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Zhang, H¹; Du, X².**ADMINISTRATIVE INFORMATION**

Support - Shaanxi Provincial Natural Science Basic Research Program Fund Shaanxi Provincial Natural Science Basic Research Program Fund Shaanxi Provincial Natural Science Basic Research Program Fund Shaanxi Provincial Natural Science Basic Research Program Fund Shaanxi Provincial Natural Science Basic Research Program Fund (2020JM-337) .

Review Stage at time of this submission - Preliminary searches.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY202370079**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 July 2023 and was last updated on 20 July 2023.**INTRODUCTION**

Review question / Objective Whether the neutrophil to lymphocyte ratio (NLR) serves as a potential indicator for the efficacy of initially unresectable hepatocellular carcinoma.

Condition being studied Hepatocellular carcinoma (HCC) is one of the common malignant tumors in the digestive system and the sixth most common malignant tumor worldwide. With the improvement of medical level, early diagnosis and treatment of HCC greatly reduces the missed diagnosis rate and mortality rate of early HCC. However, there are still a large number of HCC patients who are in the middle to late stages of initial diagnosis and lose the opportunity for radical surgery, namely unresectable hepatocellular carcinoma (uHCC). This is the main reason why HCC plunders the life and health of patients and

the long-term high mortality rate. In recent years, with the emergence and progress of targeted drugs and immune checkpoint inhibitors (ICIs), the application of Targeted therapy, immunotherapy combined with local interventional therapy has greatly improved the survival rate of patients with uHCC. Research reports show that the overall survival rate and quality of life of patients have significantly improved. However, individuals have different responses to TKI and ICI, and not all late stage patients can benefit from it. Therefore, there is an urgent need to find inexpensive and effective biomarkers related to the results of systemic combined therapy for patients with advanced uHCC. Neutrophil lymphocyte ratio (NLR) is a widely used and easily measurable clinical biomarker. Elevated NLR is believed to be associated with poor prognosis in various malignant tumors, including HCC. The role of NLR

in predicting the efficacy of systemic combination therapy in HCC patients is still unclear.

METHODS

Participant or population The patient diagnosed as initially unresectable hepatocellular carcinoma receives at least one of targeted therapy, immunotherapy, or local interventional therapy.

Intervention Neutrophil to lymphocyte ratio (NLR) was evaluated before treatment; provision of HRs and 95% CIs for neutrophil to lymphocyte ratio in OS or data necessary to calculate them.

Comparator The control group comprises those with lower level of neutrophil to lymphocyte ratio.

Study designs to be included Systematic review and meta-analysis.

Eligibility criteria To be eligible to participate in this study, articles had to meet the following inclusion criteria: 1) The patients diagnosed as initially unresectable hepatocellular carcinoma receives at least one of targeted therapy, immunotherapy, and local interventional therapy; (2) the overall survival of NLR and liver cancer patients was reported (overall survival, OS), disease-free survival (disease free survival, DFS) or relapse-free survival (recurrence free survival, RFS), other prognostic indicators; (3) reported risk ratio (HR) and 95% confidence interval (95% CI), Or it can be calculated based on the data given, and the relevant survival curves. Articles were excluded from the study if they met any of the following exclusion criteria: (1) review, case reports and non-clinical research literature; (2) the cut-off value of NLR is not clearly reported; (3) HR and 95% CI are not obtained; (4) the relevant data extracted from the given survival curve are quite different from the original text.

Information sources Databases: Embase, Pubmed, Web of Science, Cochrane Library, Wanfang, CBM, CNKI.

Main outcome(s) The association between NLR and survival outcome.

Additional outcome(s) The association between NLR and PFS outcome.

Data management Two independent reviewers will decide whether a study is eligible, by reading title and abstract. If the study is considered relevant, full-text will be read at a second phase. Any conflicts will be solved by a third independent

reviewer. Details about included and excluded studies will be depicted in a PRISMA flow-chart. A Microsoft Excel sheet will be used for data extraction. The information obtained from the studies included the year of publication, first author, country, the number of patients, age, sex, histological type, details of treatment, number of metastatic sites, study type, testing time, cutoff value for NLR, and survival outcomes, follow-up time. Survival data included the HR and 95% CI values for OS and PFS.

Quality assessment / Risk of bias analysis The quality assessment of primary studies will be performed according to Newcastle-Ottawa quality assessment Scale (NOS). The full mark is 9 points and studies labeled with more than 6 points will be regarded as high-quality researches. Publication bias was evaluated by Begg's funnel plot and Egger's test. If publication bias was observed presenting a $P < 0.05$, the nonparametric trim and fill method was applied to re-estimate a corrected effect size after adjustment for publication bias. A 2-sided $P < 0.05$ was considered statistically significant. All analyses were performed by STATA statistical software package.

Strategy of data synthesis The HR with 95% CI was used to estimate the prognostic value of NLR on OS and PFS for each study. The heterogeneity of included studies was evaluated by Cochran's I^2 test and the Higgins I^2 statistic. If the I^2 was larger than 50% or $P < 0.1$, implying significant statistical heterogeneity between studies, the random-effects model was used. Otherwise, the fixed-effect model was adopted. HRs and 95% CIs were utilized as the effect value to assess the association between NLR and OS in hepatocellular carcinoma.

Subgroup analysis Different treatments.

Sensitivity analysis Sensitivity analysis will be made.

Language restriction English.

Country(ies) involved China.

Keywords unresectable hepatocellular carcinoma, Neutrophil-to-lymphocyte ratio, prognosis.

Contributions of each author

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