Clinica Chimica Acta 477 (2018) 7–12

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Review

Prognostic significance of neutrophil to lymphocyte ratio in patients with gastrointestinal stromal tumors: A meta-analysis

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ARTICLE INFO

Keywords:
Neutrophil to lymphocyte ratio (NLR)
Gastrointestinal stromal tumors
Biomarker
Prognosis
Meta-analysis

ABSTRACT

Background: The neutrophil to lymphocyte ratio (NLR) is reported to be a prognostic factor in multiple malignancies. However, its prognostic value in patients with gastrointestinal stromal tumors (GISTs) remains controversial. This study aims to evaluate the prognostic value of preoperative NLR in GISTs.

Methods: MEDLINE, EMBASE, and, Cochrane databases were searched until February 2017. Eligible articles were defined as studies assessing the prognostic role of preoperative NLR in GISTs. The end points were overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), and clinicopathological parameters. Pooled hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using fixed-effects/random-effects models.

Results: A total of eight studies comprising 1676 patients with GISTs were included. Elevated NLR had an association with decreased DFS/RFS (HR: 2.18, 95% CI: 1.30–3.67, P = 0.003), but not OS (HR: 1.74, 95% CI: 0.63–4.84, P = 0.29). The findings from most subgroup analyses were consistent with those from the overall analysis. Moreover, high NLR was significantly correlated with male, stomach lesion, tumor size (> 5 cm), tumor rupture (+), tumor recurrence (+), mitotic index (> 5/50 HPF), and NIH risk category (high/intermediate).

Conclusions: Elevated preoperative NLR may be an unfavorable prognostic biomarker in patients with GISTs.

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms arising from the gastrointestinal (GI) tract, and account for 1–2% of all GI tumors [1]. GISTs can develop at any site of the GI tract; however, the stomach accounts for at least half of them and is the most common location [2]. They are thought to arise from the interstitial cells of Cajal (ICC), the pacemaker cells of the GI tract [3]. Radical resection without residual tumor remains the only established curative treatment for localized GISTs [4,5]. Nevertheless, postoperative recurrence rate remains high [4,6]. Presently, many tumor-specific parameters are identified as prognostic factors for GISTs, and most of these factors are based on postoperative pathological findings such as size, mitotic index, location, and tumor rupture [5,7–10]. However, only tumor size, tumor location, and mitotic index are the best prognostic indicators to predict the malignant potential of GISTs [11,12].

It is well known that inflammation can largely influence tumor development and progression [13]. Several inflammatory biomarkers, such as the Glasgow Prognostic Score (mGPS), C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) are identified as prognostic indicators in various cancers [14–17]. These tests are simple and inexpensive to perform, and they are readily available in daily oncologic practice. Recently, the preoperative NLR, which also reflects the degree of systemic inflammation, has been found to be linked to prognosis in patients with GISTs [18,19]. However, some studies failed to find the correlation between NLR and prognosis of GISTs [20,21]. Therefore, we conducted a meta-analysis to assess the prognostic effect of preoperative NLR in GISTs.

2. Materials and methods

2.1. Search strategies

We searched MEDLINE, EMBASE, and Cochrane databases from inception up to February 2017. Search terms included “gastrointestinal stromal tumors” or “GISTs”, “neutrophil lymphocyte ratio” or “NLR”, “survival” or “prognostic” or “prognosis” or “recurrence” or “clinical outcome”. The reference lists were manually retrieved for substantial

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https://doi.org/10.1016/j.cca.2017.11.029
Received 23 July 2017; Received in revised form 21 November 2017; Accepted 23 November 2017
Available online 23 November 2017

relevant studies.

2.2. Study selection

The criteria for inclusion were listed as follows: (1) GISTs was diagnosed by pathological methods; (2) assessing the association of NLR with OS and/or DFS/RFS; (3) studies supplied sufficient information for calculating hazard ratio (HR) and 95% confidence interval (CI); (4) reporting a dichotomous cut-off value for NLR; and (5) original English articles. The exclusion criteria were as follows: (1) reviews, letters, case-reports, and conference abstracts; (2) lacking essential information for calculating an HR and 95% CI; and (3) overlapping or duplicate data.

2.3. Data extraction

The following information was collected: first author's name, year of publication, study design, area of publication, number of patients, tumor stage, survival analysis methods, cut-off values, time of follow-up, outcome measures (HRs for OS, DFS/RFS, and their 95% CIs), and clinicopathological features. HRs were extracted from multivariate or univariate analyses or estimated from Kaplan-Meier survival curves [22]. The two reviewers independently reviewed all eligible studies and extracted data. Any disagreement was resolved by discussions among all coauthors.

2.4. Quality assessment

The quality assessment of primary studies was performed in accordance with the Newcastle-Ottawa Scale (NOS) [23], which included an assessment of subject selection, comparability of groups, and clinical outcome. A total of nine items were extracted, and each item scored 1. The total scores ranged from 0 to 9. If scores are ≥ 7, the study is considered as high quality.

2.5. Statistical analyses

HRs and their 95% CIs were searched in the original articles or extrapolated using methods described by Tierney and Parmar [22,24]. The log HR and standard error (SE) were used for aggregation of the survival results [24]. The associations between NLR and clinicopathologic features were expressed as odds ratios (ORs) and its 95% CIs. Heterogeneity of the HR of each study was quantified using Cochran's Q test and Higgins-I^2 statistic. A P-value < 0.1 for the Q-test or $I^2 > 50\%$ was considered statistically significant. A random effect model was used if heterogeneity was observed, while a fixed effect model was applied in the absence of inter-study heterogeneity. Subgroup analyses were conducted based on the area of publication, sample size, treatment, analysis method, and NOS score. Sensitivity analyses were carried out to evaluate result stability excluding each study. If the number of included studies was > 11, the publication bias was performed using funnel plots and with the Begg's funnel plots and Egger's tests [25,26]. All statistical analyses were conducted by Review Manager 5.3 software (Cochrane Collaboration, Copenhagen, Denmark). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Search results

The initial search yielded 36 potentially articles. After excluding duplicate articles, 22 potentially eligible studies were selected. Of these, 9 were excluded through titles and abstracts, leaving 13 articles for further evaluation. As a result, 8 eligible studies, comprising a total of 1676 patients, were included in the quantitative synthesis [18–21,27–30]. The selection process was shown in Fig. 1.

3.2. Characteristics of the included studies

All the studies were published between 2013 and 2016. The number of patients in each study varied from 67 to 448. Three studies were from China, one from Austria, one from UK, one from Canada, one from Turkey, and one from Singapore. HRs and 95% CI were extracted directly from the eight studies. The cut-off values for NLR ranged from 1.92 to 3.0. There were two studies for OS, and seven for DFS/RFS. In methodological quality of studies, the overall NOS scores ranged 6 to 8, with a median of 6.6. Table 1 lists the detailed study characteristics.

3.3. Meta-analysis

3.3.1. Impact of NLR on OS

Two studies reported the data of preoperative NLR and OS in GISTs. The results showed that the pooled HRs were significant for high NLR (HR: 1.74, 95% CI: 0.63–4.84, P = 0.29; Fig. 2), with excessive heterogeneity (P = 0.01, I^2 = 83%). Pooled HRs > 1 indicated that elevated NLR was correlated with poor OS in GISTs. However, no statistically significant difference was found between the high- and low-NLR groups.

3.3.2. Impact of NLR on DFS/RFS

Seven studies reported the data of preoperative NLR and DFS/RFS in GISTs. The pooled analysis demonstrated that elevated NLR had an association with decreased DFS/RFS (HR: 2.18, 95% CI: 1.30–3.67, P = 0.003). However, excessive heterogeneity existed between studies (P = 0.002, I^2 = 71%). Thus, the random-effects model was used (Fig. 3).

To detect the potential heterogeneity, subgroup analyses stratified by area of publication, treatment, analysis method, sample size, and NOS score. As shown in Table 2, elevated NLR significantly predict poor DFS/RFS in studies with sample sizes ≥ 200 (HR = 2.59; 95% CI = 1.71–3.90; $P < 0.001$). Stratification by analysis method, multivariate analysis demonstrated that NLR were independent prognostic factors (HR: 3.27, 95% CI: 1.94–5.50, $P < 0.001$). In the subgroup analysis by the NOS score, the negative effect of elevated NLR on DFS/RFS was observed in studies with NOS score ≥ 7 (HR: 3.25, 95% CI: 1.62–6.48, $P < 0.001$). In addition, subgroup analysis revealed that high PLR predicted poor DFS/RFS in patient with GISTs, regardless of the area (eastern and western) and treatment methods (surgery and mixed).

3.4. NLR and clinicopathological features

In the meta-analysis, we identified 11 clinical factors to explore the impact of NLR on the clinical features in GISTs. The pooled analysis demonstrated that high NLR was significantly correlated with gender (male vs. female; HR = 1.90, 95% CI: 1.57–2.31, $P < 0.001$), tumor location (stomach vs. non-stomach; HR = 0.72, 95% CI: 0.57–0.90, P = 0.004), tumor size (> 5 cm vs. < 5 cm; HR = 1.68, 95% CI: 1.35–2.08, $P < 0.001$), tumor rupture (yes vs. no; HR = 2.10, 95% CI: 1.08–4.09, P = 0.03), tumor recurrence (yes vs. no; HR = 2.79, 95% CI: 1.83–4.24, $P < 0.001$), mitotic index ($> 5/50$ HPF vs. $< 5/50$ HPF; HR = 1.79, 95% CI: 1.29–2.48, $P < 0.001$), and NIH risk category (high/intermediate vs. very low/low; HR = 1.84, 95% CI: 1.06–3.21, P = 0.03). Whereas no significant association was found with age (≥ 60 vs. < 60), cellular type (spindle vs. non-spindle), malignant potential (high/moderate vs. low), and imatinib treatment (yes vs. no). The correlation between NLR expression and clinicopathological parameters of GISTs is shown in Table 3.

4. Discussion

In the present study, we identified 8 studies involving 1676 patients that investigate the prognostic value of preoperative NLR in patients