Original Article

Comparison between neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as predictors of mortality on Fournier's gangrene cases

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ABSTRACT

Introduction: Fournier's gangrene (FG) is an infection of the subcutaneous tissue and fascia that progresses quickly and leads to necrosis. It is more prevalent in male patients and immunocompromised individuals, such as those suffering from uncontrolled diabetes. It has a high mortality rate, which makes its early identification and clinical suspicion critical. This study aimed to compare two laboratory parameters, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), and to predict the mortality of FG in a tertiary care hospital.

Methods: In a retrospective study, data was retrieved from medical records for the period from January 2014 to December 2020, of patients diagnosed with FG. Recorded data that is age, sex, comorbidities, mortality, and laboratory results (PLR and NLR) were used to assess determinants of survival.

Results: There were 23 (17.04%) nonsurvivors among the 135 subjects studied. The mean age was 50.9 ± 14.9 years and men were 103 (83%) patients. Among the participants, diabetes mellitus was the most frequent comorbidity at 74 (54.81%) patients. NLR ≥8 was statistically significant (P = 0.013) for identifying mortality, while PLR >140 was not. In multivariate analysis, NLR ≥8 was found to be a reliable predictor of the FG mortality rate (adjusted odds ratio 12.062, confidence interval 95% 2.115–68.778, P = 0.005).

Conclusion: NLR had prognosis predictive value for FG, whereas PLR did not.

INTRODUCTION

Fournier's gangrene (FG) was first described by Dr. Alfred Fournier with a clinical presentation resembling necrotizing fasciitis in the external genitalia and perineum.[1] FG is uncommon but potentially fatal and considered an urological emergency.[2] Several risk factors for mortality have been identified, including male, alcohol consumption, immunocompromised state such as human immunodeficiency virus infection, and uncontrolled diabetes.[2] However, despite these findings, the mortality remains high. According to a large-scale study of FG cases in the United States of America (US), the incidence of FG is about 1.6 per 100,000 men, with the peak incidence occurring between the ages of 50 and 79 years (3.3 per 100,000).[2,3] It is reported that the mortality rate for FG remains between 7% and 30%.[4]

FG patients often present mild symptoms in the early stages. Therefore, it is critical to recognize promptly and establish aggressive treatment for those who are at risk. Meanwhile, the inflammatory and infectious processes underlying FG affect hematologic parameters.[5] Bacteremia activates the inflammatory cascade, altering the hematological component that is naturally designed to remove bacteria.[6] Several publications have found neutrophilia, thrombocytosis, or

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lymphopenia associated with the incidence and mortality of FG.[7,8]

Neutrophils are the most critical kind of immune cell in the innate immune system, acting as the body's first line of defense against infection and illness while lymphocytes contribute significantly to the establishment of adaptive immunity. Previous studies have shown that the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) had clinical significance in determining the prognosis of FG patients.[9,10] According to Yim *et al.*, admission values of PLR > 140 and NLR >8 were linked with an 11.6-fold and 4.66-fold higher risk of death, respectively.[10] NLR and PLR are two relatively new laboratory parameters that are extensively utilized to predict disease severity in a range of inflammatory and infectious disorders.[10,11] Since FG pathophysiology involves inflammation and infection, NLR and PLR may have clinical significance of predicting mortality. Moreover, both NLR and PLR are noninvasive, low-cost, and simple to calculate markers of inflammation obtained from peripheral blood analysis.

The study aims to compare the efficacy of NLR and PLR to predict FG patient mortality. To our knowledge, this is the first study to evaluate NLR and PLR to predict FG mortality in Indonesia.

METHODS

Study objects and sampling method

This retrospective study reviewed data from January 2014 to December 2020 of all patients with a diagnosis of FG. Patients who fulfilled the following criteria were included: scrotal erythema and edema (among men), wound drainage and fluctuation, crepitus, and a progressive necrotizing process of soft tissue that resulted in gangrene. Patients who did not have emergency surgery due to medical difficulties, patients with inadequate data, patients with local superficial inflammation of the perianal or urogenital areas, and patients who refused treatment were excluded from the research. The data collected came from the medical records. Data recorded were age, sex, comorbidities, mortality, microbiology result, and hematology result.

Comorbidities were assessed through patient history taking upon admission. In addition, we collected hematology results at admission to accurately define the presence of diabetes, chronic kidney disease, and hypertension. Hemoglobin A1c (HbA1c) (%) was utilized to identify patients with diabetes, while the estimated glomerular filtration rate (GFR) calculated through the Modification of Diet in Renal Disease equation was employed to determine impaired kidney function. Vital signs, including blood pressure measurements, were also gathered to assess whether patients were hypertensive or hypotensive.

For microbiology results, each patient's wound and tissue cultures were acquired through a surgical incision, and they were also given empiric antibiotics concurrently with the cultures. The antibiotic prescription was adjusted in consideration of the culture test results. The research variables were collected after the ethics approval was received from the ethics committee (0515/LOE/301.4.2/VII/2021).

Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio

NLR and PLR assessments are performed by comparing neutrophils or platelets with lymphocytes. In several studies, this value is associated with inflammatory conditions that occur in patients. The NLR value is high if ≥8, and low if <8. Meanwhile, PLR is low if ≤140 and high if >140.[10,12] The calculation of NLR was total neutrophil count (cells/mm^3) per total lymphocyte count (cells/mm^3) and PLR was total platelet count (cells/mm^3) per total lymphocyte count (cells/mm^3).

Analysis

The results of the NLR and PLR were tested for normality and a comparative test for mortality was performed. For normally distributed data, the independent sample independent T-test was performed with a significance value of $P < 0.05$. All analyses were performed using the statistical software SPSS 21 (IBM, New York, United States).

RESULTS

The characteristics of the 135 study participants are presented in Table 1 and the culture results are in Table 2. The study group was divided into two groups: survivors and non-survivors. Patients who survived in the study were 112 (82.96%), whereas 23 (17.04%) were non-survivors. The patients were more often male (112, 82.96%) and diabetes (74, 54.81%). Hypotension, high HbA1c levels, and elevated NLR scores were significantly associated with mortality ($P < 0.05$). HbA1c ≥6.5 was associated with mortality ($P < 0.05$) and NLR score ≥8 was more prevalent in the nonsurvivor group, 55 (49.11%) versus 20 (86.96%). In addition, the NLR score was lower in the nonsurvivor group, 16.5 ± 24 versus 15.5 ± 10 ($P = 0.05$). In multivariate analysis, it was found that NLR score ≥8 was the independent risk factor for mortality in FG patients [adjusted odds ratio 12.062, confidence interval 95% 2.115–68.778, $P = 0.005$, Table 3] whereas PLR >140 had no meaningful prognostic significance. The most prevalent pathogens were *Klebsiella* spp.(18%), *Pseudomonas* spp.(18%), *Escherichia coli* (15%), *Acinetobacer* spp.(14%), and *Fusobacterium* (10%) [Table 2].

DISCUSSION

FG is a necrotizing fasciitis whose occurrence and healing process are primarily determined by the host's immune system balance.[13] Oguz *et al.* previously described the FG

Table 1: Baseline characteristics of Fournier's gangrene patients

variable	Total, *n* (%)	Survivor, *n* (%)	Nonsurvivor, *n* (%)	*P*
Patients	135	105 (77.8)	30 (22.2)	
Age	50.9±14.9	50.4±15.0	53.2±14.7	0.423
Sex				
Male	112 (82.96)	103 (91.96)	9 (39.13)	0.386
Female	23 (17.04)	20 (17.86)	3 (13.04)	
Comorbidities				
DM	74 (54.81)	63 (56.25)	11 (47.83)	0.14
CKD	31 (22.96)	29 (25.89)	2 (8.70)	
HT	12 (8.89)	9 (8.04)	3 (13.04)	
Systolic blood pressure (mmHg), median (IQR)		112 (84–90)	86 (84–90)	0.0001*
Hypertension	5 (3.7)	5 (4.8)	0	0.223
Hypotension	31 (23)	12 (11.4)	19 (63.3)	0.0001*
Serum creatinine (mg/dL), median (IQR)		0.99 (0.77–1.30)	1.10 (0.85–1.80)	0.65
HbA1c (%), median (IQR)		5.9 (5.4–6.3)	7.8 (7.2–9.3)	0.0001*
<6.5	92 (68.1)	90 (85.7)	2 (6.7)	0.0001*
≥6.5	43 (31.9)	15 (14.3)	28 (93.3)	
eGFR (mL/min/1.73 m), mean±SD		83.40 (37.85)	67.64 (43.92)	0.054
≥60	91 (67.4)	74 (70.5)	17 (56.7)	0.155
<60	44 (32.6)	31 (29.5)	13 (43.3)	
NLR Score, mean±SD		15.5±10	16.5±24	0.050*
<8	60 (44.44)	57 (50.89)	3 (13.04)	0.013*
≥8	75 (55.56)	55 (49.11)	20 (86.96)	
PLR score, mean±SD		279.2±135.9	298.9±227.7	0.696
≤140	23 (17.04)	18 (16.07)	5 (21.74)	0.580
>140	101 (74.81)	84 (75.00)	17 (73.91)	

DM=Diabetes mellitus, CKD=Chronic kidney disease, HT=Hypertension, SD=Standard deviation, NLR=Neutrophil-to-lymphocyte ratio, PLR=Platelet-o-lymphocyte ratio, eGFR=Estimated glomerular filtration rate, HbA1c=Hemoglobin A1c, IQR=Interquartile range.*Significance (*P*=<0.05)

Table 2: Culture results of Fournier's gangrene patients

Organism	*n* (%)
Klebsiella spp.	24 (18)
Pseudomonas spp.	24 (18)
Escherichia coli	20 (15)
Acinetobacter spp.	19 (14)
Fusobacterium	13 (10)
Miscellaneous	22 (16)
No growth	13 (10)
Total	135 (100)

Table 3: Multivariate analysis of factors associated with mortality

Variable	*P*	ORs	95% CI
Age	0.49	1.61	0.416–6.26
Comorbidity	0.66	1.072	0.784–1.47
Gender (male)	0.288	2.99	0.396–22.55
NLR >8	0.005*	12.062	2.115–68.778
PLR >140	0.142	4.025	0.262–25.877

NLR=Neutrophil-to-lymphocyte ratio, PLR=Platelet-to-lymphocyte ratio, ORs=Odds ratios, CI=Confidence interval. *Significance (*P*=<0.05)

healing process, stating that there are many associations with internal and external factors in the patient.[14] In terms of necrotizing soft-tissue infections (NSTIs), FG is most often categorized as a type I NSTI, with up to 80% of FG including several bacteria. Numerous frequently isolated organisms comprise the commensal flora of the anatomic area under the pelvic diaphragm, which includes the perineum, rectum, and vaginal canal. Aerobic bacteria such as *E. coli, Klebsiella pneumoniae*, and *Staphylococcus aureus* may be cultured from wounds and blood samples. Anaerobic microbes include *Bacteroides fragilis* and *Clostridium* species.[15] Other bacteria detected include *Streptococcus, Vibrio, Enterococcus, Pseudomonas, Proteus,* and *Corynebacterium*.[16,17] This concept is consistent with our research, which found that the most common pathogens were *Klebsiella* spp.(18%), *Pseudomonas* spp.(15%), *E. coli* (14%), *Acinetobacter* spp. (14%), and *Fusobacterium* spp.(10%).

There are several prognostic factors that can predict recovery or death from FG,[18,19] which include the results of NLR and PLR.[9,10] In our study, testing was carried out to assess the mortality compared to the prognostic factor. Our study participants had a mean age of 50.9 ± 14.9 years, and higher in the nonsurvivor group but not statistically significant (P = 0.423). This finding is consistent with the findings of Sorensen *et al.*, who discovered that the prevalence peaks at the age of 50 and increases with age.[20] However, in statistical tests, there were no significant results regarding the association of age with the mortality rate of FG patients. This result is different from the results of Medina Polo *et al.*, in which mortality increases with increasing age and is also associated with the comorbidities of the patients.[21]

The incidence of FG is strongly associated with comorbidities. From the results of our research, 54.81% of the cases were subjects with comorbid diabetes mellitus, and when compared to other comorbidities, 8.1% died. These findings are consistent with several previous studies: diabetes

mellitus not only increases the prevalence of FG but also increases mortality.[13] However, our analysis did not reveal a significant association between comorbidity and mortality, particularly in relation to diabetes mellitus. The results were in line with previous studies.[22,23]

It should be noted that diabetic status was obtained through history taking upon admission, which may have introduced bias into our results. To address this, we included HbA1c levels as a laboratory test to predict diabetes-associated complications in DM patients.[24] Our findings indicate that high HbA1c levels (≥6.5) were significantly associated with mortality, in line with previous studies.[24] Elevated and uncontrolled blood glucose levels, as indicated by HbA1c, may lead to vascular disease and suppressed immunity, ultimately increasing susceptibility to mortality.

The results of the evaluation of NLR in subjects showed that 55.56% of subjects with NLR ≥8 and the rest had NLR <8. Of the overall mortality rate in subjects, it was found that 14.8% had an NLR value ≥8. In the results of the comparative test, there are significant associations that indicate that the greater the NLR, the worse the prognosis of the subjects. From the results of our risk test, it was found that subjects with an NLR >8 increased the risk of death by 12.062 times compared with <8. These findings are also in line with a study by Yim *et al.*, which showed that NLR could be a prognostic factor for FG patients because the increment is associated with higher mortality.[9,10] NLR is an indicator of inflammation in patients with FG, whether there is an increase in systemic inflammation related to infection or not. The increased NLR condition could be related to the incidence of systemic infection and may be associated with the incidence of sepsis in the patient, which aggravates the disease's condition.[25,26]

From the results of the PLR laboratory, it was found that 17.04% had ≤140 while 74.81% had >140. Of the total deaths that occurred, 62.2% were subjects with a PLR >140. However, there is no significant relationship between PLR and survivability, despite previous research claiming that increasing PLR increased the mortality of FG patients by up to 11 times.[3,10] The findings of an increase in platelets in severe cases of FG were caused by an increase in platelet production, one of which was due to chronic infection.[27,28]

However, the mean NLR and PLR in the group who died were lower than in the surviving group. This study has limitations; it only involved one center, so epidemiological conditions could not be determined from this study. Thus, the next research can be carried out by involving several reference centers and epidemiological research can be carried out that is more representative of the condition of the population.

CONCLUSION

Hematological disorders in patients with FG can be used to predict the prognosis of the disease. In this study, NLR has a predictive value for FG prognosis, whereas PLR has no predictive ability for FG prognosis. If NLR levels are found to be unusually high, the patient and family may be educated about the clinical course and mortality and should get more aggressive therapy. These findings need a prospective, multi-institutional study.

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