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Pretransplant C-reactive protein as a prognostic marker in allogeneic stem cell transplantation

A PRISMA-compliant meta-analysis

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Abstract

Background: Numerous reports have explored the prognostic value of pretransplant serum C-reactive protein (CRP) in patients receiving allogeneic stem cell transplant (ASCT), but the results remain conflicting. Therefore, we performed a meta-analysis to comprehensively assess the prognostic value of pretransplant serum CRP in patients receiving ASCT.

Methods: We systematically searched eligible studies in PubMed, Embase, and Web of Science from 1999 to September 2018. The pooled hazard ratios (HRs) and their corresponding 95% CIs were used to synthetically assess the prognostic value of pre-ASCT CRP in terms of overall survival (OS), non-relapse mortality (NRM), and acute graft versus host disease (aGVHD).

Results: A total of 14 articles with 15 studies containing 3458 patients were included in this meta-analysis. The pooled results showed that high pre-ASCT CRP level was significantly related to worse OS (HR = 1.63; 95% CI: 1.34–1.98; $P < .05$), to an increased risk of NRM (HR = 2.06; 95% CI: 1.62–2.62; $P < .05$), and aGVHD (HR = 1.35; 95% CI: 1.07–1.71; $P < .05$). Additionally, sensitivity and subgroup analyses demonstrated that our pooled results were stable and reliable.

Conclusions: High pre-ASCT serum CRP was significantly associated with worse OS, as well as higher risk of NRM and aGVHD. CRP may be a candidate factor of updating the existing risk scoring systems or establishing a novel risk scoring systems, which has the potential of guiding patient selection for ASCT and proceeding with risk-adapted therapeutic strategies. However, more high-quality clinical studies and basic research are required to further validate our findings in view of several limitations in our meta-analysis.

Abbreviations: aGVHD = acute graft versus host disease, ASCT = allogeneic stem cell transplantation, BM = bone marrow, CB = cord blood cell, CRP = C-reactive protein, K = Kaplan–Meier curve analysis, M = multivariate analysis, MC = myeloablative conditioning, MHD = malignant hematological disease, Mixed = the study enrolled a mixed population of MC and RIC, NA = not available, NMHD = nonmalignant hematological disease, NOS = Newcastle–Ottawa quality scale, NRM = no-relapse mortality, OS = overall survival, PBSC = peripheral blood stem cell, RIC = reduced intensity regimen, U = univariate analysis.

Keywords: allogeneic stem cell transplant, C-reactive protein, meta-analysis

1. Introduction

Allogeneic stem cell transplantation (ASCT) is an established treatment for a variety of malignant and nonmalignant hematological diseases, but its curative effect may be discounted by many risks that are related to transplant-related morbidity and mortality.[1,2] Accurately assessing prognostic risk in advance plays a key role in guiding patient selection for ASCT and proceeding with risk-adapted therapeutic strategies, which is an important guarantee for favorable outcomes. Several prognosis scoring tools have been developed to predict outcomes following ASCT, including but not limited to the European blood and marrow transplantation (EBMT) score,[3] detailed inventories of patient health through geriatric assessment,[4,5] the hematopoietic cell transplantation specific comorbidity index (HCT-CI),[6] and the pretransplantation assessment of mortality (PAM) score.[7] Nevertheless, these tools are complex and mostly suitable for older and (or) less fit patients. Additionally, regardless of substantial advances in ASCT, such as reduced-intensity conditioning, HLA matching, and complex supportive care, the morbidity, and mortality of ASCT remain unsatisfactorily high.[4] Therefore, it would be of importance to identify simple, objective, and easily accessible markers with additional prognostic information to update the existing prognosis scoring tools or establish new models to more precisely estimate outcomes after ASCT.

Interleukin-6 (IL-6) is a cytokine with pro-inflammatory effects. It has been considered that IL-6 could enhance Th 17 differentiation, but suppress regulatory T cells in the context of ASCT, subsequently promoting the development of graft versus

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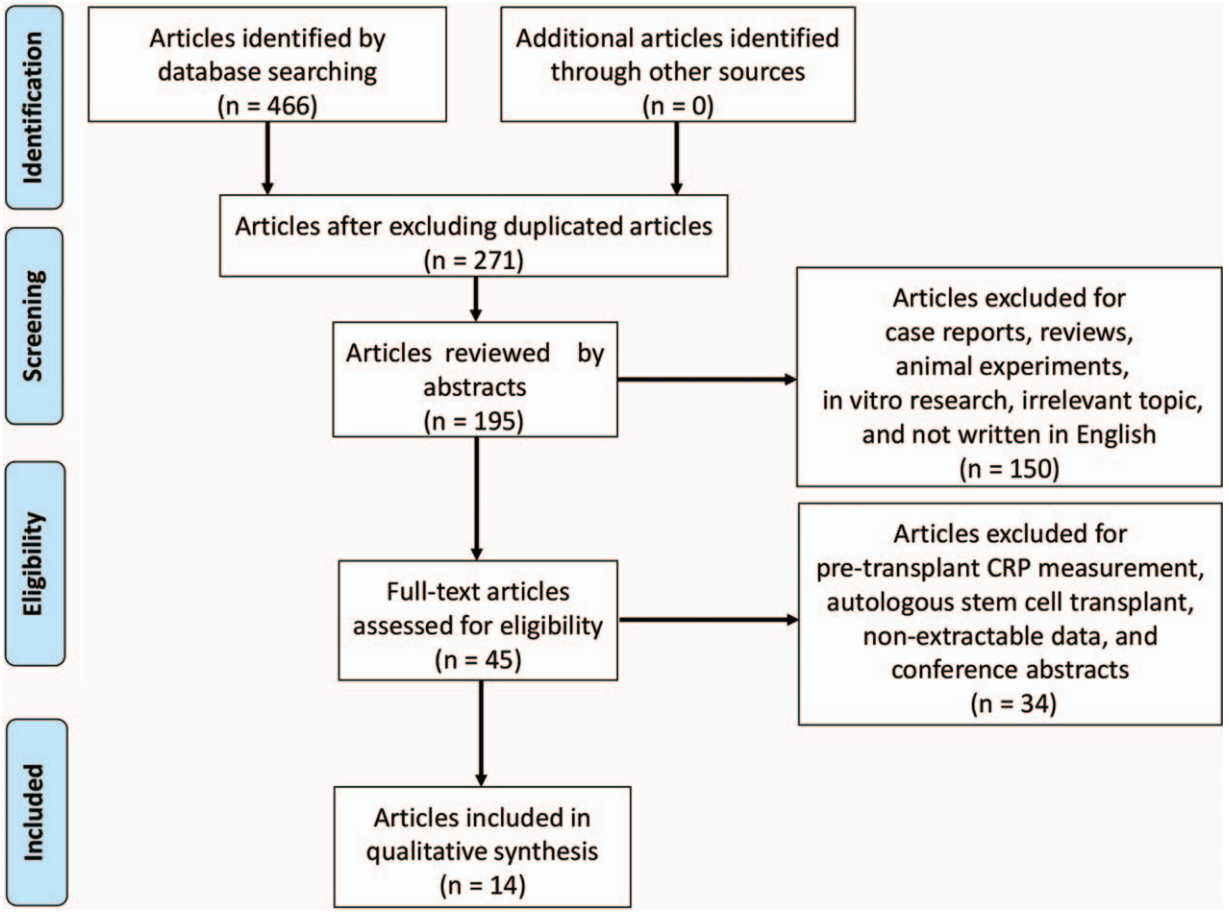

Figure 1. Flow diagram of literature identification process.

host disease (GVHD) and thus increasing the risk of non-relapse mortality (NRM).[8] Additionally, serum IL-6 is able to activate vascular endothelial gp130 and then redistribute VE-cadherin, which disrupts the adherence junctions between endothelial cells and causes capillary leakage, with subsequent fluid retention after ASCT.[9,10] Particularly, fluid retention is considered as a risk of GVHD and NRM, which may also partly account for the role of IL-6 in promoting GVHD and NRM. More importantly, there is evidence suggesting that targeting IL-6-initiated signaling is a promising strategy to prevent and treat GVHD.[11–13] NRM is an important reason for poor OS in patients with ASCT. Besides, in patients who received ASCT for hematological malignancies disease relapse and progression is another key factor affecting long-term survival. It is reported that malignant hematological cells is capable of constitutively releasing IL-6, and in turn IL-6 can promote the proliferation and survival of malignant hematological cells, subsequently which impacts the long-term survival in patients who received ASCT for hematological malignancies disease.[14–17]

C-reactive protein (CRP) is an acute-phase protein produced by hepatocytes in response to IL-6.[18] Thus, CRP can be applied as a surrogate marker of serum IL-6. In turn, CRP can also induce IL-6 expression to promote inflammatory process. In accordance with the close association between CRP and IL-6, several recent studies suggested that high level of serum pre-ASCT CRP was associated with a higher incidence of acute graft versus host disease (aGVHD),[19–22] an increased risk of NRM[1,20,21,23] and worse overall survival (OS).[20,23–26] Nevertheless, some other studies reported that there was no association of pre-ASCT CRP level with OS,[1,18,27] NRM,[9,18,28,29] and aGVHD.[9,23,29] In fact, the small sample size largely limited the statistical power and reliability of results from most previous studies that explored the association between pretransplant serum CRP and outcomes in patients with ASCT. Therefore, the relationship between pretransplant serum CRP and outcomes in patients with ASCT remain inconclusive. Herein we performed a systematic review and meta-analysis to comprehensively investigate the association of pretransplant serum CRP in patients receiving ASCT with OS, NRM and aGVHD.

2. Materials and methods

This meta-analysis was undertaken according to preferred reporting items for systematic reviews and meta-analyses statement.[30] Furthermore, this study was approved by Ethics Committee of Southeast Hospital Affiliated to Xiamen University.

2.1. Literature search

We systematically searched eligible studies in PubMed, Embase, and Web of Science from 1999 to September 2018, and we only searched for studies published in English and studies on human. The search terms included "C-reactive protein (CRP)" and "stem cell transplantation or stem cell transplant". Two reviewers performed the literature research independently.

Table 1

The main characteristics of the included studies.

Author, year	Country	Number of patients	Median age, y	Indications of ASCT	Stem cell source	Conditioning regimen	CRP cut-off, mg/L	Median follow-up time, mo
Akı, 2012	Turkey	106	29	MHD	PBSC (94.3%) BM (5.7%)	MC	10	9
Artz, 2016	USA	784	50	MHD	PBSCs (83%) BM (17%)	MC, RIC	10	38
Artz, 2008	USA	112	52	MHD	PBSC (94%) BM (6%)	RIC	18.5	NA
Fuji, 2008	Japan	224	47	MHD	PBSC (43.7%) BM (48%) CB (8.3%)	MC, RIC	15	31.3
Jordan, 2014	Denmark	349	26.7	MHD (82%) NMHD (18%)	PBSC (35%) BM (65%) CB (1%)	MC, RIC	10	NA
Kanda, 2011	Japan	112	47	MHD	PBSC (35.7%) BM (46.4%) CB (17.9%)	MC, RIC	3	23
Kataoka,2009	Japan	264	40	MHD	PBSC (32%) BM (64%) CB (4%)	MC, RIC	3	48.9
Patel, 2018	UK	253	37	MHD	PBSC (38%) BM (62%)	MC	9	60.6
Pavlu, 2010	Spain	271	34	MHD	PBSC (5.5%) BM (94.5%)	MC	9	NA
Remberge1, 2010	Sweden	205	49	MHD (81%) NMHD (19%)	PBSC (72.6%) BM (21%) CB (6.4%)	RIC	10	NA
Remberge2, 2010	Sweden	299	23	MHD (86%) NMHD (14%)	PBSC (54.5%) BM (37%) CB (8.5%)	MC	10	NA
Sakamoto, 2013	Japan	211	48	MHD (96%) NMHD (4%)	BM (NA) CB (NA)	MC, RIC	2	41.2
Sato, 2013	Japan	90	45	MHD (NA) NMHD (NA)	PBSC (33%) BM (64%) CB (3%)	MC, RIC	6	NA
Tevde, 2016	Norway	100	47.5	MHD (92%) NMHD (8%)	PBSC (95%) BM (5%)	MC, RIC	5	NA
Yamamoto, 2016	Japan	78	58.5	MHD (82.1%) NMHD (17.9%)	PBSC (3.8%) BM (60%) CB (36.2%)	RIC	3	36

ASCT = allogeneic stem cell transplantation, BM = bone marrow, CB = cord blood cell, MC = myeloablative conditioning, MHD = malignant hematological disease, Mixed = the study enrolled a mixed population of MC and RIC, NA = not available, NMHD = nonmalignant hematological disease, NOS = Newcastle–Ottawa quality scale, PBSC = peripheral blood stem cell, RIC = reduced intensity regimen.

2.2. Inclusion criteria

Eligible studies should conform to all the criteria as followed: studies on patients receiving ASCT were included, but those focusing on autologous transplant should be excluded; CRP level should be measured before conditioning; studies reported OS or NRM or aGVHD. Moreover, hazard ratio (HR) and its 95% confidence intervals (95% CIs), which estimated the association between these outcomes and CRP levels, was directly presented or could be indirectly calculated from Kaplan–Meier survival curves.

2.3. Exclusion criteria

Articles should be excluded if they matched any of the following items: case reports, meeting abstracts, editorials, or reviews; autologous stem cell transplant; CRP measurement was performed after conditioning or ASCT; animal or in vitro experiments; HR and its 95% CIs that estimated the association between CRP levels and OS or NRM or aGVHD was not available.

2.4. Data extraction and quality assessment

The following data were extracted: the first author's name, publication year, study country, the number of patients, ASCT (malignant and nonmalignant), median age, conditioning intensity, cut-off for high CRP level, follow-up time, and ending points, including OS, NRM, and aGVHD. OS and NRM were taken as primary ending points. If HR and its 95% CIs that estimated the association between CRP levels and OS or NRM or aGVHD was not directly provided, we used the Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/, freely downloaded software) to calculate it from Kaplan–Meier curves. Multivariate analyses were firstly used if multivariate and univariate survival data were all provided.

2.5. Statistical analysis

The statistical analyses of this meta-analysis fulfilled performed using Stata version 12.0 (Stata Corporation, College Station, TX). The pooled HRs and their corresponding 95% CIs were

Table 2

The association between pretransplant CRP level and outcomes in patients receiving ASCT.

Study	OS (HR, 95% CI)	NRM (HR,95% CI)	aGVHD (HR,95% CI)
Akı, 2012	1.61 (0.96–2.78)[M]	1.49 (0.68–3.23)[M]	NA
Artz, 2016	1.22 (0.98–1.53)[M]	1.52 (1.11–2.07)[M]	NA
Artz, 2008	1.7 (0.93–3.1)[M]	2.5 (1.0–6.3)[M]	4.1 (1.61–10.41)[M]
Fuji, 2008	2.0 (1.3–3.1)[M]	4.0 (2.0–8.0)[M]	1.7 (1.1–2.6)[M]
Jordan, 2014	1.35 (1.18–1.54)[M]	1.50 (1.24–1.82)[M]	1.12 (0.95–1.30)[M]
Kanda, 2011	2.65 (0.98–6.00)[K]	5.76 (1.70–19.48)[M]	NA
Kataoka,2009	1.45 (0.94–2.23)[M]	1.88 (0.90–3.90)[M]	NA
Patel, 2018	1.95 (1.4–2.7)[M]	2.47 (1.4–4.4)[M]	NA
Pavlu, 2010	2.33 (1.4–4.0)[M]	4.22 (1.6–11.2)[M]	NA
Remberge1, 2010	1.62 (1.01–2.59)[M]	1.86 (1.02–3.39)[M]	NA
Remberge2, 2010	0.96 (0.91–1.13)[K]	NA	NA
Sakamoto, 2013	NA	1.67 (0.73–3.82)[M]	1.13 (0.70–1.81)[M]
Sato, 2013	3.27 (1.22–8.75)[M]	6.21 (2.17–17.71)[M]	3.91 (1.17–13.10)[M]
Tevde, 2016	2.08 (0.88–4.95)[M]	1.04 (0.57–1.89)[M]	1.0 (0.98–1.01)[U]
Yamamoto, 2016	3.3 (1.4–7.9)[M]	3.2 (0.8–13.1)[M]	2.5 (1.0–6.0)[M]

aGVHD = acute graft versus host disease, ASCT = allogeneic stem cell transplantation, K = Kaplan–Meier curve analysis, M = multivariate analysis, NA = not available, NRM = no-relapse mortality, OS = overall survival, U = univariate analysis.

used to synthetically assess the association between pre-ASCT CRP and OS or NRM or aGVHD. The heterogeneity within the included studies was evaluated by I^2 statistic test and chi-square based Q-test. $P < .05$ and $I^2 > 50\%$ suggested significant heterogeneity existed, while $I^2 < 50\%$ suggested that there was no statistically significant heterogeneity. The random effects model was used to pool HRs when significant heterogeneity existed, while the fixed effects model was used. HR > 1 and $P < .05$ (low CRP level as reference) indicated that high CRP level was associated with a higher risk of NRM or aGVHD, and poorer OS. Subgroup analysis and meta-regression were performed to explore the sources of heterogeneity for OS and NRM according to median age (≤45 years and >45 years), cut-off of high CRP level (3, 9, and 10 mg/L), survival analysis type

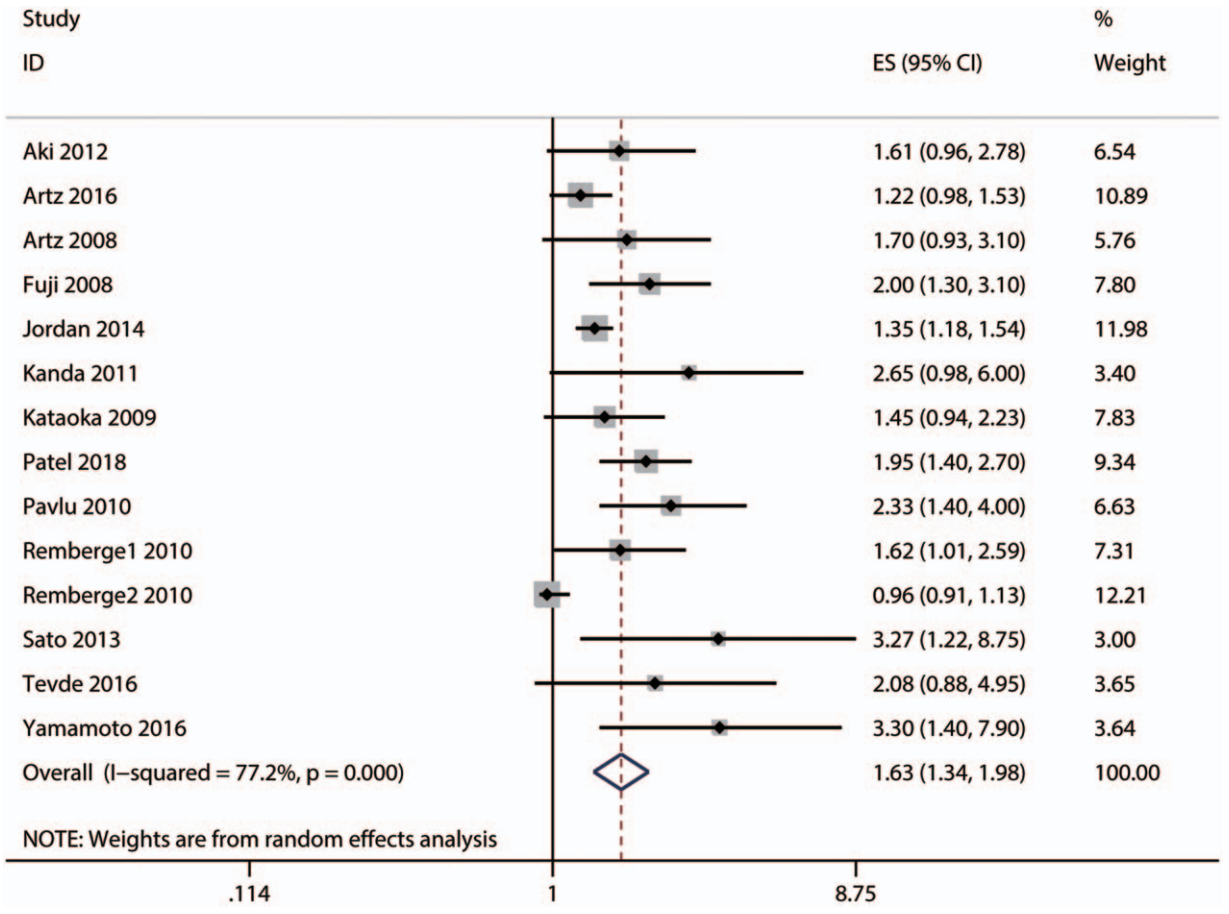

Figure 2. Forest plot of pooled HR for the association between high pre-allogeneic stem cell transplantation (ASCT) and worse overall survival (OS). HR = hazard ratio.

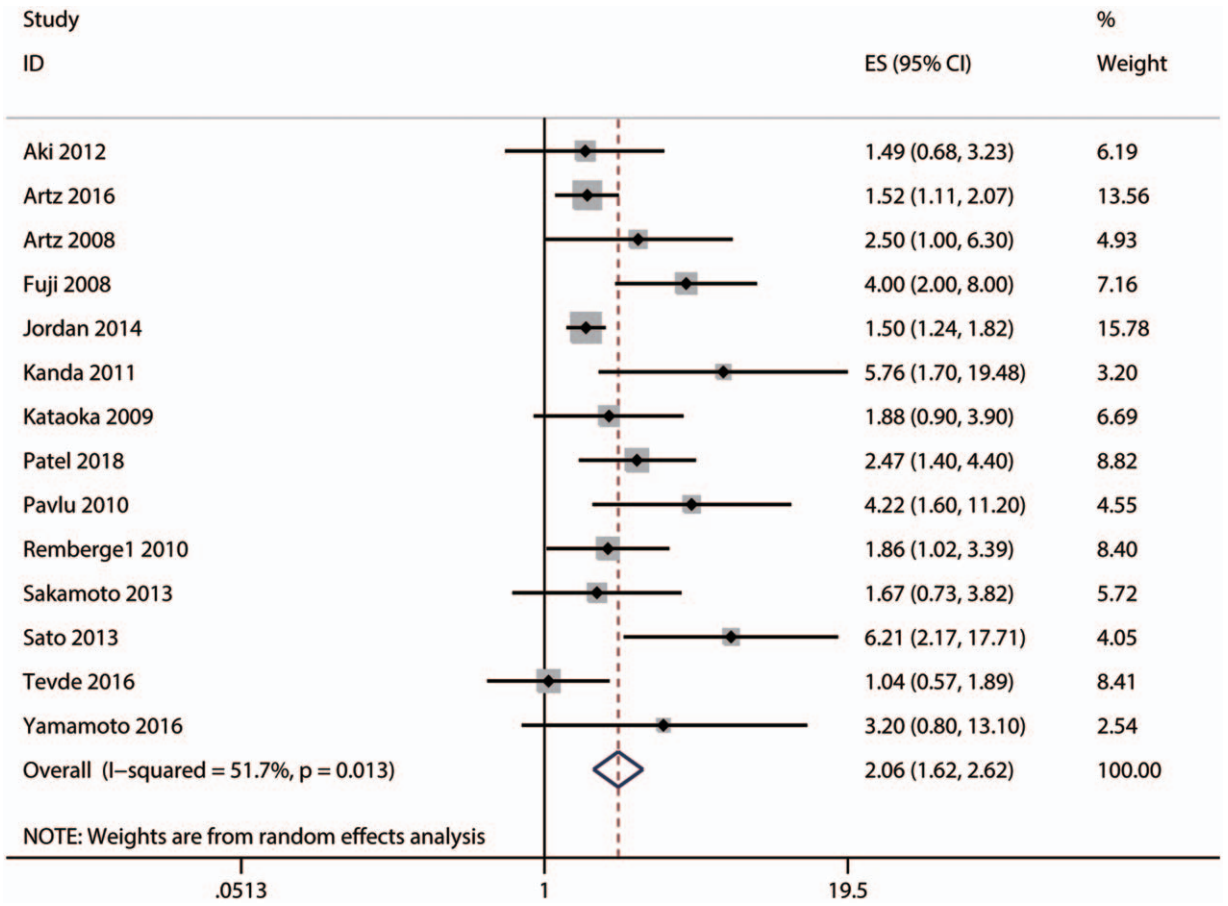

Figure 3. Forest plot of pooled HR for the association between high pre-ASCT and higher risk of non-relapse mortality (NRM). ASCT = allogeneic stem cell transplantation, HR = hazard ratio.

(multivariate analysis and Kaplan–Meier curve), and conditioning regimen (myeloablative conditioning [MC], reduced intensity conditioning [RIC], and mixed). "Mixed" means that the study included not only patients receiving MC, but also RIC. Additionally, sensitivity analysis was also conducted to further explore the sources of heterogeneity, and at the same time test the robustness of our pooled results for OS and NRM by omitting single study in each step. The Begg and Egger tests were used for publication bias evaluation.[31,32] The asymmetrical shape of Begg funnel plot or *P* value of the 2 tests (<.05) indicated that there was significant publication bias. When there was significant publication bias, we used trim-and-fill analysis to explore whether publication bias substantially affected the reliability and stability of our pooled results for OS and NRM.[33] A *P*-value <.05 was considered as statistical significance.

3. Results

3.1. Study search and study characteristics

The detailed process of study selection is described in Fig. 1. A total of 469 articles were identified from PubMed, Embase, and Web of science following the initial literature search. Firstly, we excluded 271 duplicated articles by screening titles. Then by reviewing abstracts, we further excluded 150 articles due to case reports, reviews, animal experiments, in vitro research, irrelevant topic, and not written in English. Next, we evaluated the rest of articles by full-text. In this step, we further excluded 34 articles owing to pretransplant CRP measurement, autologous stem cell transplant, non-extractable data, and conference abstracts. Finally, a total of 14 articles with 15 studies[1,9,18–25,27–29,34] containing 3458 patients were included in this meta-analysis.

The main characteristics of the included studies are exhibited in Table 1. The included studies were published from 2008 to 2017. The numbers of patients in this included studies ranged from 78 to 784. Four studies enrolled patients receiving MC, 3 studies patients receiving RIC and 8 studies enrolled not only patients receiving MC, but also patients receiving RIC. One study used 2 mg/L as the cut-off of high CRP level, 3 studies used 3 mg/L, 1 study used 5 mg/L, 1 study used 6 mg/L, 2 studies used 9 mg/L, 5 studies used 10 mg/L, 1 study used 15 mg/L, and 1 study used 18.5 mg/L. Fourteen studies analyzed the relationship between CRP level and OS, 12 of which provided HRs from multivariate analysis, and 2 only provided Kaplan–Meier curves (Table 2). Fourteen studies analyzed the relationship between CRP level and NRM, all of which provided HRs from multivariate analysis (Table 2). Seven studies reported about the relationship between CRP level and aGVHD, 6 of which were conducted by multivariate analysis and 1 by univariate analysis (Table 2).

3.2. Data synthesis

A total of 14 studies analyzed the relationship between pre-ASCT CRP level and OS.[1,9,18–25,27,28,34] Considering the significant

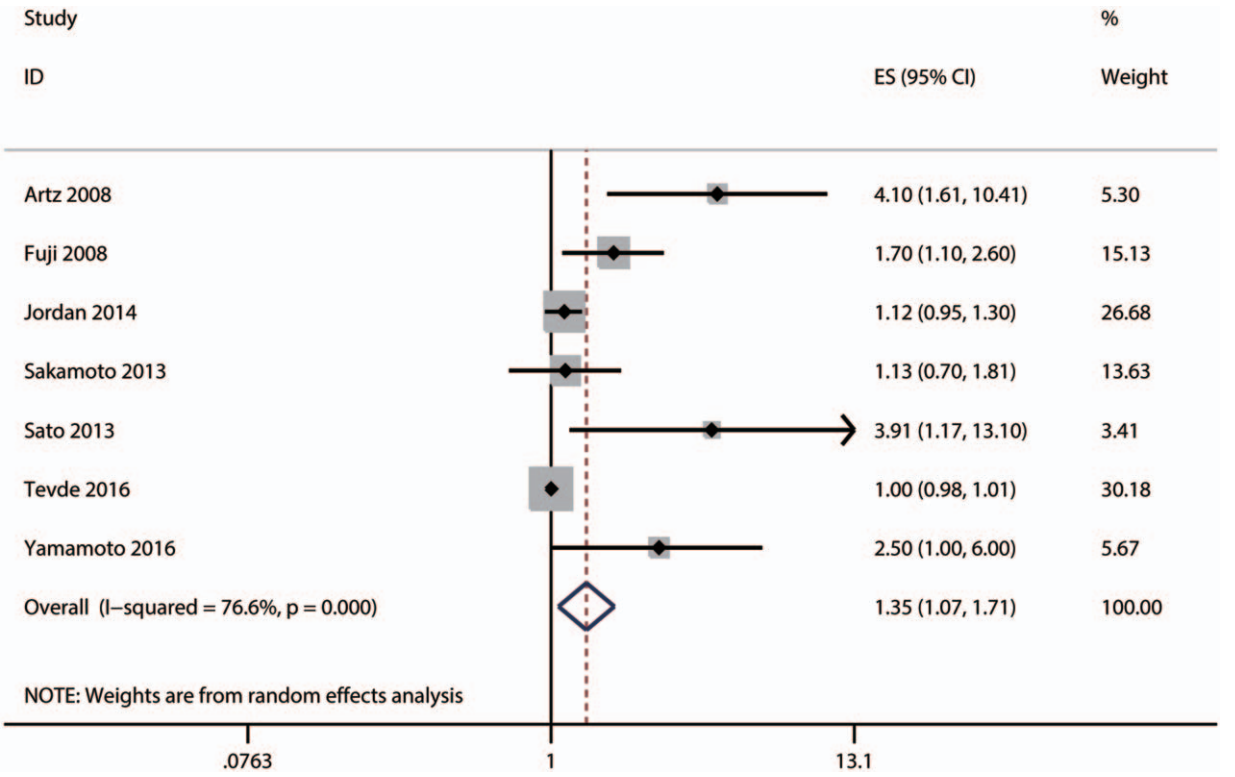

Figure 4. Forest plot of pooled HR for the association between high pre-ASCT and higher risk of acute graft versus host disease (aGVHD). ASCT = allogeneic stem cell transplantation, HR = hazard ratio.

heterogeneity ($I^2 = 77.2\%$, $P < .0001$), we calculated the pooled HR using the random-effects model. The result showed that high pre-ASCT CRP level was significantly related to worse OS (HR = 1.63; 95% CI: 1.34–1.98; $P < .05$) (Fig. 2). Fourteen studies explored the relationship between pre-ASCT CRP level and NRM.[1,9,18–25,28,29,34] The pooled HR and 95% CI were also calculated using a random-effects model due to the presence of significant heterogeneity ($I^2 = 51.7\%$, $P = .013$). The results indicated that patients with high pre-ASCT CRP level experienced an increased risk of NRM (HR = 2.06; 95% CI: 1.62–2.62; $P < .05$) (Fig. 3). Additionally, 7 studies reported about the relationship between pre-ASCT CRP level and aGVHD.[9,19–23,29] Because of the significant heterogeneity ($I^2 = 76.6\%$, $P < .0001$), the random-effects model was used to perform the pooling analysis. The result showed that there was also a positive relationship between pre-ASCT CRP level and aGVHD (HR = 1.35; 95% CI: 1.07–1.71; $P < .05$) (Fig. 4).

3.3. Meta-regression and subgroup analysis

To investigate the sources of heterogeneity for OS, we performed the meta-regression according to median age (≤45 years and >45 years), cut-off of high CRP level (3, 9, and 10 mg/L), survival analysis type (multivariate analysis and Kaplan–Meier curve), and conditioning regimen (myeloablative conditioning [MC], reduced intensity conditioning [RIC], and mixed). From meta-regression analysis, we observed that different cut-offs ($t = 3.47$, $P = .008$) and survival analysis types ($t = 3.55$, $P = .004$) could explain the major heterogeneity of the pooled analysis for OS, while median age ($t = .28$, $P = .379$), and conditioning regimen ($t = 1.99$, $P = .069$) could only explain minor heterogeneity of the pooled analysis for OS (Table 3). Subsequently, we performed subgroup analysis by cut-off of high CRP level and to survival analysis types further confirm whether the 2 factors were the source of the major heterogeneity of the pooled analysis for OS. The result showed that in the subgroups of 3 and 9 mg/L significant heterogeneity disappeared, but significant heterogeneity was still observed in the subgroup of 10 mg/L (Fig. 5), basically further confirming the substantial contribution of different cut-offs to the heterogeneity. Moreover, a close association between high CRP level and worse OS was still observed in each subgroup of different cut-offs, suggesting the robustness of our pooled result. Similarly, we also found that the significant heterogeneity completely disappeared and in any subgroup of survival analysis type (Fig. 6), confirming the result of our meta-regression. More importantly, in the subgroup of multivariate analysis we still found there was a significant association between high pre-ASCT CRP level and worse OS (1.64, 95% CI = 1.41–1.92, $P < .001$)

Table 3

Meta-regression analysis of study heterogeneity.

Factors for OS	*P*-value
Median age (≤45 y and >45 y)	.379
Cut-off of high CRP level (3, 9, and 10 mg/L)	.008
Survival analysis type (multivariate analysis and Kaplan–Meier curve)	.004
Conditioning regimen (MC, RIC and mixed)	.069
Factors for NRM	
Median age (≤45 y and >45 y)	.081
Cut-off of high CRP level (3, 9, and 10 mg/L)	.006
Conditioning regimen (MC, RIC, and mixed)	.044

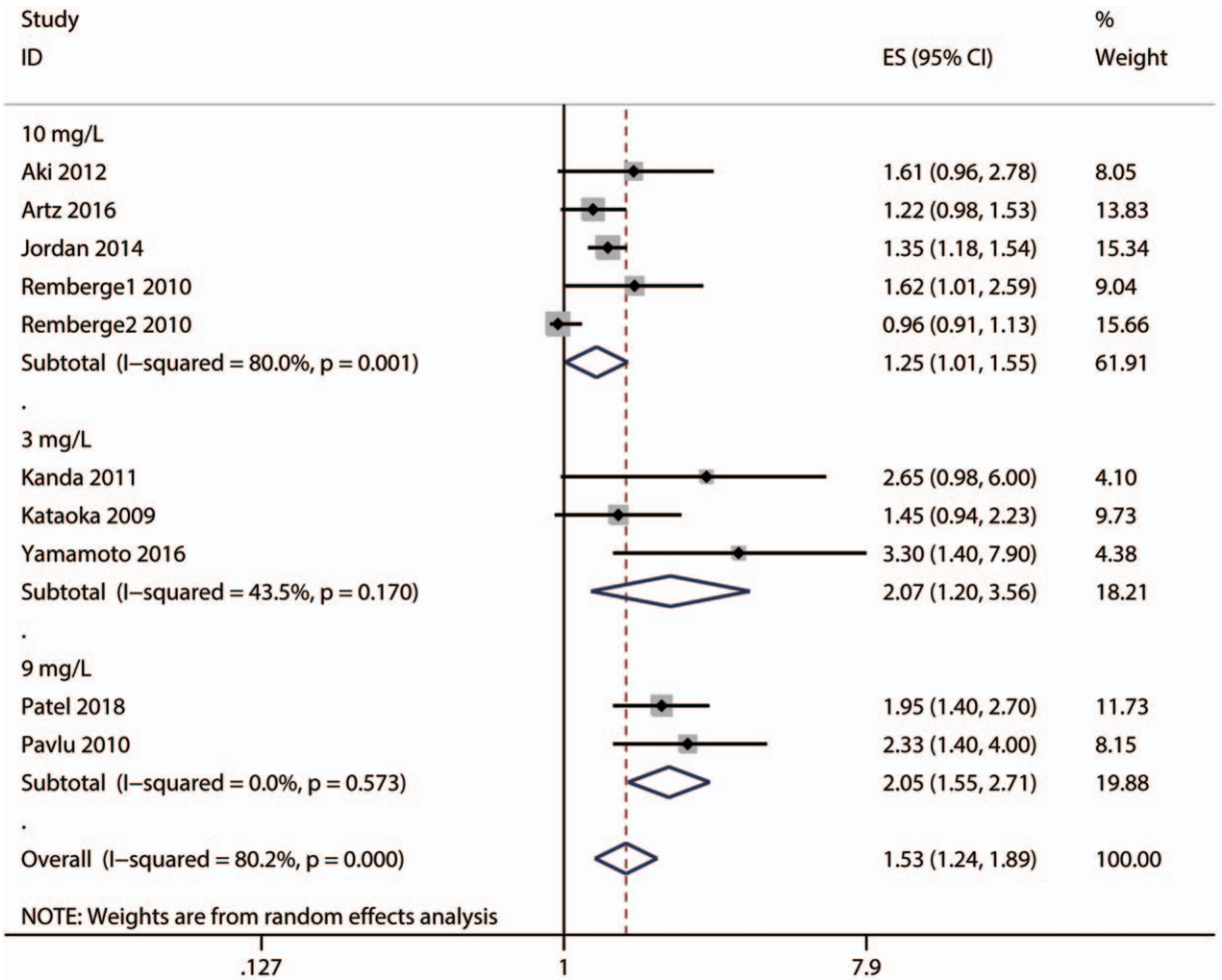

Figure 5. Subgroup analysis for OS according to different cut-offs of high CRP level. CRP = C-reactive protein, OS = overall survival.

(Fig. 6), suggesting that pre-ASCT CRP was an independent predictive factor for OS in patients receiving ASCT.

With respect to NRM, the meta-regression analysis was conducted according to median age (≤45 years and >45 years), cut-off of high CRP level (3, 9, and 10 mg/L), and conditioning regimen (myeloablative conditioning [MC], reduced intensity conditioning [RIC], and mixed). The results indicated that cut-off of high CRP level ($t = 3.87$, $P = .006$) and conditioning regimen ($t = 2.25$, $P = .044$) were the main sources of the heterogeneity of the pooled analysis, while median age ($t = .781$, $P = .081$) could only explain minor heterogeneity (Table 3). Subgroup analyses by cut-offs and conditioning regimen were also performed to further confirm whether cut-offs and conditioning regimen were the main sources of heterogeneity of the pooled analysis for NRM. As results showed, the significant heterogeneity disappeared and the positive relationship between high CRP level and increased NRM continued to exist in all subgroups of different cut-offs (Fig. 7). Similar to cut-off, no significant was observed any more in any subgroup of conditioning regimen, except in the subgroup of the mixed (Fig. 8). Moreover, high CRP level was still positively related to an increased NRM in any subgroup of different conditioning regimens (Fig. 8). In general, our subgroup analysis confirmed the results of the meta-regression that cut-off and conditioning regimen may account for the major heterogeneity of the pooled analysis for NRM.

3.4. Sensitivity analysis

Sensitivity analysis was conducted to further explore the robustness of our pooled results for OS and NRM. The results showed that the pooled HRs for OS (Fig. 9A) and NRM (Fig. 9B) did not fluctuate remarkably when sequentially omitting single trial in each step, suggesting that our pooled results were robust and credible.

3.5. Publication bias

The Begg funnel plot and Egger tests were used to explore whether publication bias existed for the pooled analyses of OS and NRM. From the results, it was observed that the Begg funnel plots for the pooled analyses of OS (Fig. 10A) and NRM (Fig. 10B) were asymmetric, suggesting that there may be significant publication bias for the pooled analyses of OS and NRM. Therefore, we tried to further investigate whether the stability and credibility of our pooled results for OS and NRM were substantially affected by publication bias using trim-and-fill analysis. Results of trim-and-fill analysis showed that the adjusted funnel plots of the pooled analyses of OS (Fig. 10C) and NRM (Fig. 10D) became symmetric, and the adjusted pooled HRs for OS and NRM still indicated that high pre-ASCT high CRP level was related to poor OS (1.44, 95% CI = 1.21–1.72, $P < .001$) and increased NRM (1.59, 95% CI = 1.23–2.06,

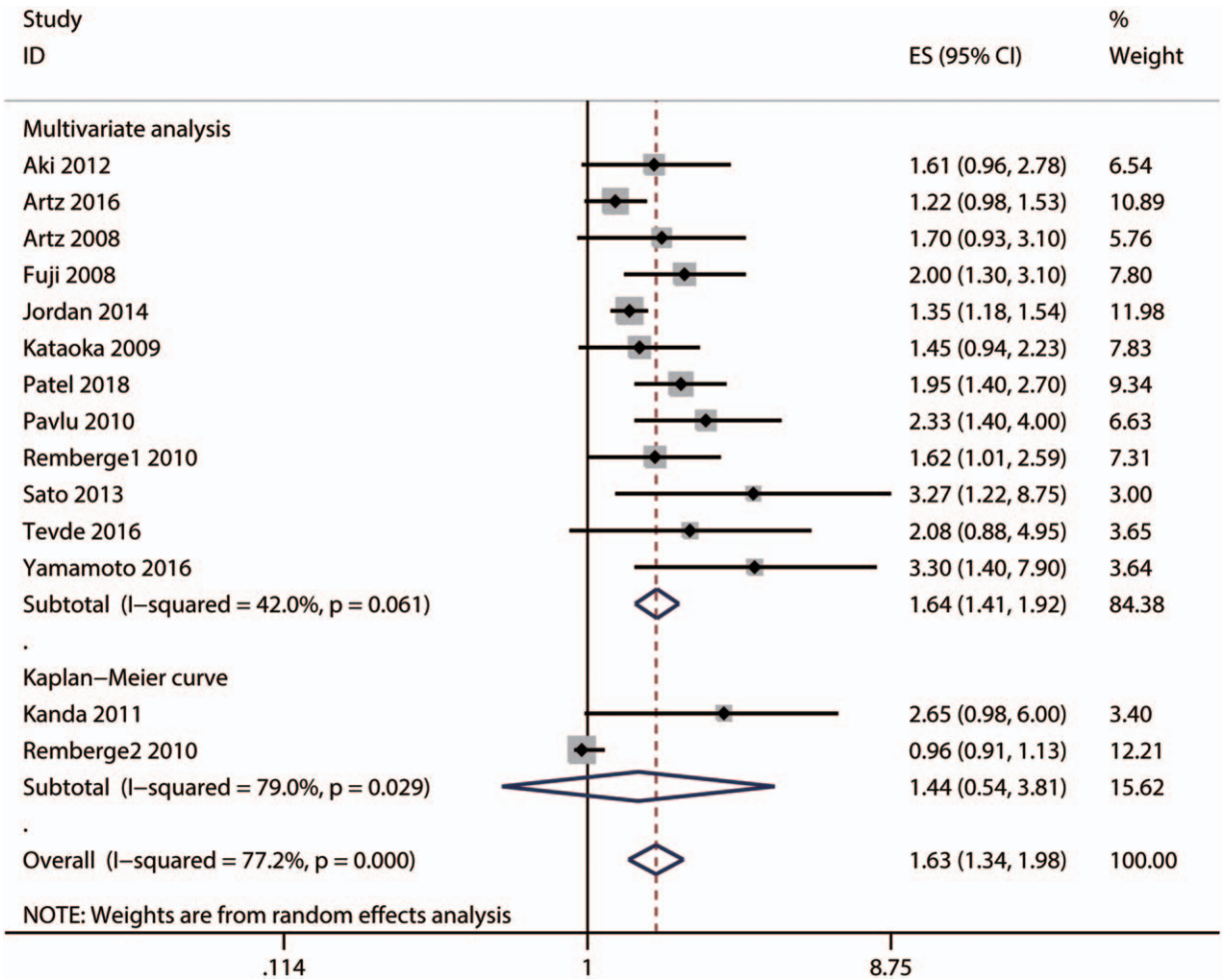

Figure 6. Subgroup analysis for OS according to different survival analysis types. OS = overall survival.

$P < .001$). Overall, trim-and-fill analysis demonstrated that the stability and credibility of our pooled HRs for OS and NRM were not substantially affected by publication bias.

4. Discussion

As far as we know, this study is the first meta-analysis to comprehensively assess the association between pretransplant CRP level and outcomes of patients with ASCT. In this study, our pooled results suggested pretransplant CRP level may be an independent predictive factor for OS, NRM, and aGVHD of patients with ASCT. Nevertheless, there was a significant heterogeneity in our pooled analysis, which might affect the reliability of the pooled results. Thus, we performed the meta-regression analysis to explore the source of heterogeneity. The results suggested that the significant heterogeneity might be caused by different cut-offs of high CRP level for OS, and by different cut-offs and conditioning regimens for NRM. Furthermore, we performed the subgroup analysis for OS by cut-offs, and subgroup analyses for NRM by cut-offs and conditioning regimen to explore whether these factors affected the reliability of the pooled results. The results of subgroup analyses further confirmed the independent predictive effect of pretransplant CRP level for OS and NRM in patients receiving ASCT.

Although mechanisms underlying the association between pretransplant CRP level and outcomes remain rather unclear, there are some clues that perhaps could explain our findings in this meta-analysis. As an essential pro-inflammation cytokine, IL-6 has been considered to be capable of enhancing Th 17 differentiation, but suppressing regulatory T cells in the context of ASCT, which subsequently promotes the development of graft versus host disease (GVHD), thereby increasing the risk of NRM.[8] Besides, serum IL-6 is able to activate vascular endothelial gp130 and then redistribute VE-cadherin, which disrupts the adherence junctions between endothelial cells and causes capillary leakage with subsequent fluid retention after ASCT.[9,10] In particular, fluid retention is considered as a risk of GVHD and NRM, which may also partly account for the role of IL-6 in promoting GVHD and NRM. More importantly, there is evidence suggesting that targeting IL-6-initiated signaling is a promising strategy to prevent and treat GVHD,[11–13] further confirming the accelerative effects of IL-6 in promoting GVHD and NRM. NRM is an important reason for poor OS in patients with ASCT. Additionally, in patients who received ASCT for hematological malignancies disease relapse and progression is another key factor affecting overall survival. It is reported that malignant hematological cells is capable of constitutively releasing IL-6, and in turn IL-6 can promote the proliferation and survival of malignant hematological cells,[14–17] subsequently impacting OS in patients with hematological malignancies disease. C-reactive protein (CRP), as an acute-phase protein in response to IL-6,[18] is considered as a surrogate marker of serum

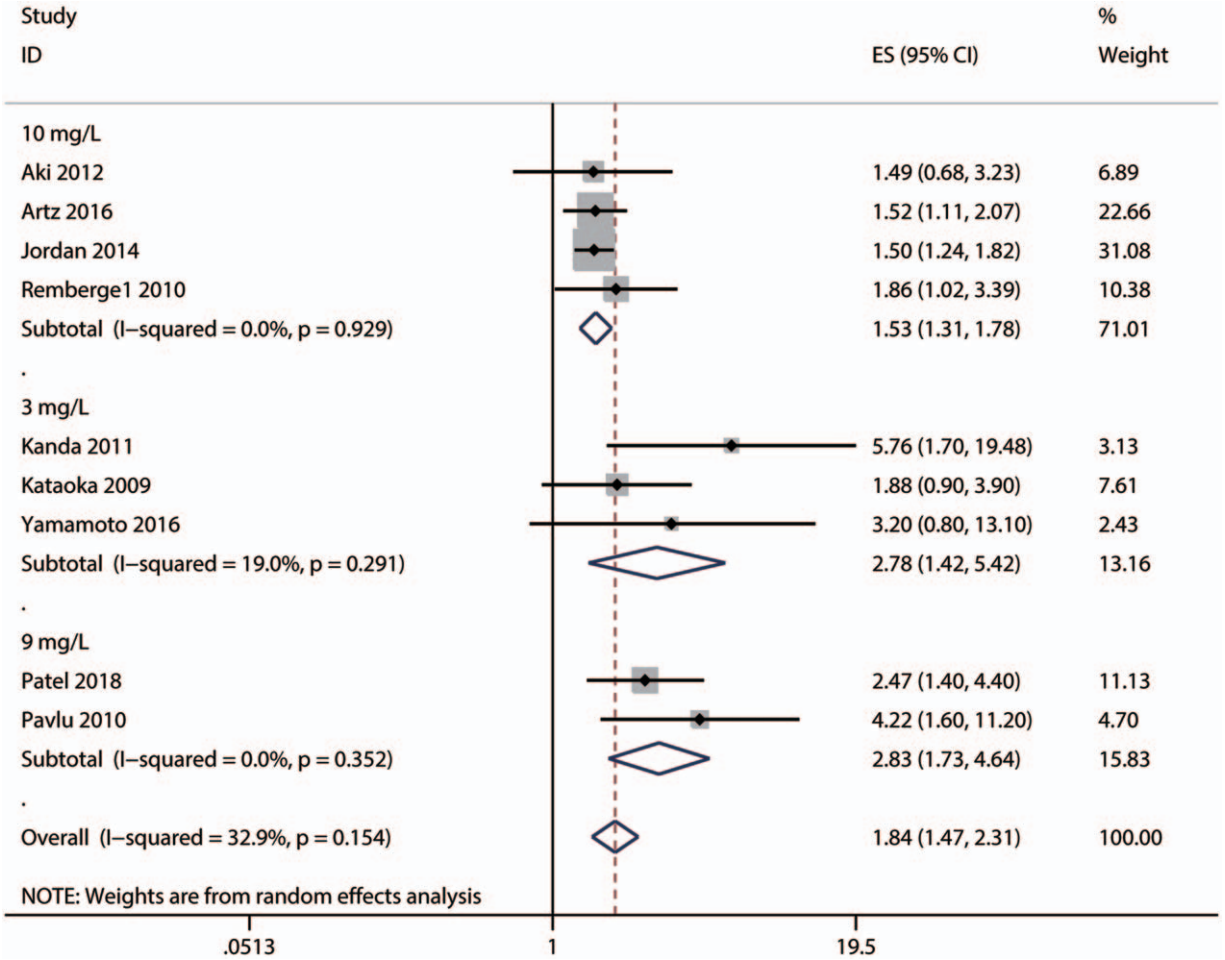

Figure 7. Subgroup analysis for NRM according to different cut-offs of high CRP level. CRP = C-reactive protein, NRM = no-relapse mortality.

IL-6.[35] Moreover, it was also reported that CRP could also induce IL-6 expression to promote inflammatory process.[36] Therefore, the mutual relationship between serum CRP level and IL-6 may partly explain the correlation between pretransplant CRP level and outcomes in patients with ASCT.

Previous studies reported that high CRP level was a risk, independent of comorbidity, of disability and diminished function in older adults, suggesting that CRP level may act as a biomarker of health status.[37,38] This may partly explain our finding that high CRP level associated with an increased NRM. As an inflammatory marker, slightly increased CRP level may mirror minute inflammation, suggesting the existence of hidden bacterial infection without detectable clinical manifestations.[34] For instance, some previous studies reported that high pretransplant CRP was closely associated with higher incidence of infection in patients following ASCT.[20,34] Actually, if a latent bacterial infection really exists before ASCT, the undetectable bacterial organisms may rapidly proliferate under post-transplant neutropenic and immunosuppressive state, under which the latent infection could evolve into the fatal infection, and ultimately cause NRM, which shortens OS in patients with ASCT.[21,39–41] In addition to latent infection, it was also considered that high pretransplant CRP level may represent the presence of minimal residual disease,[21] which is the root of disease relapse. Therefore, a latent bacterial infection and minimal residual disease clued by increased CRP level before ASCT may partly interpret the correlation between pretransplant CRP level and outcomes in patients with ASCT as well.

In general, our meta-analysis and systematic review suggested that pretransplant CRP level may be an independent predictive factor for OS, NRM, and aGVHD of patients with ASCT. Although CRP is a non-specific inflammatory marker, both disease-specific and non-specific inflammation have adverse effects on outcomes in patients receiving ASCT. Therefore, as an inexpensive and easily accessible blood index CRP may be a candidate factor of updating the existing risk scoring systems or establishing a novel risk scoring systems, which has the potential of guiding patient selection for ASCT and proceeding with risk-adapted therapeutic strategies. However, some limitations should be considered when we interpret our findings in this meta-analysis. First, significant heterogeneity existed in our meta-analysis, which probably affect the reliability of our pooled results. Although by meta-regression and subgroup analysis we identified that different cut-offs of high CRP level and conditioning regimens may be the main origin of heterogeneity, many other factors, such as ethnicity, disease types and stages, stem cell sources and follow-up time, may also introduce a degree of heterogeneity, which may affect the reliability of our pooled results. Second, the cut-offs for high CRP level were inconsistent among the included studies, limiting its practicability of clinical guidance. Third, although the roles of IL-6 in ASCT may explain the correlation between pretransplant CRP level and outcomes in

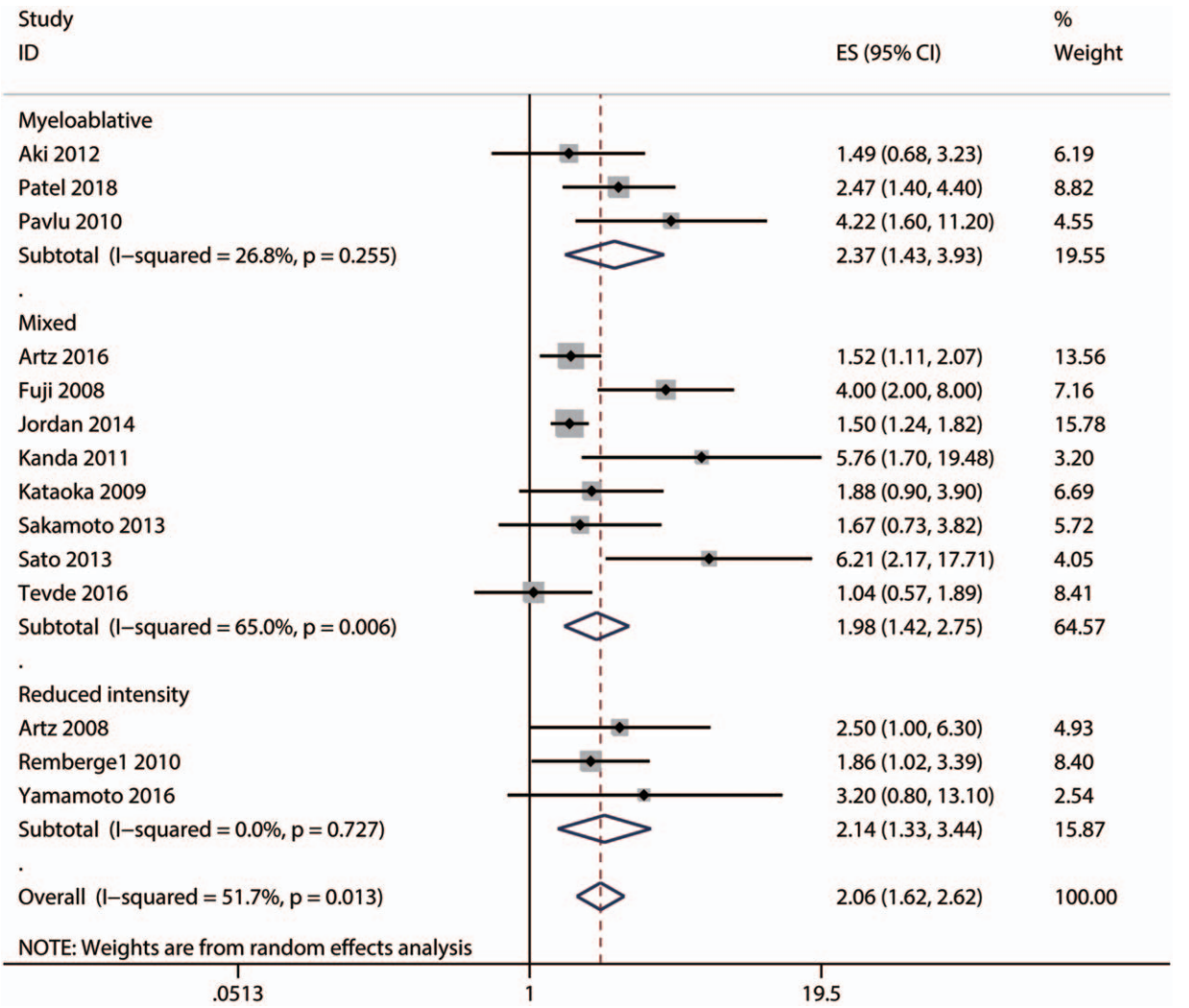

Figure 8. Subgroup analysis for OS according to different conditioning regimens. OS = overall survival.

patients with ASCT, most included studies in this meta-analysis did not definitely clarify the relationship between CRP and IL-6 in the context of ASCT. Therefore, to further elucidate the mechanisms underlying the correlation between pretransplant CRP level and outcomes in patients with ASCT, more studies are warranted to explore the mutual relationship between CRP and IL-6 in the context of ASCT. Fourth, we only included studies published in English, which may cause a degree of publication

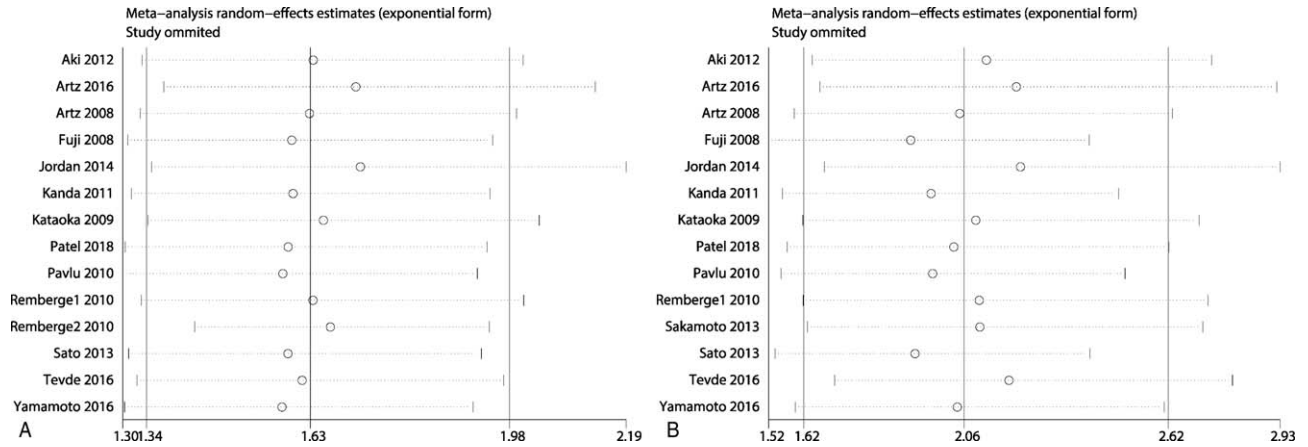

Figure 9. Sensitivity analyses for OS (A) and NRM (B). NRM = no-relapse mortality, OS = overall survival.

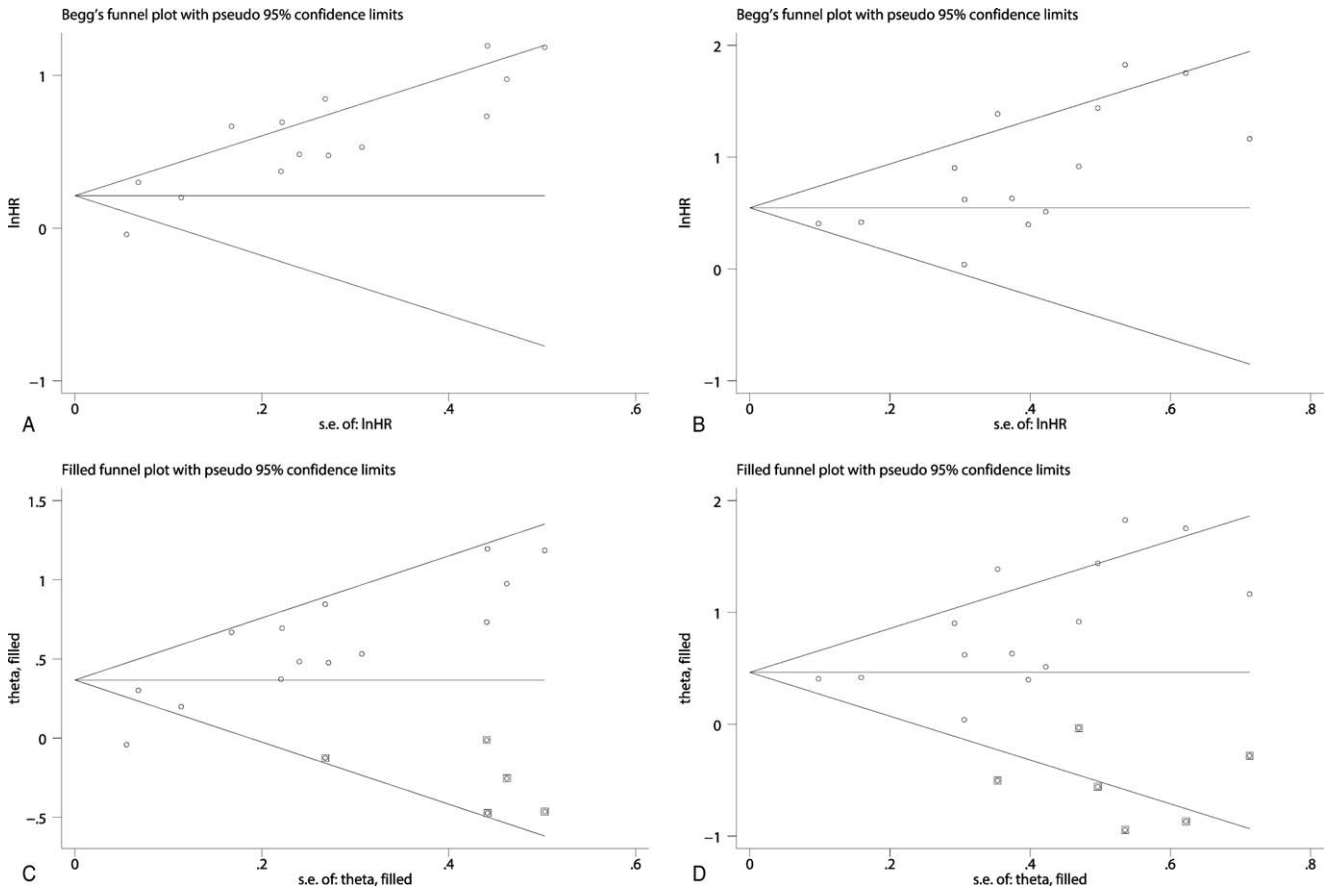

Figure 10. Begg funnel plots of publication bias assessment for OS (A) and NRM (B); the adjusted Begg funnel plots of publication bias assessment for OS (C) and NRM (D) from the trim-and-fill analysis. NRM = no-relapse mortality, OS = overall survival.

bias. At last but not least, although most studies provided HR and 95% CI from multivariate analysis, variables incorporated into Cox proportional hazard model were inconsistent from study to study, which may also introduce a degree of heterogeneity.

5. Conclusion

High pre-ASCT serum CRP was significantly associated with worse OS, as well as higher risk of NRM and aGVHD. CRP may be a candidate factor of updating the existing risk scoring systems or establishing a novel risk scoring systems, which has the potential of guiding patient selection for ASCT and proceeding with risk-adapted therapeutic strategies. However, more high-quality clinical studies and basic research are required to further validate our findings in view of several limitations in our meta-analysis.

Author contributions

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