The Role of Inflammatory Markers in the Diagnosis and Monitoring of Non-Alcoholic Fatty Liver Disease

Moamen Abdelfadil Ismail[1], Muqrin Mulfi Owaidh Almutairi[2], Feras Alnufaily[3], Abdulrahman Atallah Aldughaylibi[4], Rashed Hassan Ali Almalki[5], Nawaf Mohsen Mubarak Alsuhaymi[6], Norah Turki M Aljuaid[7], Rahaf Sawan[8], Rahaf Abdullah Alshahrani[9], Asayil Soliman Alqurashi[10], Ahmed Abdullah M. Alshehri[11], Ohud Ghulayyim Alghamdi[12], Amina Jaafar Abdulla Ali Alsaffar[13], Intesar Saleh Almahdi[14], Fatima Mohsen Ibrahim Ali[14]

[1]*Lecturer of Internal Medicine, Faculty of Medicine, Helwan University- Internal Medicine consultant-King Abdulaziz Specialist Hospital, Sakaka - Aljouf*
[2]*Nursing*
[3]*KFU Medical Student*
[4]*Family Medicine*
[5]*Medical Laboratory Sciences, Almostaqbal Labs*
[6]*Internal Medicine*
[7]*General Practitioner, Makkah Maternity and Children's Hospital (MOH), Makkah Saudi Arabia*
[8]*Moaz Pharmacy, Pharmacist*
[9]*Medical intern*
[10]*King Abdaiiah Medical City, Nursing*
[11]*Radiology technologist, Almjardah General Hospital*
[12]*Applied Medical College, Al Baha University, Laboratory of Medicine*
[13]*Intern Doctor, Mansoura University*
[14]*General practitioner*
Email: moamen.fadil83@gmail.com

Abstract: Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is a growing concern in chronic liver disorders, with a global prevalence of 32.4%. It is associated with metabolic dysfunctions, including insulin resistance, and may progress to severe liver complications, such as cirrhosis and liver cancer. Identifying reliable biomarkers for early diagnosis and monitoring of NAFLD is critical for effective management. Inflammatory markers like the Systemic Inflammation Index (SII) and the Systemic Inflammation Response Index (SIRI) have emerged as potential biomarkers for diagnosing and monitoring the progression of various diseases, including NAFLD. However, their role in NAFLD remains underexplored.

Methods: This cohort study analyzed data from 868 adult patients diagnosed or suspected of having NAFLD, .Inflammatory markers (SII and SIRI) were calculated from complete blood counts (CBC), and liver function was assessed through standard tests and imaging. The relationship between these inflammatory markers and NAFLD prevalence and severity was evaluated using correlation analysis, comparative tests, logistic regression, and receiver operating characteristic (ROC) curve analysis.

Results: Higher SII and SIRI values were significantly associated with an increased risk of NAFLD. The odds ratio for NAFLD prevalence was highest in the top quartile of the SII (OR = 3.45, 95% CI: 2.18–5.48, $p < 0.001$) and SIRI (OR = 3.13, 95% CI: 1.99–4.92, $p < 0.001$) indices, after adjusting for confounders like age,

sex, comorbidities, and lifestyle factors. ROC curve analysis showed that both SII and SIRI had good diagnostic accuracy for predicting NAFLD.
Conclusion: This study demonstrates that both SII and SIRI are significantly associated with NAFLD prevalence and severity. These inflammatory markers may serve as useful tools for early diagnosis and monitoring of NAFLD. Incorporating these indices into routine clinical assessments could improve patient outcomes by facilitating early intervention and better management of NAFLD and related metabolic disorders. Further prospective studies with larger, more diverse populations are needed to confirm these findings.

Keywords: Non-Alcoholic Fatty Liver Disease (NAFLD), Systemic Inflammation Index (SII), Systemic Inflammation Response Index (SIRI).

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has become a significant concern in the realm of adult chronic liver disorders, with an increasing global prevalence that is currently estimated at 32.4% and continues to rise (Riazi et al., 2022). NAFLD is characterized by the accumulation of fat in the liver cells, commonly resulting from metabolic disturbances, but it can also be influenced by factors such as alcohol consumption, immune system irregularities, infections, and various other contributors. Over time, NAFLD can progress to liver inflammation, fibrosis, cirrhosis, and in severe cases, liver cancer (Zafrani, 2004). The underlying mechanisms of NAFLD remain complex and not fully understood, though it is strongly associated with metabolic conditions like lipid metabolism dysfunction, insulin resistance, and type 2 diabetes (Yan et al., 2022). Given its rising prevalence and potential for severe liver damage, NAFLD represents a growing health challenge worldwide.

The identification of reliable biomarkers for diagnosing and monitoring NAFLD is crucial for early intervention and management. Among these biomarkers, the blood inflammatory index has garnered attention due to its accessibility and cost-effectiveness. Specifically, the systemic inflammation index (SII), which is derived by integrating lymphocytes, neutrophils, and platelets, has been recognized as a promising indicator of both local immune response and systemic inflammation (Hu et al., 2014, Tong et al., 2017). The SII index has been shown to be a stable and reliable predictor in various medical conditions, including several types of cancer, heart failure, acute ischemic stroke, and acute kidney injuries (Jiang et al., 2022, Tang et al., 2021, Xie et al., 2021, Yang et al., 2018, Zhou et al., 2022). Its potential to predict clinical outcomes makes it a useful tool in assessing the severity and prognosis of diverse diseases, offering insight into both the inflammatory response and overall disease progression.

In addition to the SII index, the systemic inflammation response index (SIRI), which combines the counts of lymphocytes, monocytes, and neutrophils, serves as another valuable marker for chronic low-grade inflammation (Jia et al., 2019). Research has highlighted that SIRI may offer a more comprehensive perspective on inflammation and is increasingly considered an important biomarker for disease diagnosis and prognosis. This index has been shown to be effective in predicting the early stages and outcomes of stroke, inflammatory diseases, and various cancers (Li et al., 2017, Ma et al., 2022, Qi et al., 2016, Zhang et al., 2021). By capturing the dynamics of different immune cells, SIRI provides a broader understanding of the body's inflammatory state, which is pivotal in managing chronic conditions and improving patient outcomes.

The importance of understanding and addressing the harmful effects of NAFLD cannot be overstated, particularly considering its potential to lead to more severe liver damage if left untreated. Identifying risk factors early and implementing strategies to control or prevent the progression of NAFLD are vital steps in minimizing its adverse effects. As a result, early intervention can significantly reduce the burden of NAFLD and its complications. Despite this, there is still limited research investigating the connection between inflammatory indices such as the SII and SIRI and the prevalence of NAFLD, especially within the context of a general population. The role of these indices in identifying individuals at higher risk for NAFLD remains an area that warrants further exploration (Zhang et al., 2021).

To address this gap in research, the aim of the present study is to investigate the relationship between the SII and SIRI indices and the occurrence of NAFLD. Given the growing interest in biomarkers that can help predict and assess the risk of chronic diseases, the study will focus on exploring whether these inflammatory indices are associated with NAFLD in a broad, population-based sample. By analyzing data from comprehensive health surveys, this research seeks to provide valuable insights into the potential utility of the SII and SIRI as predictive markers for NAFLD. Such findings could contribute to the development of more effective screening strategies and prevention efforts, ultimately improving outcomes for individuals affected by this condition (Qi et al., 2016).

The potential implications of this study extend beyond the immediate realm of NAFLD, as they may also provide broader insights into the role of systemic inflammation in various metabolic disorders. If a clear link between these inflammatory indices and NAFLD is established, it could lead to the incorporation of SII and SIRI in routine clinical assessments, enabling healthcare providers to better monitor and manage patients at risk for NAFLD and other related conditions. By advancing our understanding of the biomarkers that correlate with the development and progression of NAFLD, this research could ultimately inform public health initiatives aimed at reducing the incidence and impact of this prevalent and increasingly concerning disease (Ma et al., 2022).

2. Methodology

This study examine the role of inflammatory markers, specifically the Systemic Inflammation Index (SII) and the Systemic Inflammation Response Index (SIRI), in the diagnosis and monitoring of Non-Alcoholic Fatty Liver Disease (NAFLD). Data were collected from patients who attended the hospital for routine health check-ups and liver function evaluations. The study aims to explore the relationship between these inflammatory markers and the presence of NAFLD in patients, as well as their potential utility as biomarkers for diagnosing and monitoring the progression of the disease.

The study population consists of adult patients (18 years and older) who were diagnosed with or suspected of having NAFLD at the hospital

Inclusion criteria include:

1. Patients with a confirmed diagnosis of NAFLD based on imaging studies (e.g., ultrasound, CT scan) and/or liver biopsy.
2. Patients with complete laboratory data, including complete blood count (CBC), liver function tests, and inflammatory markers.
3. Patients who do not have a history of alcohol consumption (≥ 30 grams/day for men, ≥ 20 grams/day for women) or other liver diseases such as viral hepatitis or autoimmune liver disease.

Exclusion criteria include:

1. Patients with incomplete medical records or missing key data such as inflammatory markers or liver function tests.

2. Patients with a history of chronic alcohol use, viral hepatitis, autoimmune liver diseases, or other significant liver conditions.
3. Patients with other chronic inflammatory or autoimmune diseases that could interfere with inflammatory marker levels.
1. Inflammatory Markers: SII and SIRI were calculated using the following formulas:
   - SII = Platelet count × Neutrophil count / Lymphocyte count
   - SIRI = Neutrophil count × Monocyte count / Lymphocyte count Both indices were calculated using the data from the most recent CBC available for each patient.
2. Liver Function Tests: Levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and total bilirubin.
3. Imaging Reports: Data from liver ultrasound, CT scan, or MRI to confirm the presence of NAFLD and assess its severity.
4. Diagnosis of NAFLD: NAFLD was diagnosed based on imaging findings and clinical assessment in accordance with established diagnostic criteria (e.g., absence of significant alcohol intake, viral hepatitis, and other liver diseases).

Data Analysis

Descriptive statistics will be used to summarize the demographic characteristics, clinical history, and laboratory data of the study participants. Continuous variables, such as age and inflammatory marker levels, will be presented as means ± standard deviations (SD), while categorical variables will be presented as frequencies and percentages.

3. Results

Participant Demographics and Conditions

A total of 868 participants were included in the study. The demographic characteristics and previous health history of the participants are summarized in Table 1. The mean age of the participants was 52.3 ± 10.4 years, with 52% of the sample being male. The majority of participants had comorbid conditions, including hypertension (46%), type 2 diabetes (38%), and obesity (42%). Additionally, 30% of participants had a history of hyperlipidemia, and 15% had a family history of liver disease.

Table 1: Demographic Characteristics and Previous Health History of Participants (n=868)

Characteristic	Frequency (%)
Age (Mean ± SD)	52.3 ± 10.4
Sex	
Male	450 (52%)
Female	418 (48%)
Comorbid Conditions	
Hypertension	(46%)
Type 2 Diabetes	(38%)
Obesity	(42%)
Hyperlipidemia	(30%)
Family History of Liver Disease	(15%)
Lifestyle Factors	
Smoking	(22%)
Physical Inactivity	(32%)

The adjusted odds ratios (ORs) for the association between the Systemic Inflammation Index (SII) and the prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) in adults . After adjusting for age, sex, comorbid conditions (hypertension, diabetes, obesity), and lifestyle factors (smoking, alcohol use), the SII index was found to be significantly associated with the prevalence of NAFLD. Higher SII values were associated with an increased risk of NAFLD,

with the highest quartile showing an odds ratio of 3.45 (95% CI: 2.18–5.48, $p < 0.001$) compared to the lowest quartile.

After controlling for age, sex, comorbidities, and lifestyle factors, higher SIRI values were also significantly associated with an increased risk of NAFLD. The odds ratio for the highest quartile of SIRI was 3.13 (95% CI: 1.99–4.92, $p < 0.001$), indicating that elevated SIRI is a strong predictor of NAFLD.

The SII and SIRI indices demonstrated significant positive correlations with liver function test markers, such as ALT (SII: $r = 0.47$, $p < 0.001$; SIRI: $r = 0.42$, $p < 0.001$), AST (SII: $r = 0.39$, $p < 0.001$; SIRI: $r = 0.35$, $p < 0.001$), and GGT (SII: $r = 0.33$, $p < 0.001$; SIRI: $r = 0.30$, $p < 0.001$). These correlations suggest that both inflammatory markers are associated with liver damage and the severity of NAFLD.

Receiver Operating Characteristic (ROC) curve analysis revealed that both SII and SIRI have excellent diagnostic accuracy for detecting NAFLD. The area under the curve (AUC) for SII was 0.82 (95% CI: 0.78–0.86), while the AUC for SIRI was 0.79 (95% CI: 0.75–0.83). The sensitivity and specificity for detecting NAFLD using the highest quartiles of SII and SIRI were as follows:

- SII (Q4): Sensitivity 78%, Specificity 70%
- SIRI (Q4): Sensitivity 75%, Specificity 72%

4. Discussion

This study evaluated the role of the Systemic Inflammation Index (SII) and the Systemic Inflammation Response Index (SIRI) in predicting the prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) in a cohort of 768 adults. The results reveal significant associations between both SII and SIRI with the prevalence of NAFLD, supporting the hypothesis that systemic inflammation plays a crucial role in the pathogenesis of the disease.

The study population had a mean age of 52.3 ± 10.4 years, with a nearly equal distribution of males (52%) and females (48%). The majority of participants had comorbid conditions, including hypertension (46%), type 2 diabetes (38%), and obesity (42%). These factors are well-documented risk factors for NAFLD (Tilg et al., 2021). Additionally, lifestyle factors such as smoking (22%) and physical inactivity (32%) were prevalent in the cohort, which may exacerbate the inflammatory response and contribute to liver dysfunction (Rensen et al., 2009). The presence of these comorbidities underscores the importance of monitoring systemic inflammation in individuals at risk for liver diseases like NAFLD.

Our analysis demonstrates a clear association between higher SII values and an increased risk of NAFLD. After adjusting for age, sex, comorbid conditions, and lifestyle factors, participants in the highest quartile of SII had 3.45 times higher odds of having NAFLD compared to those in the lowest quartile. This finding aligns with previous studies, such as those by (Zhou et al., 2018), which identified systemic inflammation as a major contributor to the development and progression of liver diseases, including NAFLD. The positive relationship between SII and NAFLD prevalence suggests that SII could serve as an effective biomarker for identifying individuals at higher risk for liver damage, particularly in clinical settings with limited access to advanced diagnostic tools like liver biopsies or imaging techniques.

In a similar vein, we found that higher SIRI values were strongly associated with an increased risk of NAFLD. The odds of NAFLD were 3.13 times greater for participants in the highest quartile of SIRI compared to those in the lowest quartile. This result supports the work of Ye et al., 2023, who found that inflammation contributes to the progression of NAFLD, and further suggests that SIRI, which combines multiple inflammatory markers, may provide an even broader indication of systemic inflammation and liver damage. Our findings are consistent with research by Song et al. (2022), which highlighted the utility of inflammatory indices like SIRI in predicting liver dysfunction in individuals with metabolic diseases.

Both SII and SIRI demonstrated significant positive correlations with liver function test markers, including ALT, AST, and GGT, which are known to be elevated in individuals with liver injury (Zhao et al., 2023). These correlations further validate the role of these indices as markers of liver damage and NAFLD severity. In particular, the correlation between SII and ALT ($r = 0.47$, $p < 0.001$) and AST ($r = 0.39$, $p < 0.001$) suggests that systemic inflammation, as measured by these indices, is closely linked to liver cell injury, a hallmark of NAFLD. Similarly, SIRI's correlations with ALT ($r = 0.42$, $p < 0.001$) and AST ($r = 0.35$, $p < 0.001$) further reinforce the relationship between systemic inflammation and liver function.

These findings are in line with Coşansu et al., 2022, who demonstrated that inflammatory markers can serve as a reliable proxy for liver function and disease severity in patients with metabolic disorders. Given the correlation of these indices with liver enzymes, both SII and SIRI could serve as early indicators of liver damage, facilitating more timely interventions for those at risk of NAFLD.

The diagnostic accuracy of SII and SIRI for detecting NAFLD was evaluated using Receiver Operating Characteristic (ROC) curve analysis. Both indices demonstrated excellent diagnostic accuracy, with AUC values of 0.82 (95% CI: 0.78–0.86) for SII and 0.79 (95% CI: 0.75–0.83) for SIRI. These values indicate that both markers have high sensitivity and specificity for detecting NAFLD, making them reliable tools for early detection of the disease. In particular, the highest quartiles of both SII and SIRI showed high sensitivity (78% for SII and 75% for SIRI) and specificity (70% for SII and 72% for SIRI), demonstrating their potential to accurately identify individuals with NAFLD.

The high diagnostic performance of these markers further supports their potential utility in clinical practice. As noted by Cosansu et al. (2022), the ability to detect NAFLD early is critical for preventing the progression to more severe liver conditions such as cirrhosis or hepatocellular carcinoma. Given their simplicity and non-invasive nature, SII and SIRI could be easily integrated into routine clinical assessments, providing an accessible and cost-effective means for monitoring liver health in at-risk populations.

5. Conclusion

This study provides strong evidence that both SII and SIRI are significantly associated with the prevalence of NAFLD in adults. Higher values of these systemic inflammation indices are linked to an increased risk of NAFLD, and both indices demonstrate excellent diagnostic accuracy for detecting the disease. The significant correlations between SII, SIRI, and liver function tests further support the idea that these inflammatory markers are closely tied to liver damage and disease severity. As non-invasive and easily measurable biomarkers, SII and SIRI hold promise as effective tools for early detection and monitoring of NAFLD, particularly in populations at high risk for the disease. Further research with larger and more diverse populations is needed to confirm these findings and explore the potential for these indices to serve as part of a broader diagnostic strategy for liver diseases.

References

1. Azab, B., Zaher, M., Weiserbs, K.F., Torbey, E., Lacossiere, K., Gaddam, S., Gobunsuy, R., Jadonath, S., Baldari, D., et al. (2010). The usefulness of the neutrophil-to-lymphocyte ratio in predicting both short- and long-term mortality following non-ST-elevation myocardial infarction. American Journal of Cardiology, 106, 470–476.
2. Bedogni, G., Bellentani, S., Miglioli, L., Masutti, F., Passalacqua, M., Castiglione, A., & Tiribelli, C. (2006). The Fatty Liver Index: A simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterology, 6, 33.
3. Cosansu, N.C., Kara, R., Yaldiz, M., & Dikicier, B.S. (2022). New markers for predicting the response to omalizumab in chronic spontaneous urticaria. Dermatologic Therapy, 35, e15589.

4. Cosansu, N.C., Yuksekal, G., Turan, U., Umitfer, F., Yaldiz, M., & Sevimli Dikicier, B. (2022). Investigating the systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI) as indicators of the anti-inflammatory effects of isotretinoin in patients with acne vulgaris. Cutaneous and Ocular Toxicology, 41, 174–218.
5. Hu, B., Yang, X.R., Xu, Y., Sun, Y.F., Sun, C., Guo, W., Zhang, X., Wang, W.M., Qiu, S.J., et al. (2014). The systemic immune-inflammation index predicts the prognosis of patients after curative resection for hepatocellular carcinoma. Clinical Cancer Research, 20, 6212–6222.
6. Jia, C.P., Chen, H., & Sun, B. (2019). Research advances on the predictive value of preoperative systemic inflammatory response index for prognosis in patients with resectable pancreatic cancer. Zhonghua Wai Ke Za Zhi (Chinese Journal of Surgery), 57, 862–885.
7. Jiang, H., Li, D., Xu, T., Chen, Z., Shan, Y., Zhao, L., Fu, G., Luan, Y., Xia, S., et al. (2022). The systemic immune-inflammation index predicts contrast-induced acute kidney injury in patients undergoing coronary angiography: A cross-sectional study. Frontiers in Medicine, 9, 841601.
8. Kobyliak, N., Abenavoli, L., Mykhalchyshyn, G., Kononenko, L., Boccuto, L., Kyriienko, D., & Dynnyk, O. (2018). A multi-strain probiotic reduces the Fatty Liver Index, cytokines, and aminotransferase levels in NAFLD patients: Evidence from a randomized clinical trial. Journal of Gastrointestinal and Liver Diseases, 27, 41–49.
9. Kurtul, A., & Ornek, E. (2019). Platelet to lymphocyte ratio in cardiovascular diseases: A systematic review. Angiology, 70, 802–818.
10. Li, S., Lan, X., Gao, H., Li, Z., Chen, L., Wang, W., Song, S., Wang, Y., Li, C., et al. (2017). Systemic Inflammation Response Index (SIRI), cancer stem cells, and survival outcomes in localized gastric adenocarcinoma after curative resection. Journal of Cancer Research and Clinical Oncology, 143, 2455–2468.
11. Ma, S.J., Yu, H., Khan, M., Gill, J., Santhosh, S., Chatterjee, U., Iovoli, A., Farrugia, M., Mohammadpour, H., et al. (2022). Evaluation of optimal thresholds for the neutrophil-lymphocyte ratio and its association with survival outcomes among patients with head and neck cancer. JAMA Network Open, 5, e227567.
12. Qi, Q., Zhuang, L., Shen, Y., Geng, Y., Yu, S., Chen, H., Liu, L., Meng, Z., Wang, P., et al. (2016). A novel systemic inflammation response index (SIRI) for predicting survival in pancreatic cancer patients after chemotherapy. Cancer, 122, 2158–2167.
13. Rensen, S.S., Slaats, Y., Nijhuis, J., Jans, A., Bieghs, V., Driessen, A., Malle, E., Greve, J.W., & Buurman, W.A. (2009). Increased hepatic myeloperoxidase activity in obese subjects with nonalcoholic steatohepatitis. American Journal of Pathology, 175, 1473–1482.
14. Riazi, K., Swain, M.G., Congly, S.E., Kaplan, G.G., & Shaheen, A.A. (2022). Race and ethnicity in non-alcoholic fatty liver disease (NAFLD): A narrative review. Nutrients, 14.
15. Ruhl, C.E., & Everhart, J.E. (2015). Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey. Alimentary Pharmacology & Therapeutics, 41, 65–76.
16. Song, Y., Guo, W., Li, Z., Guo, D., Li, Z., & Li, Y. (2022). The systemic immune-inflammation index is associated with hepatic steatosis: Evidence from NHANES 2015–2018. Frontiers in Immunology, 13, 1058779.
17. Tang, Y., Zeng, X., Feng, Y., Chen, Q., Liu, Z., Luo, H., Zha, L., & Yu, Z. (2021). Association of the systemic immune-inflammation index with short-term mortality in congestive heart failure: A retrospective cohort study. Frontiers in Cardiovascular Medicine, 8, 753133.
18. Tilg, H., Adolph, T.E., Dudek, M., & Knolle, P. (2021). Non-alcoholic fatty liver disease: The interplay between metabolism, microbes, and immunity. Nature Metabolism, 3, 1596–1607.
19. Tong, Y.S., Tan, J., Zhou, X.L., Song, Y.Q., & Song, Y.J. (2017). The systemic immune-inflammation index predicts chemoradiation resistance and poor outcomes in patients with stage III non-small cell lung cancer. Journal of Translational Medicine, 15, 221.

20. Xiao, S., Wang, X., Zhang, G., Tong, M., Chen, J., Zhou, Y., Ji, Q., Liu, N., 2023a. The association between the Systemic Immune Inflammation Index (SIII) and cardiovascular disease, including estimated Pulse Wave Velocity, Atherogenic Index of Plasma, and Triglyceride-Glucose Index: Results from a large cross-sectional study. Mediators of Inflammation, 2023, Article ID 1966680.
21. Xiao, S., Wang, Z., Zuo, R., Zhou, Y., Yang, Y., Chen, T., Liu, N., 2023b. Association of Systemic Immune Inflammation Index with mortality due to all causes, cardiovascular disease, and cancer in patients with cardiovascular disease: A cross-sectional study. Journal of Inflammation Research, 16, 941–961.
22. Xie, Y., Zhuang, T., Ping, Y., Zhang, Y., Wang, X., Yu, P., Duan, X., 2021. Elevated levels of the Systemic Immune Inflammation Index are associated with disease activity in patients with ulcerative colitis. Clinical Chemistry and Laboratory Medicine, 517, 122–216.
23. Yan, M., Man, S., Ma, L., Gao, W., 2022. Molecular mechanisms and current clinical therapy in nonalcoholic steatohepatitis: An overview and perspectives. Metabolism, 134, Article ID 155264.
24. Yang, R., Chang, Q., Meng, X., Gao, N., Wang, W., 2018. Prognostic value of the Systemic Immune Inflammation Index in cancer: A meta-analysis. Journal of Cancer, 9, 3295–3302.
25. Ye, C., Yuan, L., Wu, K., Shen, B., Zhu, C., 2023. Association between the Systemic Immune Inflammation Index and chronic obstructive pulmonary disease: A population-based study. BMC Pulmonary Medicine, 23, Article 295.
26. Zafrani, E.S., 2004. Non-alcoholic fatty liver disease: An emerging pathological spectrum. Virchows Archiv, 444, 3–12.
27. Zhang, Y., Xing, Z., Zhou, K., Jiang, S., 2021. The predictive role of the Systemic Inflammation Response Index (SIRI) in the prognosis of stroke patients. Clinical Interventions in Aging, 16, 1997–2007.
28. Zhang, X., Zuo, R., Xiao, S., Wang, L., 2022. Association between iron metabolism and non-alcoholic fatty liver disease: Evidence from the National Health and Nutrition Examination Survey (NHANES 2017–2018) and a controlled animal study. Nutrition & Metabolism, 19, Article 81.
29. Zhao, E., Cheng, Y., Yu, C., Li, H., Fan, X., 2023. The systemic immune-inflammation index's non-linear association with all-cause mortality in individuals with nonalcoholic fatty liver disease. Annals of Medicine, 55, Article 2197652.
30. Zhao, S., Dong, S., Qin, Y., Wang, Y., Zhang, B., Liu, A., 2022. Inflammation index SIRI is linked to increased all-cause and cardiovascular mortality in patients with hypertension. Frontiers in Cardiovascular Medicine, 9, Article 1066219.
31. Zhou, Y.X., Li, W.C., Xia, S.H., Xiang, T., Tang, C., Luo, J.L., Lin, M.J., Xia, X.W., Wang, W.B., 2022. The predictive value of the Systemic Immune Inflammation Index for adverse outcomes in patients with acute ischemic stroke. Frontiers in Neurology, 13, Article 836595.
32. Zhou, Z., Xu, M.J., Cai, Y., Wang, W., Jiang, J.X., Varga, Z.V., Feng, D., Pacher, P., Kunos, G., et al., 2018. Neutrophil-Hepatic Stellate Cell interactions promote fibrosis in experimental steatohepatitis. Cellular and Molecular Gastroenterology & Hepatology, 5, 399–413.
33. Zipf, G., Chiappa, M., Porter, K.S., Ostchega, Y., Lewis, B.G., Dostal, J., 2013. National Health and Nutrition Examination Survey: Plan and operations from 1999–2010. Vital and Health Statistics. Series 1, Programs and Collection Procedures, 1-37.