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## Predictive Value of Neutrophil-to-Lymphocyte Ratio for Detecting Nonalcoholic Fatty Liver Disease in Type 2 Diabetes Mellitus Patients

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Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition characterized by insulin resistance, leading to increased blood glucose levels (hyperglycemia). Insulin resistance is a key factor in the development of nonalcoholic fatty liver disease (NAFLD), a condition defined by excessive hepatic fat accumulation that is not caused by alcohol consumption. NAFLD can progress from simple steatosis to hepatic inflammation and fibrosis. The neutrophil-to-lymphocyte ratio (NLR) is a simple biomarker for systemic inflammation. Elevated NLR values may indicate increased inflammation, such as that observed in NAFLD. This study aimed to determine differences in NLR values in T2DM patients with NAFLD and without NAFLD. This cross-sectional study used secondary data from the medical records of 88 T2DM patients from 2022 to 2024, divided into groups without NAFLD (n=45) and with NAFLD (n=43) based on ultrasonographic liver findings. The Welch t-test was applied to compare NLR values, and receiver operating characteristic (ROC) analysis was used to identify the optimal cut-off value for NLR. The NAFLD group had significantly higher NLR values (mean difference = 3.80; 95% CI: 2.75–5.24;  $p < 0.001$ ), with an AUC of 0.962 (95% CI: 0.915–1.000;  $p < 0.001$ ) and an optimal cut-off value of  $\geq 3.1964$  (sensitivity 90.7%; specificity 100%). In conclusion, NLR is significantly elevated in T2DM patients with NAFLD and demonstrates strong discriminatory ability, indicating its potential use as a simple inflammatory biomarker in T2DM managements.

**Keywords:** Inflammation, NLR, NAFLD, Type 2 Diabetes Mellitus

### INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition characterized by impaired insulin secretion and insulin resistance, leading to hyperglycemia and various complications. T2DM is a significant public health burden since its prevalence is rising worldwide in tandem with dietary changes and increased caloric intake (International Diabetes Foundation, 2017). In addition to glucose metabolic disturbances, T2DM is also strongly associated with metabolic-related liver disease, particularly nonalcoholic fatty liver disease (NAFLD) (Mantovani et al., 2020; Zhang et al., 2023).

NAFLD is commonly known as the hepatic manifestation of metabolic syndrome, characterized by the accumulation of fat in more than 5% of hepatocytes in the absence of significant alcohol intake (Lesmana et al., 2022). Previous meta-analyses report that NAFLD is found in approximately 65% of patients with T2DM (Bidang(En Li Cho et al., 2023). The two conditions share intertwined pathophysiological mechanisms in which insulin resistance plays a significant role by increasing peripheral lipolysis,

free fatty acid flux to the liver, and hepatic gluconeogenesis, ultimately aggravating steatosis and oxidative stress (Chen et al., 2021; Zhang et al., 2023).

Diagnosing and monitoring NAFLD remain clinical challenges. The gold standard for evaluation of severity remains liver biopsy, as it directly assesses steatosis, inflammation, and fibrosis. However, biopsy is invasive, carries risks of complications, and is impractical for routine evaluation or study due to large sample sizes (Lesmana et al., 2022). Therefore, USG is frequently used as a more practical, non-invasive approach with broad availability, cheaper cost, and adequate sensitivity for identifying mild to severe steatosis (Jang & Song, 2023).

Low-grade chronic inflammation is recognized as a significant factor in the association between insulin resistance and the development of NAFLD, while also aiding progression to nonalcoholic steatohepatitis (NASH) and fibrosis (Husna, 2020). The inflammatory process shifts leukocyte dynamics by increasing neutrophil activity and suppressing lymphocyte counts, as reflected in the neutrophil-to-lymphocyte ratio (NLR), a simple and

affordable biomarker of systemic inflammation (Lesmana et al., 2022). Increased NLR values have been associated with features of both T2DM and NAFLD, including hepatic inflammation, insulin resistance, and the severity of steatosis (Kaushal et al., 2025).

Previous studies have shown significant differences in NLR values between patients with and without NAFLD, as diagnosed by liver biopsy, controlled attenuation parameter (CAP), and transient elastography (TE). However, CAP and TE are costly and not widely available in healthcare facilities, and biopsy is also an invasive method (Lesmana et al., 2022; Zhao et al., 2022).

## METHOD

The study used a cross-sectional design and employed consecutive sampling from the medical records of outpatient and inpatient T2DM patients at Universitas Sebelas Maret Hospital from 2022 to 2024. Subjects included those with previously diagnosed T2DM who met the American Diabetes Association criteria and had complete liver USG results (American Diabetes Association, 2022).

Inclusion criteria were (1) adults (>18 years old) with T2DM, (2) complete laboratory data including leukocyte differential count, fasting blood glucose (FBG), random blood glucose (RBG), and hemoglobin A1c (HbA1c), and (3) USG findings confirming the presence or absence of NAFLD. Exclusion criteria included (1) significant alcohol consumption (>20 g/day), (2) viral hepatitis, (3) other chronic liver diseases (e.g., autoimmune or drug-induced), (4) malignancy, (5) acute infection, and (6) hematologic disorders that may affect leukocyte counts.

A total of 88 subjects met all criteria, including 45 without NAFLD and 43 with NAFLD. The dependent variable was the NLR, obtained from complete blood count results. The independent variable was NAFLD status, by

abdominal USG. Additional variables included age, sex, FBG, RBG, HbA1c, and type of antidiabetic therapy.

IBM Statistical Package for Social Sciences (SPSS) version 26.0 was utilized for data analysis. Descriptive statistics were presented as median (IQR) for the Mann-Whitney U test. Differences in mean NLR between groups with and without NAFLD were analyzed using Welch's t-test due to unequal variances. Statistical significance would be met if the p-value is <0.05. Additionally, our study used receiver operating characteristic (ROC) curve analysis to identify the optimal cut-off value for NLR. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret (No. 60/UN27.06.11/KEP/EC/2024).

## RESULTS AND DISCUSSION

In this study, 88 subjects passed the inclusion and exclusion criteria, with 45 in the non-NAFLD group and 43 in the NAFLD group. The NAFLD group was, by statistics, significantly older than the non-NAFLD group (56.00 (51.00–59.00) vs. 45.00 (41.00–49.50) years;  $p < 0.001$ ). Sex distribution was relatively balanced (44.3% males and 55.7% females;  $p = 0.981$ ). These findings support earlier Asia-based studies showing that sex is not a principal determinant of NAFLD prevalence among individuals with T2DM (Kaushal et al., 2025; Kong et al., 2023; Tao et al., 2025). However, evidence from a Southeast Asian study indicates a trend toward higher NAFLD prevalence among women, although this trend did not reach statistical significance (Lesmana et al., 2022). Another study reported that NAFLD incidence and severity appear to increase with age, particularly among postmenopausal women, likely due to diminished estrogen's protective influence on hepatic fibrogenesis, which exacerbates insulin resistance and hepatic fat accumulation (Cotter & Rinella, 2020).

**Table 1.**  
Basic Characteristics Data of Research Subjects

Variable	Without NAFLD (N=45)	With NAFLD (N=43)	p
Gender			0,981 <sup>1</sup>
Male	19	20	
Female	26	23	
Age (years)	45,00 (41,00–49,50)	56,00 (51,00–59,00)	<0,001 <sup>2</sup>
RBG (mg/dl)	247,00 (165,00–323,50)	190,00 (147,00–269,00)	0,058 <sup>2</sup>
FBG (mg/dl)	227,50 (176,75–255,75)	146,00 (130,00–185,75)	0,025 <sup>2</sup>
HbA1c (%)	12,10 (10,90–13,10)	9,50 (7,63–10,88)	0,021 <sup>2</sup>
Absolute Neutrophil Count (cell/mm <sup>3</sup> )	5,56 (4,07–6,69)	7,55 (6,10–11,11)	<0,001 <sup>2</sup>
Absolute Lymphocyte Count (cell/mm <sup>3</sup> )	2,68 (2,40–3,11)	1,48 (1,14–3,11)	<0,001 <sup>2</sup>

Notes: <sup>1</sup>Chi-square test and <sup>2</sup>Mann-Whitney U test were applied to describe subjects' characteristics. <sup>2</sup> Results are shown as median (IQR). \*Fasting blood glucose and HbA1c data were available only in a subset of patients (fasting blood glucose: 6 non-NANFLD; HbA1c: 11 non-NAFLD and 6 NAFLD)

As shown in Table 1, we found higher medians for FBG, RBG, and HbA1c in the non-NAFLD group. These results contradict previous studies that reported NAFLD is usually found in patients with worse glycemic control (He et al., 2024; Mantovani et al., 2022). A probable cause of a difference in HbA1c results might be liver disease; factors

such as anemia, hypersplenism, and shortened erythrocyte lifespan may lead to underestimation of glycemic levels despite ongoing hyperglycemia, resulting in lower accuracy of HbA1c percentages (Eyth et al., 2025).

**Table 2.**  
**Distribution of Antidiabetic Drug Usage**

Antidiabetic Drug	Without NAFLD (N=45)	With NAFLD (N=43)	p
Metformin (%)	27 (60,0%)	23 (48,8%)	0,293 <sup>1</sup>
Sulfonilurea (%)	15 (33,3%)	17 (39,5%)	0,545 <sup>1</sup>
Insulin (%)	24 (53,3%)	12 (27,9%)	0,026 <sup>1</sup>
GLP-1RA (%)	0 (0%)	0 (0%)	-
SGLT2-i (%)	0 (0%)	0 (0%)	-
Pioglitazon (%)	3 (6,7%)	7 (16,3%)	0,191 <sup>2</sup>
DPP-4i (%)	8 (17,8%)	0 (0,0%)	0,006 <sup>2</sup>
α-Glucosidase Inhibitor (%)	6 (13,3%)	4 (9,3%)	0,739 <sup>2</sup>

Notes: <sup>1</sup>Chi-square test is used for drug distribution, and <sup>2</sup>Fisher's Exact test if the frequency requirements are not met.

Antidiabetic drug usage further provides insight into these findings. Insulin was used significantly more in the non-NAFLD group (p = 0.026). Insulin therapy is commonly initiated in patients with severe hyperglycemia or HbA1c >9% (American Diabetes Association, 2022; Perkeni, 2021), suggesting this group has worse glycemic control despite not being diagnosed with steatosis on USG. Furthermore, a previous study found a reduction of proinflammatory cytokines after insulin therapy, which may indicate an anti-inflammatory effect and might have influenced the results in this study. Conversely, patients with NAFLD more frequently used pioglitazone, a PPAR-γ agonist known for improving liver condition and insulin sensitivity, which may contribute to differences in glycemic parameters (Lian & Fu, 2021).

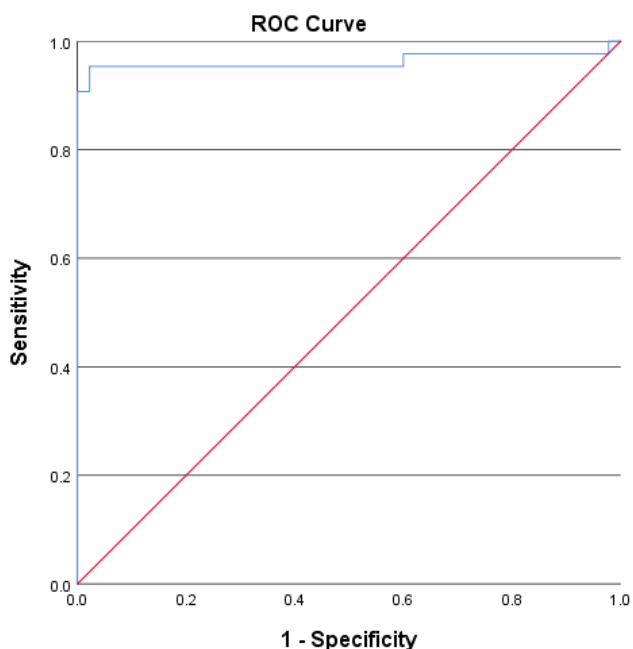
Regarding inflammatory markers, the NAFLD group demonstrated significantly higher neutrophil counts (7.55 (6.10–11.11) cell/mm<sup>3</sup> vs. 5.56 (4.07–6.69) cell/mm<sup>3</sup>; p < 0.001) and lower lymphocyte counts (1.48 (1.14–2.15) cell/mm<sup>3</sup> vs. 2.68 (2.40–3.11) cell/mm<sup>3</sup>; p < 0.001). Our findings aligned with the theory that chronic inflammation plays a role in NAFLD pathogenesis. Insulin resistance promotes lipolysis and increases free fatty acids, leading to hepatic fat accumulation and oxidative stress, which activate inflammatory pathways (Chen et al., 2021; Grander et al., 2023). These mechanisms led to elevated proinflammatory cytokines, such as TNF-α and IL-1β, which trigger neutrophil recruitment and, in tandem with lymphopenia, thereby increase the NLR (Chen et al., 2021; Kaushal et al., 2025). Lesmana et al. further demonstrated the association among NLR, TNF-α, and HOMA-IR,

reinforcing NLR's role as an alternative biomarker of subclinical inflammation in metabolic liver disease (Lesmana et al., 2022).

**Table 3.**  
Comparison of Mean NLR Using Welch's t-test in Subjects With and Without NAFLD

Variable	Mean±SD	Mean difference (95% CI)	p
<b>NLR</b>			
Without NAFLD	2,09±0,48	-3,604 (-4,915–-2,293)	<0,001
With NAFLD	5,70±4,24		

Welch's t-test showed a significantly different average NLR between the groups (5.70 ± 4.24 vs. 2.09 ± 0.48; p < 0.001). This finding is consistent with multiple prior studies by Kaushal et al., Zhao et al., and Lesmana et al., which reported higher NLR in NAFLD and its association with both steatosis and fibrosis severity (Kaushal et al., 2025; Lesmana et al., 2022; Zhao et al., 2022). The present study strengthens the evidence that NLR reflects systemic inflammation in patients with T2DM and NAFLD.



**Figure 1.** NLR ROC curve in differentiating Subjects with and without NAFLD

**Table 4.**

Classification based on NLR cut-off value of 3.196

NAFLD status	NLR $\geq$ 3,196	NLR < 3,196	Total
With NAFLD	39	4	43
Without NAFLD	0	45	45
Total	39	49	88

ROC curve analysis yielded an AUC of 0.962 (95% CI: 0.911–1.000;  $p < 0.001$ ), indicating excellent discriminatory capability of NLR in distinguishing subjects with and without NAFLD. However, our ROC analysis findings should be interpreted cautiously, as they may reflect spectrum bias related to USG usage as well as the modest sample size. The optimal cut-off value was 3.196, producing 90.7% sensitivity and 100% specificity. This cut-off is higher than those reported in previous studies (ranging from 1.57 to 2.15) (Lesmana et al., 2022; Tang et al., 2025), a difference possibly attributable to the diagnostic method used. While CAP, TE, and biopsy are more sensitive for mild steatosis, USG typically detects only more severe steatosis. USG, while widely used in clinical practice, has limited sensitivity for detecting mild steatosis and provides no information on fibrosis of inflammatory activity. Therefore, the NAFLD group in this study may represent subjects with more severe hepatic fat accumulation, which could lead to NLR having lower diagnostic performance in patients with mild steatosis.

, the NAFLD group was older and less likely to receive insulin therapy compared to the non-NAFLD group. Aging is known to be associated with an increase in

circulating levels of proinflammatory markers, often referred to as inflammaging, which may lead to independent elevation of NLR. In addition, insulin therapy has been shown to decrease inflammatory cytokines, thus exerting anti-inflammatory effects. Therefore, the observed differences in NLR between the two groups may reflect the age and antidiabetic treatment rather than NAFLD alone. As no multivariable adjustment was performed, the independent contribution of NLR to NAFLD risk cannot be definitively established.

Overall, our findings demonstrate the central role of inflammation in NAFLD pathogenesis among patients with T2DM and the potential utility of NLR as an adjunctive biomarker to aid risk stratification, particularly where advanced imaging modalities are unavailable. Nonetheless, these findings should be interpreted cautiously, considering the study's limitations: (1) the distribution of NAFLD severity was limited, with most cases being grade 1; (2) some laboratory data, particularly glycemic parameters, were incomplete; and (3) unmeasured confounders such as dietary patterns, insulin resistance indices, and genetic factors were not assessed. Further studies incorporating more comprehensive clinical variables and more sensitive diagnostic modalities are warranted.

## CONCLUSIONS

This study found significant differences in NLR values from T2DM patients with NAFLD and without NAFLD. Higher NLR values in the NAFLD group suggest an association with elevated systemic inflammation. NLR may serve as a complementary inflammatory marker for initial screening, but should not be interpreted as a standalone diagnostic tool.

## SUGGESTION

NLR may be considered a supportive inflammatory biomarker to assist in early NAFLD identification among T2DM patients, particularly in healthcare settings with limited access to advanced hepatic imaging. Future studies should confirm the proposed cut-off value using larger and more diverse populations, incorporate more sensitive diagnostic modalities and multivariable models that are required to determine whether NLR independently predicts NAFLD. Additional research would be needed to evaluate the effects of metabolic, therapeutic, and genetic factors on NLR and NAFLD progression.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

## REFERENCES

- American Diabetes Association. (2022). Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. *Clinical Diabetes*, 40(1), 10–38. [[Crossref](#)] [[Publisher](#)]
- Chen, W., Chen, K., Xu, Z., Hu, Y., Liu, Y., Liu, W., Hu, X., Ye, T., Hong, J., Zhu, H., & Shen, F. (2021). Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio Predict Mortality in Patients with Diabetic Foot Ulcers Undergoing Amputations. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 14, 821–829. [[Crossref](#)] [[Publisher](#)]
- Cotter, T. G., & Rinella, M. (2020). Nonalcoholic Fatty Liver Disease 2020: The State of the Disease. *Gastroenterology*, 158(7), 1851–1864. [[Crossref](#)] [[Publisher](#)]
- En Li Cho, E., Ang, C. Z., Quek, J., Fu, C. E., Lim, L. K. E., Heng, Z. E. Q., Tan, D. J. H., Lim, W. H., Yong, J. N., Zeng, R., Chee, D., Nah, B., Lesmana, C. R. A., Bwa, A. H., Win, K. M., Faulkner, C., Aboona, M. B., Lim, M. C., Syn, N., ... Loomba, R. (2023). Global prevalence of non-alcoholic fatty liver disease in type 2 diabetes mellitus: an updated systematic review and meta-analysis. *Gut*, 72(11), 2138–2148. [[Crossref](#)] [[Publisher](#)]
- Eyth, E., Zubair, M., & Naik, R. (2025). Hemoglobin A1C. *Laboratory Screening and Diagnostic Evaluation: An Evidence-Based Approach*, 403–408. [[Crossref](#)] [[Publisher](#)]
- Grander, C., Grabherr, F., & Tilg, H. (2023). Non-alcoholic fatty liver disease: pathophysiological concepts and treatment options. *Cardiovascular Research*, 119(9), 1787–1798. [[Crossref](#)] [[Publisher](#)]
- He, Y., Xiao, F., Yi, B., & Lu, J. (2024). Prevalence and associated factors of MAFLD in adults with type 2 diabetes. *PLOS Global Public Health*, 4(12), e0003572. [[Crossref](#)] [[Publisher](#)]
- Husna, F. N. (2020). *Uji Aktivitas Alginat Dari Sargassum Duplicatum Dengan Ekstrak Buah Okra Dan Ekstrak Kulit Buah Manggis Terhadap Penyembuhan Luka Terbuka Pada Mencit Diabetik*. [[Publisher](#)]
- International Diabetes Foundation. (2017). Diabetes Atlas 8th edition 2017. In *IDF Diabetes Atlas, 8th edition*.
- Jang, W., & Song, J. S. (2023). Non-Invasive Imaging Methods to Evaluate Non-Alcoholic Fatty Liver Disease with Fat Quantification: A Review. *Diagnostics (Basel, Switzerland)*, 13(11). [[Crossref](#)] [[Publisher](#)]
- Kaushal, S., Ganju, N., Mokta, K. K., Mokta, J. K., & Gulepa, R. (2025). Prevalence of non-alcoholic fatty liver disease and left ventricular diastolic dysfunction in newly diagnosed type II diabetes mellitus: an observational, cross-sectional study. *PANACEA JOURNAL OF MEDICAL SCIENCES*, 15(2), 433–437. [[Crossref](#)] [[Publisher](#)]
- Kong, L., Yang, Y., Li, H., Shan, Y., Wang, X., & Shan, X. (2023). Prevalence of nonalcoholic fatty liver disease and the related risk factors among healthy adults: A cross-sectional study in Chongqing, China. *Frontiers in Public Health*, 11, 1127489. [[Crossref](#)] [[Publisher](#)]
- Lesmana, C. R. A., Kencana, Y., Rinaldi, I., Kurniawan, J., Hasan, I., Sulaiman, A. S., & Gani, R. A. (2022). Diagnostic Value of Neutrophil to Lymphocyte Ratio in Non-Alcoholic Fatty Liver Disease Evaluated Using Transient Elastography (TE) with Controlled Attenuated Parameter (CAP). *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 15, 15. [[Crossref](#)] [[Publisher](#)]
- Lian, J., & Fu, J. (2021). Pioglitazone for NAFLD Patients With Prediabetes or Type 2 Diabetes Mellitus: A Meta-Analysis. *Frontiers in Endocrinology*, 12. [[Crossref](#)] [[Publisher](#)]
- Mantovani, A., Byrne, C. D., Zheng, M. H., & Targher, G. (2020). Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: A meta-analysis of observational studies. *Nutrition, Metabolism and Cardiovascular Diseases*, 30(8), 1236–1248. [[Crossref](#)] [[Publisher](#)]
- Mantovani, A., Lombardi, R., & Dalbeni, A. (2022). Glucose-lowering agents and reduced risk of incident non-alcoholic fatty liver disease: new insights. *Hepatobiliary Surgery and Nutrition*, 11(1), 15660–15160. [[Crossref](#)] [[Publisher](#)]
- Perkeni. (2021). *Pedoman Pengelolaan dan Pencegahan Diabetes Mellitus Tipe 2 di Indonesia* (2nd ed.). PB Perkeni. [[Publisher](#)]
- Tang, Y., Deng, Y., Zhang, G., Wang, Y., Wang, J., Wu, J., & Gu, M. (2025). Inflammatory markers as predictors of liver fibrosis in type 2 diabetes patients with metabolic dysfunction-associated fatty liver disease. *Frontiers in Endocrinology*, 16, 1556646. [[Crossref](#)] [[Publisher](#)]
- Tao, J., Wang, L., Wang, H., & Tan, J. (2025). Non-linear relationship between liver fibrosis and femoral neck bone mineral density in metabolic dysfunction-associated fatty liver disease patients with type 2 diabetes mellitus. *Journal of Diabetes Investigation*. [[Crossref](#)] [[Publisher](#)]
- Zhang, D., Zhang, L., Chen, S., Chen, R., Zhang, X., & Bai, F. (2023). Prevalence and Risk Factors of Metabolic-Associated Fatty Liver Disease Among Hospital Staff. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 16, 1221–1234. [[Crossref](#)] [[Publisher](#)]
- Zhao, Y., Xia, J., He, H., Liang, S., Zhang, H., & Gan, W. (2022). Diagnostic performance of novel inflammatory biomarkers based on ratios of laboratory indicators for nonalcoholic fatty liver disease. *Frontiers in Endocrinology*, 13, 981196. [[Crossref](#)] [[Publisher](#)]