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Prognostic value of neutrophil-to-lymphocyte ratio in end-stage liver disease: A meta-analysis

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Abstract

BACKGROUND

The neutrophil-to-lymphocyte ratio (NLR) is commonly utilized as a prognostic indicator in end-stage liver disease (ESLD), encompassing conditions like liver failure and decompensated cirrhosis. Nevertheless, some studies have contested the prognostic value of NLR in ESLD.

AIM

To investigate the ability of NLR to predict ESLD.

METHODS

Databases, such as Embase, PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Weipu, and Wanfang, were comprehensively searched to identify studies published before October 2022 assessing the prognostic ability of NLR to predict mortality in patients with ESLD. Effect sizes were calculated using comprehensive meta-analysis software and SATAT 15.1.

RESULTS

A total of thirty studies involving patients with end-stage liver disease (ESLD) were included in the evaluation. Among the pooled results of eight studies, it was observed that the Neutrophil-to-Lymphocyte Ratio (NLR) was significantly higher in non-survivors compared to survivors (random-effects model: standardized mean difference = 1.02, 95% confidence interval = 0.67-1.37). Additionally, twenty-seven studies examined the associations between NLR and mortality in ESLD patients, reporting either hazard ratios (HR) or odds ratios (OR). The combined findings indicated a link between NLR and ESLD mortality (random-effects model; univariate HR = 1.07, 95%CI = 1.05-1.09; multivariate HR = 1.07, 95%CI = 1.07-1.09; univariate OR = 1.29, 95%CI = 1.18-1.39; multivariate OR = 1.29, 95%CI = 1.09-1.49). Furthermore, subgroup and meta-regression analyses revealed regional variations in the impact of NLR on ESLD mortality, with Asian studies demonstrating a more pronounced effect.

CONCLUSION

Increased NLR in patients with ESLD is associated with a higher risk of mortality, particularly in Asian patients. NLR is a useful prognostic biomarker in patients with ESLD.

INTRODUCTION

End-stage liver disease (ESLD) is defined as the final stage of liver disease caused by various factors. Globally, cirrhosis and liver cancer are ranked as the eleventh and sixteenth leading causes of death, respectively, accounting for 3.5% of all deaths each year worldwide^[1]. The burden of ESLD is expected to increase in the future^[2]. Because liver transplantation remains the only curative treatment for ESLD, it is crucial to identify predictors of ESLD prognosis to differentiate between patients who require immediate transplantation and those who can be managed with intensive medical care for a longer period.

The neutrophil-to-lymphocyte ratio (NLR) is a readily measurable parameter that has been shown to reflect disease severity^[3]. NLR has been widely used as a biomarker for prognostic evaluation of patients with various diseases and has diagnostic value in

distinguishing among certain conditions^[4]. For example, NLR has shown promise in predicting poor prognosis in cancer patients^[4]. Because Kupffer cells and inflammatory cells, such as macrophages, T lymphocytes, neutrophils, and dendritic cells, have been found to contribute to liver inflammation and fibrosis in patients with liver disease^[5], NLR is often utilized as a prognostic factor in these patients. NLR has also been associated with prognosis in patients with hepatocellular carcinoma, suggesting its potential as a prognostic indicator after liver transplantation^[6,7]. Moreover, NLR has been used to predict the prognosis of patients with other liver diseases, such as acute-on-chronic liver failure (ACLF) and decompensated liver cirrhosis (DC)^[8-10], although the prognostic value of NLR in patients with ACLF and DC remains unclear. Most studies indicate that NLR is linked to poor prognosis in patients with ACLF or DC, although other studies have reported no association^[11]. Most of these studies, however, focused solely on patients with ACLF or DC, with few examining whether NLR is a prognostic factor for ESLD, the broader condition.

The objective of this systematic review and meta-analysis was to thoroughly assess the correlation between NLR and prognosis in patients with ESLD. The aim was to identify a reliable and easily measurable parameter that could help identify patients in need of immediate liver transplantation.

MATERIALS AND METHODS

Literature search

Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2009 statement guidelines^[12] were followed to report the results of this systematic review. The protocol was registered in the Prospective Register of Systematic Review [CRD42022367423].

The databases OVID Embase, PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Weipu, and Wanfang were systematically searched for studies on the associations of NLR with ESLD published from 1 January 1980 to 30 October 2022 in English or Chinese. Search terms included “end-stage liver

disease"tOR "liver cirrhosis"rOR "hepatic cirrhosis"rOR "liver fibrosis"bOR "liver failure"iOR "hepatic failure"iOR "liver transplantation"aOR "hepatic transplantation"aOR "liver transplant"aAND "neutrophil-lymphocyte ratio"lOR "neutrophil-to-lymphocyte"tOR ro-lympThe full search strategy is described in Appendix 1.

Study Selection

Studies were selected if they were (1) observational studies, including cross-sectional, cohort, and case-control studies; (2) included adults aged ≥ 18 years; (3) involved patients who were diagnosed with ESLD; and (4) measured NLR in both survivors and non-survivors or reported a hazard ratio (HR) or odds ratio (OR) reflecting the association between NLR and mortality. Conference abstracts, case reports, systematic reviews, dissertations, expert opinions, and editorials or commentaries were excluded, as were studies that included fewer than 100 participants and studies published in Chinese journals limited to the Chinese Scientific and Technical Papers and Citation Database, the Chinese Science Citation Database, and the Chinese core journal criterion of Peking University. If multiple studies involved the same dataset, the study with the larger number of participants was included. After removing duplicates, two authors (CXH and TYM) independently reviewed the titles and abstracts to remove irrelevant studies. The full texts of the remaining studies were examined with a record of reasons for exclusion. A third author (LXH) resolved disagreements when necessary.

Definition of ESLD

ESLD was defined as chronic or acute-on-chronic liver failure according to the standard criteria of the Asian Pacific Association for the Study of the Liver (APASL)^[13] or the European Association for the Study of the Liver^[14]. Included were patients with liver cirrhosis who were diagnosed pathologically or by clear ultrasound with at least an index clinical complication of decompensation and candidates for liver transplantation

due to liver failure or cirrhosis. Patients aged < 18 years and patients with acute liver failure or other terminal diseases were excluded.

Data extraction

Data were extracted from included articles using a standardized form in Microsoft Excel. Data extracted from these studies included the name of the first author; the year of publication; the location of the study; the number of patients analyzed, as well as their sex and mean or median age; the etiology of ESLD; the mean or median NLR and NLR cutoff value; the primary outcome of the study; and univariate and/or multivariate HRs or ORs, along with their associated 95% confidence intervals (CIs). Two authors (CXH and TYM) independently extracted these data, with disagreements resolved by consensus.

Evaluation of study quality

Two authors (CXH and TYM) independently assessed the quality of each study using the Newcastle-Ottawa Scale. This tool consists of three items, selection, comparability and outcome/exposure, which included four, two, and three sub-items, respectively, to which star-based scores were assigned. Studies with scores ≥ 6 were considered high-quality studies, those with scores of 4-5 were regarded as having a moderate risk of bias, and those with scores < 4 were regarded as having a high risk of bias.

Statistical analyses

Statistical analyses were performed using Stata 15.1 (Stata Corp, College Station, TX, United States) and Comprehensive Meta-analysis software (2.0). The main pooled outcomes were the HRs or ORs with their 95%CIs of the associations between NLR and ESLD. HRs and ORs were analyzed separately, as were univariate and multivariate HRs and ORs.

The heterogeneity of the studies was assessed using I^2 statistics, with I^2 values of 25%, 50%, 75%, and $\geq 75\%$ indicating low, moderate, high, and very high heterogeneity,

respectively^[15]. If heterogeneity was high or very high, a random-effects model was used. Study heterogeneity and some potential moderators were explored using subgroup analyses and meta-regression. These variables included the mean age of the patients (categorized as < 50 or > 50 years), location (categorized as Asia or non-Asian regions), etiology, and duration of follow-up. Publication bias was assessed by visual inspection of funnel plots, and by Begg's and Egger's tests. When necessary, trim-and-fill analyses and sensitivity analyses were performed.

All statistical tests were two-sided, with the level of significance set at $P < 0.05$.

RESULTS

Literature search

A search of the databases yielded 5510 studies. Analysis using EndNote Version 9.0 software found that 1132 of these studies were duplicates. The remaining 4378 studies were screened by reading their titles and abstracts, resulting in the removal of 4247 studies. A full-text review of the remaining 131 studies resulted in the inclusion of 30 of these studies. The literature search strategy is described in a PRISMA flow diagram (Figure 1).

Characteristics of eligible studies

The 30 studies consisted of 21 published in English and nine published in Chinese. Table 1 shows the main characteristics of the included studies.

All studies were published after 2014, with the largest number, seven, published in 2021. The studies included were from three continents, with the largest number, 22, from Asia. Sixteen studies included patients with ACLF, 13 included patients with acute decompensation (AD), and one included patients with both ACLF and AD. Eighteen studies analyzed patients with hepatitis B virus (HBV)-related ESLD. The mean quality assessment score of the 30 studies was 7.4 (range: 5–9).

Eight studies provided NLR data for both survivors and non-survivors. Twelve studies used logistic regression analysis to determine the association between NLR and

mortality in patients with ESLD, whereas 15 studies used Cox regression analysis to determine this association.

Effect of NLR

Univariate HR: Thirteen studies reported the association between NLR and mortality as univariate HR, with a meta-analysis finding that increased NLR was predictive of increased mortality (Figure 2, Panel A, HR = 1.07, 95%CI = 1.05-1.09). There was significant heterogeneity among these studies ($I^2 = 89.4\%$, $P < 0.001$). Subgroup (Table 2) and meta-regression (Supplementary Table 1) analyses showed that patient age, sex ratio, region, population, primary outcome, and etiology of ESLD did not affect the prognostic value of NLR. On publication bias tests, Begg's test was non-significant, whereas Egger linear regression indicated possible bias (Supplementary Figure 1, $P < 0.05$). Using trim-and-fill analyses, two studies were imputed into the meta-analysis, but this did not significantly change the results (Supplementary Figure 2, HR = 1.06, 95%CI = 1.04-1.08). Sensitivity analysis showed similar results when each study was excluded.

Multivariate HR: Thirteen studies also reported the association between NLR and mortality as multivariate HR, with a meta-analysis finding that increased NLR was predictive of increased mortality (Figure 2, Panel B, HR = 1.07, 95%CI = 1.04-1.09). There was significant heterogeneity among these studies ($I^2 = 89.1\%$, $P < 0.001$). Similar to the results of univariate HR analysis, subgroup (Table 2), and meta-regression (Supplementary Table 1) analyses showed that age, sex ratio, population, primary outcome, and etiology of ESLD did not affect the prognostic value of NLR. In contrast, subgroup analysis revealed that studies in Asia (HR = 1.87, 95%CI = 1.06-1.11) and studies not in Asia (HR = 1.03, 95%CI = 1.00-1.06) yielded significant effects ($P = 0.005$). Both Begg and Egger test showed possible publication biases (Supplementary Figure 3, $P < 0.05$). By trim-and-fill analyses, two studies were imputed into the meta-analysis, but this did not significantly change the results (Supplementary Figure 4, HR = 1.06,

95%CI = 1.04-1.08). Sensitivity analysis showed similar result when each study was excluded.

Univariate OR: Eleven studies reported the association between NLR and mortality as univariate OR, with a meta-analysis showing that increased NLR was predictive of increased mortality (Figure 2, Panel C, OR = 1.29, 95%CI = 1.18-1.39). There was significant heterogeneity among these studies ($I^2 = 91.3\%$, $P < 0.001$). Subgroup (Table 2) and meta-regression (Supplementary Table 1) analyses showed that age, sex ratio, region, population, primary outcome, and etiology of ESLD did not affect the prognostic value of NLR. In the publication bias test, Begg's test was non-significant ($p=0.81$). However, Egger's linear regression showed the possible presence of bias (Supplementary Figure 5, $P < 0.05$). No study was imputed into the meta-analysis by trim-and-fill analyses (Supplementary Figure 6). Because the number of studies was small, the possibility of publication bias could not be completely excluded. Sensitivity analysis showed similar results when each study was excluded.

Multivariate OR: Four studies reported the association between NLR and mortality as multivariate OR, with a meta-analysis indicating that increased NLR was predictive of increased mortality (Figure 2, Panel D, OR = 1.29, 95%CI = 1.09-1.49). There was significant heterogeneity among these studies ($I^2 = 93.4\%$, $P < 0.001$). Because the number of studies was not adequate, subgroup and meta-regression analyses were not performed. In publication bias tests, Begg test was not significant ($P = 0.81$), whereas Egger linear regression showed possible bias (Supplementary Figure 7, $P < 0.05$). No study was imputed into the meta-analysis by trim-and-fill analyses. Because the number of studies was small, the possibility of publication bias could not be excluded completely. Sensitivity analysis showed similar result when each study was excluded.

Comparison of NLR in survivors and non-survivors

4 Eight studies compared NLR in surviving and non-surviving patients with ESLD. A meta-analysis showed that NLR was significantly higher in non-survivors than in survivors (Supplementary Figure 8, random-effects model: SMD = 1.02 95%CI; 0.67–1.37).

DISCUSSION

To our knowledge, this systematic review is the first to report a relationship between NLR and mortality in patients with ESLD. The pooled results of this study indicated that NLR was associated with mortality (random-effects model; univariate HR = 1.07, 95%CI = 1.05-1.09; multivariate HR = 1.07, 95%CI = 1.07-1.09; univariate OR = 1.29, 95%CI = 1.18-1.39; multivariate OR = 1.29, 95%CI = 1.09-1.49). Furthermore, the pooled results of eight studies showed that NLR levels were significantly higher in non-survivors than in survivors with ESLD (random-effects model: SMD = 1.02, 95%CI = 0.67-1.37).

Mortality rates are high in patients with ESLD, such as liver failure and decompensated cirrhosis. Systemic inflammatory reactions are closely related to the severity and prognosis of liver disease in patients with severe cirrhosis, with the occurrence of systemic inflammatory response syndrome increasing mortality rates in patients with cirrhosis^[16]. It is therefore crucial to identify and treat infections and systemic inflammation in patients with ESLD. Although routine tests, including measurements of C-reactive protein and procalcitonin (PCT) concentrations and white blood cell (WBC) counts, are commonly used to assess bacterial infection and systemic inflammation, these tests may not fully meet the demands of patients with ESLD. High serum total bilirubin concentrations in these patients can influence the diagnostic sensitivity of PCT^[17]. Additionally, patients with ESLD often have lower baseline WBC counts, which can impair the predictive value of WBC in detecting infections. A study included in this review confirmed that NLR is superior to WBC or PCT for assessing infection in patients with ACLF^[9]. NLR may also be a useful indicator of systemic inflammatory response syndrome or infection in patients with decompensated

cirrhosis^[18]. Taken together, these findings suggest that NLR strongly correlates with infection and systemic inflammatory response syndrome in patients with ESLD and that NLR may be predictive of mortality. These findings are consistent with the majority of the included studies and the final pooled results.

NLR has also been shown to be an indicator of inflammation in other conditions, such as colorectal cancer and myocardial infarction^[19]. Peripheral neutrophil counts have been reported to serve as markers for both acute and chronic inflammation^[20]. Activation of these neutrophils can inhibit T lymphocyte activation through the production of reactive oxygen and arginase^[21]. Peripheral T-lymphocyte subsets were found to be significantly lower in ACLF patients than in healthy controls^[22], and lower lymphocyte cell counts have been associated with poorer immune responses in patients with chronic liver disease^[23]. These findings suggest that NLR may be a practical indicator that reflects the balance between inflammation and immune reactions. Furthermore, the inflammatory process has been shown to play a significant role in the development of liver fibrosis and cirrhosis. A meta-analysis suggested that NLR may be a marker of the degree of fibrosis and predictor of prognosis in patients with chronic liver disease^[24]. NLR may also be predict of for prognosis in patients with ESLD.

Subgroup and meta-regression analyses revealed that the predictive value of NLR was not influenced by patient age, sex ratio, or the etiology of ESLD, suggesting that NLR is a reliable predictor of ESLD prognosis across different patient populations. NLR is considered a cost-effective and practical tool for predicting mortality in critically ill patients with liver failure and for screening patients with severe liver disease. Unlike other prognostic biomarkers, neutrophils and lymphocytes can be easily obtained and measured in clinical practice. Subgroup analysis of multivariate HR from 13 studies showed that NLR was strongly associated with mortality in Asian patients with ESLD, possibly due to the high prevalence of hepatitis B infection in Asian populations. HBV-ACLF patients exhibit lower levels of circulating lymphocytes and significantly higher levels of liver infiltrating lymphocytes^[25]. Subgroup analysis, however, did not find significant differences in NLR between patients with HBV and those with mixed

etiology. This may have been due to confounding factors and high heterogeneity in the mixed etiology group.

It is worth mentioned, the severity of the neutropenia and the overall status of the patient should be taken into account. Profound neutropenia may signify a more severe inflammatory or immunocompromised state, potentially affecting the NLR's ability to reflect the underlying inflammatory process accurately. In these patients, it can potentially impact the accuracy of NLR as a marker of systemic inflammation. Future research should focus on large-scale longitudinal studies to assess the predictive value of the NLR in ESLD patients with neutropenia, subgroup analyses to account for specific clinical characteristics, mechanistic studies to understand the underlying pathophysiology.

While NLR was identified as the strongest independent predictor in this study, other ratios such as platelet-to-lymphocyte ratio (PLR) and platelet-to-neutrophil ratio (PNR) have also been investigated for prognosis in liver diseases. However, study have shown that NLR had good predictive ability for mortality, higher than PNR^[26]. In the setting of ESLD, PLR and PNR may be less reliable due to various thrombocytopenia mechanisms associated with advanced liver dysfunction. This is aruably a more direct assessment of the disease stage and prognosis in decompensated cirrhosis patients. For this reason, this article focused on NLR rather than PLR or PNR, though future studies could explore whether a combination of ratios provides even stronger predictive ability than individual markers alone.

The present review and meta-analysis had several limitations. First, there was high heterogeneity among the studies included in this analysis, similar to other prognostic reviews, despite the use of a random-effects model. Second, most of the included studies reported positive results, which may have introduced latent publication bias, although Begg's test and Egger's test did not show significant biases. Moreover, the number of studies that utilized multivariate OR analysis to assess the association between NLR and mortality was too small for determination of publication bias. Third, the critical cut-off value of NLR for determining prognosis remains unclear. Due to

limitations in the original studies, the present analysis could not determine an exact ideal cut-off value.

CONCLUSION

This meta-analysis highlights the significance of NLR as a valuable prognostic biomarker in patients with ESLD, with higher NLRs indicating an increased risk of mortality. These findings especially emphasize the strong association between higher NLRs and prognosis in the Asian patients with ESLD. The continuing absence of a critical cut-off value of NLR for determining prognosis suggests the need for additional research to clarify this matter.

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