Meta-Analysis of Observational Studies in Epidemiology

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Prognostic significance of neutrophil–lymphocyte ratio (NLR) in patients with ovarian cancer

A systematic review and meta-analysis

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Abstract

The prognostic role of neutrophil to lymphocyte ratio (NLR) in patients with ovarian cancer remains inconsistent. This meta-analysis was conducted to evaluate the predictive value of this biomarker for prognoses in ovarian cancer patients.

We systematically searched PubMed, Web of Science, and Embase for eligible studies embracing multivariate results. The Newcastle-Ottawa Scale were used to assess the study quality. Pooled hazard ratios (HRs), and 95% confidence intervals (CIs) were calculated.

Ten studies involving 2919 patients were included in this meta-analysis. In multivariate analysis, the group with higher NLR had worse overall survival (OS) (HR = 1.34, 95% CI = 1.16–1.54) and shorter PFS (HR = 1.36, 95% CI = 1.17–1.57) than the control group. Furthermore, PLR values higher than the cut-off were associated with not only poorer OS (HR = 1.97, 95% CI = 1.61–2.40) but also more unfavorable PFS (HR = 1.79, 95% CI = 1.46–2.20). Univariate analysis also indicated the same results. Additionally, subgroup analysis showed that when the cut-off values for NLR and PLR were higher, their predictive effects became stronger.

This comprehensive meta-analysis suggested that the values of inflammatory marker of NLR was associated with ovarian cancer survival. Therefore, inflammatory markers can potentially serve as prognostic biomarkers.

Abbreviations: NLR = neutrophil to lymphocyte ratio, OC = ovarian cancer, OS = overall survival, PFS = progression-free survival, PLR = platelet-lymphocyte ratio, RFS = recurrence-free survival.

Keywords: meta-analysis, NLR, prognosis

1. Introduction

Ovarian cancer is a commonly diagnosed gynecologic malignancy and one of the most common cancers with high degree of malignancy with a poor prognosis worldwide.[1,2] Due to the widely applied cancer antigen-125 (CA-125) and cancer antigen-199(CA-199) screening and multi-parameter imaging, more and more localized ovarian cancers are diagnosed.[3–5] Nevertheless, a large proportion of patients are diagnosed at advanced-stage in this world, which would be the leading cause of cancer-related mortality, in where curative treatment, such as resection is not feasible. Hence, prognosis predictors are urgently needed to instruct individualized treatment. Besides conventional histopathological variables and CA-125 level are applied to predict oncologic outcomes, some blood biomarkers, such as albumin, hemoglobin have been reported to be prognosis predictors and enrolled in prognosis models in some reports.

An increasing body of evidence shows that systemic inflammation activation exerted by cancer cells anticipates tumor progression via inducing cancer proliferation and metastasis or promoting angiogenesis.[6] Systemic inflammatory responses are closely associated with cancer initiation, progression and metastasis, and thus, inflammatory markers, including the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), have been studied and found to be related to cancer mortality and employed as useful prognostic indicators in many solid tumors. The neutrophil–lymphocyte ratio (NLR), which has been considered as a member of the marker of the systemic inflammation response, is valuable for predicting the prognosis of various cancers.[7,8] Several previous meta-analyses on NLR in patients with ovarian cancers have identified that elevated NLR was significantly correlated with the inferior overall survival (OS), progression-free survival (PFS), and recurrence-free survival (RFS) for patients with ovarian cancer.[9–13] however, studies were not exclusive to patients undergoing potentially curative resection and the value of NLR in this patient cohort is unclear. Moreover, NLR's value in guiding the use of adjuvant treatment following potentially curative surgery is uncertain. This systematic review and meta-analysis were therefore performed to estimate the prognostic value of NLR in patients undergoing potentially curative resection and to identify any correlation with histo-pathological T-stage.

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XY and LW contributed equally to this work.

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2. Patients and methods

2.1. Search protocol

Thomson Reuters Web of Science, Ovid MEDLINE(R), and PUBMED databases were searched for relevant articles. The following search terms were used: (neutrophil lymphocyte ratio OR neutrophil-lymphocyte ratio OR neutrophil lymphocyte OR neutrophil-lymphocyte-ratio OR NLR) AND "ovarian cancer" (OR "ovarian carcinoma") AND "prognosis" (OR "overall survival" OR "progression-free survival"). All databases were searched from January 2000 to April 2018, and the search was updated on October 2018. Bibliographies in each candidate publication were also searched to identify other potentially eligible studies. Furthermore, because this study is a meta-analysis without directly involving the handing or inclusion of personal data, ethical approval was not necessary.

2.2. Selection criteria

Two independent investigators carefully screened the candidate publications. Studies were considered eligible if they satisfied all of the following criteria:

(1) original articles including patients with histopathologically diagnosed ovarian cancer;
(2) studies providing pretreatment values of NLR and cut-off values; and
(3) studies reporting the relationship between pretreatment NLR and prognostic outcomes, with enough data to analyze hazard ratio (HR) and 95% confidence interval (CI) for PFS or OS.

Overlapping or duplicate articles, review articles, letters, case reports, conference abstracts, and laboratory studies based on animal models or cancer cell lines were eliminated.

2.3. Data extraction and quality assessment

Information from the included publications was carefully extracted by 2 independent authors. In addition, any conflict was addressed by joint consensus. Full-text manuscript data was obtained by author (KM), and 50% of articles underwent independent review (AP), with discrepancies verified by consensus. For each study, baseline data (author, year of publication, country, study period, total number of patients, gender, pTNM stage, neoadjuvant chemotherapy, adjuvant chemotherapy, and NLR categorization thresholds) were recorded. Outcomes were described as odds ratios (OR) with 95% confidence intervals. Where these were not reported, the methods described by Parmar and Rogers were used to extract data from Kaplan–Meier curves, or percentage survival. Two investigators used the Newcastle-Ottawa-Scale (NOS) to evaluate the quality of the included study, and articles with NOS scores ≥6 were defined as high-quality studies.

2.4. Statistical analysis

Statistical analyses were performed using RevMan statistical package (Review Manager (RevMan) Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity between studies was measured by calculating the I2 statistic that was calculated for an objective measure of heterogeneity. A fixed-effect meta-analysis was performed in all cases, and where there was appreciable heterogeneity ($I2 > 50\%$ or Chi-squared P value $<.10$), a random-effect model was used. Corresponding funnel plots of Ln standard error as a function of effect size were used to examine the effect of publication bias visually and were statistically tested using Eggers test; P values $>.05$ were taken as indicative of no publication bias.

3. Results

3.1. Patients' characteristics

The flow diagram for selection of literature is shown in Figure 1. Through the primary searching of database, a total of 597 records were returned. Three hundred sixty-eight of these were reserved after excluding the duplicate studies. And 326 records were excluded after screen of the titles and abstracts. Among the 21 full-text paper evaluated for eligibility, 8 of them were excluded due to they were reviews or meta-analysis animal studies and conference abstracts Ultimately, 10 retrospective observational cohort studies involving 2400 patients were selected for subsequent meta-analysis.[10,14–22]

3.2. Characteristics of the included studies

The characteristics of the enrolled studies are presented in Table 1. All studies were retrospective cohort studies. The areal distributions were China (2 articles) and Japan (6 articles). Quality assessment demonstrated that the quality of the included studies was relatively high (total quality scores ≥6) (Table 2).

3.3. Impact of NLR on OS and PFS in patients with ovarian cancer

All 10 studies embraced the data of OS and the data of PFS. As presented in Figures 2 and 3, we identified that ovarian cancer patients with an elevated NLR had a significantly higher overall mortality (hazard ratio HR 2.36, 95% confidence interval CI 1.91–2.91, $P < .001$) and progression (HR 1.82, 95% CI 1.51–2.18, $P < .001$) than those with a low pretreatment NLR. Since no obvious heterogeneity was identified among these studies, the data was analyzed using a fixed-effect model ($I2 = 36.0\%$, 28.5% and 11.2%, $P = .258$, .184, and .952).

3.4. Publication bias

Publication bias and sensitivity analysis Visual inspection of the funnel plot was performed to determine publication bias in the included studies, and the results revealed evident symmetry for NLR regarding OS and PFS analyses, suggesting the lack of obvious publication bias (Fig. 4). These results were also confirmed using the Begg and Egger tests. Furthermore, a sensitivity analysis was performed by assessing the potential impact of each article on pooled HRs. The results showed that no studies had excessive influence on the stability of the pooled effect of comparisons. Therefore, this meta-analysis is robust.

4. Discussion

Presently, the estimate of oncologic outcomes in patients with ovarian cancer mainly relies on conventional clinicopathological variables, such as TNM stage, CA125 and CA199 levels. These parameters, reflecting cancer behavior and presentation in biology, may not represent the actual burden of patients with

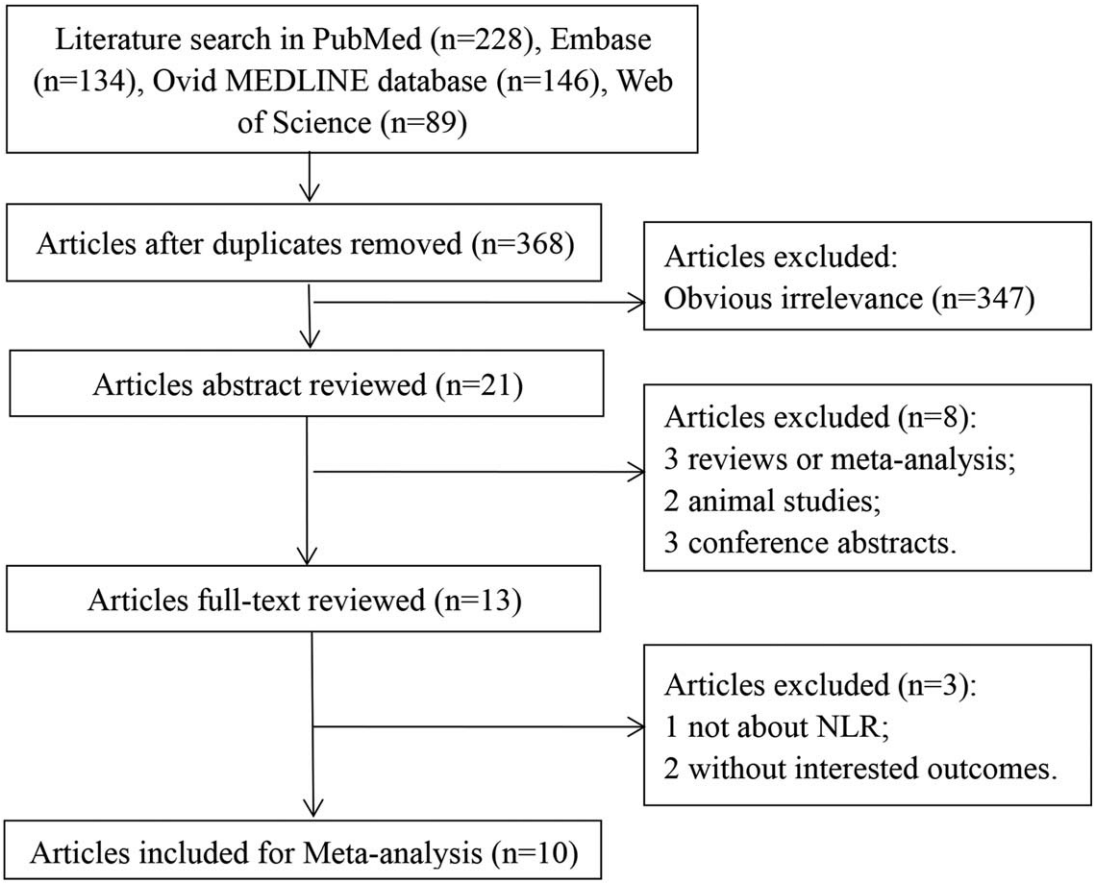

Figure 1. Flow diagram of study identification.

Table 1

Information of references enrolled in this study.

Study	Area	Type of cancer, stage	n	Age, yrs	Intervention	Cut-off value of NLR	Follow-up period, yrs	Adjusted factors
Asher 2011	United Kingdom	Primary cancer, I-IV	232	55 (15–81)	Chemotherapy or Surgery	2.4	8	None
Cho 2009	South Korea	Metastatic cancer, NR	393	63.5 (39–80)	Hepatic resection	2.3	10	Number of regional lymph node metastases, status of neoadjuvant chemotherapy
Feng 2016	China	Primary cancer, I-III	394	62.3 (33–83)	Chemoradioth-erapy followed by surgery	3.6	5.5	Pretreatment TNM stage, pathological TNM stage, vascular invasion, pretreatment CA125
Kwon BS 2018	South Korea	Primary cancer, I-IV	145	67±12	Surgery	3.2	2.5	Gender, maximum tumor diameter, tumor type, pathological differentiation, WBC count, platelet count, CA125, CA19-9, GPS, Stage
Miao 2016	China	Metastatic cancer, IV	141	62 (36–72)	Chemotherapy	3	5	Gender, age, location of primary tumor, metastasis number, hemoglobin, globulin, GPS
Thvaramara 2011	Thailand	Metastatic cancer, NR	190	63 (27–86)	Chemotherapy	2.5	1.7	Detection of unresectable tumor, the number of organs affected by metastasis, CA125, molecular targeted therapy
Wang 2015	China	Primary cancer, I-III	435	68 (26–90)	Surgery	2.7	5	Stage, tumor diameter, lymphatic involvement, venous involvement, lymph node metastasis
Wang, 2016	China	Primary cancer, III	206	56.7 (37–78)	Chemotherapy with Colorectal resection	2	9	Tumor size, vessel invasion
Williams 2014	USA.	Primary cancer, III	139	61.4 (30–77)		3.5	5	Tumor size, lymphatic involvement
Zhang 2015	China	Primary cancer, I-IV	125	62.3 (31–80)		3	6.7	TNM stage, pretreatment CA125

Table 2

Quality assessment of the included studies with Newcastle-Ottawa quality assessment scale.

Study	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Asher 2011	☆	☆	☆	–	–	☆	☆	☆	6
Cho 2009	☆	☆	☆	–	☆☆	☆	☆	☆	8
Feng 2016	☆	☆	☆	–	☆☆	☆	☆	☆	8
Kwon BS 2018	☆	☆	☆	–	☆☆	☆	–	☆	7
Miao 2016	☆	☆	☆	–	☆☆	☆	☆	☆	8
Thvaramara 2011	☆	☆	☆	–	☆☆	☆	–	☆	7
Wang 2015	☆	☆	☆	–	☆☆	☆	☆	☆	8
Wang, 2016	☆	☆	☆	–	☆	☆	☆	☆	7
Williams 2014	☆	☆	☆	–	☆	☆	☆	☆	8
Zhang 2015	☆	☆	☆	–	☆	☆	☆	☆	8

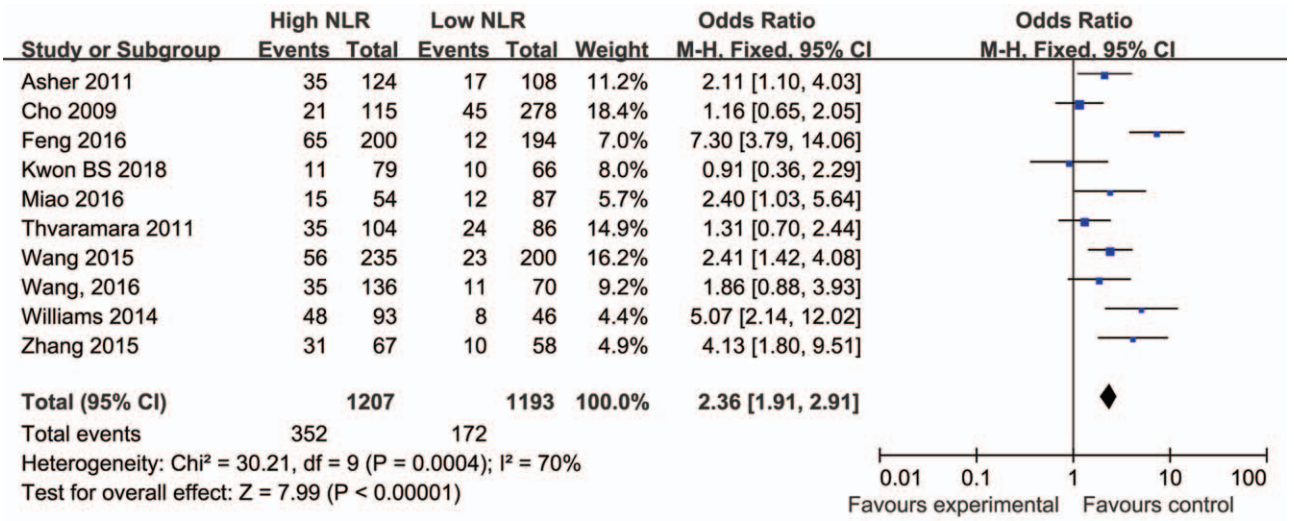

Figure 2. Forest plots showing the association between neutrophil to lymphocyte ratio and overall survival among ovarian cancer patients.

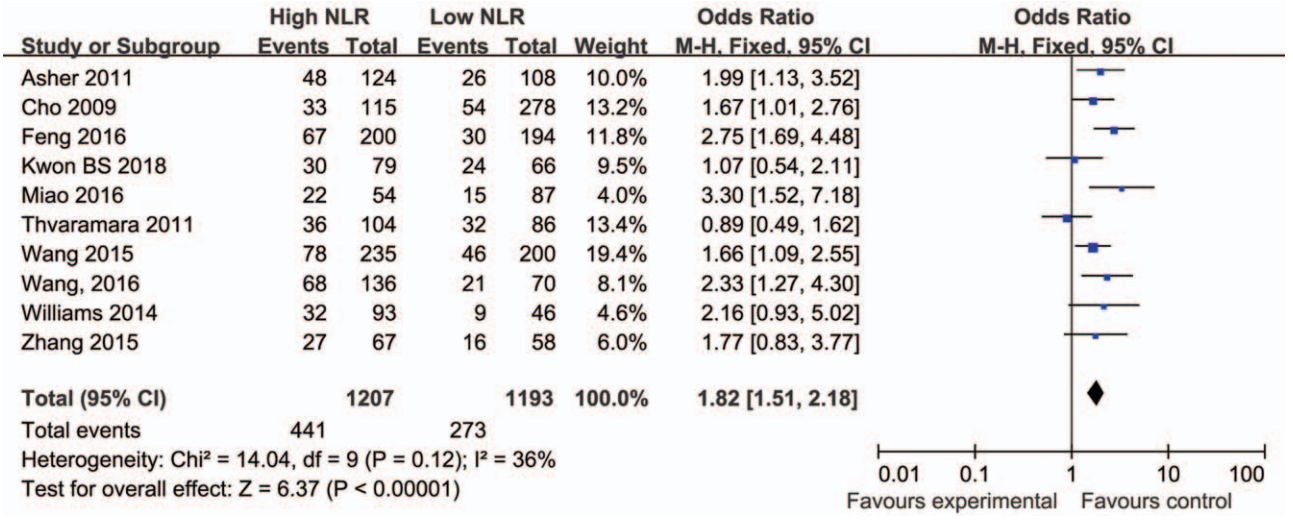

Figure 3. Forest plots showing the association between neutrophil to lymphocyte ratio and progressive free survival among ovarian cancer patients.

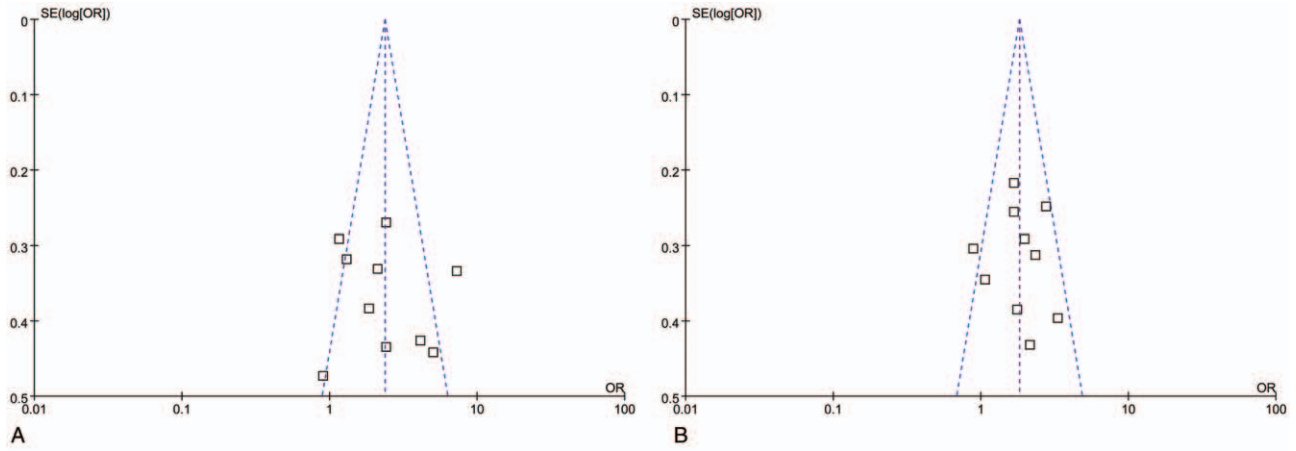

Figure 4. Funnel plot for publication bias. (A) correlation of NLR with overall survival; (B) correlation of NLR with progression-free survival. NLR = neutrophil to lymphocyte ratio.

ovarian cancer. The blood-based indexes can serve as complementary items for the predictive models in patients with ovarian cancer. Recently, The NLR has been proposed to be significant prognosis predictors in kinds of malignances including breast, colorectal, esophageal, lung and pancreas.[23–27] Yet, the cutoff value of the NLR is inconsistent in these above studies, which reduces its clinical applicability, we think the impact of the NLR has been explored as a continuous explanatory variable and it is affected by the patients baselines and therapeutic approaches. Reported pooled hazard ratios for NLR and OS have ranged from 1.40 in esophageal cancer to 2.61 in pancreatic cancer, compared with 2.5 in this study. However, the significance and consistence of the prognostic role of NLR remain to be determined in patients with ovarian cancer.

This meta-analysis is the first to examine exclusively the prognostic value of NLR in patients undergoing difference treatments for ovarian cancer. The principal findings were that no fewer than 60% of patients had an elevated NLR after treatment, in keeping with other cancer meta analyses (range 36.5–59.8%).

The mechanism underlying the potential prognostic value of NLR is mainly due to the significance of the infiltrated neutrophils and lymphocytes. The systemic inflammatory response from cancer cells promotes the infiltration of neutrophils, which benefits cancer progression via secreting interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor α (TNF-α) and vascular endothelia growth factor (VEGF).[28] VEGF is a proangiogenic factor contributes to cancer development especially through angiogenesis. Moreover, increased TNF-α and IL-10 issue in lymphocyte count decrease and lymphocyte dysfunction also. Additionally, the production of an effective angiogenesis cytokine, vascular endothelial growth factor, is also promoted by elevated neutrophils, hence, the cancer growth is further increased.[29] It is well known that lymphocyte depletion is likely reflection of an impaired T-lymphocyte-mediated antitumor response, which represents an adverse prognostic trait. In general, the relative ratio of elevated neutrophils and decreased lymphocytes could be a scientific marker for evaluating the systemic inflammatory response and outcome of individuals. And so, NLR is valuable as a potential indicator of prognosis to some degree.

This meta-analysis has a number of inherent limitations. Heterogeneity existed between studies, which may be explained by a number of factors, not least the variation in NLR critical values and patient characteristics including disease stage, age and treatment. All studies analyzed were retrospective in methodology, and cohort in nature, providing pooled rather than individual patient data. Not all reported extractable data, limiting the number available for analysis.

In conclusion, since all of the included studies were published recently, investigating the associations between NLR with oncologic outcomes for patients with ovarian cancer is the present hotspot. In spite of limitations, the present meta-analysis stands for the most comprehensive and informative study focusing on this issue.

Author contributions

Conceptualization: Xinming Yin, HongBo Yang.
Data curation: Xinming Yin, HongBo Yang.
Formal analysis: Xinming Yin.
Funding acquisition: Hui Yang.
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Validation: HongBo Yang.
Writing – original draft: Xinming Yin, HongBo Yang.
Writing – review & editing: HongBo Yang.

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