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Efficacy of Non-invasive Serum Markers in Predicting the Prognosis of Fournier Gangrene

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What's known on the subject? and What does the study add?

Fournier's gangrene is a life-threatening urological emergency. Prediction of mortality and morbidity is important to decide the intensity of treatment. Therefore, many non-invasive methods are being investigated. Biochemical non-invasive serum markers such as aspartat aminotransferaz (AST)/alanin aminotransferaz (ALT), albumin/globulin, neutrophil/lymphocyte, and platelet/lymphocyte ratios are used to demonstrate general inflammatory conditions. Among these parameters AST/ALT and neutrophil/lymphocyte ratios appear to be useful in initial evaluation of the prognosis of patients with Fournier gangrene.

Abstract

Objective: Fournier gangrene is a true urological emergency. This study aimed to evaluate the efficacy of biochemical diagnostic markers in predicting the prognosis of patients who presented to the hospital with Fournier gangrene.

Materials and Methods: Sixty-eight male patients who underwent aggressive debridement and drainage for Fournier gangrene were included in the study. The patients were divided into two groups: Group 1 comprised patients who died and group 2 comprised those who survived. Fournier Gangrene Severity index (FGSI), Uludağ FGSI (UFGSI), and age-adjusted Charlson Comorbidity index (ACCI) scores, and urea, creatinine, sodium, potassium, hemogram, aspartat aminotransferaz (AST)/alanin aminotransferaz (ALT), total protein, albumin, globulin, alkaline phosphatase and lactate dehydrogenase values of all patients were recorded. The AST/ALT, albumin/globulin, neutrophil/lymphocyte, and platelet/lymphocyte ratios (PLR) were also noted.

Results: The mean age of all patients was 59.04±13.99 (25-89) years. The FGSI, UFGSI, and ACCI scores of the patients in group 1 were found to be significantly worse than those in group 2. When we evaluated systemic inflammation parameters, there was a statistically significant difference between the groups in terms of the AST/ALT and neutrophil/lymphocyte ratios (NLRs) (p=0.042 and 0.023, respectively), but no significant difference was found in relation to the albumin/globulin and PLRs.

Conclusion: Non-invasive serum markers, such as AST/ALT and NLR, appear to be useful in evaluating the prognosis of patients with Fournier gangrene. Therefore, we recommend the use of these ratios in the initial evaluation of this patient group.

Keywords: Fournier gangrene, serum markers, prognosis, mortality

Introduction

Fournier's gangrene is a necrotizing fasciitis that rapidly progresses and affects the deep and superficial tissues of the perineum and ano-genital areas. This disease, which can lead to fatal results when diagnosed late, can sometimes be confused with benign processes (1,2).

Patients with Fournier's gangrene usually present with discomfort, swelling, and pain in the ano-genital region. In addition to being male, these patients may have a medical history of known risk factors for Fournier's gangrene, such as diabetes mellitus, cardiovascular disease, peripheral vascular disease, presence of malignancy, and/or alcohol overuse. Fournier's gangrene is a urological emergency that usually presents with

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sepsis when unmanaged with aggressive surgical intervention and intensive medical treatment (3). There are many factors that determine the prognosis of Fournier's gangrene. Laor et al. (4), in a study published in 1995, found that the Fournier Gangrene Severity Index (FGSI) was an extremely helpful tool in predicting disease-related prognosis. This index includes measurements of body temperature, heart and respiratory rate, serum electrolyte, creatinine and bicarbonate levels, hemoglobin/hematocrit, and white blood cell count. A study published in 2010 by Yilmazlar et al. (5) modified this index by including age score and an extent of disease score and obtained the Uludağ FGSI (UFGSI), which has been used in many studies to evaluate the prognosis of Fournier gangrene. Another widely used prognostic tool is the age-adjusted Charlson Comorbidity Index (ACCI), which was proposed by Charlson et al. (6). This index includes different scores for each comorbidity. The authors suggested that an ACCI score of >5 was associated with higher mortality rates.

The early systemic effects of Fournier's gangrene are the result of an excessive inflammatory reaction of the body against this progressive infectious course. Among these biochemical markers, a high aspartat aminotransferaz (AST)/alanin aminotransferaz (ALT) (De Ritis) ratio is associated with liver diseases and many cancers and a poor prognosis in terms of systemic inflammation (7,8).

The albumin/globulin ratio is a frequently used marker in routine health examinations, with a low value of this ratio indicating greater severity of inflammation. In malnourished patients, inflammation can cause malnutrition, whereas malnutrition can cause an inflammatory response (9).

The neutrophil/lymphocyte ratio (NLR) is an important indicator of systemic inflammatory response and is found to be higher in inflammation. NLR is a simple tool to rapidly assess the inflammatory level of a patient (10,11).

Another useful parameter is the platelet/lymphocyte ratio (PLR). This ratio is a significant indicator of the systemic inflammatory response at increased levels (12,13).

In the current study, we aimed to evaluate the effectiveness of biochemical diagnostic markers in predicting the prognosis of patients admitted to the hospital with Fournier's gangrene.

Materials and Methods

Of 82 patients, 68 fournier cases whose file information could be accessed were included in the study. In the current study, 68 male patients who underwent aggressive surgical debridement and drainage for Fournier gangrene between 2014 and 2021 were retrospectively evaluated. Since our study was retrospective and only laboratory data were evaluated, ethics committee approval was not obtained. The patients included in the study were divided into two groups, group 1 and group 2, in accordance with the presence or absence of mortality during the postoperative follow-up.

The body mass index (BMI), comorbidities, duration of symptoms and hospitalization, number of debridement procedures, revision date, need for total parenteral nutrition support, need for blood transfusion, infectious agents, skin percentage of Fournier gangrene, FGSI, UFGSI and ACCI scores, and urea, creatinine, sodium, potassium, hemogram, AST, ALT, globulin, albumin, total protein, alkaline phosphatase and lactate-dehydrogenase values of all patients were recorded. The AST/ALT ratio, albumin/globulin ratio, NLR, and PLR were also noted.

Aggressive resection including the area of necrosis was performed in all patients. Unilateral or bilateral orchiectomy was also performed in all patients due to necrosis. A surgical procedure was performed by the general surgery clinic in seven patients with perianal abscesses and one patient due to incarcerated hernia. The wound care of the postoperative patients was performed with vacuum-assisted closure and conventional rivanol dressing.

Statistical Analysis

In the statistical analysis of the patient data, for descriptive statistics, categorical variables were expressed as absolute numbers and percentages, and continuous variables were expressed as mean ± standard deviation. The normal distribution of continuous variables was tested using histograms and the Kolmogorov-Smirnov test. The independent-samples t-test was used for independent variables and the paired t-test for dependent variables that were normally distributed. The chi-square test was used for the analysis of categorical variables. A p-value of <0.05 was considered statistically significant. Univariate analysis was performed on the appropriate parameters of the patients with $p<0.05$.

Results

The results of all 68 patients were analyzed. There were 12 patients in group 1 and 56 patients in group 2. The mean age of all patients was 59.04±13.99 (25-89) years, and the mean duration of symptoms at the time of admission was 8.99±10.34 (1-72) hours. The mean duration of hospitalization was 16.62±8.84 (2-60) days, and 17.6% of the patients died during perioperative care.

The mean BMI was 26.49±3.75 (20-34) kg/m^2, and 25% of the patients had hypertension, 50% had diabetes mellitus, 16.2% had atherosclerotic heart disease, 22.1% had acute renal failure, 8.8% had chronic renal failure, 4.4% had pneumonia, 7.4% had

abnormal liver function test results, and 8.8% had a history of malignancy. The demographic data and comorbidities of the patients are shown in Table 1 by group. The FGSI, UFGSI, and ACCI scores of the patients in group 1 were found to be significantly worse than those in group 2. When evaluated in terms of systemic inflammation parameters, there was a statistically significant difference between the groups in terms of the AST/ALT ratio and NLR (p=0.042 and p=0.023, respectively), but no significant difference was observed in relation to the albumin/globulin ratio and PLR (Table 2).

The mean skin percentage of Fournier gangrene was 3.37±2.47% (1-10). In the pre-operative wound culture of the patients, *Escherichia coli* was isolated in 23.5% of the patients, *Enterococcus* species in 11.8%, *Streptococcus* species in 7.4%, *Acinetobacter baumannii* in 5.9%, *Klebsiella* species in 5.9%, *Pseudomonas* species in 5.9%, *Candida* in 5.9%, *Staphylococcus* species in 4.4%, and *Proteus* species in 1.5%. No methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococci* were detected. During perioperative care, 11.8% of the patients required total parenteral nutrition and 20.6% required blood transfusion. The number of debridement procedures following the initial surgery was 2.7 for group 1 and 2.5 for group 2.

Table 1. Demographic data and comorbidities of the study groups

	Group 1 (n=12)	**Group 2 (n=56)**	**p**
Age (years) (mean ± SD)	64.67±17.01 (min: 25, max: 89)	58.3±13 (min: 29, max: 82)	0.212
Duration of symptoms (hours) (mean ± SD)	6.42±3.15 (min: 2, max: 10)	9.54±11.25 (min: 1, max: 72)	0.081
Body mass index (kg/m²) (mean ± SD)	25.67±4.33	26.66±3.63	0.409
Hypertension (n/%)	4/33.3	13/30.2	0.340
Diabetes mellitus (n/%)	8/66.6	26/46.4	0.477
Atherosclerotic heart disease (n/%)	2/16.6	9/19.6	0.960
Acute renal failure (n/%)	4/33.3	11/24.4	0.422
Chronic renal failure (n/%)	2/16.6	4/7.1	0.285
Abnormal liver function test results (n/%)	0/0	5/8.9	0.577
Malignancy (n/%)	5/41.6	1/1.7	0.001*
Number of debridement procedures	2.75±1.71 (min: 1, max: 7)	2.52±1.51 (min: 1, max: 8)	0.670

*: Statistically significant, chi-square test, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2. Clinical scores and laboratory findings of the study groups

	Group 1 (n=12) (mean ± SD)	**Group 2 (n=56) (mean ± SD)**	**p**
FGSI score	7.58±5.07 (min: 0, max: 15)	2.64±2.59 (min: 0, max: 12)	0.006*
ACCI score	5.75±3.49 (min: 2, max: 15)	3.07±1.74 (min: 0, max: 8)	0.023*
UFGSI score	10.00±5.77 (min: 2, max: 19)	4.73±3.33 (min: 1, max: 19)	0.009*
AST/ALT ratio (De Ritis ratio)	1.58±0.57 (min: 1.07, max: 3.14)	1.19±0.33 (min: 0.64, max: 2.40)	0.042
Albumin/globulin ratio	1.08±0.69 (min: 0.59, max: 3.00)	1.18±0.59 (min: 0.47, max: 4.20)	0.646
Neutrophil/lymphocyte ratio	10.71±6.94 (min: 3.98, max: 22.82)	5.80±5.60 (min: 0.40, max: 24.25)	0.023*
Platelet/lymphocyte ratio	171.79±144.56 (min: 3.00, max: 558.00)	165.73±176.69 (min: 5.1, max: 871.70)	0.901

*: Statistically significant, chi-square test, SD: Standard deviation, Min: Minimum, Max: Maximum, FGSI: Fournier Gangrene Severity index, ACCI: Age-adjusted Charlson Comorbidity index, UFGSI: Uludağ FGSI, AST: Aspartat aminotransferaz, ALT: Alanin aminotransferaz

Discussion

Fournier gangrene is a type I necrotizing fasciitis of the perineum and anogenital regions. Rapid progression of inflammation and infection causes thrombosis of small blood vessels, which leads to ischemia and necrosis of adjacent soft tissue and fascia planes. Fournier gangrene is a relatively rare urological emergency, representing only 0.02% of all hospitalizations, although its incidence is increasing with an aging population and a higher prevalence of diabetes (14). Necrotizing fasciitis often stems from infection of the anorectum (30-50%), urogenital tract (20-40%), anogenital skin, or perineal skin (20%). Sorensen et al. (15) reported an overall incidence rate of 1.6 cases per 100.000 men/year. He emphasized that this incidence peaks at 3.3 cases per 100.000 men per year in persons over 50 years of age (15,16).

The main aims of the management of Fournier gangrene are early patient resuscitation, broad-spectrum antibiotherapy, and aggressive debridement and drainage of necrotizing tissues. Treatment aims to prevent systemic toxicity, stop infective progression, and eliminate the causative multi-bacterial agents. The urgent and aggressive debridement of necrotic and devitalized tissues is the main step in preventing the spread of infection. Early aggressive debridement is crucial, and even a delay of a few hours is directly related to the risk of death (17,18). Frequent wound monitoring and repeated debridement are essential for the control of infection. It has been reported that an average of 3.5 debridements are required for sufficient infection control (19). In our study, we started broad-spectrum antibiotics in all patients, as recommended by the infectious diseases clinic, and we performed aggressive excision and drainage of necrotic tissue. The number of debridement procedures performed following initial surgery was 2.7 for group 1 and 2.5 for group 2.

The most important factor determining the prognosis of Fournier gangrene is the presence of comorbidities (20). Some prognostic tools, such as FGSI, UFGSI, and ACCI, are used for this purpose. The most widely used prognostic scoring system is FGSI, in which a score of greater than 9 has been associated with over 75% mortality, whereas a score of 9 has a 78% probability of survival (21). In UFGSI, a score >9 is associated with a 94% likelihood of death, whereas a score <9 is correlated with an 81% probability of survival. As stated for both FGSI and UFGSI, which are similar scoring systems, greater tissue and site involvement correlates with worse pronosis (4-6). Erol et al. (22) reported that the ACCI score was higher and the life expectancy was 10 years shorter among non-survivors than among survivors. Higher ACCI scores may be correlated with a worse outcome, which may also indicate mortality (22). ACCI can be useful in the evaluation of patients' outcomes with Fournier gangrene. In our study, the scores of the patients in group 1 were found to be significantly worse in all these scoring systems.

The systemic inflammatory response is an important part of disease progression in critical illness and is often associated with septicemia and increased mortality. ALT is considered a liver-specific enzyme, whereas AST is expressed in a variety of tissues (7). AST increased more than ALT in conditions of increased proliferation rate, tissue damage, and tumor cell turnover. Therefore, the De Ritis rate is considered to indicate systemic changes such as tumor proliferation and systemic inflammation (23). Serum albumin level is used to reflect nutritional status and serum globulin to evaluate chronic inflammation severity. Moreover, both albumin and globulin concentrations are influenced by many factors, e.g., the volume status of body fluid. Recently, the albumin-globulin ratio has begun to be accepted as a new prognostic marker (24-27). NLR is a marker that has proven its prognostic value in cardiovascular diseases, infections, inflammatory diseases, and various types of cancer (28,29). NLR is thought to reflect the balance between neutrophils and lymphocytes. Previous literature has shown that a high NLR is associated with an increased concentration of various proinflammatory cytokines that can cause cellular DNA damage (30-32).

Several studies have examined the relationship between PLR and disease-specific mortality. However, no study has explored the relationship between PLR and all-cause mortality in the general population. PLR has emerged as an informative marker revealing changes in platelet and lymphocyte counts due to acute inflammatory and prothrombotic conditions (33). In the current study, when evaluated in terms of systemic inflammation parameters, there was a statistically significant difference between the groups in terms of the AST/ALT ratio and NLR (p=0.042 and p=0.023, respectively), but no significant difference was detected in the albumin/globulin ratio and PLR. According to the findings of our study, we believe that the AST/ALT ratio and NLR are useful in predicting prognosis in the rapid evaluation of patients with Fournier gangrene.

Study Limitations

There were a few limitations to our study, including the single-center and retrospective design. Multicenter studies with a larger number of patients may provide more information. Nevertheless, we believe that our study can shed light on future studies.

Conclusion

Because Fournier gangrene is a urological emergency that can be fatal, prompt evaluation of patients and early and aggressive intervention are crucial. Non-invasive serum markers, such as AST/ALT and NLR, appear to be useful in initial evaluation of the prognosis of patients with Fournier gangrene. Therefore, we recommend the use of these ratios in the initial evaluation of this patient group.

Ethics

Ethics Committee Approval: Since our study was retrospective and only laboratory data were evaluated, ethics committee approval was not obtained.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: A.T., Design: Ö.G., Data Collection or Processing: A.A., Analysis or Interpretation: Y.A., Ş.C., Literature Search: M.B., Writing: Ö.G.

Conflict of Interest: The authors declare no conflict of interest.

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