant.

Results: A total of twenty-four patients, 14 (58.3%) males and 10 (41.7%) females, were included in this study. No statistically significant correlations were found between the calculated indices and patients' clinical outcomes. The length of intensive care unit stay was strongly and positively correlated with age ($r = 0.672$ and $p < 0.001$), and the length of hospital stay was moderately and inversely correlated with preoperative albumin levels ($r = -0.584$ and $p = 0.003$).

Conclusion: SII and PIV had no statistically significant interactions with FG.

Key Words: Fournier's gangrene, Systemic immune-inflammation index, Pan-immune-inflammation value, Colostomy, Albumin.

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INTRODUCTION

Fournier's gangrene (FG) is an infectious disease characterised by necrotizing fasciitis of the external genitalia and perianal region. Although not very common, FG plays an important part in surgical emergencies due to its high morbidity and mortality. Therefore, it is a pathology that requires rapid diagnosis and treatment in which dramatic results can be obtained with appropriate treatment modalities.¹

This disease was first described by Bauriène in 1764. The disease was renamed after a French dermatologist, Jean Alfred Fournier, who defined the disease in 1883 as a progressive gangrenous disease involving the penis and scrotum.²

FG can affect all age groups, from newborns to the elderly. The disease is relatively more common, especially in male patients and those over the age of fifty. In addition, FG is observed more frequently, especially in areas with low socioeconomic status.³

The diagnosis is made according to the clinical findings, and a multidisciplinary approach is required in the treatment. In the early period, aggressive debridement and broad-spectrum antibiotic therapy for potential microorganisms form the basis of the treatment. Delayed intervention, ineffective surgical debridement, an inability to administer appropriate antibiotics, and especially the presence of comorbid diseases, such as uncontrolled diabetes mellitus (DM), are considered responsible for higher mortality rates.⁴

Therefore, the clinical and laboratory parameters with particular emphasis on prognostic biomarkers of FG patients were investigated in this study. Moreover, the effects of those parameters on patients' clinical processes were examined based on the current literature. The objective of this study was to find out the outcomes of FG patients using clinical data and prognostic biomarkers based on the current literature.

METHODOLOGY

A total of twenty-four patients, who were diagnosed with and treated for FG between January 2018, and January 2022, consecutively, in the General Surgery Clinic, University of Health Sciences, Gulhane Training and Research Hospital, Ankara, Turkey, were included in this retrospective study. Demographic data, comorbidities, patient body-mass indices (BMIs), preoperative laboratory parameters, such as white

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blood cell counts (WBC), neutrophil (Neu) counts, lymphocyte (Lym) counts, platelet (Plt) counts, monocyte (Mon) counts, haemoglobin (Hb) levels, C-reactive protein levels (CRP), and albumin levels (Alb), American Society of Anesthesiologists (ASA) scores, treatment and operative strategies, tissue culture results, the length of hospital stay, the duration of follow-up at the intensive care unit (ICU), as well as the evaluation of surgical complications according to the Clavien-Dindo classification system, were retrieved from patients records and daily progress reports, which were later analysed in detail.⁵ Patients younger than 18 years of age, those with missing hospital records and postoperative follow-up data, those with benign diseases related to the perianal or anal region, and those with other malignant diseases were excluded from the study. The pan-immune-inflammation value was calculated as previously described [$PIV = (Neu \times Plt \times Mon) / Lym$].⁶ The systemic immune-inflammation index was similarly calculated as previously described [$SII = Plt \times Neu / Lym$].⁷ All data collection processes and data analyses were carried out with the approval of the local Ethics Committee (Decision Number: 2022/18).

The normal distribution of continuous variables was investigated using visual (histograms, stem & leaf plots, probability plots) and analytical methods (Shapiro-Wilk's test as the sample size was less than 30.) Descriptive analyses were presented using means \pm and standard deviations for the normally distributed parametric variables and medians as well as interquartile ranges (IQR) for the non-normally distributed and ordinal variables. Parameters that were normally distributed within two independent groups were compared with the Student's t-test. Parameters that were not normally distributed within two independent patient groups, as well as ordinal variables, were compared with the Mann-Whitney U test. Dichotomous and categorical variables in two groups were compared with Pearson's chi-squared test. Fisher's exact test was used where appropriate. The correlation between parametric variables was evaluated using the Pearson correlation test, and the strength of the correlation was determined and demonstrated according to the calculated correlation coefficients. The correlation between one parametric and one nonparametric variable, as well as between two nonparametric variables, was evaluated using Spearman's rank test, and the strength of the correlation was determined and demonstrated according to the calculated Spearman's Rho values. The level of statistical significance was determined as $p < 0.05$. All analyses were performed using IBM SPSS Statistics® Statistical Software Program version 25 (IBM Corporation, 1 New Orchard Road, Armonk, New York, United States).

RESULTS

A total of twenty-four patients, 14 (58.3%) males and 10 (41.7%) females, were included in the study. The mean ages of the female and male patients were 59.4 ± 18.7 and $60.1 \pm$

17.7, respectively. No significant difference could be observed between the male and female patients in terms of laboratory tests, BMI results, ASA scores, or comorbidities. Moreover, there was no significant difference between the male and female patients in terms of treatment strategies or complications.

Eleven (45.8%) patients needed a diverting colostomy, and thirteen (54.2%) patients could be treated without the need for a diverting colostomy over the course of their treatment. Laboratory tests, demographic data, and comorbidities did not exhibit any statistically significant difference between those two patient groups, except for preoperative albumin levels, as preoperative albumin levels of patients without a need for colostomy were significantly higher than those with colostomies (2.80 ± 0.40 vs. 2.40 ± 0.47 , $p=0.035$, respectively). However, the length of hospital stay (16 (8-65) vs. 32 (17-50), $p=0.001$, respectively) and the duration of follow-up at the ICU (0 (0-12) vs. 5 (0-35), $p=0.009$, respectively) were significantly longer in patients with colostomy, with a significantly higher number of consecutive operations during follow-up (4 (2-12) vs. 5 (4-10), $p=0.001$, respectively, Table I). Although the patients who needed colostomy were demonstrated to have higher ASA scores ($p=0.045$), no significant differences were observed between the two groups in terms of treatment strategies or complications (Table II). Most of all, no mortality was observed in any of the patients during follow-ups.

The duration of follow-up at the ICU was strongly and positively correlated with patient age ($p < 0.001$, Spearman's Rho = 0.672), the number of operations performed ($p < 0.001$, Spearman's Rho: 0.725), as well as the length of hospital stay ($p < 0.001$, Spearman's Rho = 0.695), whereas it was strongly and inversely correlated with albumin levels ($p=0.001$, Spearman's Rho = -0.641). Similarly, the length of hospital stay was strongly and positively correlated with the number of operations performed ($p < 0.001$, Spearman's Rho = 0.863) and the duration of follow-up at the ICU ($p < 0.001$, Spearman's Rho = 0.695), whereas it was moderately and inversely correlated with patient preoperative albumin levels ($p=0.003$, Spearman's Rho = -0.584).

SII and PIV were analysed and compared for all patients in all study groups. Median SII did not significantly differ, neither between females and males [4959 (1157-23023) vs. 4289 (1182-12195), respectively, $p=0.725$, Table I] nor between patients with colostomy and without colostomy [4661 (1857-12195) vs. 3966 (1157-23023), respectively, $p=0.569$, (Table I)]. Likewise, neither gender difference nor colostomy need was associated with PIV [59425.4 (4845.2-156380.9) in females vs. 102521.1 (6468.3-1192319.4) in males, respectively, $p=0.266$, and 88172.4 (4845.2-257769.2) in patients with colostomy vs. 74063.8 (6468.3-1192319.4) in those without colostomy, respectively, $p=0.955$ (Table I)]. In addition, treatment variables indicated no statistically significant correlations with SII or PIV.

Table I: Clinical data of the patients compared according to the need for colostomy.

	No Colostomy (n=13)	Colostomy (n=11)	p
Age (Mean \pm SD)	59.6 \pm 16.5	59.7 \pm 20.2	0.988
Number of operations [Median (min-max)]	4 (2-12)	5 (4-10)	0.001
White blood cell count [Median (min-max)]	16.8 (7.1-51.7)	21.6 (6.9-30.0)	0.361
Haemoglobin level (g/dl) (Mean \pm SD)	12.2 \pm 1.8	12.5 \pm 1.8	0.719
Neutrophil count (10^6 / L) [Median (min-max)]	15.7 (5.1-49.1)	18.6 (9.1-23.0)	0.706
Lymphocyte count (10^6 / L) (Mean \pm SD)	1.09 \pm 0.50	0.96 \pm 0.54	0.552
Platelet count (10^9 / L) (Mean \pm SD)	287.5 \pm 86.9	260.2 \pm 94.4	0.468
CRP Level (Mean \pm SD)	237.3 \pm 71.4	294.0 \pm 125.9	0.205
Presence of type II DM			0.916
None	5 (20.8 %)	4 (16.7 %)	
Present	8 (33.3 %)	7 (29.2 %)	
Presence of hypertension and/or CAD			0.562
None	5 (20.8 %)	3 (12.5 %)	
Present	8 (33.3 %)	8 (33.3 %)	
Presence of type II DM and at least one additional comorbidity			0.113
None	10 (41.7 %)	5 (20.8 %)	
Present	3 (12.5 %)	6 (25.0 %)	
Days of ICU stay [Median (min-max)]	0 (0-12)	5 (0-35)	0.009
Duration of hospitalisation (days) [Median (min-max)]	16 (8-65)	32 (17-50)	0.001
Albumin level (mg/dl) (Mean \pm SD)	2.80 \pm 0.40	2.40 \pm 0.47	0.035
Body mass index (Mean \pm SD)	29.4 \pm 7.1	28.0 \pm 3.7	0.566
Systemic immune-inflammation index [Median (min-max)]	3966 (1157-23023)	4661(1857-12195)	0.569
Pan-Immune Inflammation Value [Median (min-max)]	74063.8	88172.4	0.955
	(6468.3-1192319.4)	(4845.2-257769.2)	

*Min: Minimum; Max: Maximum; CRP: C-Reactive protein; DM: Diabetes mellitus; CAD: Coronary artery disease; ICU: Intensive care unit. SD: Standard deviation. To compare continuous parametric variables in two independent groups, Student's T-test was used. To compare continuous nonparametric variables in two independent groups, Mann-Whitney Test was used. Frequency distribution of type II DM, Hypertension and/or CAD as well as type II DM and at least one additional comorbidity among patients with and without colostomy were presented by using cross-tabulations. The Pearson chi-square test or (when chi-square test assumptions do not hold due to low expected cell counts) Fisher's exact test, where appropriate, was used to compare these proportions in different groups. A p-value of less than 0.05 was considered to show statistical significance.

Table II: Treatment-associated features of the patients compared according to the need for colostomy.

	No colostomy (n=13)	Colostomy (n=11)	p
Gender of the patients			0.628
Male	7 (29.2 %)	7 (29.2 %)	
Female	6 (25.0 %)	4 (16.7 %)	
ASA score of the patients			0.045
ASA I-II	10 (41.7 %)	4 (16.7 %)	
ASA III-V	3 (12.5 %)	7 (29.2 %)	
Type of the operation			0.347
Drainage	1 (4.2 %)	0 (0.0 %)	
Drainage and VAC	12 (50.0 %)	11 (45.8 %)	
The need for additional urologic surgery			>0.999
Not necessary	12 (50.0 %)	10 (41.7 %)	
Necessary	1 (4.2 %)	1 (4.2 %)	
Tissue Culture Results			0.132
Escherichia coli	6 (25.0 %)	6 (25.0 %)	
Enterococcus spp.	5 (20.8 %)	0 (0.0 %)	
Klebsiella spp.	2 (8.3 %)	3 (12.5 %)	
Staphylococcus spp.	0 (0.0 %)	1 (4.2 %)	
Streptococcus spp.	0 (0.0 %)	1 (4.2 %)	
Clavien-Dindo classification system			0.113
Clavien-Dindo Type I	4 (16.7 %)	3 (12.5 %)	
Clavien-Dindo Type II	0 (0.0 %)	5 (20.8 %)	
Clavien-Dindo Type III	1 (4.2 %)	1 (4.2 %)	
Grafting			0.576
None	12 (50.0 %)	9 (37.5 %)	
Present	1 (4.2 %)	2 (8.3 %)	
Type of antibiotics used			0.760
Piperacillin and Tazobactam combinations	4 (16.7 %)	5 (20.8 %)	
Meropenem combinations	6 (25.0 %)	4 (16.7 %)	
Other combinations (Ampicillin, cefoperazone + sulbactam, ceftriaxone +metronidazole, Imipenem and others)	3 (12.5 %)	2 (8.3 %)	

*ASA: American Society of Anesthesiologists; VAC: Vacuum-assisted wound closure; spp: several species. Frequency distribution of genders, patient ASA scores, type of the operation, the need for additional urologic surgery, tissue culture results, postoperative surgical complications according to Clavien-Dindo classification system, grafting as well as types of antibiotics used with respect to the need for colostomy were presented by using cross-tabulations. The Pearson chi-square test or (when chi-square test assumptions do not hold due to low expected cell counts) Fisher's exact test, where appropriate, was used to compare these proportions in different groups. A p-value of less than 0.05 was considered to show statistical significance.

DISCUSSION

FG is a life-threatening disease that may rapidly progress to sepsis and septic shock, which dictates urgent intervention.⁸ Typical medical treatment interventions may include the intravenous administration of broad-spectrum antibiotics determined by the results of repeated tissue and/or abscess cultures, as well as high-dose nutritional protein-energy support.⁹ Additionally, common operative treatment strategies that are used more often may include diversion of intestinal contents by ileostomy or colostomy, effective multiple surgical debridement and drainage, vacuum-assisted wound closure (VAC) therapy, and grafting/flapping. However, rather than using them separately, a combination of both treatment modalities is generally utilised. Indeed, almost all of the mentioned treatment options were selected individually for the patients included in this study.

Martinschek *et al.*¹⁰ indicated the importance of appropriate antibiotic therapy and ICU stay in FG, with a particular emphasis on the use of hyperbaric oxygen therapy. In a report of a difficult FG case with an unknown type-II DM by Pastore *et al.*,¹¹ a multistep approach consisting of immediate surgical debridement and negative-pressure wound therapy tailored to hyperbaric oxygen therapy was demonstrated to be beneficial. Hyperbaric oxygen therapy was repeatedly reported to be useful in the treatment of FG, though none of the patients in this study received hyperbaric oxygen therapy, which might be regarded as a limitation for this study.

Iacovelli *et al.* suggested that the utilisation of VAC therapy did not result in any significant improvements in local FG;¹² however, it provided an actual advantage in early wound closure in disseminated FG. Contrary to the findings in the study by Iacovelli *et al.*, it was revealed in this study that no significant difference could be observed for VAC therapy in any study group.

Low platelet counts, low haemoglobin and creatinine levels, and a higher number of reoperations but no other laboratory parameters were demonstrated to be significantly associated with the risk for complications in FG.¹³ Similarly, Lin *et al.* also indicated in their study that WBC count was not related to patient prognosis in FG.¹⁴ Correspondingly, no significant associations could be demonstrated between the groups for any laboratory parameters in this study.

It was previously suggested by Doluoglu *et al.* that low albumin levels were significantly associated with poor prognosis in FG.¹⁵ Moreover, it was stated that elderly patients had a higher risk for FG and worse outcomes might develop following treatment.¹⁶ Likewise, patient age was shown to be older, and the number of operations, the length of ICU stay during follow-up, as well as the length of hospitalisation, were all shown to be significantly higher in patients with low albumin levels in this study.

Hatipoglu *et al.* presented their five-year experience in patients with FG, indicating that median BMI was 26.54 ± 3.93 and BMI was not associated with any variables or recurrence in FG.¹⁷ The results of this study also indicated that the BMI did not significantly differ between different patient subgroups in FG. However, it is widely accepted that the patients with a high BMI are prone to many infectious diseases due to the metabolic syndrome or occult diabetes. Therefore, patients with a high BMI always constitute a potential risk group for FG. The results in this study might not be significant due to the low number of patients.

It was stated in the literature that diverting colostomy was a controversial issue in FG. Several other options, such as the use of a rectal tube or bowel management tube, were proposed for faecal diversion.¹⁸ Nevertheless, several authors previously recommended diverting colostomy, especially in high-risk patients.¹⁹ Similarly, patients with diverting colostomy constituted 45.8% of all patients included in the study, and the presence of diverting colostomy was found to be associated with higher ASA scores, as well as longer ICU and hospital stays, which is consistent with current studies for high-risk patients in the literature.

An ever-increasing number of studies that investigate the association of SII and PIV with disease prognosis and the outcome suggested true relevance in various malignant, rheumatological, and inflammatory diseases.^{6,7,20-22} SII and PIV were demonstrated to significantly increase in hidradenitis suppurativa, a disease of the intertriginous skin that is characterised by chronic inflammation.²³ However, a detailed search of the current literature did not reveal any studies investigating the importance or relevance of SII and PIV in FG, necrotizing fasciitis, or in diseases with soft tissue necrosis. Therefore, to the best of the authors' knowledge, this is the first and only study that investigated the relevance of these prognostic biomarkers in FG. Yet, this study did not reveal any statistically significant associations for SII or PIV with clinical parameters or patient outcomes.

Ballard *et al.* stated that computed tomography (CT) was critically important in the detailed evaluation of anatomical planes in FG.²⁴ However, imaging findings were not analysed in this study, mostly because the imaging modalities (CT scans, magnetic resonance imaging, and ultrasonography) used in the follow-up of the patients with FG were found to demonstrate substantial heterogeneity. Therefore, the analysis of the imaging modalities in patients with FG was beyond the scope of this manuscript. In addition, although the utilisation of Fournier's Gangrene Severity Index (FGSI) in clinical practice was recommended by others, that index was not commonly used in the authors' daily clinical practice and was therefore intentionally ignored in the preparation of this manuscript. Early recognition of FG in the local period and urgent radical surgery were suggested to make a significant contribution to recovery.³ In this study, however, no analysis was performed in terms of local phase separation of

FG or the time from admission to surgery. The retrospective, single-centre design with a limited number of patients may comprise other limitations of the present study. Nevertheless, it should not be neglected that FG is rather rare, and only a minute portion of current literature includes such studies.

CONCLUSION

FG is a life-threatening and rapidly progressive disease. It is essential to benefit from broad-spectrum antibiotic regimens, as well as treatment modalities such as VAC therapy, diverting colostomy, and grafting. Low albumin levels and increasing age are risk factors that may influence the course of FG. However, SII and PIV were studied for the first time in FG, and no statistically significant associations were found. Still, there is a need for prospective studies with larger patient populations.

ETHICAL APPROVAL:

This study was approved by the Ethics Committee of Gulhane Training and Research Hospital (Date: 02.03.2022, Study Number: 2022/18).

COMPETING INTEREST:

The authors have no competing interest to declare.

PATIENTS' CONSENT:

Informed consent was obtained from participants in this study.

AUTHORS' CONTRIBUTION:

BU: Data acquisition and analysis, interpretation, drafting, and final approval.

SAK: Conception and design, interpretation, critical revision, and final approval.

MZB: Design, critical revision, and final approval.

MSC: Analysis and interpretation, drafting, and final approval.

OH: Interpretation, critical revision, and final approval.

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