Clinical Value of the Monocyte-to-Lymphocyte Ratio for Determining Number of Debridements in Treatment of Fournier's Gangrene

Monosit-Lenfosit Oranının Fournier Gangreni Tedavisinde Debridman Sayısına Karar Vermede Klinik Etkisi

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▌▌▌▌▌▌▌ **ABSTRACT**

Aim: Fournier's gangrene (FG) is a rapidly progressive, fulminant necrotizing fasciitis of the anogenital region. Treatment of FG consists of aggressive surgical debridements. The current scoring systems in FG focus on mortality. However, simple biomarkers could be useful. Here we aim to investigate the clinical usefulness of monocyte-to-lymphocyte ratio (MLR) in determining the number of debridements in FG patients.

Method: Fifty-nine patients were diagnosed with FG and operated in the emergency unit between 2010 and 2016. The patients were separated into a single-debridement group and a multiple-debridement group. The groups were compared in terms of mean age, gender, duration of symptoms, predisposing factors, wound culture positivity, MLR values at admission, treatment protocols, and mortality rates.

Results: The two groups differed significantly in wound culture results and colostomy status (p=0.001 and p=0.008). There was no significant difference in mortality rate (p=0.749). Furthermore, there were no significant differences between the groups in terms of predisposing factors or duration of symptoms (p=0.069 and p=0.091). The multiple-debridement group had a significantly higher MLR value (p<0.001). MLR under the cut-off value of 0.549 had 79.4% sensitivity and 76% specificity in the prediction of number of debridements. Furthermore, MLR value could predict the number of debridements independently from other factors (p<0.001).

Conclusion: MLR value was significantly higher in patients who underwent multiple debridements. Thus, MLR shows promise as a single-parameter biomarker for FG severity. Future studies should focus on this parameter using a larger number of FG patients.

Keywords: Fournier's gangrene, debridement, monocyte, lymphocyte

▌▌▌▌▌▌▌ **ÖZ**

Amaç: Fournier gangreni (FG) anorektal bölgenin klinik olarak çok hızlı kötüleşen, ölümcül nekrotizan fasiitidir. FG tedavisinin temelini agresif cerrahi debridman oluşturur. Güncel skorlama sistemleri FG'de mortalite üzerine yoğunlaşmıştır. Bununla birlikte serum belirteçleri yararlı olabilir. Bu çalışmada FG hastalarındaki debridman sayısını belirlemede monosit-lenfosit oranının (MLO) klinik etkisini ortaya koymayı amaçladık.

Yöntem: 2010-2016 yılları arasında hastanelerimiz acil servisinde FG tanısıyla tanı konup opere edilen 59 hasta çalışmaya dahil edildi. Tek debridman uygulanan grup 1 ve birden çok debridman uygulanan hastalar grup 2 olarak iki gruba ayrıldılar. Grupların ortalama yaş, cinsiyet, semptom süresi, predispozan faktör, yara kültür pozitifliği, kolostomi durumu, yatış anındaki MLO'lar, tedavi protokolleri, mortalite oranları karşılaştırıldı.

Bulgular: İki grup arasında yara kültür sonuçları ve kolostomi durumları arasında istatistiksel anlamlı fark bulundu (p=0,001 ve p=0,008). Mortalite oranları arasında anlamlı fark bulunamadı (p=0,749). Predispozan faktörler ve semptomların süresi arasında gruplar arası anlamlı fark bulunamadı (p=0,069, p=0,091). Grup 2'de MLO anlamlı oranda yüksekti (p<0,001). 0,549 cut-off değerinde MLO debridman sayını öngörmede %79,4 sensitivite ve %76 oranında spesifiteye sahipti. Ayrıca MLO debridman sayını diğer faktörlerden bağımsız olarak öngörebilmekteydi (p<0,001).

Sonuç: MLO değeri birden çok debridman yapılan hastalarda anlamlı oranda yüksek bulundu. Bu sonuç, MLO'nun tek bir parametre olarak FG ciddiyetini göstermesi bakımından önemlidir. Gelecekte düzenlenebilecek daha yüksek hasta popülasyonlu çalışmalar parametrenin gücünü gösterebilmeleri açısından önem kazanmıştır.

Anahtar Kelimeler: Fournier gangreni, debridman, monosit, lenfosit

Anuk et al.
Determining Number of Debridements in Treatment of Fournier's Gangrene

39

Introduction

Fournier's gangrene (FG) is a rare, rapidly progressive, fulminant form of necrotizing fasciitis of the perineum, genitalia and perianal region. It is a polymicrobial infection of aerobic and anaerobic bacteria and characterized by obliterative endarteritis of subcutaneous tissue leading to gangrene.[1,2] Although first described by French physician H. Baurienne in 1764, the disease was named after French venereologist Jean Alfred Fournier, who presented in 1883 the case of a young male with perineal gangrene of sudden onset.[3] FG affects mainly males (the male/female rate is 10:1) and patients over 50 years of age.[1] The principal therapeutic approaches for FG are aggressive surgical debridements, with the administration of wide-spectrum antibiotics and supportive drugs.[3] Nevertheless, FG continues to have a high mortality rate. Despite being a well-described entity, the disease has a mortality rate ranging from 20% to 50%.[2] Many of the underlying etiologic factors have been described in the literature. These include diabetes mellitus, malignant conditions, chronic alcoholism and other immunosuppressive conditions.[4]

There are several scoring systems for mortality prediction in FG. Acute Physiology and Chronic Health Evaluation (APACHE) II is a commonly used scoring system predicting the mortality of critical patients. Another is Fournier's Gangrene Severity Index (FGSI), which is specific for FG. Uludağ Fournier's Gangrene Severity Index (UFGSI) is a new scoring system that was established in Uludağ University in Turkey.[5] However, all systems focus on mortality and are too complicated to be easily calculated under urgent conditions.

To our knowledge, the monocyte-lymphocyte ratio (MLR) has not as yet been used for the prediction of FG's debridements. Here we investigated the factors affecting the number of debridements and the ability of MLR to predict debridements number in FG patients.

Materials and Methods

After the approval of the local institution's ethics committee, 59 patients admitted to the emergency care units of Kafkas University, Kars State Hospital and Dışkapı Yıldırım Beyazıt Training and Research Hospitals for perineal pain, swelling and purulent flow were investigated between years 2010 to 2016 (Approval number: 27.04.2016/51). The patients were operated on after being diagnosed with FG by the general surgery unit. For the 59 patients included in the study, full medical information was obtained from a computer database. Age, gender, duration from beginning of the symptoms to admission, predisposing factors, laboratory results, and MLRs were encoded. The patients were then sorted into two groups: those who had undergone one debridement (single debridement group) and those who had undergone two or more debridements (multiple debridement group). The groups' age, gender, time of complaint, predisposing factors, MLR values at admission, wound culture results which were obtained by wound swabs during first debridement, treatment protocols and mortality rates during this early period after admission were compared. Patients who had active infection, had used antibiotherapy in the last week, who had hematological or immunological disorders, who had recently had a blood transfusion or whose data were missing, were excluded from the study. The leukocyte count and monocyte count percentages were measured by an automated hematology analyzer (Coulter Counter Model S-Plus Jr, Coulter Electronics, Hialeah, FL). The reference interval of monocyte and of lymphocyte were 300-900 per mm[3] and 900-3.700 per mm[3] respectively.

Statistical Analysis

The data analysis was performed using the Statistical Package for the Social Sciences for Windows, version 22 (SPSS Inc, Chicago, IL, USA). Whether the distributions of continuous variables were normal was determined using the Kolmogorov-Smirnov test. Data are shown as mean ± standard deviation or median (minimum-maximum), where applicable. The differences between the groups were compared using the student's t-test or Mann-Whitney U test, where appropriate. Categorical data were analyzed by the Pearson's chi-square test where appropriate. The cut-off values of parameters for discrimination of the groups were determined using receiver operating characteristic (ROC) analysis. At each value, the sensitivity and specificity for each outcome under study were plotted, thus generating an ROC curve. A p-value less than 0.05 was considered statistically significant.

Logistic regression analysis was used to assess the differences between groups. The coefficient of regression and the 95% confidence interval for each independent variable were also calculated.

Results

The median age of the patients was 53 years (ranging from 23 to 87) and the male/female ratio was 2.1. The median duration of symptoms was 5.0 (0-21) days. Only 14 patients had predisposing factors. Patients demographic characteristics were given on Table 1. In the single debridement group, three patients had predisposing factors. In the multiple debridement group, five patients had perianal abscesses and perianal fistulas. One patient also had rectal traumatic laceration, and three patients had previously reported FG operations. One patient in

40

Anuk et al.
Determining Number of Debridements in Treatment of Fournier's Gangrene

this group had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy and one patient had urogenital infection. These results did not show statistical significance in terms of predisposing factors between groups (p=0.069).

Groups were compared with wound culture results and there was statistical significance between groups (p=0.001). In the single debridement group, only one patient had a documented *Escherichia coli* positive wound culture. However, in the multiple debridement group, 10 patients had *Escherichia coli*, three patients had an *Acinetobacter* infection, one patient had a *Candida albicans* positive culture result, and one had an *Methicillin-resistant Staphylococcus aureus* infection.

Thirty patients had undergone simple debridement, 12 patients had undergone debridement and colostomy, 13 patients had undergone major debridement, one patient had undergone penilectomy, one patient had been discharged before treatment without permission and two had undergone debridement and vacuum-assisted closure (VAC) application. Twenty-five patients had one debridement and 34 patients had had two or more debridements. One patient had undergone colostomy in the single debridement group and 11 patients had undergone colostomy in the multiple debridement group, these two groups were significantly for this trait (p=0.008). Age, gender, and duration of symptoms were compared between the two groups and the three parameters showed a homogenous distribution (p=0.286, 0.248 and 0.091). The mortality rate was 6.8% (four patients). Two of these patients were in the single debridement group and two were in the multiple debridement group. There was no statistically significant difference in the mortality rates between the groups (p=0.749). Comparisons between groups were given on Table 2.

The median MLR values of the single and multiple debridement groups were 0.33 (0.09-0.91) and 0.81 (0.25-2.30) respectively, which was significantly higher in the multiple debridement group (p<0.001) (Figure 1). ROC curve analysis returned a below cut-off value for MLR (0.549)

in an area of 0.881 [95% confidence interval (CI): 0.794-0.968], with a 79.4% sensitivity, 76% specificity, 81.8% positive predictive value and 73.1% negative predictive value for predicting number of debridements (Figure 2).

When age, gender, culture positivity, duration of symptoms, predisposing factors and MLR value were analyzed together for predicting number of debridements, the MLR value could predict the number of debridements independently from the other factors (p<0.001).

Table 1. Patients' demographic characteristics

Parameters	Number
Male/female ratio	40/19
Age	53 (23-87)
Patients with predisposing factors	14/59 (23.7%)
Exitus patients	4/59 (6.8%)
Patients had one debridement/patients had ≥2 debridements	25/34
Total number of patients	59 (100%)

Table 2. Comparisons between groups

Parameters	Group 1	Group 2	p
Number of patients	25	34	0.241
Male/female ratio	19/6	21/13	0.248
Age (median-minimum-maximum)	47 (23-84)	56 (23-87)	0.286
Patients with predisposing factors	3/25	11/34	0.069
Duration of complaints (days)	7 (0-15)	4 (0-21)	0.091
MLR value	0.33 (0.09-0.91)	0.81 (0.25-2.30)	<0.001
Colostomy	1/25	11/34	0.008
Exitus	2/25	2/34	0.749
Culture positivity	1/25	15/34	0.001

MLR: Monocyte-lymphocyte ratio
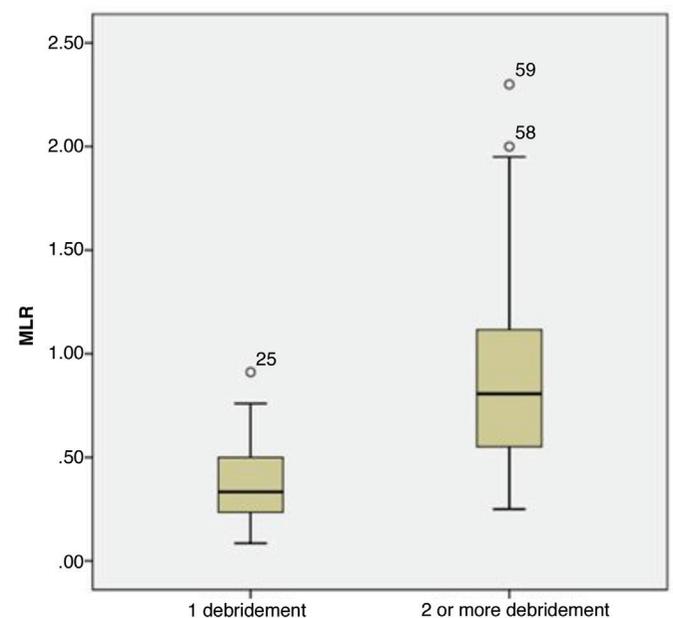
Figure 1. Monocyte-lymphocyte ratio distribution between groups
MLR: Monocyte-lymphocyte ratio

Anuk et al.
Determining Number of Debridements in Treatment of Fournier's Gangrene

41
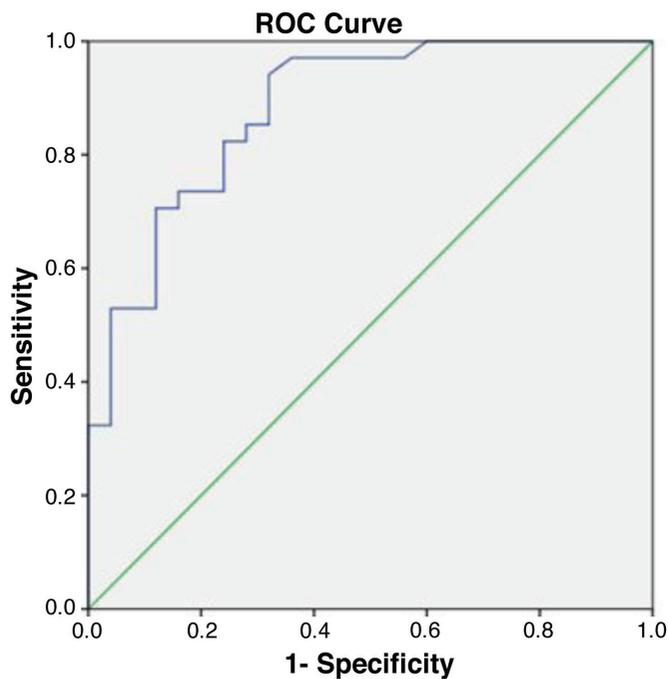
ROC Curve

Figure 2. Monocyte-lymphocyte ratio value assessed by receiver operating characteristic curve analysis
ROC: Receiver operating characteristic

Discussion

FG is a surgical emergency for which the main therapy is aggressive debridement. However, adequate treatment does not reduce the high mortality rates. Although recent technological improvements in antimicrobial agents has increased the spectrum and efficacy of these drugs, early surgical intervention remains the principal therapy for FG because tissue necrosis can rapidly progress (up to 2 cm/h) and sepsis leading to death quickly can develop.[6,7]

Many underlying conditions contribute to the formation of FG, such as diabetes mellitus, immunosuppression, local trauma, genitourinary infections, acquired immunodeficiency and malignancy. All of these conditions lead to a decline in the host immunity and contribute to polymicrobial infection.[1] When FG was first discussed in the literature, the disease was described as an idiopathic condition. However, most cases were related to an identifiable cause, like perianal and urinary tract infections, with the most common initial port of entry being local trauma.[1,2] In our study, predisposing factors and wound culture results were compared between the single and multiple debridement groups, wound culture result positivity showed statistical significance. However, in our study wound culture result showed aerobic culture positivity than anaerobic colonies than expected.

We first assessed the ability of MLR to predict of the number of surgical debridements in FG patients. The MLR has been were used to predict the progress of patients with different inflammatory events, such as malignancy and chronic diseases.[8,9,10,11] It is relatively straight forward to use and calculate the MLR under urgent conditions.

Our study has some limitations, such as its retrospective nature and limited patient number. Thus, these results should need to be compared with studies analyzing a larger number of patients. Nevertheless, as a single parameter, MLR, was able to predict the number of debridements. Based on this finding, we propose that future studies with larger patient numbers should investigate this trait further in FG patients.

Many scoring systems have been proposed for predicting the mortality rate of FG patients, including important indexes such as APACHE II, FGSI, the Laboratory Risk Indicator for Necrotizing Fasciitis and UFGSI.[1,3,5] However, under urgent conditions, it is not always easy to calculate multiple parameters. Therefore, several studies have focused on reducing the number of parameters in order to facilitate mortality prediction in FG.[12,13] One such parameter for predicting mortality in FG was assessed by Kahramanca et al.[3], who found that the neutrophil-lymphocyte ratio and platelet-to-lymphocyte ratio were useful for determining FG prognosis.[3]

As early and aggressive surgical therapy remains the most effective treatment, we focused on the number of surgical debridements. Our data show that MLR value was significantly higher in the multiple debridements group. By ROC curve analysis, we found that MLR returned a below cut-off value of 0.549 in an area of 0.881 (95% CI: 0.794-0.968), with 79.4% sensitivity and 76% specificity for predicting the number of debridements in FG patients. However, the mortality rate was not statistically different between groups, which may be because of the low mortality rate of the study.

Previous studies have suggested that improved survival of patients with FG is dependent on early diagnosis and adequate surgical treatment,[14,15] although early diagnosis is not dependent only on a physician's early diagnosis and intervention. Many patients seek treatment in advanced phases of the infection, usually after formation of necrotizing fasciitis. Sugihara et al.[16] reported in a study of 379 patients that surgical treatment within 2 days after admission reduced the mortality rates of FG. In our study, the mean duration of symptoms was 5 days (0-21) days, which is longer than the periods described in other studies.[6] However, we did not find any statistically significant difference between our two groups.

Determining whether surgical debridement is necessary in FG is mostly based on the surgical team's opinion after wound examination. Reappearance of the necrosis shows

42

Anuk et al.
Determining Number of Debridements in Treatment of Fournier's Gangrene

that the initial debridement was insufficient, so repeated interventions may be necessary. Most studies describe an initial debridement followed by repeated procedures.[17] In our study, 57.6% of our patients had undergone two or more debridements (n=34). Earlier studies have described many factors contributing to the clinical progress of FG. These include diabetes mellitus, local trauma, alcoholism, malignancy and chronic liver disease.[18,19] Patients with multiple debridements usually have underlying conditions, leading to positive wound culture results.

In our study, the mean age of patients was 53 and the male/female ratio was 2.1, which are compatible with the existing literature.[1,3] The mortality rate in our study was 6.8% (four patients), which is low compared with other studies;[1,3] this could be due to the patient numbers or early intervention by the experienced surgical team. Thirty patients underwent simple debridement; 12 patients underwent debridement and colostomy; and 13 patients underwent major debridement. Fecal or urinary diversion procedures should be undertaken to diminish additional bacterial overload of affected areas. In another study, 19 of 37 patients had undergone diverting colostomy.[20] Another study found that the fatality rate was lower in the enterostomy group than in the control group.[21] VAC devices and hyperbaric oxygen therapy are commonly used in FG treatment in modern surgical practice, thereby supporting the wound healing process.[1,4] In our study, two patients underwent debridement and VAC application. However, we could not use hyperbaric oxygen due to lack of technical device in our center.

Laor et al.[22], who presented the FGSI score, reported that the number of debridements was not associated with patient outcomes. However, Chawla et al.[23] reported a higher number of debridements in the mortality groups. Although Göktaş et al.[17] reported a 20% higher mortality rate in a group that had required multiple debridements than patients that had required a single debridement, this did not reach statistical significance. Our mortality data were similar to those of Göktaş et al.[17].

FG is a special genital form of idiopathic necrotizing fasciitis with a mortality rate of around 50%. Here we showed that the MLR is significantly higher in patients requiring multiple debridements compared to those requiring single debridements. In our analyses, MLR had a 79.4% sensitivity and 76% specificity for predicting the number of debridements. When compared with commonly used FG indexes, this single parameter appears to be a good indicator of the disease severity. Future studies with a greater number of patients and focused on MLR in FG patients should now be performed.

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Anuk et al.
Determining Number of Debridements in Treatment of Fournier's Gangrene

43

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