

ความแม่นยำของอัตราส่วนของนิวโทรฟิลและเกล็ดเลือดต่อลิมโฟไซต์ทำนายการเสียชีวิตจากภาวะติดเชื้อขั้นได้ผิวหนังลึกถึงระดับพังผืดในผู้ป่วยเบาหวาน

วรรณกร ประภาสจจะเวทย์¹ สันติ เลิศวรรณวิทย์² ธนา บุญสินสุข¹

¹ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ

²หน่วยงานศัลยกรรม โรงพยาบาลสมุทรปราการ

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บทคัดย่อ

ค่าอัตราส่วนของเม็ดเลือดขาวนิวโทรฟิลต่อเม็ดเลือดขาวลิมโฟไซต์ (NLR) และค่าอัตราส่วนเกล็ดเลือดต่อเม็ดเลือดขาวลิมโฟไซต์ (PLR) เป็นค่าตัวแปรการอักเสบของร่างกายในการประเมินการตอบสนองของระบบภูมิคุ้มกันต่อการติดเชื้อและการอักเสบที่ใช้อย่างแพร่หลาย โดยพบว่าค่า NLR และ PLR ที่สูงขึ้นส่งผลต่อการพยากรณ์โรคที่ไม่ดีในโรคต่างๆ นอกจากนี้ NLR และ PLR ยังสามารถประเมินความเสี่ยงต่อการเสียชีวิตจากการติดเชื้อขั้นได้ผิวหนังลึกถึงระดับพังผืดได้ อย่างไรก็ตาม ในผู้ป่วยเบาหวานอาจไม่สามารถใช้ NLR และ PLR ในการประเมินนี้ได้เนื่องจากภาวะภูมิคุ้มกันบกพร่อง ดังนั้น ในงานวิจัยนี้จึงมีวัตถุประสงค์เพื่อศึกษาความแม่นยำของ NLR และ PLR ในการประเมินปัจจัยเสี่ยงต่อการเสียชีวิตของผู้ป่วยโรคเบาหวานที่มีการติดเชื้อขั้นได้ผิวหนังลึกถึงระดับพังผืด โดยเก็บข้อมูลย้อนหลังจากเวชระเบียนของผู้ป่วยเบาหวานชนิดที่ 2 ที่มีภาวะการติดเชื้อขั้นได้ผิวหนังลึกถึงระดับพังผืดของรยางค์ล่าง ตั้งแต่เดือนมกราคม พ.ศ. 2559 ถึงเดือนธันวาคม พ.ศ. 2564 ที่ศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ สยามบรมราชกุมารี มหาวิทยาลัยศรีนครินทรวิโรฒ และโรงพยาบาลสมุทรปราการ ผลการวิจัยพบว่า มีผู้ป่วยเข้าร่วมการศึกษาทั้งหมด 180 ราย เป็นเพศชายและเพศหญิง เพศละ 90 ราย อายุเฉลี่ย 63.7 ± 12.1 ปี จากการวิเคราะห์ข้อมูลแบบตัวแปรเดียว พบว่าปัจจัยที่ส่งผลต่อการเสียชีวิตคือ อายุ ≥ 60 ปี ($p=0.017$) ผู้ป่วยโรคไต ($p=0.007$) NLR ($p=0.006$) จำนวนเกล็ดเลือดน้อยกว่า 150,000 เกล็ด/ไมโครลิตร ($p=0.007$) ระดับน้ำตาลในเลือดมากกว่า 200 มก./ดล. ($p=0.033$) และค่าครีเอตินินมากกว่า 2 มก./ดล. ($p<0.001$) จากการวิเคราะห์เส้นโค้งที่ใช้วัดถึงประสิทธิภาพ (ROC curve) เพื่อทำนายการเสียชีวิตโดยการใช้ NLR พบว่าจุดตัดที่ดีที่สุดคือ 14.3 (AUC 0.632; ความเชื่อมั่นร้อยละ 95 = 0.541-0.723, $p=0.007$) โดยมีความไวเท่ากับร้อยละ 60.6 และความจำเพาะเท่ากับร้อยละ 66.7 อย่างไรก็ตาม พบว่า PLR ไม่สามารถประเมินความเสี่ยงต่อการเสียชีวิตได้ (AUC 0.447; ความเชื่อมั่นร้อยละ 95 = 0.349-0.545, $p=0.278$) จากการวิเคราะห์ข้อมูลแบบหลายตัวแปรพบว่า จำนวนเกล็ดเลือดที่น้อยกว่า 150,000 เกล็ด/ไมโครลิตร $NLR \geq 14.3$ และค่าครีเอตินินมากกว่า 2 มก./ดล. เป็นปัจจัยเสี่ยงในการเสียชีวิต โดยสรุป $NLR \geq 14.3$ มีความสัมพันธ์กับความเสี่ยงที่เพิ่มขึ้นของการเสียชีวิตในผู้ป่วยเบาหวานที่มีการติดเชื้อขั้นได้ผิวหนังลึกถึงระดับพังผืด อย่างไรก็ตาม NLR ไม่สามารถเป็นเครื่องมือที่ดีพอเนื่องจากมีความแม่นยำต่ำ ในขณะที่ PLR ไม่สามารถประเมินความเสี่ยงต่อการเสียชีวิตได้

คำสำคัญ: การติดเชื้อขั้นได้ผิวหนังลึกถึงระดับพังผืด; การเสียชีวิต; ค่าอัตราส่วนของเม็ดเลือดขาวนิวโทรฟิลต่อเม็ดเลือดขาวลิมโฟไซต์; ค่าอัตราส่วนเกล็ดเลือดต่อเม็ดเลือดขาวลิมโฟไซต์; โรคเบาหวาน

ผู้สนับสนุนผลงาน:

ธนา บุญสินสุข

ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ

62 หมู่ 7 ถนนรังสิต-นครนายก ตำบลองครักษ์ อำเภองครักษ์ จังหวัดนครนายก 26120

อีเมล: thanab@g.swu.ac.th

Accuracy of neutrophil-lymphocyte and platelet-lymphocyte ratios as predictors of mortality in diabetic patients with necrotizing fasciitis

Wannakorn Prapasajchavet¹, Santi Lertvanavit², Thana Boonsinsukh¹

¹Department of Surgery, Faculty of Medicine, Srinakharinwirot University

²Department of Surgery, SamutPrakan Hospital

Abstract

The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are widely recognized markers of systemic inflammation and immune responsiveness to infection. Elevated NLR and PLR levels are associated with poor prognoses in various conditions, including necrotizing fasciitis (NF). However, their accuracy in predicting mortality in diabetic patients with NF, who often exhibit immune dysfunction, remains unclear. This study aimed to evaluate the predictive accuracy of NLR and PLR for mortality in diabetic patients with NF. The retrospectively reviewed the medical records of type-2 diabetic patients with lower extremity NF treated at Her Royal Highness Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University, and Samut Prakan Hospital from January 2016 to December 2021. A total of 180 patients were included in the study, comprising 90 men and 90 women, with a mean age of 63.7 ± 12.1 years. Univariate analysis identified significant factors associated with mortality, including age ≥ 60 years ($p=0.017$), renal disease ($p=0.007$), NLR ($p=0.006$), platelet count $<150 \times 10^3/\mu\text{L}$ ($p=0.007$), blood glucose >200 mg/dL ($p=0.033$), and creatinine >2 mg/dL ($p<0.001$). Receiver operating characteristic (ROC) curve analysis revealed that the optimal cut-off point for NLR was 14.3 (AUC 0.632; 95% CI 0.541-0.723, $p=0.007$), with a sensitivity of 60.6% and specificity of 66.7%. In contrast, PLR did not demonstrate predictive value for mortality (AUC 0.447; 95% CI 0.349-0.545, $p=0.278$). Multivariate analysis indicated that a platelet count $<150 \times 10^3/\mu\text{L}$, NLR ≥ 14.3 , and creatinine >2 mg/dL were significant risk factors for mortality. In conclusion, NLR ≥ 14.3 was independently associated with an increased risk of mortality in diabetic patients with NF; however, its low accuracy limits its usefulness as a reliable prognostic test. Conversely, PLR was not found to be a predictor of mortality.

Keywords: necrotizing fasciitis; mortality; neutrophil-lymphocyte ratio; platelet-lymphocyte ratio; diabetes mellitus

Corresponding Author:

Thana Boonsinsukh

Department of Surgery, Faculty of Medicine, Srinakharinwirot University

62 Village No.7, Rangsit-Nakhon Nayok Road, Ongkharak District, Nakhon Nayok 26120, Thailand

E-mail: thanab@g.swu.ac.th

Introduction

Necrotizing fasciitis (NF) or Necrotizing soft tissue infection (NSTI) is a rapidly progressing skin and soft tissue infection with a significant risk of being a life-threatening condition. Despite current knowledge and intensive care, the mortality rate from necrotizing fasciitis remains high, ranging from 5.9% to 22.1%¹⁻³. Various factors are associated with NF, including diabetes, chronic renal failure, cirrhosis, age >60 years, creatinine >2 mg/dL, leukocytosis, platelet count <150×10³/μL, hyponatremia, hyperglycemia and high lactate level¹⁻⁴.

The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are parameters of systemic inflammation that are widely used as markers of immune responsiveness to infection and inflammation⁵⁻⁶. They can be calculated from basic laboratory parameters that are low-cost and easy to use. The elevation of NLR and PLR tends to be indicative of poor prognostic outcomes for various conditions such as cancer, acute or chronic inflammatory conditions, thromboembolic diseases, and trauma⁷⁻⁹. Furthermore, NLR and PLR are utilized to predict mortality attributable to NF¹⁰⁻¹³.

NLR and PLR may not accurately predict mortality in diabetic patients with NF because they have immune dysfunction, which is associated with a reduced response of T cells, neutrophil function, and disorders of humoral immunity¹⁴. In addition, higher NLR is related to the increased prevalence of other diseases in diabetic patients, such as cardiovascular

disease, cerebrovascular disease, diabetic kidney disease, and diabetic retinopathy¹⁵. To the best of our knowledge, no studies have reported on the association between NLR and PLR with mortality in the diabetic population.

Objectives

This study aims to evaluate the accuracy of NLR and PLR in predicting factors of mortality in diabetic patients with NF.

Materials and Methods

Study design

The medical records of patients with NF who were treated at Her Royal Highness Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University, and Samut Prakan Hospital from January 2016 to December 2021, were retrospectively reviewed. Type-2 diabetic patients diagnosed with NF of the lower extremities by surgical exploration were enrolled. Patients under the age of 18, with other skin infections, with NF in other body regions and with immunodeficiency disorders (human immunodeficiency virus and pulmonary tuberculosis) were excluded. The Srinakharinwirot University Ethics Committee of Human Research approved the study with reference number SWUEC/E-197/2564E.

NF was diagnosed by a surgeon with an intraoperative finding of necrotic tissue of the muscle fascia. The treatment of NF included fluid resuscitation, early aggressive surgical debridement of necrotic tissue, broad-spectrum intravenous antibiotics, and local wound care. A pus swab culture was

collected to identify pathogens. The wound was re-inspected 24 hours later to ensure the adequacy of the initial debridement. Amputation was performed on irreversible necrotic tissue, infection control, or in a situation of rapid deterioration or threat to life.

Demographic data and outcomes were collected, including age, gender, comorbidity (hypertension, dyslipidemia, renal failure, cirrhosis), laboratory findings during admission (hemoglobin, white blood cell count, neutrophil count, lymphocyte count, platelet count, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, blood glucose, serum sodium, serum creatinine and serum lactate, and serum albumin), microbiological data, major amputations (above-knee and below-knee amputation), minor amputations (foot amputation, toe amputation), and mortality.

Statistical analysis

Statistical analysis was performed using SPSS (version 23) software (Statistical Procedures for Social Sciences; Chicago, Illinois, USA). Demographic data were presented as means or median, S.D., and percentage. The differences between variables were tested using an independent sample *t*-test or Mann-Whitney *U* test for quantitative variables, and a Chi-squared test or Fisher's exact test was used for categorical data. A *p*-value of less than 0.05 was considered statistically significant. An odds ratio with a 95% confidence interval that did not include unity was considered significant. Statistically

significant clinical scales were tested through receiver operating characteristics (ROC) curve analysis to determine a threshold above which associated mortality was indicated. The cut-off point was identified by the maximum value of the Youden index ($J = \text{sensitivity} + \text{specificity} - 1$). Sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio, and accuracy were all calculated.

Results

A total of 180 patients were enrolled in the study. Patient characteristics are shown in Table 1. There were 90 men and 90 women, with the mean age being 63.7 ± 12.1 years. The most common comorbidity was hypertension. The mean hemoglobin, white blood cell count, and platelet count were 10.4 ± 2.2 g/dL, $20.3 \pm 9.9 \times 10^3/\mu\text{L}$, and $333.7 \pm 145.6 \times 10^3/\mu\text{L}$, respectively. A mean neutrophil-lymphocyte ratio of 17.6 ± 15.4 and platelet-lymphocyte ratio of 274.5 ± 214.5 were ascertained. The mortality rate was 26.7%, while 146 patients had a positive culture. There were 91 patients with monomicrobial infection and 55 patients with polymicrobial infection. *Streptococcus* spp. was the most common pathogen, with others including *Staphylococcus* spp., *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Acinetobacter baumannii*, *Diphtheroid* spp., *Proteus* spp., *Enterobacter* spp., *Klebsiella pneumoniae*, *Aeromonas hydrophila*, and *Morganella morganii*.

Table 1 Demographic data of patients (n=180)

Characteristics	
Gender	
Male	90 (50%)
Female	90 (50%)
Age (years; mean±S.D.)	63.7±12.1
Comorbidity (%)	
Hypertension	138 (76.7)
Renal disease	90 (50)
Dyslipidemia	79 (43.9)
Cirrhosis	10 (5.6)
Laboratory findings during the admission (mean±S.D.)	
Hemoglobin (g/dL)	10.4±2.2
WBC count (x10 ³ /μL)	20.3±9.9
Neutrophil count (x10 ³ /μL)	17.6±9.5
Lymphocyte count (x10 ³ /μL)	1.7±1.3
NLR	17.6±15.4
PLR	274.5±214.5
Platelet count (x10 ³ /μL)	333.7±145.6
Sodium (mEq/L)	131.1±6.1
Blood glucose (mg/dL)	272.7±148.8
Lactate (mmol/L)	2.2±1.9
Creatinine (mg/dL)	2.2±2.3
Albumin (g/dL)	2.3±0.7
Microbiological culture (%)	
No growth	34 (18.9)
Monomicrobial infection	91 (50.6)
Polymicrobial infection	55 (30.5)
Pathogens (%)	
<i>Streptococcus</i> spp.	38 (24.4)
<i>Staphylococcus</i> spp.	34 (21.8)
<i>Enterococcus faecalis</i>	15 (9.6)
<i>Pseudomonas aeruginosa</i>	13 (8.3)
<i>Escherichia coli</i>	11 (7.1)
<i>Acinetobacter baumannii</i>	7 (4.5)
Others ^a	38 (24.3)

Table 1 Continued

Characteristics	
Amputation (%)	112 (62.2)
Above-knee amputation	14 (7.8)
Below-knee amputation	41 (22.8)
Foot amputation	11 (6.1)
Toe amputation	45 (25)
Mortality (%)	48 (26.7)

^aOthers - *Diphtheroid* spp., *Proteus* spp., *Enterobacter* spp., *Klebsiella pneumoniae*, *Aeromonas hydrophila*, and *Morganella morganii*.

Abbreviations: S.D., standard deviation; WBC, white blood cell; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio.

In the univariate analysis, there were six significant predictive factors for mortality (Table 2), which were age ≥ 60 years ($p=0.017$), renal disease ($p=0.007$), neutrophil-lymphocyte ratio ($p=0.006$), platelet count $<150 \times 10^3/\mu\text{L}$ ($p=0.007$), blood glucose >200 mg/dL ($p=0.033$), and creatinine >2 mg/dL ($p<0.001$). There were no significant differences between the two groups in

terms of gender, hypertension, dyslipidemia, cirrhosis, microbiological culture, hemoglobin, white blood cell count, neutrophil count, lymphocyte count, platelet-lymphocyte ratio, hyponatremia (<130 mEq/L), Lactate >2 mmol/L, hypoalbuminemia (<2 g/dL), major amputation, and laboratory risk indicator for necrotizing fasciitis (LRINEC) score, except C-reactive protein (CRP) ≥ 6 .

Table 2 The comparison between survivors and non-survivors

Variables	Survivors (n=132)	Non-survivors (n=48)	p-value
Male (%)	62 (47)	28 (58.3)	0.178
Age ≥ 60 years (%)	73 (55.3)	36 (75)	0.017*
Comorbidity (%)			
Hypertension	99 (75)	39 (81.3)	0.381
Renal disease	58 (43.9)	32 (66.7)	0.007*
Dyslipidemia	60 (45.5)	19 (39.6)	0.483
Cirrhosis	6 (4.5)	4 (8.3)	0.327
Microbiological culture (%)			
Monomicrobial infection	65 (49.2)	26 (54.2)	0.559
Polymicrobial infection	42 (31.8)	13 (21.1)	0.542

Table 2 Continued

Variables	Survivors (n=132)	Non-survivors (n=48)	p-value
Hemoglobin (g/dL; mean±S.D.)	10.4±2.2	10.4±2.3	0.992
WBC count (x10 ³ /μL; mean±S.D.)	20.2±9.8	20.8±10.2	0.711
Neutrophil count (x10 ³ /μL; mean±S.D.)	17.4±9.6	18.2±9.3	0.600
Lymphocyte count (x10 ³ /μL; mean±S.D.)	1.7±1.2	1.6±1.7	0.703
NLR (mean±S.D.)	16.1±15.1	21.7±15.6	0.006*
NLR ≥14.3 (%)	52 (39.4)	32 (66.7)	0.001*
PLR (mean±S.D.)	278.7±194	263±165	0.278
Platelet count <150 x10 ³ /μL (%)	6 (4.5)	8 (16.7)	0.007*
Sodium <130 mEq/L (%)	51 (38.6)	20 (41.7)	0.713
Blood glucose >200 mg/dL (%)	86 (65.6)	22 (47.8)	0.033*
Lactate >2 mmol/L (%)	12 (30.8)	14 (53.8)	0.063
Creatinine >2 mg/dL (%)	30 (22.9)	25 (52.1)	<0.001*
Albumin <2 g/dL (%)	18 (28.6)	16 (39)	0.267
Major amputation (%)	43 (32.6)	12 (25)	0.329
LRINEC score, except CRP ≥6 (%)	59 (45.4)	27 (57.4)	0.156

*Significant at the level of p -value < 0.05

Abbreviations: S.D., standard deviation; WBC, white blood cell; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; major amputations, above-knee and below-knee amputations; LRINEC, laboratory risk indicator for necrotizing fasciitis score; CRP, C-reactive protein.

The receiver operating characteristics (ROC) curve analysis was used to define a threshold for NLR and PLR (Figure 1). The threshold was determined for the value with maximal sensitivity and specificity. For NLR, a cut-off point of 14.3 (AUC 0.632; 95%CI 0.541-0.723, $p=0.007$) was accurate in predicting mortality with sensitivity (60.6%), specificity (66.7%), positive predictive value (83.3%), negative predictive value (38.1%), positive likelihood ratio (1.82), negative likelihood

ratio (0.091), and accuracy (62.2%). In contrast, PLR (AUC 0.447; 95%CI 0.349-0.545, $p=0.278$) and LRINEC score, except CRP (AUC 0.536; 95%CI 0.442-0.629, $p=0.471$) did not show a predictive factor in mortality.

Significantly, the multivariate logistic regression analysis identified platelet count <150 x10³/μL, NLR ≥14.3, and creatinine >2 mg/dL as significant risk factors associated with mortality (Table 3).

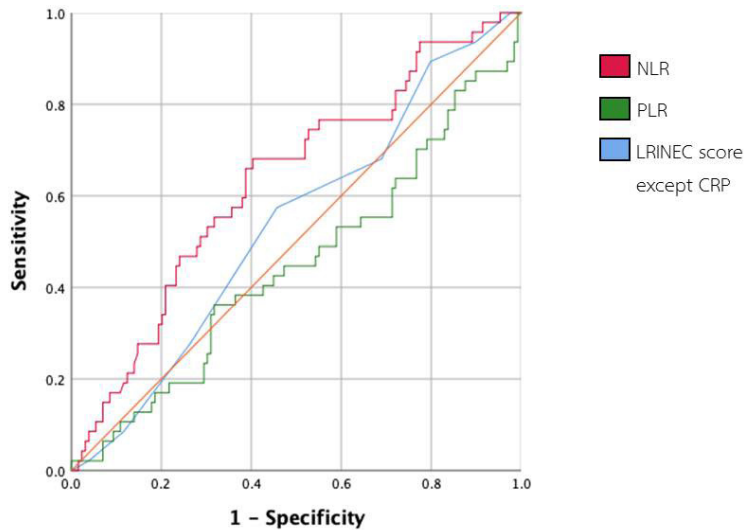


Figure 1 The receiver operating characteristic (ROC) curves of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and laboratory risk indicator for necrotizing fasciitis (LRINEC) score except C-reactive protein (CRP) in predictors of mortality.

Table 3 Significant predictors for mortality in diabetic patients with necrotizing fasciitis by multivariate analysis

Variables	Odds ratio	95%CI	p-value
Platelet count $<150 \times 10^3/\mu\text{L}$	4.2	1.38-12.83	0.014
NLR ≥ 14.3	3.08	1.54-6.16	0.006
Creatinine $>2 \text{ mg/dL}$	3.66	1.82-7.35	0.006

Significant at the level of $p\text{-value} < 0.05$

Abbreviations: 95%CI, 95% confidence intervals; NLR, neutrophil-lymphocyte ratio.

Discussion

The overall mortality rate of NF was 5.9-22.1%¹⁻³. The mortality in this study was rather high (26.7%) because it included only diabetic patients, which is a risk factor for death. The other risk factors associated with mortality in NF include chronic renal failure, cirrhosis, age >60 years, creatinine $>2 \text{ mg/dL}$, leukocytosis, platelet count $<150 \times 10^3/\mu\text{L}$, hyponatremia, hyperglycemia and high lactate level¹⁻⁴. This study found that platelet count $<150 \times 10^3/\mu\text{L}$,

NLR ≥ 14.3 , and creatinine $>2 \text{ mg/dL}$ were associated with mortality in diabetic patients.

Recent studies have identified several inflammatory markers that could predict the prognosis of inflammatory conditions or malignancies. The NLR was derived from absolute neutrophil count divided by absolute lymphocyte count. The PLR was derived from platelet count divided by absolute lymphocyte count. These ratios represented inflammatory process-induced neutrophilia, thrombocytosis,

and cortisol-induced lymphopenia^{5,6,13}. Normal NLR and PLR values were in the range of 1.53-1.7 and 117.05-132.4, respectively¹⁶⁻¹⁸. The elevation of NLR and PLR can predict poor prognostic outcomes for various conditions, including NF⁷⁻¹³.

Previous studies reported that the cut-off points for NLR, which provide the best accuracy in predicting the mortality of NF, were 7.5-11.1^{10,13,19}. Wu et al. showed that $\text{NLR} \geq 11.1$ has a sensitivity of 77.8% and a specificity of 69%¹⁰. In diabetic patients with NF, our study found that $\text{NLR} \geq 14.3$ was accurate in predicting mortality with acceptable sensitivity (60.6%) and specificity (66.7%). Unfortunately, NLR was not a good prognostic test because there was poor accuracy and area under the ROC curve. Power et al. reported that the “sensitivity + specificity” should be at least 1.5 for useful tests, while our NLR has a value of 1.273²⁰. NLR varied in diabetic patients. There could be a decrease due to diabetes being associated with a reduced response of T cells, neutrophil function, and disorders of humoral immunity¹⁴. It is well known that hyperglycemia and the duration of diabetes serve as major risk factors for diabetic microvascular complications. The diabetic microenvironment activates local and systemic inflammatory responses, contributing to the activation of a large number of inflammatory cells, including neutrophils, lymphocytes, and platelets²¹. Therefore, NLR could be increased in diabetic microvascular diseases such as cardiovascular disease, cerebrovascular disease, diabetic kidney disease, and diabetic retinopathy¹⁵.

Wu et al. demonstrated that PLR at a cut-point value of 196 (AUC: 0.679; sensitivity: 59.3%; specificity: 73.8%) can predict mortality in NF¹⁰. By contrast, Ravindhran et al. found that PLR did not demonstrate value as a diagnostic biomarker for mortality in NF. Our study showed similar results in that PLR did not function as a predictor of mortality.

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is a tool for detecting early cases of NF²². There are six laboratory biomarkers, including white blood cells, hemoglobin, creatinine, glucose, serum sodium, and C-reactive protein (CRP). Van Stigt et al. found that patients who died as a result of NF had a significantly higher median LRINEC score, while Ravindhran et al. reported that $\text{LRINEC} \geq 6$ was a predictor of outcomes in NF^{13,23}. However, the LRINEC score was not widely used because CRP was performed only in patients who were highly suspected of having an infection, and it was not available at all hospitals¹⁰. Our hospital diagnosed NF by clinical, ultrasound, and surgical exploration, resulting in CRP not being checked as a routine. Based on our research, the LRINEC score, except CRP, was not associated with an increased risk of mortality.

Previous studies reported amputation rates between 7.1-26%^{1-3,10,12}. Our amputation rate was extremely high at 62.2% overall, and major amputations (above-knee and below-knee amputations) were 30.6%. There could be macrovascular and microvascular changes, comprised of immune responses, increased susceptibility to infections, and

impaired wound healing in diabetic patients²⁴. Supporting this notion, Paul et al. found that diabetes mellitus has a strong association with amputation^{12,25}. However, Khamnuan et al. and Horn et al. reported that amputation was not associated with survival rate, which is consistent with the current study^{1,3}.

This study had several limitations. First, it was a retrospective study based on information from medical records and chart reviews. Thus, the data were limited, had some bias, and involved missing information. Second, the small sample size limited the validation of the study results. Finally, the demographic data for each endemic area were different and might not apply to all populations. Future systematic and theoretical analyses are required to resolve this issue.

Conclusion

$\text{NLR} \geq 14.3$ was found to be independently associated with an increased risk of mortality in diabetic patients with NF, whereas PLR did not demonstrate functionality as a predictor of mortality. However, it appears that NLR fails in terms of being an effective prognostic test with low accuracy for predicting mortality in diabetic patients with NF (sensitivity + specificity < 1.5).

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Data Availability

The data used to support the finding of this study are available from the corresponding author upon request.

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References

1. Khamnuan P, Chongruksut W, Jearwattananok K, et al. Necrotizing fasciitis: Risk factors of mortality. *Risk Manag Healthc Policy* 2015;8:1-7. doi:10.2147/RMHP.S77691.
2. van Stigt S, Knubben M, Schrooten T, et al. Prognostic factors for mortality in 123 severe cases of necrotizing fasciitis in 5 hospitals in the Netherlands between 2003 and 2017. *Eur J Trauma Emerg Surg* 2022;48:1189-95. doi:10.1007/s00068-021-01706-z.
3. Horn DL, Shen J, Roberts E, et al. Predictors of mortality, limb loss, and discharge disposition at admission among patients with necrotizing skin and soft tissue infections. *J Trauma Acute Care Surg* 2020;89:186-91. doi:10.1097/TA.0000000000002636.

4. Kobayashi L, Konstantinidis A, Shackelford S, et al. Necrotizing soft tissue infections: delayed surgical treatment is associated with increased number of surgical debridements and morbidity. *J Trauma* 2011; 71:1400-5. doi:10.1097/TA.0b013e31820db8fd.
5. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. *Bratisl Lek Listy* 2021;122:474-88. doi: 10.4149/BLL_2021_078.
6. Song M, Graubard BI, Rabkin CS, et al. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. *Sci Rep* 2021;11:464. doi: 10.1038/s41598-020-79431-7.
7. Gawinski C, Michalski W, Mróz A, et al. Correlation between lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte Ratio (PLR) and tumor-Infiltrating lymphocytes (TILs) in left-sided colorectal cancer patients. *Biology (Basel)* 2022;11:385. doi:10.3390/biology11030385.
8. Kurtipek E, Büyükterzi Z, Büyükterzi M, et al. Endothelial dysfunction in patients with pulmonary thromboembolism: Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio. *Clin Respir J* 2017;11:78-82. doi:10.1111/crj.12308.
9. Niu S, Pei Y, Hu X, et al. Relationship between the neutrophil-to-lymphocyte ratio or platelet-to-lymphocyte ratio and deep venous thrombosis (DVT) following femoral neck fractures in the elderly. *Front Surg* 2022;9:1001432. doi:10.3389/fsurg.2022.1001432.
10. Wu H, Li C, Liu S, et al. Is Neutrophil lymphocyte ratio, platelet lymphocyte ratio or red blood cell distribution width associated with risk of mortality in patients with necrotizing fasciitis. *Infect Drug Resist* 2023;16:3861-70. doi:10.2147/IDR.S413126.
11. Johnson SR, Benvenuti T, Nian H, et al. Measures of admission immunocoagulopathy as an indicator for in-hospital mortality in patients with necrotizing fasciitis: A retrospective study. *JB JS Open Access* 2023 28;8:e22.00106. doi:10.2106/JBJS.OA.22.00106.
12. Paul P, Vineed S, Chisthi MM, et al. Neutrophil to lymphocyte ratio: A useful predictor of amputation in patients with necrotizing fasciitis: diagnostic accuracy study, 24 August 2022, PREPRINT (Version 1) available at Research Square. doi: 10.21203/rs.3.rs-1978771/v1.
13. Ravindhran B, Rajan S, Kerketta D, et al. Neutrophil to lymphocyte Ratio (NLR) and Platelet to lymphocyte ratio (PLR) versus laboratory risk indicator for necrotizing fasciitis (LRINEC) as predictors of outcome in necrotising fasciitis. *Indian J Surg* 2020;82:325-30. doi:10.1007/s12262-019-01929-w.

14. Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. *Indian J Endocrinol Metab* 2012;16:S27-36. doi:10.4103/2230-8210.94253.
15. Wan H, Wang Y, Fang S, et al. Associations between the neutrophil-to-lymphocyte ratio and diabetic complications in adults with diabetes: A cross-sectional study. *J Diabetes Res* 2020;2020:6219545. doi:10.1155/2020/6219545.
16. Forget P, Khalifa C, Defour JP, et al. What is the normal value of the neutrophil-to-lymphocyte ratio? *BMC Res Notes* 2017;10:12. doi:10.1186/s13104-016-2335-5.
17. Moosazadeh M, Maleki I, Alizadeh-Navaei R, et al. Normal values of neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and platelet-to-lymphocyte ratio among Iranian population: Results of Tabari cohort. *Caspian J Intern Med* 2019;10:320-5. doi:10.22088/cjim.10.3.320.
18. Lee JS, Kim NY, Na SH, et al. Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea. *Medicine (Baltimore)* 2018;97:e11138. doi:10.1097/MD.00000000000011138.
19. Yim SU, Kim SW, Ahn JH, et al. Neutrophil to lymphocyte and platelet to lymphocyte ratios are more effective than the Fournier's gangrene severity index for predicting poor prognosis in Fournier's gangrene. *Surg Infect (Larchmt)* 2016;17:217-23. doi:10.1089/sur.2015.126.
20. Power M, Fell G, Wright M. Principles for high-quality, high-value testing. *Evid Based Med* 2013;18:5-10. doi:10.1136/eb-2012-100645.
21. Li J, Wang X, Jia W, et al. Association of the systemic immuno-inflammation index, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio with diabetic microvascular complications. *Front Endocrinol (Lausanne)* 2024;15:1367376. doi:10.3389/fendo.2024.1367376.
22. Wong CH, Khin LW, Heng KS, et al. The LRINEC (Laboratory Risk indicator for necrotizing fasciitis) score: A tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med* 2004;32:1535-41. doi:10.1097/01.ccm.0000129486.35458.7d.
23. van Stigt S, Knubben M, Schrooten T, et al. Prognostic factors for mortality in 123 severe cases of necrotizing fasciitis in 5 hospitals in the Netherlands between 2003 and 2017. *Eur J Trauma Emerg Surg* 2022;48:1189-95. doi:10.1007/s00068-021-01706-z.

24. Kim HJ. Investigating diabetic foot pathophysiology and amputation prevention strategies through behavioral modification. *J Wound Manag Res* 2023; 19:167-72. doi:10.22467/jwmr.2023.02747.
25. Paul P, Prabhakaran I, Chisthi M. Mortality from necrotizing fasciitis: A cross-sectional study. *Int Surg J* 2020;7:1036-41. doi:10.18203/2349-2902.isj20201036.