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Neutrophil-lymphocyte ratio and Fournier gangrene severity index are not prognostic factors of mortality in Fournier gangrene patients

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ABSTRACT

BACKGROUND

Fournier gangrene (FG) is a life-threatening disease, commonly found in diabetic and immunocompromised patients. Recent studies suggested the use of new parameters apart from the commonly used Fournier gangrene severity index (FGSI), such as the neutrophil-lymphocyte ratio (NLR), the clinical use of which remains questionable. Therefore, we aimed to evaluate the role of the NLR and FGSI as a prognostic factor of mortality in patients with FG.

METHODS

This is an analytical study with a retrospective approach involving 109 adult patients diagnosed with FG. Data were collected regarding medical history, symptoms, physical examination findings, and laboratory tests. The FGSI score and NLR were determined. Bivariate analysis was performed using chi-square test and independent t-test. Overall survival between groups was compared using Kaplan–Meier survival estimates and Cox regression test.

RESULTS

Of the 109 patients, 90 survived (82.5%, group 1) and 19 died (17.43%, group 2). The cut-off point of NLR among the patients was 10.9, with a 73.7% sensitivity and 60% specificity. The area under curve value was 0.65 (95% CI; 0.524-0.754; $p < 0.05$). The Kaplan Meier survival analysis showed that NLR was as an independent prognostic factor of mortality in FG patients (HR 5.177; 95% CI; 1.092-8.471; $p < 0.05$), but Cox regression analysis showed that NLR and FGSI were not significant prognostic factors of mortality ($p = 0.09$ and $p = 0.179$; respectively).

CONCLUSION

This study demonstrated that NLR and FGSI are not important as prognostic tools for FG mortality.

Keywords: Fournier gangrene, prognostic factor, neutrophil, lymphocyte, neutrophil-lymphocyte ratio

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INTRODUCTION

Fournier gangrene (FG) is a rare type of necrotizing fasciitis that affects the perineal, genital, or anorectal region. It is characterized by widespread soft tissue necrosis and systemic toxicity of the superficial fascia and subcutaneous tissues.⁽¹⁾ Even though it is quite uncommon, constituting only 0.02% of all hospital admissions, it is considered a urological emergency as it has a high mortality rate, at 20 to 50% in most reported series.^(2,3) In recent years, the incidence of Fournier gangrene is increasing with the increase in diabetes prevalence and the number of immunocompromised patients due to various causes.⁽⁴⁾ Previous studies have determined the possible risk factors for predicting the prognosis of Fournier gangrene patients, such as comorbidities, Fournier gangrene severity index (FGSI) score and disease severity.⁽⁵⁻⁷⁾ Parameters to determine the severity and prognosis of the disease have been suggested, one of which is the FGSI, commonly used to assess the severity of the disease by evaluating clinical and laboratory parameters, such as temperature, heart rate, respiratory rate, serum sodium, serum potassium, serum creatinine, serum bicarbonate, hematocrit and white blood cell count.⁽⁸⁾ Since its introduction, the score has been validated by many studies, but its accuracy remains questionable.^(9,10) Nevertheless, it is the only well-known tool to assess severity.⁽¹⁰⁾ Recent findings have suggested simple and promising parameters by utilizing normal laboratory findings. There is an increasing interest in predicting the prognosis of the patients with a simple blood test since studies began suggesting a correlation between inflammatory status and disease prognosis. One of the most commonly used parameter is the neutrophil-lymphocyte ratio (NLR).⁽¹¹⁾ Findings regarding its potential use in predicting the prognosis of Fournier gangrene patients have been reported. A retrospective study showed that the FGSI scoring system was not associated with determining poor prognosis. However, high NLR and high platelet to

lymphocyte ratio (PLR) were associated with predictors of mortality in patients with Fournier's gangrene.⁽¹⁰⁾ In contrast, another retrospective observational analytical study of patients diagnosed with Fournier fasciitis (FF) showed that FF severity, as measured by NLR and PLR, does not correspond to the severity measured by the FGSI.⁽¹²⁾ Other studies utilized the NLR cutoff-values of 13.71 (sensitivity 83.3% and specificity 86.6%)⁽¹³⁾ and 8 (sensitivity 72.2%, specificity of 52.3%), respectively.⁽¹⁴⁾ The present study included FGSI in the analysis of NLR as mortality predictors. Therefore, the aim of this study was to determine the role of NLR and FGSI as prognostic factors of mortality in patients with FG.

METHODS

Research design

This was an analytical study with a prospective approach utilizing secondary data taken from the medical records of Dr. Soetomo General-Academic Hospital from January 2012 to November 2020.

Research subjects

Fournier gangrene was defined as an acute necrotic infection involving the scrotum, penis or perineum. A total of 109 adult patients aged 18 and above with Fournier gangrene or fasciitis necroticans and complete laboratory examination data including neutrophil and lymphocyte counts were included in the study. Patients with a history of malignancy or chemoradiation were excluded, as were also those with incomplete or unclear data in the medical records.

Data collection

The data collected and presented included patient age, diagnosis, lesion location, comorbidities, FGSI, bacterial culture results, surgical interventions, and survival status.

Statistical analysis

The collected data were grouped and displayed descriptively in the form of tables and

narratives. Bivariate analysis was performed using chi-square test and independent t-test. The association between the binary marker of NLR and the risk of mortality was evaluated using a survival curve. Mortality was defined as disease related death during the hospital stay and survival was measured in days. The separation between the curves of patients with a high NLR and those with a low NLR indicated the prognostic ability of the marker represented by a receiver operating characteristic (ROC) curve.⁽¹⁵⁾ The performance of the marker was evaluated by the area under the curve (AUC), which is a measure of the ability of a tool to discriminate whether a condition is present or not. An AUC value of 0.5 indicates that the test has no discriminating ability, whereas an AUC of 1.0 indicates perfect discrimination.⁽¹⁶⁾ Overall survival was compared between groups using Kaplan–Meier survival estimates and the proportional-hazards Cox regression. The statistical significance was set at $p < 0.05$ for all analyses.

Ethical clearance

The ethical committee of the research and development center of Dr. Soetomo General Academic Hospital approved this study under number 0725/109/4/V/2021.

RESULTS

Baseline characteristics

A total of 109 patients with mean age of 50.31 ± 14.75 years had mean NLR of 15.86 ± 12.75 . Only 25 patients had an FGSI score of more than 9. The scrotal area was the most commonly affected area ($n=55$, 50.46%) compared to other areas. Most patients also suffered from diabetes mellitus ($n=40$, 36.7%) leading to infections caused mainly by *Pseudomonas aeruginosa* ($n=23$, 21.1%), *Klebsiella pneumoniae* ($n=21$, 19.27%), and *Acinetobacter baumannii* ($n=20$, 18.35%). Most patients were treated with debridement and necrotomy, followed by incision and drainage of

the abscess ($n=55$, 50.46%), after which most patients survived ($n=90$, 82.57%). The differences in clinical parameters between the survivors and non-survivors are shown in Table 2. The FGSI scores in the two groups did not show significant differences ($p=0.248$), but the NLR did show significant differences between the two groups ($p=0.021$) (Table 2).

NLR and FGSI value as a prognostic marker

In this study, the NLR cut-off point among the patients was 10.9, with 73.7 % sensitivity and 60 % specificity, as shown in Figure 1. The AUC was 0.65 (95% CI; 0.524-0.754; $p < 0.05$). The Kaplan-Meier curve in Figure 2 shows that the NLR cut-off value of 10.9 has a significant impact on the patient's mortality rate (95% CI; 29.7-19.7; $p < 0.05$). The univariate Kaplan Meier survival analysis indicated that NLR can be used as an independent predictor for mortality in Fournier gangrene patients (HR 5.177; 95% CI; 1.092-8.471; $p < 0.05$). However, the Cox regression showed that NLR and FGSI score were not significant as a prognostic factor of mortality in FG patients (the p values of NLR and FGSI were $p=0.09$ and $p=0.179$; respectively) (Table 3).

DISCUSSION

Fournier gangrene is a rare and serious condition that can be found in immunocompromised patients.⁽¹⁷⁾ Even though FGSI has been validated in numerous studies, its use in clinical settings is oftentimes questionable. There is still a high mortality rate ranging from 20 to 50% among Fournier gangrene patients due to sepsis,⁽¹⁷⁾ which is one of the main causes of mortality and extended length of stay in patients with urological infections, including Fournier gangrene.⁽¹⁸⁾ To reduce the severity of the disease, the utilization of inexpensive and simple laboratory parameters, such as white blood cell parameters, erythrocyte sedimentation rate, and C-reactive protein, are necessary.^(19,20) The use of NLR as a parameter

Table 1. Characteristics and clinical features of the subjects (n=109)

Variables	n (%)
Age (years)	50.31 ± 14.79
NLR	15.86 ± 12.75
FGSI	
> 9	25 (23.0)
< 9	84 (70.0)
Diagnosis	
Fournier gangrene	53 (48.62)
Fournier gangrene and perianal abscess	33 (30.28)
Fournier gangrene and scrotal abscess	22 (20.18)
Fournier gangrene and perianal fistula	1 (0.92)
Affected Region	
Penoscrotal	12 (11.01)
Penoscrotal and perianal	2 (1.83)
Penoscrotal and suprapubic	2 (1.83)
Perianal	27 (24.77)
Perianal and scrotum	8 (7.34)
Scrotum	55 (50.46)
> 2 regions	3 (2.75)
Comorbidities	
Diabetes mellitus	40 (36.70)
Diabetes mellitus and hypertension	21 (19.27)
Diabetes mellitus and chronic kidney disease	7 (6.42)
Diabetes mellitus and hepatitis B infection	1 (0.92)
Hypertension	8 (7.34)
Chronic Kidney Disease	4 (3.67)
No comorbidities	28 (25.67)
Bacterial culture	
<i>Pseudomonas aeruginosa</i>	23 (21.10)
<i>Klebsiella pneumoniae</i>	21 (19.27)
<i>Staphylococcus epidermidis</i>	12 (11.01)
<i>Acinetobacter baumannii</i>	20 (18.35)
<i>Gemella morbillorum</i>	2 (1.83)
<i>Escherichia coli</i>	13 (11.93)
<i>Candida spp</i>	8 (7.34)
<i>Clostridium perfringens</i>	5 (4.59)
<i>Fusobacterium necrophorum</i>	5 (4.59)
Survival intervention	
Debridement-necrotomy	48 (44.04)
Debridement-necrotomy and incision-drainage	55 (50.46)
Debridement-necrotomy and graft	3 (2.75)
Debridement-necrotomy and urinary diversion	3 (2.75)
Survival status	
Survived	90 (82.57)
Dead	19 (17.43)

Data presented as n (%), except for age and NLR (mean ± SD); NLR: Neutrophil-to-lymphocyte ratio; FGSI: Fournier Gangrene Severity Index

has been suggested by many studies. Kaushik et al.⁽²¹⁾ recommended its use as a diagnostic marker and predictor in septic patients. Its greatest strengths are its efficiency in time, cost, and application compared to other examinations.

Neutrophils are one of the main immune cells against pathogens and their crucial function is to produce enzymes during the acute inflammatory phase. Neutrophils are able to lyse infected cells, produce free radicals, and induce the production

Table 2. Differences in clinical parameters between the survivors and non-survivors

Variables	Survivors (n=90)	Non-survivors (n=19)	p value
Age (years)	49 ± 14.9	54 ± 13.8	0.208
FGSI			
≤ 9	75 (89.3)	9 (10.7)	0.248
>9	17 (68.0)	8 (32.0)	
NLR			
≤10.9	52 (91.2)	5 (8.8)	0.021
>10.9	38 (73.1)	14 (16.9)	

Data presented as n (%), except for age mean ± SD; NLR: Neutrophil-to-lymphocyte ratio; FGSI: Fournier Gangrene Severity Index

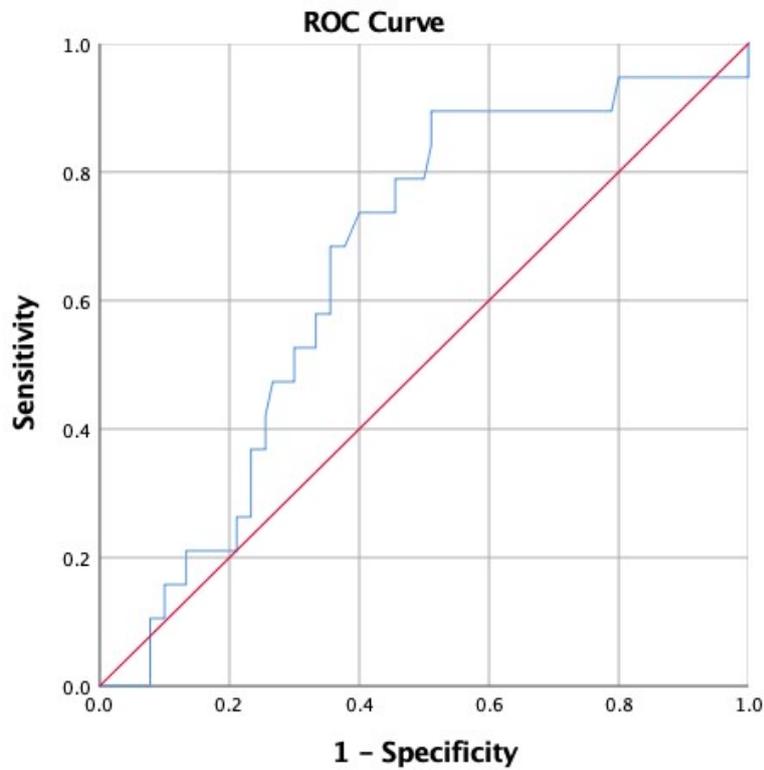
of pro-inflammatory cytokines.⁽²²⁾ The coordination of the transition from innate to adaptive immunity is handled by the lymphocytes. Both innate and adaptive immunity are core components of the body's immune system against pathogens.⁽²³⁾ The ratio of the neutrophil and lymphocyte numbers indicates a transition between innate and adaptive immunity. The relatively low number of lymphocytes could cause a cytokine storm and severe inflammation, leading to a worse prognosis. Our study showed the potential role of NLR as a prognostic marker for Fournier gangrene patients, since patients with a high NLR had a 5.17-times greater risk of mortality than those with a low NLR. This finding is in line with the study by George et al. in 2020 who discovered a significant difference in NLR among septic patients with multiple organ dysfunction syndrome (MODS). They found that most septic patients with MODS had a high NLR. The NLR is deemed superior to a white blood cell count.⁽²⁴⁾ A study with a large sample size conducted by Li et al.⁽²⁵⁾ also showed the predictive capability of NLR in septic patients. However, a study by Ni et al.⁽²⁶⁾ suggested that NLR does not significantly predict septic inpatients with a long hospital stay. The

difference between these findings may have been caused by other factors in these studies which could affect the patients' NLR. The increased NLR in septic patients is difficult to use as a predictive tool, considering that there are many factors affecting neutrophil and lymphocyte counts. However, it can still be used as a mortality predictor in septic patients. The ROC curve, Kaplan-Meier, and hazard ratio findings in this study are in line with those of the study by Yim et al.⁽¹⁰⁾ which suggested that NLR is a useful independent predictor that is associated with increased mortality in FG patients. In our study, Cox regression showed that NLR and FGSI score had no significant prognostic value for mortality in FG patients. Another study showed that the FGSI scoring system was not found to be valuable in determining prognosis, but that the NLR and PLR were valuable.⁽²⁷⁾ One other study showed similar results, in that the FGSI scoring system was not associated with determining poor prognosis, but that high NLR and high PLR were associated with predictors of mortality in patients with FG.⁽¹⁰⁾ In our study, a high FGSI score (>9) was generally associated with the non-surviving group; however, multivariable Cox regression analyses found this not to be statistically significant.

Table 3. Multivariate Cox regression analysis

Variables	Coefficient	Hazard Ratio	p value
Age (years)	0.017	1.017	0.356
FGSI score	0.081	1.328	0.179
NLR	-0.033	2.043	0.09

NLR: Neutrophil-to-lymphocyte ratio; FGSI: Fournier Gangrene Severity Index



Diagonal segments are produced by ties.

Figure 1. Receiver operator characteristic curve for neutrophil to lymphocyte ratio (NLR), area under the curve = 0.65 (95% CI; 0.524-0.754; $p < 0.05$, sensitivity = 73.7, specificity = 60.0

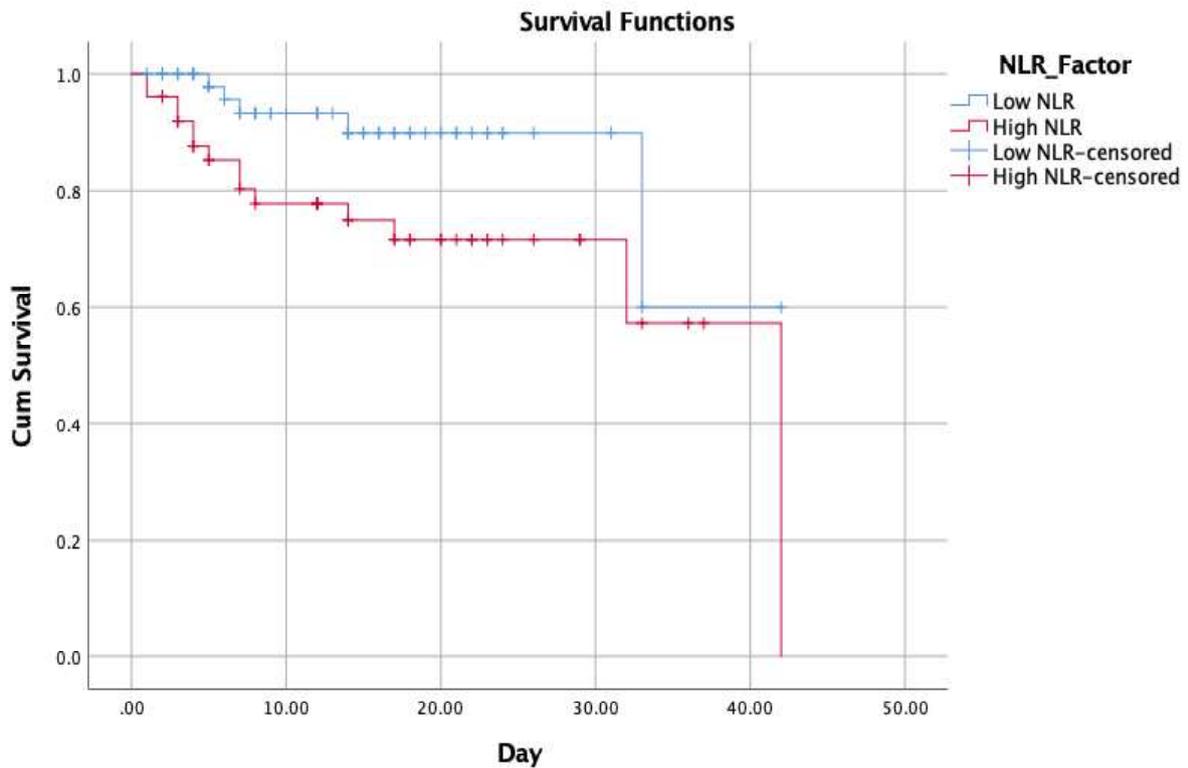


Figure 2. Kaplan-Meier survival curves for the overall survival indicating the value of NLR as a survival predictor

The present study is limited by its retrospective design and use of secondary data. Most samples included in this study had a high NLR ratio, indicating that most included patients were classified as severe. The inclusion of more patients with different disease severity should be performed in future studies. This study showed the utility of the NLR in FG. The NLR can be examined with high availability and low cost. This marker could be an ideal and simple biomarker to predict the outcome of mortality in patients with FG.

CONCLUSIONS

This study demonstrated that a high NLR and FGSI cannot be used as an indicator of poor prognosis of mortality in FG patients.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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CONTRIBUTORS

MAR, FH, YPK contributed to concept and design; MAR, FH contributed to data collection and analysis. MAR and FR contributed to writing manuscript and critical review. All authors have read and approved the final manuscript. 

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