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NEUTROPHIL TO LYMPHOCYTE RATIO AS A PROGNOSTIC MARKER IN GALLBLADDER CARCINOMA: META-ANALYSIS

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ABSTRACT
The neutrophil to lymphocyte ratio (NLR) as prognostic factor of tumors are reported by many studies. By this meta-analysis, we have evaluated NLR prognostic role in gallbladder carcinoma (GBC). Pubmed and Embase were searched for relevant studies. Study data and characteristics were extracted. Prognostic role of NLR was analyzed using hazard ratio (HR) and 95% confidence interval (95%CI). Total of 4 observational studies with 892 patients were included for this meta-analysis. The pooled HR of 1.79 (95% CI: 1.51-2.13, P<0.01) showed patients having elevated NLR to have shorter overall survival (OS) after treatment. This meta-analysis suggests patient's survival with gall bladder cancer can be predicted using elevated NLR.

BACKGROUND
Gallbladder carcinoma (GBC) is most prevalent cancer of biliary tract but quite rare worldwide.[1] In recent years this carcinoma has attracted many public attention because of poor prognosis. Epidemiological studies show GBC patients' having less than 10% 5 year overall survival (OS).[2] This may be due to lack of treatment options, absence of effective marker for prognosis, late diagnosis and nonspecific symptoms. If there was presence of ideal marker for identifying patients' with poor prognosis, to improve OS of GBC aggressive measures can be adopted.

Previous studies showed involvement of inflammation in progression and genesis of tumors.[3] Systemic inflammation is represented by neutrophil and lymphocyte presence in peripheral blood. The NLR as potential prognostic marker has been investigated in many cancers. Stotz et al.[4] Investigated NLR prognostic implications in patients of primary operable and inoperable pancreatic cancer and found that poor prognosis was indicated by increased NLR regardless of therapeutic modality. Sharaiha et al.[5] found NLR to be potential prognostic marker in recurrence and death after esophagectomy. Similar findings were found in renal cancer[6], colorectal cancer[7], hepatocellular carcinoma[8], lung cancer[9,10] and gastric cancer.[5] Therefore elevated NLR can be applied in poor prognosis of malignancy patients. GBC is supposed to be malignancy related to inflammation.[11] On the basis of fact that NLR in other cancers is an effective prognostic indicator, it may show a similar relation in GBC. However, studies about NLR and GBC prognosis associations were rare. So, this meta-analysis aims to examine the relation between NLR and GB prognosis in GBC.

METHODS AND MATERIALS
Search strategy
Searching of PubMed and Embase was done with keywords on the terms "NLR," "neutrophil-to-lymphocyte ratio," or "neutrophil lymphocyte ratio" and "gallbladder cancer," "gallbladder carcinoma".

Inclusion and exclusion criteria
Following criteria was applied for inclusion in meta-analysis: (1) pretreatment NLR was measured; (2) NLR and OS association was reported in patients having gallbladder carcinoma; (3) 95% CI and hazard ratio (HR) was reported; and (4) all included patients only had gallbladder carcinoma and were diagnosed by pathological examination.

Publications excluded were: (1) studies which did not had HR or 95% CI and (2) letters, reviews, expert opinions, or case reports.

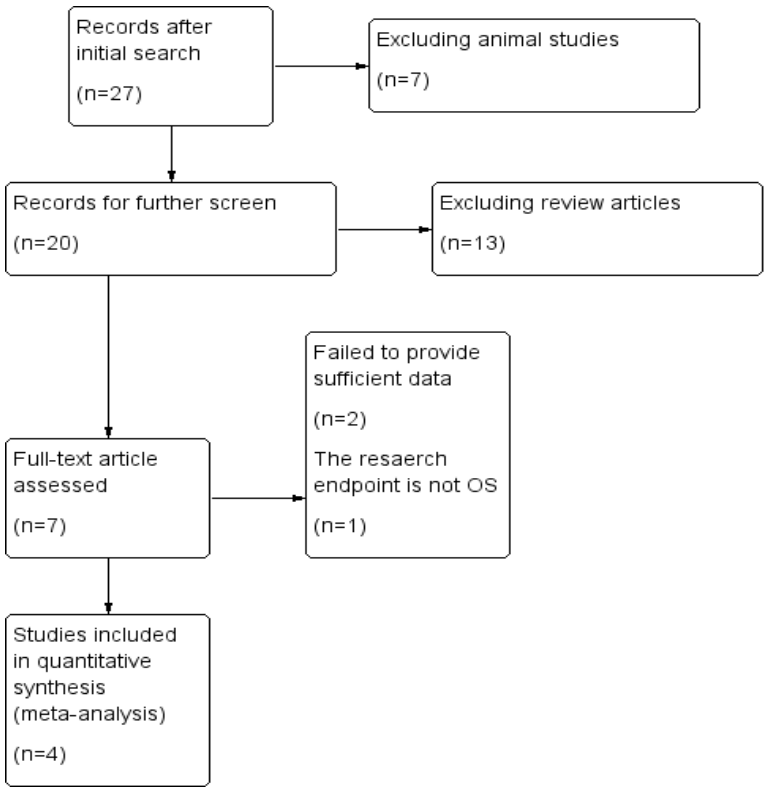


Figure 1: A flow chart outlining study selection.

Data Collection

Two master's degree students of internal medicine (Dr. Arun Bhattarai and Dr. Prateek Rajkarnikar) independently extracted data after analyzing eligible criteria for relevant studies using standardized data extraction table. The following information was extracted from each study: Author name, journal of publication, year of publication, country of study done, enrollment criteria, characteristics of patients, sampling time, cut-off value for NLR, predominant treatment (surgical or non-surgical) and HRs with 95% confidence interval (CI). Any disagreement was resolved by mutual discussions.

Statistical analysis

From each study HRs with 95% CI were extracted and a pooled HR was calculated. Multivariate analysis was chosen in study having both univariate and multivariate analyses in same study for the meta-analysis. Test of heterogeneity was performed using Cochran's Q test and Higgins I-squared statistic. $P \geq 0.10$ and $I^2 \leq 50\%$ were considered the values that indicated homogeneity, and a fixed-effects model was used. Begg's funnel plot and Egger's linear regression test were used to evaluate publication bias. All statistical analyses were carried out using RevMan 5.2 and STATA 11.0.

RESULTS

Selection and characteristics of included studies

A flow chart of the literature search is shown in Fig. 1. The initial search algorithm retrieved a total of 27 studies. After the first review, 20 studies related to the NLR and the prognosis of GBC were further evaluated. Of those studies, 13 reports were excluded as they were only review articles; 2 articles did not provide sufficient data for estimating the HR and 95% CI; and articles endpoint was not OS. Thus, 4 studies[12–15] published between 2014 and 2016 were included in our meta-analysis. The characteristics of the included studies are summarized in Table 1. A total of 892 patients were included. The studies came from the USA (n = 1), China (n = 2) and Canada (n=1). The NLR was calculated on the basis of pretreatment laboratory data using the white blood cell (WBC) counts from the included studies. Three of the 4 studies used multivariate analysis.[12]

Meta-analysis results

As heterogeneity test showed minimum heterogeneity (I^2= 2%, p = 0.38) between the studies, a fixed-effects model was used for the analysis. A pooled HR of 1.79 (95% CI: 1.51-2.13, P<0.01) showed that patients with an elevated NLR were expected to have shorter OS after treatment (Fig. 2). Because of relatively minor heterogeneity, further meta-regression or subgroup analysis was not conducted.

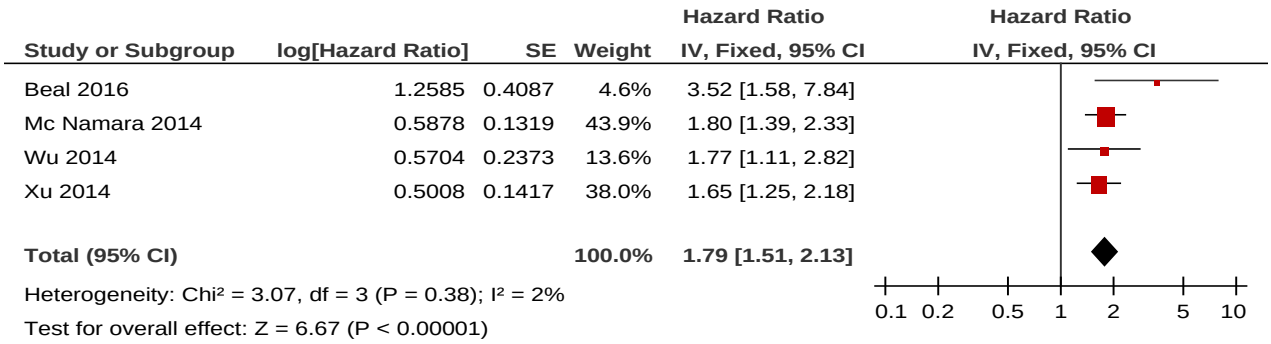
Publication bias

A publication bias estimate was used to evaluate the reliability of the meta-analysis results. A funnel plot (Fig. 3) was constructed, and the Begg's test and Egger's test showed that Pr > |z| = 0.734 and P > |t| = 0.179, respectively. Hence the results revealed absence of publication bias in this meta-analysis and indicated a positive outcome.

Study	Year	Country	Treatment	HR(95%CI)	Multivariate analysis	Result	Endpoint
Mc Namara[13]	2014	Canada	Surgery & Non-surgical	1.80(1.39-2.34)	Yes	Positive	OS
Beal[12]	2016	USA	Surgery	3.52(1.58-7.85)	No	Positive	OS
Xu[14]	2014	China	Surgery	1.65(1.25-2.17)	Yes	Positive	OS
Wu[15]	2014	China	Surgery	1.769(1.111-2.818)	Yes	Positive	OS

Study	Sample	Sample of elevated NLR	NLR cut-off	Sampling Time
Mc Namara[13]	304	163	3	Pretreatment
Beal[12]	187	42	5	Pretreatment
Xu[14]	316	209	2.6	Pretreatment
Wu[15]	85	45	2.3	Pretreatment

Table 1: Characteristics of all identified studies. "OS": overall survival.



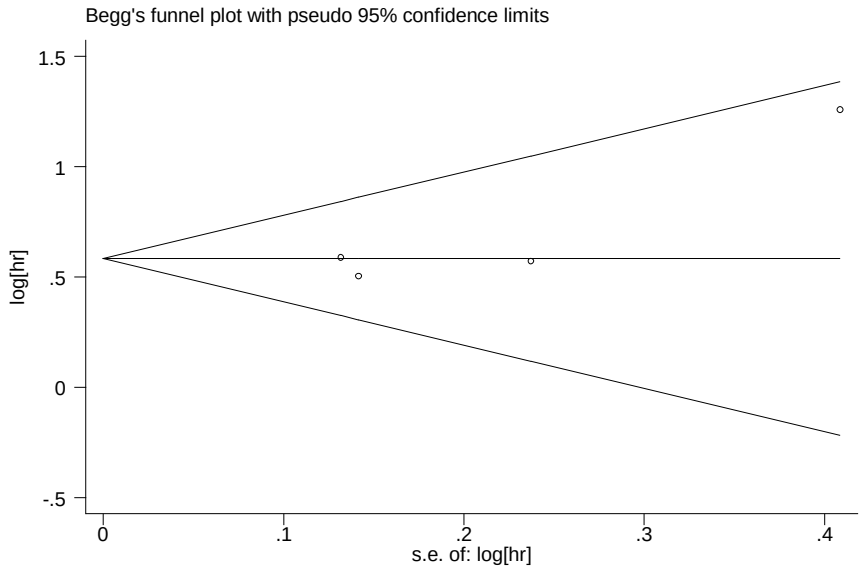


Figure 2: Forest plot of HR and 95%CI for each study.

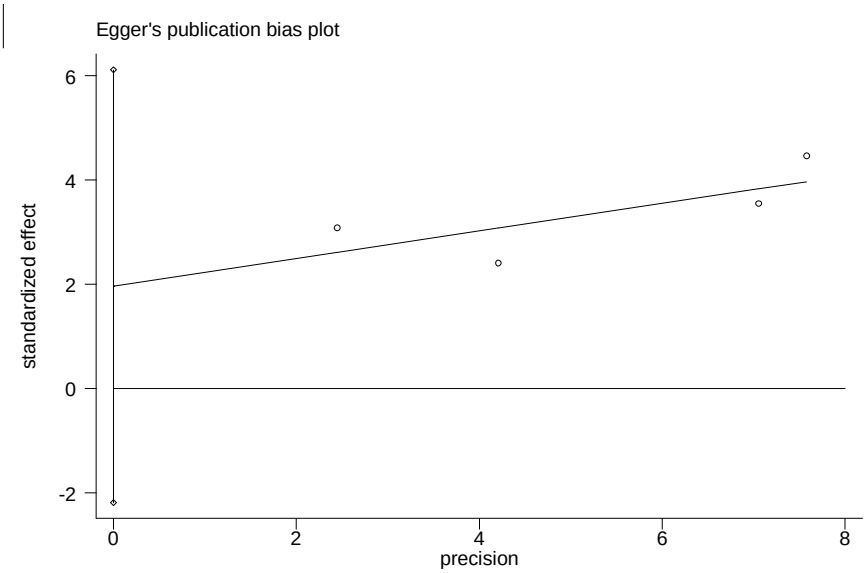


Figure 3: Begg's (a) and Egger's (b) funnel plot for the assessment of potential publication bias.

DISCUSSION

Systemic inflammation is represented by neutrophil and lymphocyte presence in peripheral blood. The NLR as potential prognostic marker has been investigated in many cancers. Stotz et al.[4] investigated NLR prognostic implications in patients of primary operable and inoperable pancreatic cancer and found that poor prognosis was indicated by increased NLR regardless of therapeutic modality. Sharaiha et al.[5] found NLR to be potential prognostic marker in recurrence and death after esophagectomy. Similar findings were found in renal cancer[6], colorectal cancer[7], hepatocellular carcinoma[8], lung cancer[9,10] and gastric cancer.[5]

The NLR is available in peripheral blood and is drawing attention of many researchers. NLR elevation is generally due to lymphopenia and neotrophilia. Lymphopenia hints disease severity and linked with immune escape by tumor cells from tumor-infiltrating lymphocytes (TIL).[16,17] Elevated levels of tumor infiltrating lymphocytes seen in primary tumor site have shown to be associated with good prognosis. Ability of tumor cells to inhibit cytotoxic T lymphocyte infiltration through production of immunosuppressive cytokines like IL—10, transforming growth factor–β (TGF—β), or vascular endothelial growth factor (VEGF), and reducing IL-2 which maintains cytotoxic T lymphocyte function.[18] On the other hand, neutrophils are known to be source of circulating VEGF and are related to vascular invasion and metastasis in cancer by angiogenesis.[19] In vitro culture of healthy donor neutrophil was found to be able to inhibit lymphocytic cytolytic ability and strength of inhibition was dependent on number of neutrophil. Favorable immune environment is generated by elevated NLR which promotes host immune suppression and vascular invasion. Therefore, an elevated NLR is associated with poor prognoses.

This meta-analysis includes 4 observational studies with 892 patients and first to acknowledge the prognostic role of pretreatment NLR from peripheral blood in gallbladder carcinoma. From the results, poor prognosis and shorter OS is predicted by elevated NLR gallbladder carcinoma patients. Some limitations of this meta-analysis requires for keen interpretation of the results. First, only 4 observational studies were included and due to insufficient data, studies having negative results were excluded. Second, the cut-off value of high NLR was different in each included study (Table 1), that might have contributed to minor heterogeneity. Third, some studies only had Kaplan-Meier curve and not report HR or 95% CI. Theoretically, these factors could be obtained through estimation from the curve, but that approach can be inaccurate. Therefore, articles that did not meet these criteria were removed from analysis.

CONCLUSION

This meta-analysis indicates elevated NLR could be used in poor survival prediction of patients having gallbladder carcinoma which is low cost and easily available. However due to limitation of the study, conduction of more multi-centre prospective cohorts is needed to validate the role of the NLR in carcinoma.

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