The relationship of HbA1c and neutrophil-lymphocyte ratio (NLR) to prognostics of Fournier's gangrene assessed using scoring Fournier's Gangrene Severity Index (FGSI)

RR Bono Pazio[a*], Syah Mirsya Warli[b], Dhirajaya Dharma Kadar[b], Iqbal Pahlevi Adeputra Nasution[c], Adi Muradi Muhar[d]

[a]Department of Surgery, Faculty of Medicine, University of North Sumatra, Medan, Indonesia
[b]Division of Urology, Department of Surgery, Faculty of Medicine, University of North Sumatra, H. Adam Malik Hospital, Medan, Indonesia
[c]Division of Pediatric Surgery, Department of Surgery, Faculty of Medicine, University of North Sumatra, H. Adam Malik Hospital, Medan, Indonesia
[d]Division of Digestive Surgery, Department of Surgery, Faculty of Medicine, University of North Sumatra, Medan, Indonesia

Abstract

Introduction: Fournier's Gangrene, a life-threatening necrotizing fasciitis, primarily affects individuals over 50 years old, with risk factors including diabetes, alcoholism, and urogenital instrumentation. This study investigates the relationship between Hemoglobin A1c (HbA1c), Neutrophil-Lymphocyte Ratio (NLR), and the prognostic implications for Fournier's Gangrene, using the Fournier's Gangrene Severity Index (FGSI) for assessment.
Methods: A cross-sectional, correlational analytical study utilized secondary data from medical records at RSUP H. Adam Malik from January 2015 to July 2023, focusing on the correlation between HbA1c, NLR, and FGSI scores in Fournier's Gangrene prognosis.
Results: Out of 100 samples, high HbA1c and NLR levels were significantly associated with worse FGSI scores, indicating a poorer prognosis for Fournier's Gangrene. Statistical analysis revealed a moderate correlation between HbA1c levels and FGSI scores and a weak correlation for NLR, considering their prognostic significance.
Discussion: The findings affirm the critical role of HbA1c in monitoring glycemic control and its direct correlation with Fournier's Gangrene severity, suggesting the necessity of effective diabetes management. Similarly, NLR's association with inflammation severity underscores its utility in prognostic assessment.
Conclusion: Elevated HbA1c and NLR levels are significant predictors of adverse outcomes in Fournier's Gangrene, with HbA1c being a more robust prognostic indicator compared to NLR.

Keywords: Fournier's Gangrene, HbA1c, Neutrophil-Lymphocyte Ratio, FGSI, prognosis, diabetes mellitus

1. Introduction

Fournier's Gangrene can attack individual from various age , however own predilection For attack individual over 50 years old . A number of factor risk happen *Fournier's Gangrene* including alcoholism , diabetes, age advanced , cancer , malnutrition , instrumentation or urogenital trauma, and history disease vessels blood peripheral (Farma P., 2023) Men in relationships sex with fellow type are at greater risk high , esp For caused infection related with *Methicillin-Resistant Staphylococcus aureus* (MRSA) . (Chernyadyev et al., 2018).

HbA1c, also known as hemoglobin A1c, is the parameter used For measure average blood sugar levels during three month final . HbA1c generally used For monitor control blood sugar in patients with

diabetes mellitus . Diabetes mellitus is comorbidity at a time factor risk morbidity and mortality *Fournier's gangrene* (FG). Disease This found in 10-60% of individuals with Fournier's gangrene. As many as 66% of mortality in FG occurred in DM sufferers . In DM, it happens damage macrovascular and microvascular chronic progressive . On FG, it happened damage microvascular progressive tissues and organs in a way acute, so damage microvascular chronic already _ occurs in patients with diabetes mellitus significant worsens the prognosis of FG. Faeni et al (2021) report that diabetes mellitus is related with FGSI score >9 (p=0.036). Other studies state that for DM patients with FGSI >9, the probability of survival is only 25%. Therefore, it can be concluded that an increase in HbA1c is related to prognosis *Fournier's gangrene* the bad (Faeni et al. , 2021; Faswati and Herawati, 2022; Noegroho et al. , 2023).

NLR is ratio between amount neutrophils (cells blood white plays a role in response inflammation) and lymphocytes (cells blood white plays a role in system immunity) in blood patient . NLR has used as a marker of inflammation systemic and has been proven own mark predictive in various condition medical conditions , including sepsis. Sepsis is complications serious that can be occurs in Fournier 's *Gangrene* , and strong inflammation often happen in condition. Therefore NLR can used For evaluate level inflammation and identify patient with risk tall (Lewis *et al.*, 2021).

The FGSI score is tools used to measure level severity *Fournier's Gangrene* . This score combine various clinical and laboratory parameters , incl temperature body , pressure blood , level consciousness , and laboratory parameters like blood sugar levels and levels electrolytes . FGSI score can be help doctor in assess the patient's prognosis and determine action proper medical care . Study about connection between HbA1c and NLR with FGSI score in patients *Fournier's Gangrene* has become focus attention in effort increase understanding about factors that influence the prognosis of the condition This . Result of research This has give rapid development about case This (de Souza *et al.*, 2020).

A number of study show that patient with high HbA1c levels tend has a better prognosis bad in case *Fournier's Gangrene* . High blood sugar levels can hinder response immunity body to infection , so worsen development of gangrene. Besides that's an increase blood sugar levels can also promote growth bacteria pathogen . Therefore good blood sugar control is very important in management *Fournier's Gangrene* (Chernyadyev *et al.*, 2018).

Temporary that NLR has also identified as factor potential prognostic _ useful in *Fournier's Gangrene* . Patient with high NLR tend own more inflammation _ serious , that can be influence development disease . NLR can also used For identify patient with risk tall For complications like sepsis. However , it's important For remembered that *Fournier's Gangrene* is condition complex medical conditions , and other factors can also occur affect prognosis. Therefore _ that , research more carry on required For understand with more Good connection between HbA1c, NLR, and FGSI scores in case *Fournier's Gangrene* (Demir *et al.*, 2018).

Fournier's Gangrene is condition serious and deadly medical needs attention medical. Study about connection between HbA1c and NLR with FGSI score can be give development in increase understanding about factors that influence the patient's prognosis with *Fournier's Gangrene* . High HbA1c levels can worsen development of gangrene, while NLR is high can indicated more inflammation critical (El-Qushayri *et al.*, 2020). However, it's important For do study more carry on For confirm findings this and understand role Other factors in the prognosis *of Fournier's Gangrene* . Above the background behind above , researcher interested For research relationship between HbA1c and NLR prognostic Graded Fournier 's *Gangrene* use FGSI *scoring*.

2. Methods

This type of research is correlation analytic with a cross-sectional *design sectional*) . The data that will be used is secondary data taken from medical records. In this study, we wanted to know the relationship between HbA1c and NLR prognostic Graded Fournier 's *Gangrene* using FGSI *scoring* at RSUP H. Adam Malik, Research This done at home Sick General Adam Malik Hajj Center Medan with agreement Commission Ethics USU Health Research . Research and data collection will done start from month January 2015 until with month July 2023.

The population of this study were all *Fournier's Gangrene patients* at Haji Adam Malik Hospital, Medan. The inclusion criteria for this study were patients diagnosed with Fournier's Gangrene in the emergency room of HAM Hospital for the period 1 January 2015 until . July 31 2023, complete medical record data including patient identity and laboratory examination. Meanwhile, the exclusion criteria in this study were incomplete data from laboratory examination results, patients with comorbidities (acute/chronic kidney disorders, heart disease, stroke), and patients with immunodeficiency or who were taking steroid drugs.

The data that has been collected and grouped based on variables will then be processed and analyzed using the *SPSS (Statistics) program Packages for Social Science) ver 22* . For categorical data , analysis is correlation done with the Spearman test . The p value <0.05 and r> 0.5 is a positive correlation. Subject mapping was carried out based on NLR levels, HbA1c and FGSI scores, then *true calculations were carried out positive* , *true negative* , *false positive* , *false negative* . Calculation result *is true positive , true negative , false positive ,* and *false negative values* are then entered into the formula to find the sensitivity, specificity , positive predictive value, and negative predictive value (Monaghan *et al* . , 2021). Analyst *Kaplan Meier* for analysis prognostic of the case *Fournier's Gangrene* with FGSI scoring . The results of the analysis are presented in the form of tables, graphs and narratives.

3. Results

In study This has collected as many as 100 samples met criteria study . Characteristics sample can seen in Table 1.

Table 1. Characteristics sample with *Fournier's Gangrene* based on FGSI

Characteristics	FGSI		p *value*
	< 9 (n = 66) (mean ± SD)	≥ 9 (n = 34) (mean ± SD)	
Age (years)	54.32 ± 10.56	55.74 ± 12.97	0.181
Temperature (°C)	37.43 ± 0.76	37.40 ± 1.02	0.762
Heart rate (x/ minute)	95.17 ± 9.82	99.85 ± 15.00	0.254
Respiratory rate (x/ minute)	21.02 ± 2.11	21.35 ± 2.42	0.505
Sodium content (mmol/l)	131.45 ± 4.88	128.26 ± 6.98	<0.001
Potassium level (mmol/l)	3.98 ± 0.64	3.84 ± 0.78	0.247

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creatine (mg/dL)	1.32 ± 0.70	1.95 ± 1.16	0.007
Hematocrit (%)	34.34 ± 6.87	32.06 ± 7.87	0.120
Leukocytes (/mm^3)	14,127.73 ± 5,006.68	17,409.41 ± 12,226.78	0.236
bicarbonate (mmol/l)	18.83 ± 5.54	16.25 ± 3.72	0.031

*Mann- Whitney

A total of 66 patients had FGSI <9 (66%), while 34 had FGSI ≥ 9 (34%). Characteristics sample with FGSI <9 ie age 54.32 ± 10.56 years , temperature 37.43 ± 0.76 °C , HR 95.17 ± 9.82 x/ minute , RR 21.02 ± 2.11 x/ minute , sodium 131.45 ± 4.88 mmol/l, potassium 3.98 ± 0.64 mmol/l, hematocrit 34.34 ± 6.87 % , creatine 1.32 ± 0.70 mg/dL, leukocytes 14,127.73 ± 5,006.68 /mm^3 , and bicarbonate 18.83 ± 5.54 mmol/I. Characteristics sample with FGSI ≥ 9 ie Age 55.74 ± 12,97 years , Temperature 37.40 ± 1.02 °C , HR 99.85 ± 15.00 x/ minute , RR 21.35 ± 2.42 x/ minute , sodium 128.26 ± 6,98 mmol/ L, potassium 3.84 ± 0.78 mmol/ L, creatine 1.95 ± 1.16 mg /dL, hematocrit 32.06 ± 7.87 %, leukocytes 17,409.41 ± 12,226.78 /mm^3 , and bicarbonate 16.25 ± 3.72 mmol/I. Sodium, creatine and bicarbonate levels different significant between FGSI<9 group with FGSI ≥9 group (p < 0.05).
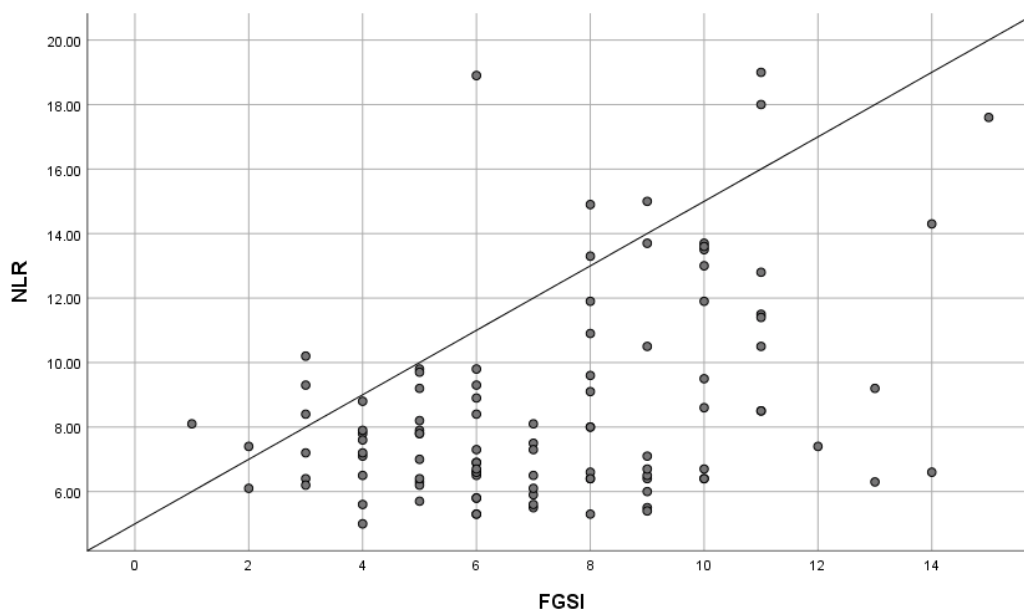
Table 2. HbA1c levels and NLR values based on FGSI

| Parameter	FGSI		r	p value
	< 9 (n = 66) (mean ± SD)	≥ 9 (n = 34) (mean ± SD)		
HbA1c (%)	6.79 ± 1.50	9.06 ± 2.33	0.538	<0.001
NLR	7.77 ± 2.34	10.23 ± 3.89	0.312	0.003

*Mann-Whitney
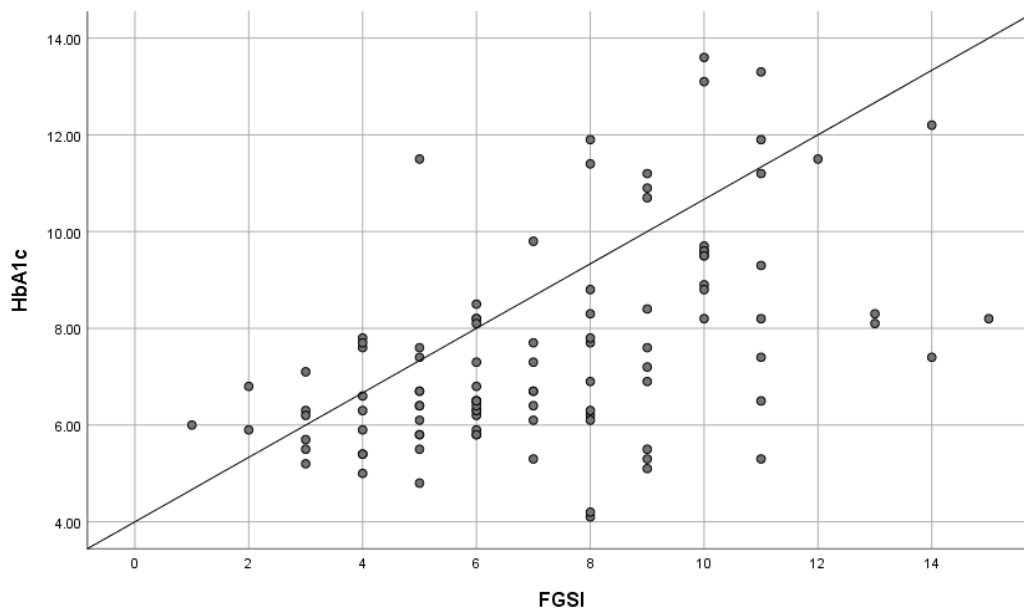
Figure 1. *Scatter plots* For correlation between HbA1c and FGSI

Figure 2. *Scatter plots* For correlation of NLR with FGSI

Based on Table 2, values average HbA1c levels in the group with FGSI <9 is 6.79 ± 1.50, whereas for FGSI ≥9 is 9.06 ± 2.33. Average value of NLR in the FGSI <9 group was 7.77 ± 2.34, while in the FGSI

≥9 group it was 10.23 ± 3.89. By statistics , differences HbA1c levels and NLR values between second group considered significant (p <0.001). Correlation between HbA1c and NLR levels against FGSI score is 0.538 (correlation moderate) and 0.312 (correlation weak).
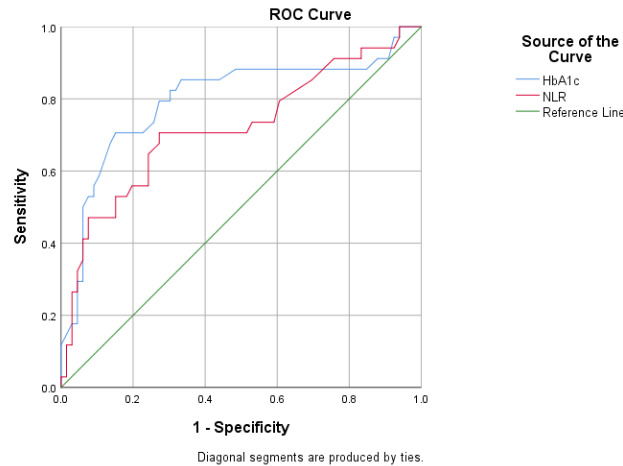
Figure 3. ROC curve of HbA1c and NLR levels

Analysis ROC curve of HbA1c and NLR levels as predictor FGSI ≥ 9 can seen in Figure 3.1. Based on Table 3, AUC value of HbA1c and NLR levels were 0.797 (*good accuracy*) and 0.719 (*good accuracy*).
Table 3 *Area Under Curve* (AUC) value of HbA1c and NLR levels as predictor FGSI ≥ 9

Parameter	AUC	p value
HbA1c	0.797	<0.001
NLR	0.719	<0.001

Table 4. Cut-off, sensitivity, specificity, values predictive positive, and value predictive negative from HbA1c and NLR levels as predictor FGSI ≥ 9

Parameter	*Cut-off*	Sensitivity	Specificity	PPV	NPV
HbA1c	≥ 7.50	85.7%	81.5%	61.5%	85.0%
NLR	≥ 8.15	70.6%	71.2%	55.8%	82.4%

In Table 4, you can seen that mark *cut-off* of HbA1c as predictor of FGSI ≥ 9 is 7.50 with sensitivity , specificity , PPV, and NPV respectively sequentially namely : 85.7%, 81.5%, 61.5%, and 85.0%. The cut-off value of NLR as predictor of FGSI ≥ 9 is 8.15, with sensitivity , specificity , PPV, and NPV respectively sequentially namely 70.6%, 71.2%, 55.8%, and 82.4%.

4. Discussion

Based on previous study, DM had reported as one of the factor risk from FG. This matter because more gangrene condition tend occurs in individuals with condition immunosuppression . There have been cases of

FG in DM sufferers reported range between 32% to 66%. Diabetes condition _ significant give impact on immunity somebody . Disturbances that occur covers interference with abilities destruction intracellular pathogen , disorder adhesion neutrophils , disorders chemotaxis , and interference immunity cellular (Nisbet and Thompson, 2002).

HbA1c levels are something indicator important to control glycemic in duration of 2 to 3 months in patients with DM. Normal HbA1c levels ie range between 5.7% to 6.4%. Levels ≥6.5% indicate control poor glycemic . _ Until moment This is only study by Sen et al. ever _ report role HbA1c levels in determine the prognosis in FG. In studies the , analysis performed on 18 patients with DM, and 20 non-DM patients . The result found that in the mean HbA1c in the group with DM , namely 8.9 ± 1.1. Then done in DM group , carried out distribution become two group that is patient with HbA1c <7% (n = 12) and patients with HbA1c ≥7% (n = 6). Average HbA1c levels in the group DM patients with HbA1c ≥7% was 11.8 ± 1.4. On the other hand , the mean HbA1c in the group DM patients with HbA1c <7% was 6.6 ± 0.4. Next , found that the length of treatment more long and broad lesion more greater in the DM group with HbA1c ≥7%. From the results , Sen et al. conclude that HbA1c levels can become predictor on patient prognosis with FG(Sen *et al.*, 2016)

In study this , we aim For look for connection between HbA1c levels with FGSI scoring . Therefore FGSI ≥9 has reported give probability mortality as much as 75%, then we do analysis to HbA1c level against FGSI ≥9. Result of study This found that mean HbA1c in the group with FGSI ≥9 more tall compared to with FGSI <9 group (9.06 ± 2.33 vs 6.79 ± 1.50; r = 0.538; p < 0.001). We also found out there is correlation positive currently between HbA1c levels with FGSI score . This matter indicated that enhancement HbA1c levels will impact on improvement FGSI score , and vice versa . Analysis accuracy from HbA1c levels against FGSI scores were also performed and found that HbA1c has good accuracy _ as predictor of FGSI (AUC = 0.797; p < 0.001). *Cut-off* value from HbA1c levels as predictor of FGSI ≥9 was 7.5. The sensitivity , specificity , PPV, and NPV of the cut-off ≥7.5% against FGSI ≥9 were 85.7%, 81.5%, 61.5%, and 85.0%. The findings in our research indicate that HbA1c levels have good sensitivity and specificity _ as predictor against FGSI ≥9.

Neutrophils is cells that play a role important in line First For eradication infection . Cell This classified as *innate immune system* . On the other hand , lymphocytes is classified cells _ as *adaptive immune system* . From the results studies previous , comparison ratio between neutrophils and lymphocytes (NLR) have reported as indicator important in determine the patient 's prognosis with FG. Studies Yim et al. report that NLR >8 is associated with enhancement risk mortality as high as 4.66 times (Yim *et al.*, 2016).

For moment this , report about NLR relationship with FGSI scores are very limited . Guemes -Quinto et al. report that an increase in NLR does not impactful or not have correlation to FGSI score , so No influential to mortality patient . Unfortunately , studies the Still classified weak because studies the only included a total of 45 patients (Guemes-Quinto *et al.*, 2023). In studies in 2017 by Saum et al. also reported that NLR value does not impact on length of treatment stay patient with FG (OR [95%CI] = 0.49 [-0.2 – 1.2]; p = 0.162) (Ghodoussipour *et al.*, 2018).

In study by Pehlivanli and Aydin, concluded that combination between NLR and FGSI can predict mortality from FG case . In studies the group _ mortality have the NLR value is 22.30 ± 30.31, whereas NLR value in the group that did not experience mortality is 6.95 ± 6.31. FGSI value in the group mortality was 14.40 ± 2.19, while in group without mortality is 6.78 ± 2.49. Although Pehlivanli and Aydin concluded that a combination of NLR and FGSI can made as predictor of FG, however No There is studies correlation is carried out between these two parameters (Pehlivanll and Aydin, 2019).

Based on results our findings, on average The NLR value found in the FGSI ≥9 group was 10.23 ± 3.89, while in the FGSI <9 group it was 7.77 ± 2.34. Findings This significant in a way statistics (p < 0.05). Correlation test results show that there is correlation weak positive between NLR value with FGSI score . Findings the indicated that enhancement NLR levels will impact on the FGSI score , and vice versa . Next ,

analyze strength predictions of the NLR was carried out and found that the NLR has good accuracy _ as predictor FGSI score ≥9 (AUC = 0.719). The cut-off value of NLR as predictor of FGSI ≥9 was 8.15 (sensitivity = 70.6%, specificity = 71.2%, PPV = 55.8%, and NPV = 82.4%).

Previous study also stated a statistically significant mean difference between SFGSI (p<0.0001) and quickSOFA (qSOFA) scores (p=0.002) in determining the survival rate of FG patients. The sensitivity and specificity of the SFGSI score in predicting mortality were 90.1% and 88.3% respectively, whereas the sensitivity and specificity of the qSOFA score were 88.2% and 86.2%. E. Coli comprised 56.2% of the bacteria, followed by S. Haemolyticus, S. Aureus, P. Aeruginosa, and K. Pneumoniae. On the basis of bacterial culture results, P. Aeruginosa had the highest fatality rate (100%) followed by S. Aureus (75%), S. Haemolyticus (30%), and E. Coli (20%), in that order (Warli et al., 2024).

5. Conclusion

Characteristics samples in groups with FGSI <9 was sodium 131.45 ± 4.88 mmol/l, creatine 1.32 ± 0.70 mg/dL, and bicarbonate 18.83 ± 5.54 mmol/I. Characteristics samples in groups with FGSI ≥9 was sodium 128.26 ± 6.98 mmol/l, creatine 1.95 ± 1.16 mg/dL, and bicarbonate 16.25 ± 3.72 mmol/I. The HbA1c value with a cut-off is more than 7.50 meaningful compared to NLR value , with with sensitivity , specificity , PPV, and NPV respectively sequentially namely : 85.7%, 81.5%, 61.5%, and 85.0% compared with NLR value with cut-off 8.15, where mark sensitivity , specificity , PPV, and NPV respectively sequentially namely 70.6%, 71.2%, 55.8%, and 82.4%.

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