Original Article

Prognostic value of baseline C-reactive protein in diffuse large B-cell lymphoma: a systematic review and meta-analysis

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Background: C-reactive protein (CRP) is an inflammatory marker of great significance for progression and prognosis of diffuse large B-cell lymphoma (DLBCL). However, previous studies reported the inconsistent findings of the relationship between CRP levels and survival in DLBCL patients. This meta-analysis was performed to investigate the predictive value of baseline CRP in the prognosis of DLBCL.

Methods: Relevant studies on baseline CRP and prognosis of DLBCL were searched from PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform, and other databases. The search time was from establishment of the database to December 2022. The studies that reported the baseline CRP level, DLBCL confirmed by pathology, data on the relationship between CRP and overall survival (OS) or progression-free survival (PFS), and published in English or Chinese were included in this meta-analysis. No evidence showed the risk of bias of the included studies. Random-effects meta-analysis were conducted to calculate hazard ratio (HR). Stata15.0 software was used for the meta-analysis.

Results: A total of 11 studies with 2,314 patients were included. All included studies were of high quality. The result of prognosis in patients with CRP and DLBCL was HR =2.48 [95% confidence interval (CI): 1.52 to 4.07]. The subgroup analysis showed that the risk of death was higher in both groups (HR =2.58, 95% CI: 2.10 to 3.18, random effects model I^2=39.7%). There was a significant difference between group 1 and group 2 (P=0.000).

Conclusions: Current evidence suggests that baseline CRP is a potential predictor of DLBCL patients and has potential prognostic value in clinical practice, improving the survival rate and quality of life of DLBCL patients. Additionally, OS appears to be strongly influenced by potential country specific differences, which may be related to racial differences and specific lifestyles.

Keywords: C-reactive protein (CRP); diffuse large B-cell lymphoma (DLBCL); prognosis; meta-analysis

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive and heterogeneous group of diseases and the most common subtype of non-Hodgkin lymphoma (1). Although the majority of DLBCL patients treated achieve complete response, 30–40% either do not respond to this treatment or experience relapse, and prognosis for these patients is poor (2). Prognostic biomarkers provide basic information for predicting treatment outcomes and survival and therefore play a vital role in achieving reliable and accurate treatment predictions. Currently, *CD97B* mutation, CD30 expression and T-cell immunoglobulin mucin molecule-3 (Tim-3) expression have been confirmed as prognostic biomarkers of DLBCL (3), but these indicators are not widely used clinically due to technical limitations or difficulty in obtaining them (4,5). Hence, there is a need for prognostic clinical markers that are cost-effective, simple, and readily available. Inflammation is a marker of cancer and its progression, and C-reactive protein (CRP) is an inflammatory marker of great significance for progression and prognosis of malignant tumors (6), which include DLBCL. The previous meta-analysis evaluated the relationship between CRP levels and survival in DLBCL patients, though the findings have been inconsistent (7,8). According to Troppan *et al.*, high CRP levels at diagnosis of DLBCL as an independent poor prognostic factor for clinical outcome. Adding CRP to the well-established prognostic models such as the R-IPI score might improve their predictive ability (9). The previous study revealed that pre-therapy CRP can be a potential prognostic marker for patients with DLBCL (10). In this meta-analysis, literature on the relationship between CRP and overall survival (OS) and progression-free survival (PFS) in DLBCL patients was collected, and a meta-analysis was conducted for quantitative evaluation. We present this article in accordance with the MOOSE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1157/rc).

Highlight box

Key findings

- The baseline CRP level is a potential predictor of DLBCL, with potential prognostic value in clinical practice and may improve the survival rate and quality of life of DLBCL patients.

What is known and what is new?

- *CD97B* mutation, CD30 expression and Tim-3 expression have been confirmed as prognostic biomarkers in DLBCL.
- CRP is an inflammatory marker that is of great significance for progression and prognosis of malignant tumors.

What is the implication, and what should change now?

- The meta-analysis results showed that a high baseline CRP level predicts lower OS in DLBCL patients, and CCRP is a predictive biomarker for DLBCL patients. This marker is convenient and minimally invasive for quantifying CRP by blood tests, and its key role in cancer prognosis may lead to clinical application.

Methods

Search strategy

The Newcastle-Ottawa Scale (NOS) was used to rate the caliber of the included studies (11). The NOS scale consisted of nine elements, which were grouped into three categories: selection, comparability, and outcome/exposure. The study quality was classified as low, medium, or high based on scores of 0–3, 4–6, and 7–9, respectively. Literature about the association between baseline levels of CRP and prognosis of DLBCL was retrieved from PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform, and other databases from establishment until December 2022. According to the characteristics of the database, a joint search of subject words and free words was conducted (C-reactive protein OR CRP) AND (diffuse large B-cell lymphoma OR DLBCL) AND (prognosis OR survival OR survival); English search form: (C-reactive protein OR CRP) AND (diffuse large B-cell lymphoma OR DLBCLOR) AND (prognosis OR survival OR survival rate). By reading the title and abstract, irrelevant literature was eliminated. After reading the full text, relevant articles were further screened according to inclusion and exclusion criteria, and the references of selected literature were manually searched.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

(I) Patients with DLBCL confirmed by pathology;
(II) Patients received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as induction therapy;
(III) Studies reported baseline CRP level;
(IV) Data on the relationship between CRP and OS or PFS provided;

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(V) Published in English or Chinese.

If the following exclusion criteria were met, documents were excluded:

(I) Dissertation, conference abstract;
(II) Irrelevant research or animal research;
(III) Studies without sufficient data;
(IV) Confounding factors were not adjusted;
(V) Repeated publication of literature.

Data extraction and literature quality evaluation

The retrieved literature was imported into EndNote20 literature management software for deduplication. Two researchers independently screened the articles according to the title and abstract and eliminated those that failed to meet the inclusion criteria. If there was any disagreement in the screening process, the literature was reviewed and discussed until a consensus was reached. If there was any disagreement, the opinions of a third party were consulted. The basic characteristics and effect size data were extracted from each study: first author, year of publication, study area, sample size, study duration, follow-up time, CRP value, patient age, survival outcome, hazard ratio (HR) and 95% confidence interval (CI) for OS and/or PFS. Two researchers independently used the NOS to evaluate the quality of the included literature (12). In cases of disagreement during the evaluation process, consultation or third-party advice was sought.

Statistical analysis

A meta-analysis was performed using Stata15.0 software (StataCorp LP, College Station, TX, USA). The chi-square test was used to evaluate the heterogeneity among the studies; heterogeneity was considered to be significant at $P<0.1$. Statistical I^2 was used to quantitatively evaluate heterogeneity, with $I^2 \geq 50\%$ indicating heterogeneity between studies. In this case, a random effects model was used for analysis, and a forest map was drawn. Subgroup analysis was performed to explore potential sources of heterogeneity, and sensitivity analysis was used to test the stability of results. The stability of the results was ensured by removing each study in turn to observe changes in the population effect. Funnel plots and Egger's test were used to check publication bias in the literature. All tests were bilateral, and $P<0.05$ was considered statistically significant. Due to the enough sample size in this meta-analysis, Begg's test is not suitable. Continues variables of CRP were measured using HR with a 95% CI for each outcome. The HR values were extracted from multiple Cox regression analyses of included studies.

Results

Basic characteristics and quality evaluation of the included literature

A total of 206 studies were retrieved, 97 studies were excluded after repeated screening, and 73 studies were excluded based on title and abstract review. Thirty-six papers were included in the full-text screening, including 1 meta-analysis and 2 dissertations. In 16 studies, the study index was not OS, PFS or other survival indicators, and in 12 studies, the study index was not the pretreatment CPR level. Four papers focused on diseases other than DLBCL. Finally, a total of 11 studies were included for the meta-analysis (9,13-22), as shown in *Figure 1*.

The basic characteristics of the included studies were compiled. The 11 studies included a total of 2,314 DLBCL patients: 4 studies in China, 2 studies in South Korea, 2 studies in Australia, and 1 study each in Japan, the Netherlands and Israel. The mean follow-up time was 38.2 months, four articles provided HRs for PFS, and 11 studies analyzed the direct or indirect association between CRP and OS. After scoring according to the NOS scale, the literature quality score ranged from 7 to 9, with an average of 7.8 points; 11 studies scored ≥7, indicating good study quality. The basic characteristics and quality evaluation of the 11 studies included are shown in *Table 1*.

Meta-analysis of prognosis in patients with CRP and DLBCL

The 11 studies described the relationship between baseline CRP and OS in the 2,314 DLBCL patients. The heterogeneity test results were as follows: $P=0.000$, $I^2=80.8\%$, with significant heterogeneity between groups. A random effects model was used for analysis. The results of the meta-analysis showed HR =2.48, 95% CI: 1.52 to 4.07, and the differences were statistically significant, suggesting that a high baseline CRP level correlates with low OS in DLBCL patients (*Figure 2*).

A total of four studies described the relationship between baseline CRP and PFS in 602 patients with DLBCL. Heterogeneity test results were $P=0.000$, $I^2=92.4\%$, with no heterogeneity between groups, using random effects model

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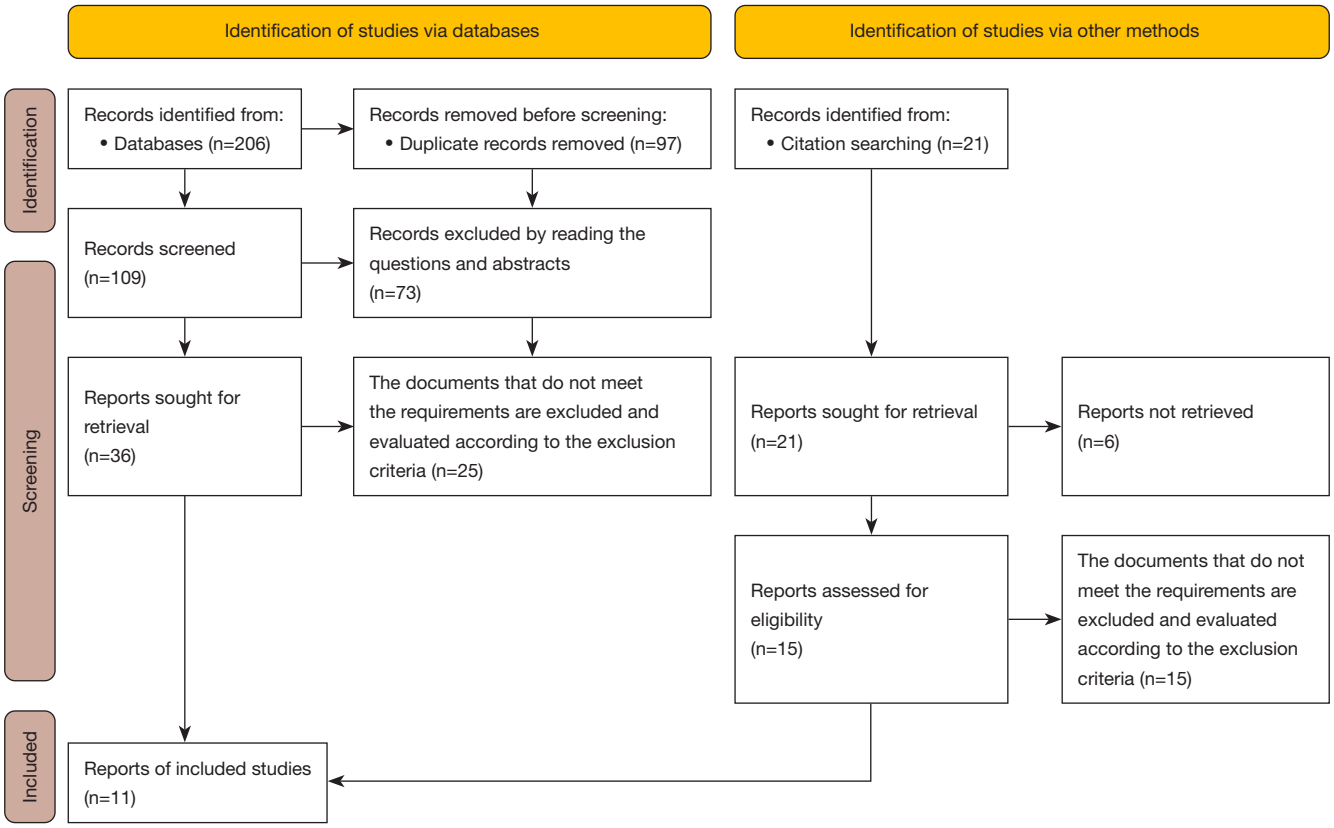

Figure 1 Literature screening flow chart.

Table 1 Basic characteristics and quality evaluation of the 11 included studies

First author	Year	Country	Sample size, n	Value of CPR (mg/L)	Age (years)	Study period	Follow-up time (months)	Survive index	Quality score
Adams	2015	Holland	104	10.0	66	2004–2013	43.7	OS, PFS	9
Wang	2016	China	156	20.0	59	2006–2015	29	OS, PFS	8
Jung	2021	South Korea	186	15.0	58	2006–2018	32.5	OS, PFS	8
Kobayashi	2016	Japan	465	10.0	–	2006–2014	32	OS	8
Shin	2012	South Korea	85	13.0	69	2004–2009	30	OS	8
Tadmor	2013	Israel	91	–	66	1996–2010	30	OS	8
Melchardt	2015	Australia	515	29.0	65	2004–2014	53	OS	8
Troppan	2014	Australia	477	15.0	68	2004–2013	–	OS, PFS	8
Cao	2012	China	94	8.0	56	2006–2009	–	OS	7
Zhu	2020	China	198	–	60	2011–2018	–	OS	8
Huang	2016	China	106	19.0	55	2007–2014	65	OS	7

CRP, C-reactive protein; OS, overall survival; PFS, progression-free survival.

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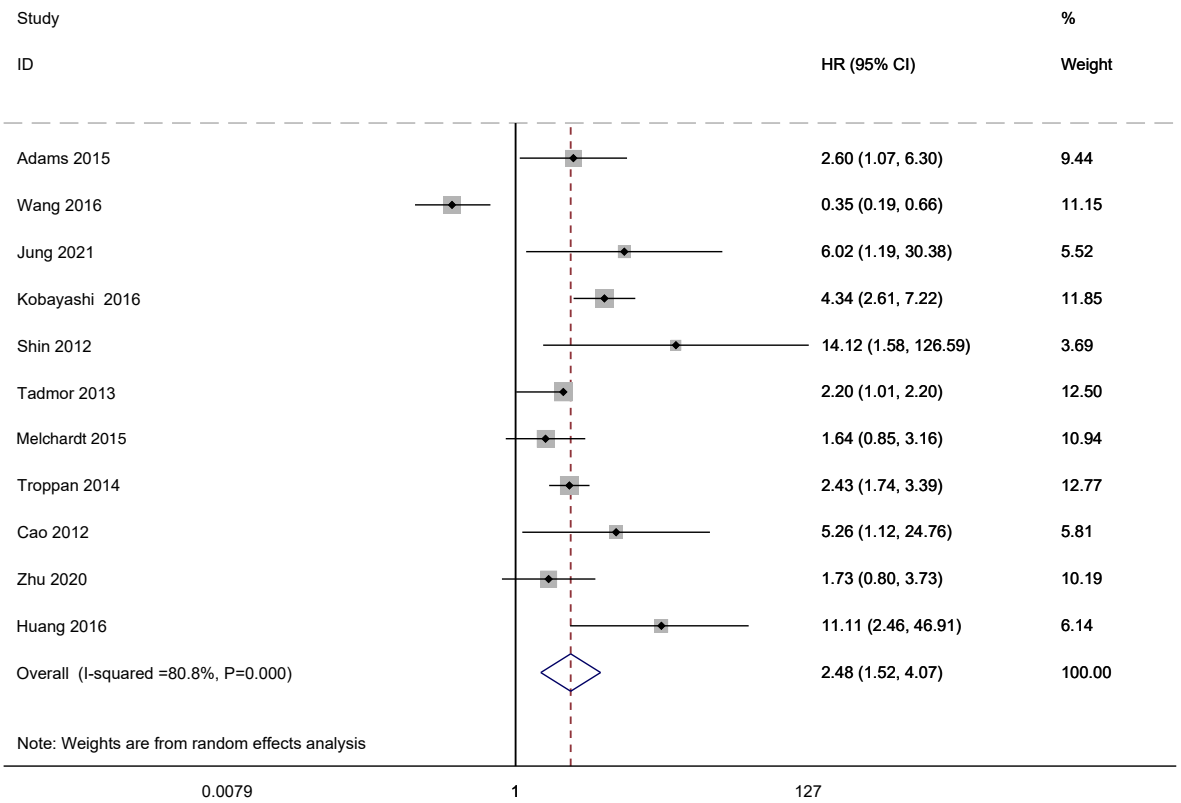

Figure 2 Correlation between baseline CRP level and OS in DLBCL patients. HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; OS, overall survival; DLBCL, diffuse large B-cell lymphoma.

analysis. The results of the meta-analysis showed effect size =0.46, 95% CI: –0.62 to 1.54; the differences were not statistically significant, suggesting that high baseline CRP is not associated with low PFS in DLBCL patients (*Figure 3*).

Subgroup analysis

The study of subgroups was conducted based on the study area. Studies were grouped according to study area: one group representing domestic research and two groups representing foreign research. The risk of death was higher in two groups (HR =2.58, 95% CI: 2.10 to 3.18, random effects model I^2=39.7%). As there was a significant difference between group 1 and group 2 (P=0.000), different study areas were the main source of heterogeneity, as shown in *Figure 4*.

Research according to treatment options was explored. Group 1 representatives were treated with R-CHOP. Group 2 representatives received standard R-CHOP protocol, CHOP like protocol or the third-generation protocol containing anthracycline, but all received combined treatment including monoclonal antibody rituximab. There is an increased risk of death in two groups (HR =2.51, 95% CI: 2.05 to 3.08, random effects model I^2=55.9%). There is a significant difference between group 1 and group 2 (P=0.001), so the treatment regimen was the main cause of non-heterogeneity, as shown in *Figure 5*.

Regarding baseline CRP thresholds, group 1 had a CRP critical value of less than 15 mg/L, and group 2 had a CRP critical value of more than 15 mg/L. Risk of death was increased in both groups (HR =4.10, 95% CI: 2.70 to 6.22, fixed effect model I^2=0.0%; HR =1.86, 95% CI: 1.51 to 2.30, random effect model I^2=84.5%). There was a significant difference between group 1 and group 2 (P=0.001), with CRP critical grouping a major source of heterogeneity, as shown in *Figure 6*.

Sensitivity analysis

In sensitivity analysis, the effect size of each study was

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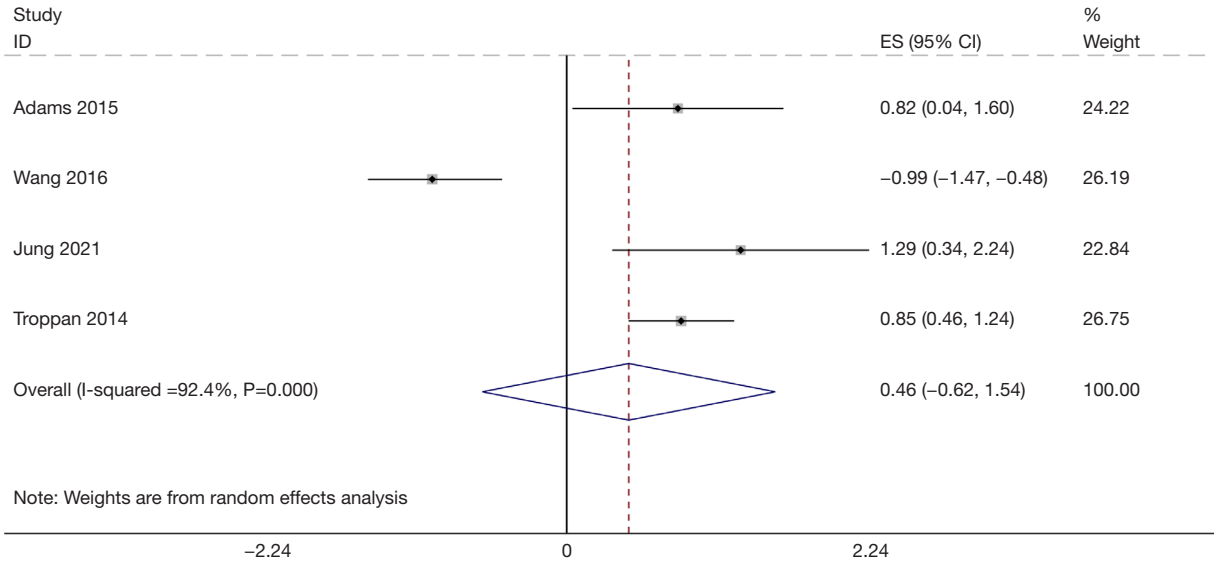

Figure 3 Correlation between baseline CRP level and PFS in DLBCL patients. ES, effect size; CI, confidence interval; CRP, C-reactive protein; PFS, progression-free survival; DLBCL, diffuse large B-cell lymphoma.

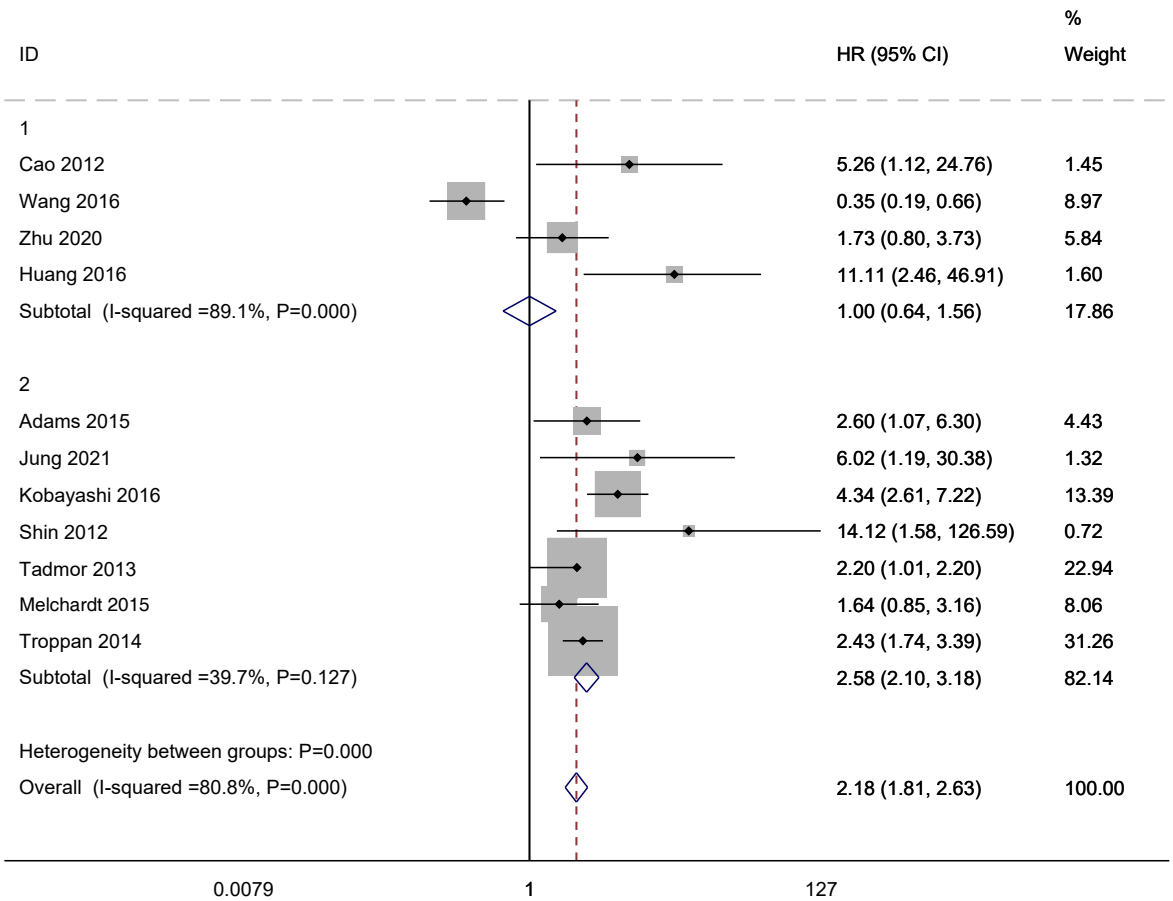

Figure 4 Comparison of different study areas. HR, hazard ratio; CI, confidence interval.

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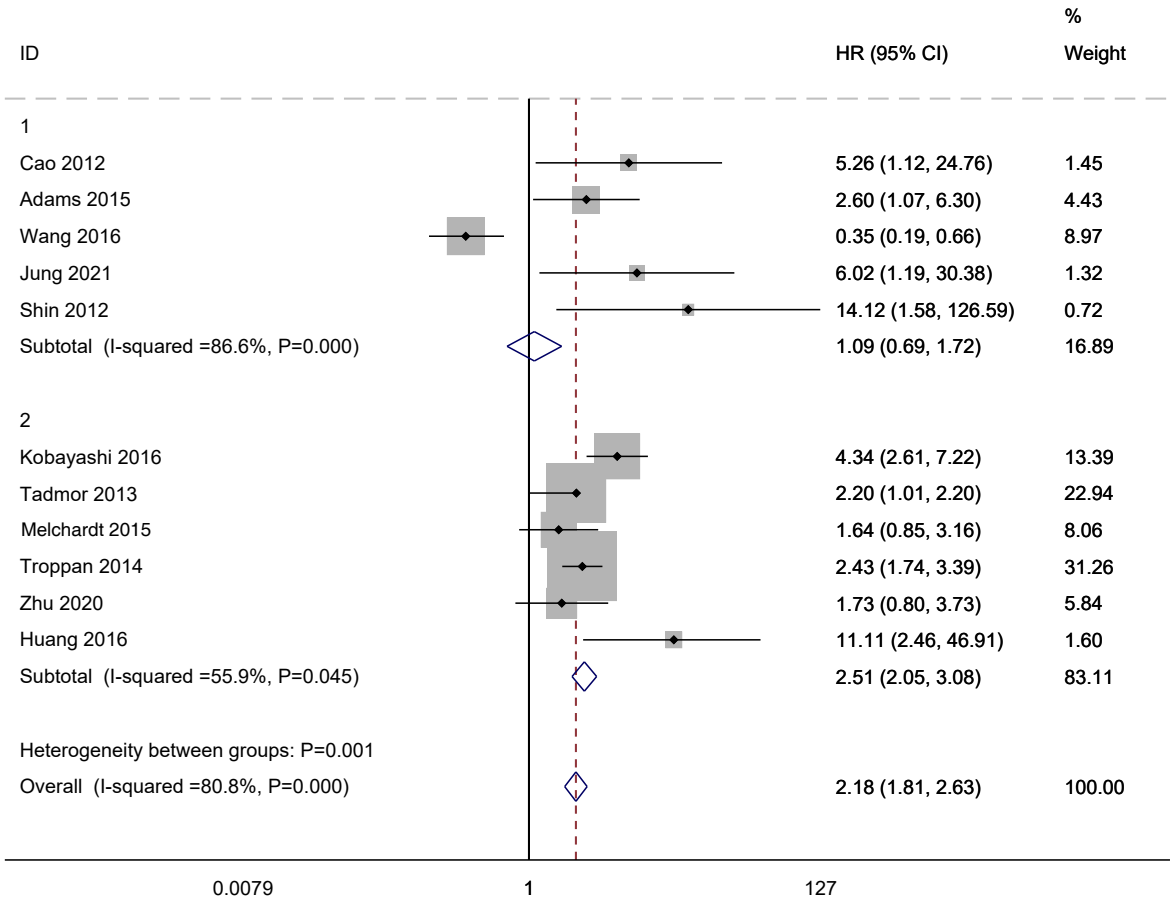

Figure 5 Comparison of different treatment regimens. HR, hazard ratio; CI, confidence interval.

deleted one by one and combined again to analyze the degree of influence of individual studies on the overall effect size. We found that after excluding one study, heterogeneity significantly decreased (I^2=49.5%), while the merged HR did not show significant changes, indicating stable research results, as shown in *Figure* 7.

Publication bias

The inclusion and exclusion criteria were strictly followed. The asymmetry of the left and right sides of the funnel plot suggested the existence of publication bias, which may be due to the difficulty in publishing articles with negative results. In addition, differences in other factors (treatment plan, age and underlying diseases) were causes of publication bias. At the same time, Egger's test result showed no serious publication deviation (P>0.05). Based on the above results, the main conclusion of the meta-analysis is reliable, as shown in *Figure 8*.

Discussion

CRP has been identified as a prognostic factor for a variety of solid and hematological malignancies. Elevated CRP levels have been found to be associated with poor OS in many types of cancer, including digestive tract tumors, urinary tract tumors, soft tissue sarcomas, pancreatic cancer, and small cell lung cancer (23). The prognostic effect of CRP on DLBCL remains controversial and uncertain, and the purpose of this meta-analysis was to organize and analyze previously published studies. The results of this meta-analysis showed a high baseline CRP level to be associated with low OS. Due to heterogeneity, the prognostic value of CRP remained stable and reliable after subgroup analysis and sensitivity analysis based on study area, treatment regimen, CRP threshold value and sample

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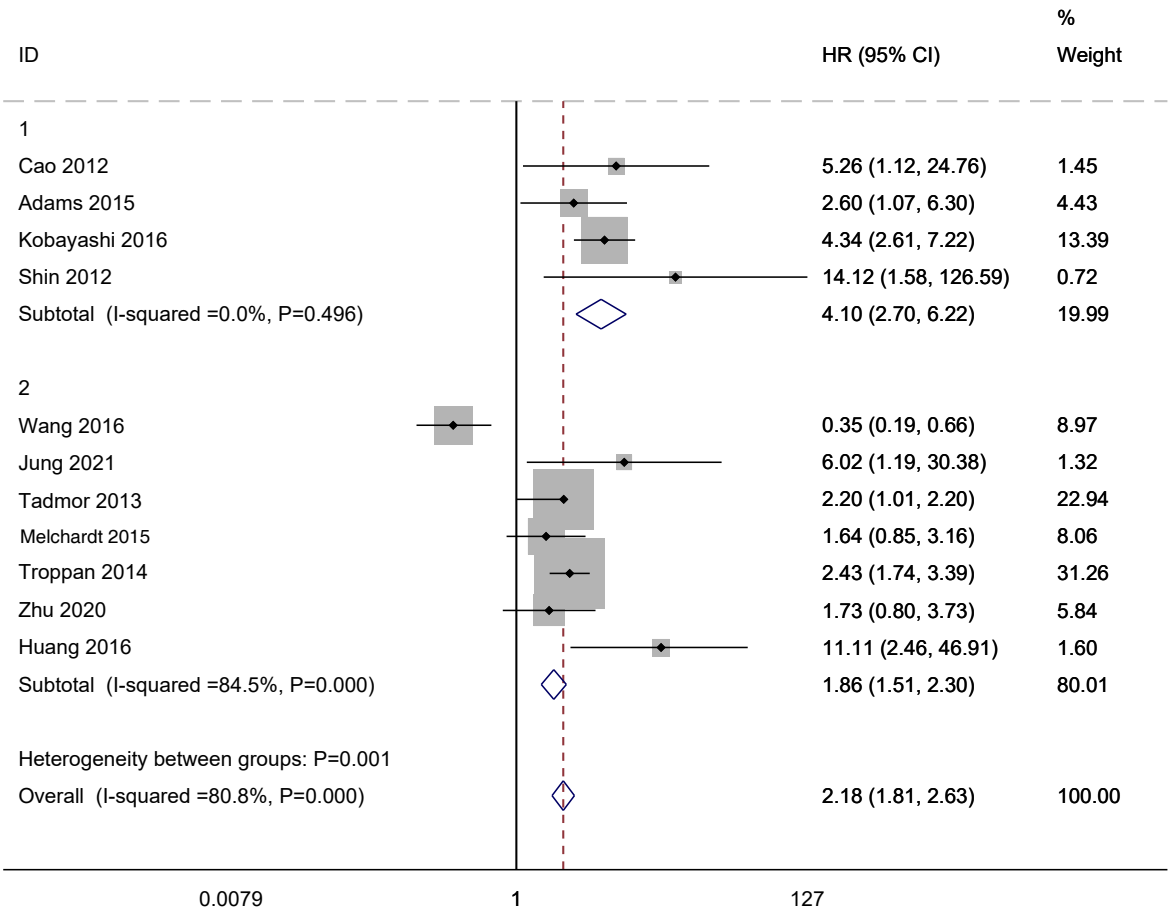

Figure 6 Group comparison of different CRP threshold values. HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein.

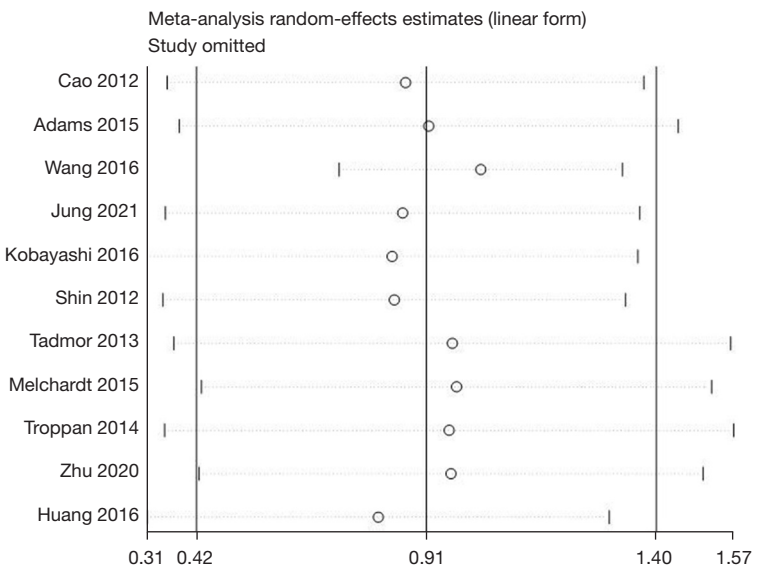

Figure 7 Sensitivity analysis of OS. OS, overall survival.

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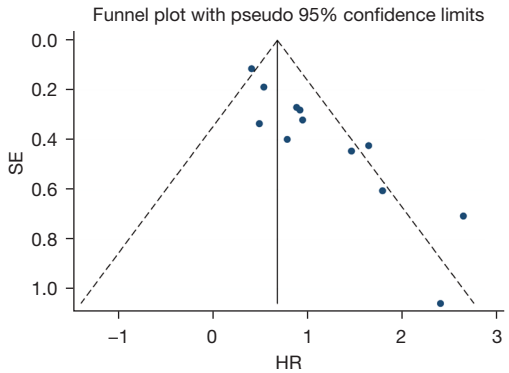

Figure 8 Funnel diagram. SE, standard error; HR, hazard ratio.

size. Therefore, CRP is an important prognostic indicator for DLBCL patients and has potential prognostic value in clinical practice. In addition, because CRP is routinely measured in most medical laboratories, along with complete blood counts and classified white blood cell counts, it is possible for CRP to be validated in DLBCL in clinical practice.

CRP testing is noninvasive, easy to detect, inexpensive, repeatable, and can track tumor status in real time, making it a hot topic in the emerging field of noninvasive tumor markers. Various meta-analyses have shown that CRP has significant prognostic value for solid tumors, including gynecological tumors (24), urinary tract tumors (25), lung cancer (26), and colorectal cancer (27). Additionally, CRP is associated with low OS in various tumors, consistent with the results of this meta-analysis, which showed that CRP was associated with low OS in DLBCL. The results of a meta-analysis investigating the association between CRP and DLBCL also showed that the pretreatment CRP value is a prognostic marker for DLBCL (10), These studies provide more evidence that CRP is a potential predictor of DLBCL patients. One study reported that the CRP/albumin ratio (CAR) plays an important prognostic role in DLBCL. A high CAR indicates low survival, which to some extent supports our findings that a high CAR usually suggests high CRP when albumin levels are fixed (28). He *et al.* found that high CRP can effectively reflect disease changes in DLBCL patients and is related to tumor stage, which may be one of the poor prognostic factors of DLBCL (29). In the study of Qiu *et al.*, among DLBCL patients receiving CHOP, the therapeutic effect in the low CRP expression group was significantly better than that in the high expression group, indicating that high CRP leads to poor prognosis by influencing the therapeutic effect (30).

In this study, subgroup analysis was conducted to determine the source of heterogeneity, and the results of subgroup analysis grouped by the study area suggest that heterogeneity related to OS appears to be strongly influenced by potential country specific differences, which may be related to racial differences and specific lifestyles. Subgroup analysis using a CRP of 15 mg/L as the critical value suggests heterogeneity. In populations with a CRP ≥15 mg/L, OS reported a higher risk of death, and CRP <15 mg/L was also associated with poor OS. The main reason for the difference in critical values is that some studies use median CRP levels as the critical value, just to balance the number of individuals in the high CRP and low CRP groups. If applied clinically, a unified cut-off value must be used, therefore more high-quality prospective clinical studies are needed to determine the most suitable baseline CRP threshold for different cancers.

Various inflammatory parameters are associated with the development and progression of cancer. Routine diagnostic CRP, an acute-phase protein, is produced by the liver in response to interleukin-6 and other cytokine stimulation (31). There are several possible potential mechanisms to explain the association between elevated CRP and adverse survival outcomes. First, chronic inflammation can promote carcinogenesis and contribute to the occurrence or progression of cancer. As the circulating concentration of vascular endothelial growth factor is directly related to CRP (32), increased circulating CRP may reflect the phenotype or aggressiveness of a tumor (33). Second, to synthesize large amounts of CRP, tumor growth can induce various cytokines and chemokines that stimulate liver cells (34), and rapid tumor growth can trigger an immune response, with release of many inflammatory factors. Therefore, the concentration of circulating CRP levels becomes elevated, which may reflect tumor phenotype or aggressiveness (35). Third, elevated CRP identifies patients with impaired T-lymphocyte response, as poor tumor infiltration appears to be associated with poor outcomes, and elevated CRP concentration has recently been shown to correlate negatively with T-lymphocyte subgroup infiltration, which may lead to tumorigenesis and progression of DLBCL (36). So, elevated CRP is associated with poor survival outcomes.

Our meta-analysis provides potential prognostic biomarkers for DLBCL patients; however, there are some limitations to the current study. First, although the number of articles included was reasonable, heterogeneity was relatively high and could not be completely eliminated.

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This heterogeneity may be partly explained by inclusion of three variables in the meta-regression analysis. This may be caused by baseline characteristics of the patient, such as age, disease stage, and underlying diseases that may affect prognosis. Second, the optimal thresholds for CRP included varied widely, ranging from 8 to 29 mg/L, possibly because different CRP measurements and kits were used at different hospitals. This may be one of the reasons for the high heterogeneity in the subgroup results. Third, the results of this study were based on published research data, without obtaining detailed individual data for analysis. Moreover, the number of included studies was limited, and the sample size was small. All were retrospective studies, which may lead to bias. Finally, some researchers do not publish adverse results because they believe they are meaningless, leading to some inevitable publication bias. Therefore, we will continue to use the pruning and filling methods to obtain adjustment results to illustrate the association.

Conclusions

Overall, our meta-analysis results suggest that high baseline CRP predicts lower OS in DLBCL patients and that CRP is a predictive biomarker in DLBCL. Quantification of CRP through blood tests is convenient and minimally invasive, and its key role in cancer prognosis may contribute to its clinical application. The present study was unable to determine the role of CRP in treatment response and tumor recurrence and accurate threshold values for CRP. To address these limitations, better quality prospective longitudinal studies of the role of CRP as a prognostic indicator are needed to confirm the observations.

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Footnote

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Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1157/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1157/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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