Int J Clin Exp Med 2015;8(9):15340-15350
www.ijcem.com /ISSN:1940-5901/IJCEM0011366

*Original Article*

# Prognostic value of interim $^{18}$F-FDG-PET in diffuse large B cell lymphoma treated with rituximab-based immune-chemotherapy: a systematic review and meta-analysis

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Received June 13, 2015; Accepted September 7, 2015; Epub September 15, 2015; Published September 30, 2015

**Abstract:** The prognostic value of an interim fluorine-18-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) for diffuse large B-cell lymphoma (DLBCL) has been assessed by different groups. However, studies have suggested that the use of rituximab could limit the predictive value of interim $^{18}$F-FDG PET for DLBCL. To clarify the prognostic value of interim $^{18}$F-FDG PET in DLBCL patients treated with rituximab based immunochemotherapy, we searched for relevant studies in PubMed, the Cochrane Library and EMBASE. A random versus fixed effects model was applied according to the heterogeneity. According to the literature search strategies, 11 studies were identified. The pooled HR comparing PFS between patients with positive and negative results was 2.96 (95% CI=2.25-3.89). The patients in interim 18F-FDG PET negative group had a higher CR rates than that in interim 18F-FDG PET positive group (RR=5.53, 95% CI=2.59-11.80). Consistent evidence favoring interim $^{18}$F-FDG PET-based treatment assessment should be considered in the management of patients with DLBCL.

**Keywords:** $^{18}$F-FDG PET, DLBCL, prognosis, meta-analysis

## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent type of non-Hodgkin's lymphoma (NHL). The combination of the anti-CD20 monoclonal antibody rituximab with standard doses of cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) has dramatically improved clinical outcomes of patients with DLBCL. Nevertheless, significant proportions of patients show disease progression or relapse after a good initial response. The International Prognostic Index (IPI) is the most widely used tool for identifying patients at different degrees of risk [1], but there is different outcome of individual patients within the same IPI prognostic group. Response to treatment may be another important predictor of outcome with the advantage of addressing the management for the individual patient. In 2007, the International Workshop Criteria (IWC) integrated fluorine-18-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) results after completion of therapy into the response assessment for DLBCL [2, 3]. Thus, $^{18}$F-FDG PET is actually considered the "gold standard" for initial staging and evaluation of response after treatment. However, this information can only be obtained belatedly and cannot be used to guide treatment strategies. In recent years, there is an increasing interest in using interim $^{18}$F-FDG PET performed after 1-4 cycles of chemotherapy to predict response to induction treatment and to drive consolidation therapy. The prognostic value of an interim $^{18}$F-FDG PET has been assessed by different groups and can predict survival in the era of CHOP therapy for DLBCL [4-8]. However, the use of rituximab could limit the predictive value of interim $^{18}$F-FDG PET for DLBCL, the positive predictive value of interim $^{18}$F-FDG PET scans has been subject to inconsistent results after post-rituximab treatment in DLBCL. Some reports suggest that $^{18}$F-FDG PET

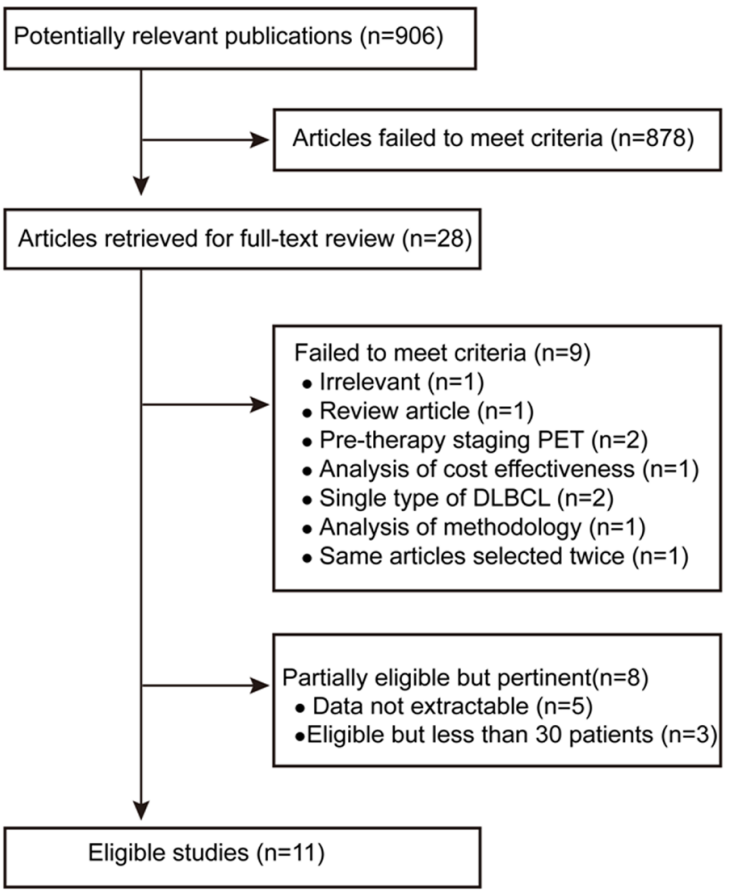


**Figure 1.** Systematic literature search selection process.

scans performed early during treatment, after two to four cycles of R-CHOP, could help identify high-risk patients who are likely to relapse [5, 6, 9-12]. Other studies have shown that positive interim $^{18}$F-FDG PET is not predictive of a worse outcome in DLBCL [13-16]. These discrepancies on the predicting value of interim $^{18}$F-FDG PET may either be because of the heterogeneity of the visual criteria used so far or reflect the different clinical profiles (e.g., treatment strategies, response, and prognosis).

Therefore, although interim $^{18}$F-FDG PET has been shown to be the strongest prognostic factor in patients with Hodgkin lymphoma (HL), while in DLBCL there are discordant results [17-19]. To better define the prognostic value of interim $^{18}$F-FDG PET for patients with DLBCL treated with rituximab based chemotherapy, we conducted a systematic review to assess its potency in predicting treatment outcomes and to estimate the effects of a positive interim $^{18}$F-FDG PET scan on PFS, paying particular attention to the clinical applicability of the reported results.

## Methods

### *Literature search*

We did a systematic literature search involving PubMed, the Cochrane Library database and EMBASE with no language restrictions. The conference proceeding of the American Society of Hematology, the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) for relevant clinical trials were also manually searched. To complement the search, we examined the reference lists of eligible studies and relevant review articles. Two reviewers (Z.D, F.C) independently screened abstracts and further examined full-text articles of all potentially eligible citations.

### *Inclusion and exclusion criteria*

In this analysis, the studies evaluated $^{18}$F-FDG PET between the second and the fourth cycle of first-line rituximab-chemotherapy for newly diagnosed patients with DLBCL were included. We included both prospective and retrospective studies. The number of the enrolled patients was more than 30 and included at least 5 patients who progressed during chemotherapy or relapsed through clinical follow-up. Many studies did not meet all the inclusion criteria, but did partially include a relevant patient population, we included it only if subgroup data on $^{18}$F-FDG PET were separately extractable. We excluded studies that did not provide adequate information to allow the calculation of hazard ratio (HR) with PFS.

### *Data abstraction*

Two board-certified hematologists (Z.D, F.C) independently performed data extraction. We extracted the following information from eligible studies: first author, year of publication, journal, patient demographic and clinical characteristics such as IPI, disease stage, therapeutic interventions, interim $^{18}$F-FDG PET results, and final clinical outcomes. In each study, PFS was considered endpoints for sur-

**Table 1.** Summary of studies included in the meta-analysis

| Author | Year | Country | Study design | No of patients | Median age (range), yrs | Median follow-up (range), mos | No of chemotherapy course before PET | $^{18}$FDG-PET analysis method |
|---|---|---|---|---|---|---|---|---|
| Safar et al. | 2012 | France | Retrospective | 112 | 59 (20-79) | 38 (4.4-73) | 2 | Visual (3-PS)/SUV assessment |
| Casasnovas et al. | 2011 | France | Prospective | 102 | 45 (18-59) | 19 (3-28) | 2 and 4 | Visual (IHP criteria)/SUV assessment |
| Fuertes et al. | 2013 | Spain | Prospective | 50 | 55 (21-29) | 47 (2-72) | 2 or 3 | Visual (3-PS/5-PS)/SUV assessment |
| Yang et al. | 2011 | Korea | Prospective | 161 | 61 (17-85) | 31 (0.4-71) | 3 or 4 | Visual IHP |
| Itti et al. | 2013 | France | Retrospective | 114 | 56 (23-80) | 39 (12-74) | 2 | Visual (5-PS)/SUV assessment |
| Gonzalez-Barca et al. | 2013 | Spain | Prospective | 69 | 60 (18-79) | 29 (6-53) | 2 | Visual (IHP criteria) |
| Cashen et al. | 2011 | USA | Prospective | 50 | 58 (29-80) | 34 (16-44) | 2 or 3 | Visual (IHP criteria) |
| Pregno et al. | 2012 | Italy | Retrospective | 88 | 55 (18-80) | 26 (8-67) | 2 or 3 or 4 | Visual (5-PS) |
| Moskowitz et al. | 2010 | USA | Prospective | 98 | 47 (20-75) | 44 (25-80) | 4 | Visual (IHP criteria) |
| Cox et al. | 2012 | Italy | Prospective | 85 | NA | 36 (5-68) | 3 | Visual (5-PS) |
| Yoo et al. | 2011 | Korea | Retrospective | 155 | 56 (16-85) | 20 (4-73) | 2 or 3 or 4 | Visual (IHP criteria) |

Abbreviations: NA, not available.

**Table 2.** Clinical characteristics of the studies of rituximab-based immunochemotherapy for DLBCL

| Author | Clinical Staging | Prognostic index (case) | Therapy regimen (case) | Use of Rituximab (%) | Interim $^{18}$F-FDG PET (+)/(-) |
|---|---|---|---|---|---|
| Safar et al. | I-II: 21<br>III-IV: 91 | aaIPI: 0 (6); 1 (39); 2 (41); 3 (26) | R-CHOP21 (57)<br>R-CHOP14 (24)<br>R-ACVBP14 (31) | 100 | 42/70 |
| Casasnovas et al. | I-II: 4<br>III-IV: 98 | aaIPI: 1 (5); 2 (79); 3 (17)<br>Bulky disease (21) | R-ACVBP14 (50)<br>R-CHOP14 (52) | 100 | 40/62 |
| Fuertes et al. | I-II: 28<br>III-IV: 22 | IPI: 1 (24); 2 (12); 3 (9); 4-5 (5) | R-CHOP21 (50) | 100 | 12/38 |
| Yang et al. | I-II: 94<br>III-IV: 67 | IPI: 1 (75); 2 (33); 3 (27); 4-5 (26)<br>Bulky disease (27) | R-CHOP21 (161)<br>Additional IFRT (53) | 100 | 43/116 |
| Itti et al. | I-II: 20<br>III-IV: 94 | aaIPI: 0 (7); 1 (33); 2 (50); 3 (24) | R-CHOP21 (63) R-CHOP14/R-ACVBP14 (51)<br>Additional IFRT (4) | 100 | 51/63 |
| Gonzalez-Barca et al. | I-II: 24<br>III-IV: 45 | IPI: 0-2 (46); 3-5 (23)<br>Bulky disease (17) | R-CHOP-14 (69)<br>Additional IFRT (4) | 100 | 34/35 |
| Cashen et al. | III: 15 IV: 35 | IPI: 0-1 (7); 2 (9); 3 (18); 4-5 (16) | R-CHOP21 (50) | 100 | 24/26 |
| Pregno et al. | I-II: 29<br>III-IV: 59 | aaIPI: 0-2 (53); 3 (25)<br>Bulky disease (27) | R-CHOP21 (31)<br>R-CHOP14 (57)<br>Additional IFRT (14) | 100 | 25/63 |
| Moskowitz et al. | I-II: 14<br>III-IV: 83 | aaIPI: 1 (21); 2 (49); 3 (29)<br>Bulky disease (33) | R-CHOP14 (97) | 100 | 38/59 |
| Cox et al. | I-II: 33<br>III-IV: 52 | aaIPI: 1 (14); 2 (33); 3 (38) | R-CHOP14 (43)<br>R-CHOP21 (31)R-MACOP-B (11)<br>Additional IFRT (19) | 100 | 24/61 |
| Yoo et al. | I-II: 64<br>III-IV: 91 | aaIPI: 0 (6); 1 (39); 2 (41); 3 (26) | R-CHOP21 (155) | 100 | 55/100 |

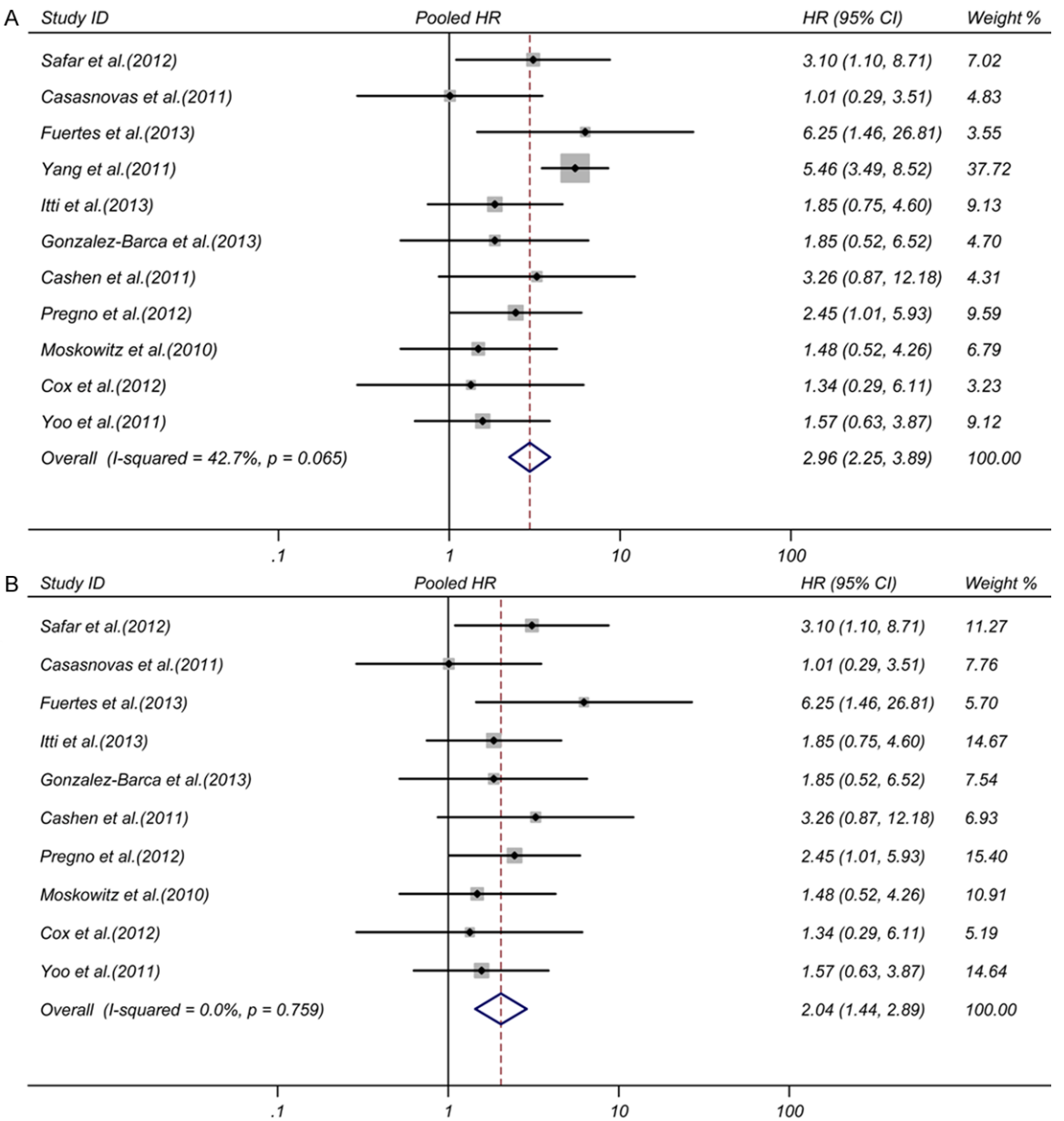


**Figure 2.** Meta-analysis of PFS between two groups of DLBCL patients (interim $^{18}$F-FDG PET positive vs negative) receiving R-chemo. Forest plots to show the pooled HR of $^{18}$F-FDG PET -based response criteria (A). After adjustment for heterogeneity, Forest plot showing the pooled HR of $^{18}$F-FDG PET -based response criteria between two groups of DLBCL patients (interim $^{18}$F-FDG PET positive vs negative) receiving R-chemo (B). Squares on the hazard ratio plot are proportional to the weight of each study, which is based on the inverse variance (IV) method. Hazard ratios are presented with 95% confidence intervals (CIs).

vival analysis. We assessed the effect of treatment for each study using HR and their 95% confidence interval (95% CI) as the main effect size estimate. For those studies that reported the value of HR and its standard error straightforward, these data would be extracted directly. For those studies that did not report the HR but provided sufficient data on survival, the log HRs and variances were estimated based on the methodology published by Parmar *et al*. [20]. In cases in which the only available data were presented in the form of graphical survival curves, the freely available Engauge Digitizer software version 4.1 (SourceForge, http://digitizer. sourceforge.net/) was used to extract survival rates at specified time points, assuming that the rate of patient censoring was constant throughout the follow-up period. HR was then calculated using data points for each group. Reviewers were not blinded to the name of the journal.

**Table 3.** Sensitivity analysis for pooled HR of PFS for interim $^{18}$F-FDG PET

| Excluded study | HR (95% CI) | $I^2$% | *P*-value of Cochran Q test |
|---|---|---|---|
| Safar et al. (2012) | 2.95 (2.22-3.92) | 48.4 | 0.04 |
| Casasnovas et al. (2011) | 3.12 (2.36-4.14) | 37.7 | 0.11 |
| Fuertes et al. (2013) | 2.88 (2.18-3.80) | 45.1 | 0.06 |
| Yang et al. (2011) | 2.040 (1.44-2.89) | 0.00 | 0.76 |
| Itti et al. (2013) | 3.10 (2.33-4.13) | 44.8 | 0.06 |
| Gonzalez-Barca et al. (2013) | 3.03 (2.29-4.01) | 46.7 | 0.05 |
| Cashen et al. (2011) | 2.94 (2.23-3.90) | 48.4 | 0.04 |
| Pregno et al. (2012) | 3.02 (2.26-4.03) | 47.9 | 0.05 |
| Moskowitz et al. (2010) | 3.11 (2.34-4.13) | 42.5 | 0.07 |
| Cox et al. (2012) | 3.04 (2.30-4.01) | 45.1 | 0.06 |
| Yoo et al. (2011) | 3.15 (2.36-4.20) | 41.5 | 0.08 |

Inconsistencies between reviewers were either clarified by the authors or resolved by consensus.

*Statistical analysis*

To quantitatively compare the predictive value of interim $^{18}$F-FDG PET, pooled HRs comparing PFS between patients with positive and negative results were adopted as the primary indicators of meta-analysis to predict the outcome of patients after chemotherapy. For binary data, the risk ratio (RR) was used as an indication of treatment effect, and the Mantel-Haenszel method and DerSimonian-Laird method were used to pool RR for fixed effects and random effects model, respectively; Response was defined according to the International Working Group Criteria. The impact of heterogeneity on the pooled estimates of the individual outcomes of the meta-analysis was assessed by the $I^2$ test, the Cochran Q statistic (the heterogeneity could be accepted if $P > 0.05$ and $I^2 < 50\%$) and Galbraith plot for heterogeneity. The potential for publication bias was assessed using the Begg rank correlation method and the Egger weighted regression method. All the reported *P* values were two-sided. *P* values less than 0.05 were regarded as statistically significant. Statistical analyses were carried out using STATA 10.0 (STATA Corporation, College Station, TX, USA, 2009).

## Results

*Study selection and characteristics*

906 potentially related references were identified, of which 28 were considered potentially eligible and were retrieved for further assessment. After excluding 17 publications, 11 studies eligible for this review [12, 15, 16, 21-28] (**Figure 1**). The remaining 11 studies, which included 1081 adult patients, met all inclusion and exclusion criteria and were included in the systematic research and meta-analysis (**Table 1**). All patients included in these trials were diagnosed DLBCL by accurate histologic diagnosis. One study reported interim $^{18}$F-FDG PET results at completion of both second cycle and fourth cycle of chemotherapy, we only abstracted data on the second cycle in this study [12]. Five study evaluated interim $^{18}$F-FDG PET at varied timing ranging from the second to fourth cycle [15, 22, 23, 26, 28]. Four study categorized patients by the $^{18}$F-FDG PET -positive or negative based on visual analysis and SUV analysis respectively, we only abstracted data based on visual analysis in these studies [12, 21, 22, 24]. The induction regimens used included four standard regimen: R-CHOP14 (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone every 14 days), R-CHOP21 (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone every 21 days), R-ACVBP14 (rituximab plus doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone every 14 days) and R-MACOP-B (rituximab plus methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin every 21 days) (**Table 2**).

*Progression-free survival*

To evaluate the predictive value of interim $^{18}$F-FDG PET based on eleven studies with a total 1081 patients, the pooled HR comparing PFS between patients with positive and negative results was 2.96 (95% CI, 2.25-3.89), which implies that PFS in patients with a positive $^{18}$F-FDG PET result was significantly shorter than those with a negative result (**Figure 2A**). There low heterogeneity was found in the pooled HR synthesis of $^{18}$F-FDG PET data ($I^2$=42.7%, *P*=0.065). Galbraith plot was used to determine the heterogeneity source and found that Yang *et al*. were the sole outlier. This heterogeneity could be attributed to the result of the study by Yang *et al*. [23] (HR=5.46; 95% CI, 3.49-8.52). After omitting this study, heteroge-

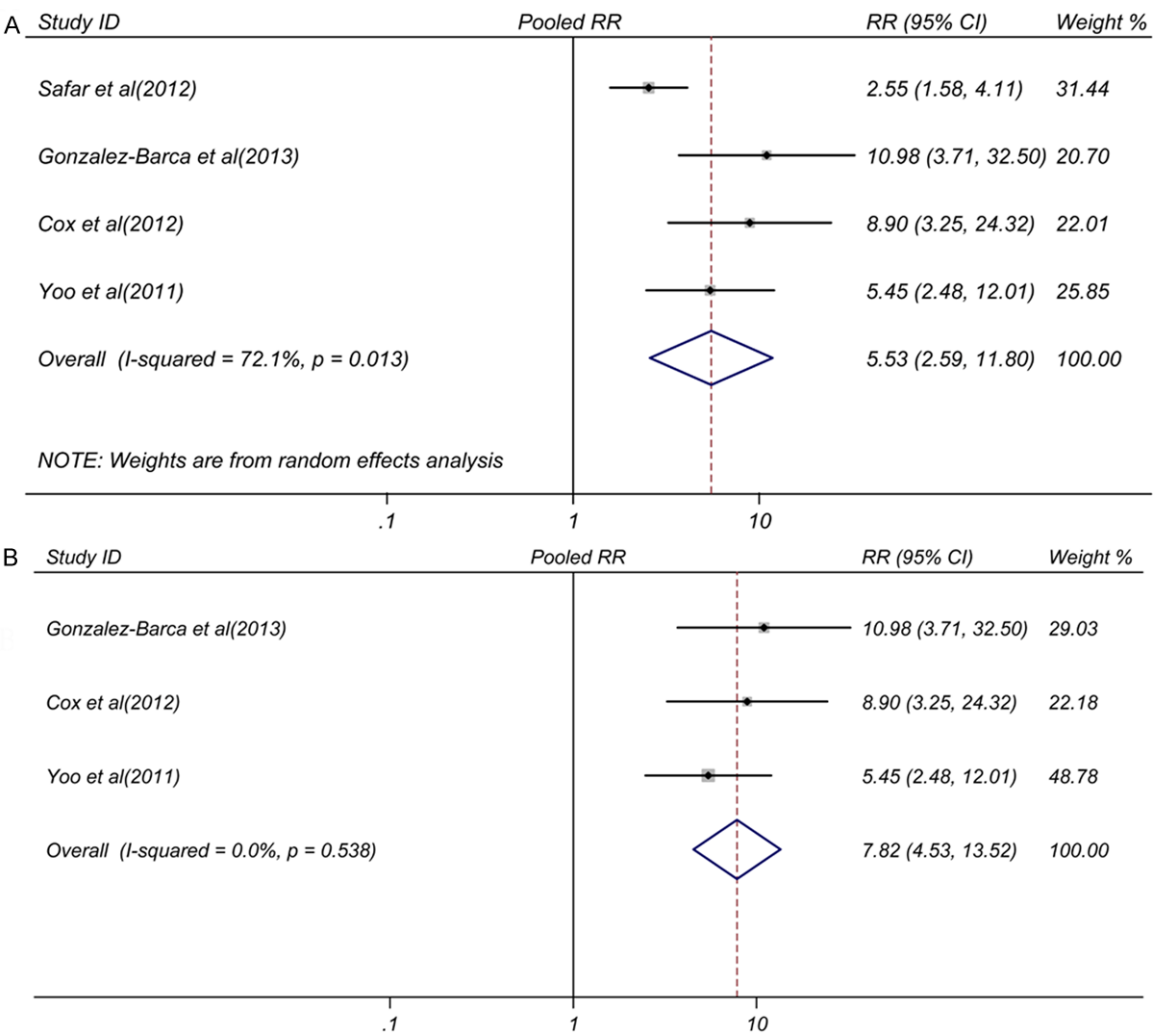


**Figure 3.** Meta-analysis of CR between two groups of DLBCL patients (interim $^{18}$F-FDG PET positive vs negative) receiving R-chemo. Forest plots showing the pooled Risk ratios (RR) of $^{18}$F-FDG PET -based response criteria. RR are presented with 95% confidence intervals (CIs) (A). After adjustment for heterogeneity, Forest plots showing the pooled Risk ratios (RR) of PET-based response criteria between two groups of DLBCL patients (interim $^{18}$F-FDG PET positive vs negative) receiving R-chemo (B). Squares on the risk ratio plot are proportional to the weight of each study, which is based on the Mantel-Haenszel (M-H) method. Risk ratios are presented with 95% confidence intervals (CIs).

neity greatly decreased from 42.7% to 0.00%, and the significant correlation was observed as well (HR=2.04, 95% CI=1.44-2.89) (**Figure 2B**). Sensitivity analysis revealed that recalculating pooled estimates of HR of PFS after excluding each study were robust and stable in the direction of the original study results (**Table 3**).

*Complete remission rates*

The data for 421 available patients were analyzed for CR. Among all patients, 62 of 155 patients in the interim $^{18}$F-FDG PET positive group responded to R-chemo treatment, compared with 235 of 266 patients in the interim $^{18}$F-FDG PET negative group. The patients in interim $^{18}$F-FDG PET negative group had a higher CR rates than that in interim $^{18}$F-FDG PET positive group (RR=5.53, 95% CI=2.59-11.80) (**Figure 3A**). There substantial heterogeneity was present in pooling rate of CR ($I^2$=72.1%; *P*=0.013). Galbraith plot was used to determine the heterogeneity source and found that Safar *et al.* were the sole outlier. This heterogeneity could be attributed to the result of the study by Safar *et al*. [21]. After omitting this study, heterogeneity greatly decreased from 72.1% to 0.00%, and the significant correlation was observed as well (RR=7.82, 95% CI=4.53-13.52) (**Figure 3B**). Sensitivity analysis revealed

**Table 4.** Sensitivity analysis for pooled CR rates of interim $^{18}$F-FDG PET

| Excluded study | RR (95% CI) | $I^2$% | *P*-value of Cochran Q test |
|---|---|---|---|
| Safar et al. (2012) | 7.82 (4.53-13.52) | 0.00 | 0.54 |
| Gonzalez-Barca et al. (2013) | 3.99 (2.74-5.80) | 68.9 | 0.04 |
| Cox et al. (2012) | 4.46 (3.01-6.59) | 75.5 | 0.02 |
| Yoo et al. (2011) | 4.74 (3.15-7.11) | 80.6 | 0.06 |

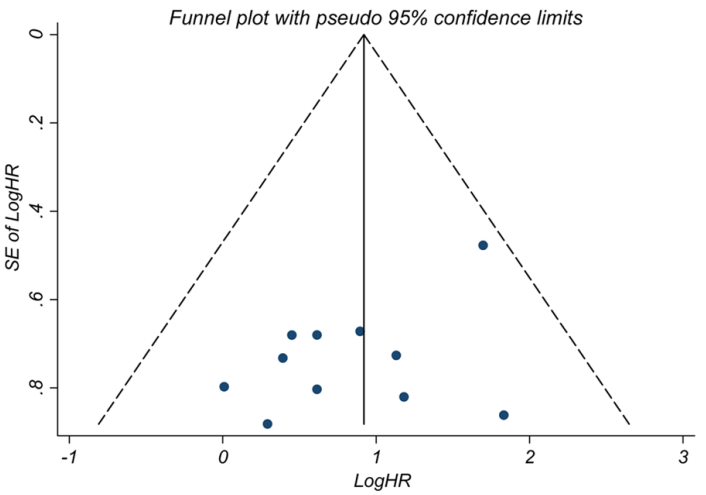


**Figure 4.** Funnel plot comparing log (HR) versus the standard error of log HR.Closed circles represent trials included in the meta-analysis. The line in the center indicates the summary log HR. The other lines represent the 95% confidence intervals (CIs).

that recalculating pooled estimates of RR of CR after excluding each study were robust and stable in the direction of the original study results (**Table 4**). This results imply that interim $^{18}$F-FDG PET was strongly predictive of outcome under rituximab plus chemotherapy.

*Publication bias*

The funnel plots showed minimal evidence of publication bias among eleven studies (**Figure 4**). However, the statistical tests also showed evidence of publication bias (Begg-Mazumdar: Kendall's tau=0.00, *P*=1.00; Egger: bias=-2.78, *P*=0.021). Galbraith plot was used to determine the heterogeneity source and found Yang *et al.* [23] was the sole outlier. After omitting that, significant correlation with no heterogeneity was observed as well (**Figure 2B**). Publication bias was also found in pooling rate of CR through begg's test (Begg-Mazumdar: Kendall's tau=1.70, *P*=0.09; Egger: bias=100.53, *P* < 0.01). From Galbraith plot, we saw Safar *et al.* [21] was the outlier. After omitting that, significant correlation with no heterogeneity was observed as well (**Figure 3B**).

## Discussion

The prognostic value of an interim $^{18}$F-FDG PET scan in primarily DLBCL, has been addressed in previous studies. All have found an association between a negative early $^{18}$F-FDG PET result and prolonged PFS and event-free survival [5-7, 9, 29, 30]. These studies were, however, mostly performed before the rituximab era and exhibit clinical heterogeneity. Recently, some studies have suggested that the use of rituximab could limit the predictive value of interim $^{18}$F-FDG PET for DLBCL [28, 31]. Therefore, there was a need to clarify the impact of interim $^{18}$F-FDG PET in patients with DLBCL treated with the current standard of care (e.g., immune-chemotherapy). Our study focused on a large cohort of patients with DLBCL treated with rituximab-based immune-chemotherapy and an interim $^{18}$F-FDG PET scan was performed after two to four cycles of treatment. We found that interim $^{18}$F-FDG PET was strongly predictive of outcome under rituximab plus chemotherapy. The patients in interim $^{18}$F-FDG PET negative group had a higher CR rates than that in interim $^{18}$F-FDG PET positive group. PFS in patients with a positive $^{18}$F-FDG PET result was significantly shorter than those with a negative result. These results confirm previous data and contradict the suggestion that the prognostic value of interim $^{18}$F-FDG PET may be lost if rituximab is used. Although study quality was limited in some studies, as demographic and clinical characteristics of included patients were reasonably comparable over the studies, our results should generally be applicable to DLBCL patients receiving standard full course R-CHOP or comparable regimens. However, our study still has important limitations. For instance, the meta-analysis included 1081 DLBCL patients from 11 studies who had stage I-IV disease and various prognosis (IPI scores ranged from 0 to 5). Median follow-up ranged from 19 to 46.8 month, and FDG-PET was performed after 2, 3 or 4 cycles of therapy, inconsistent timing of interim $^{18}$F-FDG PET/CT may

have limited the predictive value of $^{18}$F-FDG PET in this study. Also, studies were heterogeneous in how $^{18}$F-FDG PET result was interoperated, the visual interpretation including the International Harmonization Project (IHP) criteria, the 5-point scale (5PS) and the 3-point scale (3PS).

The interim $^{18}$F-FDG PET has emerged as a powerful predictive method of assessing DLBCL. However, a major drawback of the interim $^{18}$F-FDG PET analysis appeared to be the absence of uniform criteria and the false positive rate in the modern therapeutic era, especially post-rituximab treatment of DLBCL. As for the $^{18}$F-FDG PET evaluation criteria, a recent report from Horning *et al* sounds an additional note of caution for the use of interim $^{18}$F-FDG PET in clinical decision making [32]. A panel of three expert nuclear medicine physicians reviewed the $^{18}$F-FDG PET scans collected after 3 cycles of R-CHOP in the Eastern Cooperative Oncology Group E3404 study. Agreement among the 3 reviewers was only 68% and 71% when they interpreted the interim scans according to modified IHP criteria and the London Deauville criteria, respectively. Lin *et al.* found that an SUV-based assessment improved the PPV of interim $^{18}$F-FDG PET in DLBCL over that achieved with visual assessment [33]. However, it may prove difficult to reproduce any SUV-based criteria reliably when scan conditions are not controlled in a research setting. Given that reporting of interim $^{18}$F-FDG PET can vary significantly even in a controlled research setting, further standardization of interim $^{18}$F-FDG PET interpretation is clearly needed.

Although interim $^{18}$F-FDG PET is attractive as a tool for monitoring metabolic activity of tumors, frequent false-positive results might limit its usefulness. There are numerous potential explanations for the number of false-positive scans. FDG as a marker is not highly specific and shows uptake in infectious and inflammatory processes. It is possible that the use of immunotherapy may increase lesion inflammation; in addition, antibody-mediated cellular cytotoxicity and complement activation are important mechanisms in rituximab's activity. Han *et al*. [15, 31] and Pregno *et al*. [15] have found that fewer than half of patients with a positive interim $^{18}$F-FDG PET scan result will relapse after a standard course of immune-chemotherapy. Thus, intensification of therapy based on interim $^{18}$F-FDG PET would lead to overtreatment of a substantial portion of patients. On the other hand, because $^{18}$F-FDG PET imaging relies on metabolic changes that occur in the tumor, some patients who present with a highly proliferative disease and respond quickly to chemotherapy may present with a negative interim $^{18}$F-FDG PET but relapse shortly thereafter. This could explain why some patients with negative interim $^{18}$F-FDG PET scans relapse.

In conclusion, although the use of $^{18}$F-FDG PET to monitor patients with DLBCL is a promising technique, it still requires reproducible and universal interpretation criteria to permit reliable conclusions to be made for the routine use of this imaging procedure. In addition, interim $^{18}$F-FDG PET results alone should not be used to change patient management during therapy with rituximab-containing regimens outside of clinical trials. In the future, prospective trials should be performed to clearly determine the role of interim PET, and to evaluate risk-adapted therapy based on the results of interim $^{18}$F-FDG PET.

## Acknowledgements

This study was supported by national natural science foundation of China (No. 81301960, 81171653, 81302047, 81402518), natural science foundation of Jiangsu province (BK20-11246, BK2011247, BK20130243), the project of Six batch of major talent summit (BRA2010037), society development plans, department of science and technology Changzhou (CJ20112020, CJ20130010, CJ201400-39, CZ20110024, CS20102020, CE20125026) and the Innovative Talents Training Project of Changzhou Health Bureau.

## Disclosure of conflict of interest

None.

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