Systematic Review and Meta-Analysis

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Effect of pre-transplantation serum ferritin on outcomes in patients undergoing allogeneic hematopoietic stem cell transplantation

A meta-analysis

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Abstract

Background: Pre-transplantation serum ferritin (SF) has been considered to be a potential prognostic biomarker in patients undergoing allogeneic hematopoietic stem cell transplantation (allogeneic HSCT), but this conclusion remains controversial. Thus, we performed a meta-analysis to investigate the prognostic significance of pre-transplantation SF in patients undergoing allogeneic HSCT.

Methods: We systematically searched PubMed, Embase, and Web of Science up to September 2017, and finally identified a total of 25 eligible studies with 4545 patients.

Results: The pooled results of our meta-analysis showed that high pre-transplantation SF was markedly related to worse overall survival (OS) [hazard ratio (HR) = 1.82; 95% confidence interval (95% CI): 1.47–2.26; $P < .001$], nonrelapse mortality (NRM) (HR = 2.28; 95% CI: 1.79–2.89; $P < .001$), and progression-free survival (PFS) (HR = 1.72; 95% CI: 1.27–2.33; $P < .001$). In addition, high pre-transplantation SF was closely associated with a lower incidence of chronic graft versus host disease (cGVHD) (OR = 0.74, 95% CI: 0.58–0.96; $P < .05$), and a higher incidence of blood stream infections (BSIs) (OR = 1.67, 95% CI: 0.93–3.01; $P = .09$). However, no significance relationship was found between elevated pre-transplantation SF and acute graft versus host disease (aGVHD) (OR = 1.08, 95% CI:.72–1.62; $P = .70$).

Conclusion: In patients undergoing allogeneic HSCT for hematological malignancies, elevated pre-transplantation SF was significantly associated with worse OS and PFS, higher incidence of NRM and BSI, and lower incidence of cGVHD, but it had no effect on aGVHD. Considering the limitations in our meta-analysis, more prospective and homogeneous clinical studies are needed to further confirm our findings.

Abbreviations: aGVHD = acute graft versus host disease, AML = acute myeloid leukemia, BSI = blood stream infection, cGVHD = chronic graft versus host disease, CI = confidence interval, HR = hazard ratio, HSCT = allogeneic hematopoietic stem cell transplantation, MDS = myelodysplastic syndromes, NRM = nonrelapse mortality, OR = odds ratio, OS = overall survival, SF = serum ferritin.

Keywords: hematopoietic stem cell, meta-analysis, serum ferritin, transplantation

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allogeneic HSCT) has been widely considered as an effective treatment for hematological malignancies, but favorable outcomes after allogeneic HSCT may be neutralized by several transplant-associated morbidities and mortality.[1] Hence, it is urgent to develop practical prognostic tools for predicting outcomes in patients with allogeneic HSCT, to encourage physicians appropriately to decide whether to treat individual patients with allogeneic HSCT, or to make preventive therapeutic schedules to mitigate relevant risks. A high iron burden is a common pre-transplantation abnormality, which might be partly attributed to multiple blood transfusions and hemolysis and can lead to liver function damage, hepatic sinusoidal obstruction syndrome, infection, and other problems, thus substantially influencing transplant-associated mortality and long-term survival.[2–5] Although liver biopsy is the gold standard for evaluating iron overload, serum ferritin (SF) is commonly used to assess the body's iron stores, due to its easy availability and the high procedural risks of liver biopsy. In addition, a recent study indicated that SF measured shortly before allogeneic HSCT is a reliable biomarker for iron overload, despite the fact that it is an acute-phase protein and its serum level can be influenced by acute infections, inflammations, and even malignant status.[6]

Furthermore, many studies have reported that pre-transplantation SF is a predictive biomarker for outcomes of patients with allogeneic HSCT. For instance, numerous studies indicated that elevated pre-transplantation SF was associated with inferior

Editor: Ahmet Emre Eskazan.

The authors report no conflicts of interest.

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Medicine (2018) 97:27(e10310)

Received: 9 November 2017 / Received in final form: 11 January 2018 / Accepted: 13 March 2018

http://dx.doi.org/10.1097/MD.0000000000010310

overall survival (OS)[7–9] and progression-free survival (PFS),[6,10,11] as well as a higher risk of nonrelapse mortality (NRM)[5,8,12] and blood stream infection (BSI).[9,13] In addition, several studies showed that there was an inverse relationship between raised pre-transplantation SF and chronic graft-versus-host disease (cGVHD).[14,15] Nevertheless, several studies on this topic reported conflicting results, indicating that high pre-transplantation SF might not be an independent prognostic marker in patients with allogeneic HSCT.[16–18] Considering the limited sample sizes of single studies regarding this topic, it is necessary to conduct a meta-analysis to further assess the prognostic value of elevated pre-transplantation SF in patients with allogeneic HSCT. A meta-analysis has been performed previously in this regard and indicated that elevated SF was correlated with lower OS and a higher incidence of NRM.[19] However, the previous meta-analysis did not include many recently published studies and only assessed the relationship of SF to OS and the NRM rate, but not PFS and post-transplantation GVHD and BSI, which increase the risk of transplant-related mortality and long-term survival. Furthermore, the previous meta-analysis did not separate allogeneic HSCT from autologous HSCT, which might introduce substantial heterogeneity to the pooled results. Therefore, we conducted this updated meta-analysis to more comprehensively investigate the prognostic significance of pre-transplantation elevated SF level in patients with hematological malignancies undergoing allogeneic HSCT.

2. Materials and methods

2.1. Ethics and dissemination

Ethical approval and informed consent are not required, as the study will be a literature review and will not involve direct contact with patients or alterations to patient care.

2.2. Study search strategy

We systematically searched PubMed, Embase, and Web of Science using the terms "ferritin" or "iron overload," and "stem cell transplantation" from January 2000 to September 2017. We restricted the search to English published studies and human studies. Two independent reviewers performed the literature research.

2.3. Study selection criteria

The inclusion criteria were as follows: only allogeneic HSCT, ferritin level must be measured before allogeneic HSCT, OS or PFS or NRM or acute graft versus host disease (aGVHD)/cGVHD or BSIs were reported, and hazard ratio (HR), or odds ratio (OR) and their 95% confidence intervals (95% CIs) could be obtained directly, or sufficient data or survive curves were available to calculate the above estimates. The exclusion criteria were as follows: in vitro studies, case reports, conference abstracts, editorials, and reviews, and studies on patients with autologous HSCT.

2.4. Data extraction and quality assessment

The following information was extracted: the first author's name, country of research, study type, recruitment time, mean age of patients, disease type, case number, cut-off for SF, follow-up, OS, PFS, NRM, and aGVHD/cGVHD or BSI. The outcomes of interest included OS, PFS, NRM aGVHD/cGVHD, and BSI. If the studies did not directly provide HRs for OS, PFS, or NRM, the Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/, freely downloaded software) was used to extract the survival data from Kaplan–Meier curves.[20]

The Newcastle–Ottawa quality scale (NOS) was applied to assess the quality of the included studies. It evaluated the included studies in terms of the selection of participants, comparability, and ascertainment of outcome. The NOS score ranged from 0 (minimum) to 9 (maximum). A higher final score indicated a better methodological quality. A study with a score of 6 or higher was considered high-quality.

2.5. Statistical analysis

The statistical analyses of this meta-analysis were performed using Stata version 12.0 (Stata Corporation, College Station, TX). The pooled HRs and ORs and their corresponding 95% CIs were calculated to assess the association between SF and patient outcomes. The heterogeneity across the included studies was tested by the Cochran Q and Higgins I^2 statistics. $P < .05$ and $I^2 > 50\%$ indicated significant heterogeneity, whereas $I^2 < 25\%$, and $25\% < I^2 < 50\%$, indicated no heterogeneity and moderate heterogeneity, respectively. A random effects model was applied when statistical heterogeneity was detected; Otherwise, the fixed effects model was used. $HR > 1$ (low SF used as reference) indicated a higher risk of poor outcomes for high SF, and it was considered statistically significant if the 95% CI did not include 1 and $P < .05$. A sensitivity analysis was performed by sequentially deleting a single study in each step. The pooled results were considered stable if the HR did not significantly change with exclusion of the individual study. Publication bias was evaluated by Begg test and Egger tests, with funnel plot analysis. $P < .05$ with funnel plot asymmetry was considered a statistically significant publication bias.[21,22]

3. Results

3.1. Study search and study characteristics

The detailed process of study selection is described in Fig. 1. A total of 2197 studies were identified from PubMed, Embase, and Web of science after the initial literature search. After checking titles and abstracts, we eliminated 316 duplicated studies. In addition, 1814 studies including case reports, reviews, animal studies, irrelevant, and non-English studies were excluded, leaving 47 full-text articles for further evaluation. After that, 3 studies published by the same institution, 3 studies that enrolled patients undergoing autologous HSCT, 5 studies without extractive data, and 36 studies published in conference abstracts were excluded. Finally, a total of 25 studies were included in our meta-analysis.[4–18,23–32]

In all the included studies, a total of 4545 patients were enrolled between 1988 and 2013. Most of the included studies were retrospective, and only 1 study was prospective. Among the included studies, 22 enrolled mixed groups of patients, who suffered from acute myeloid leukemia (AML), acute lymphoblastic leukemia, chronic myeloid leukemia, chronic lymphoblastic leukemia, or myelodysplastic syndromes (MDS), 3 studies involved MDS only, and 1 study was involved AML only. More detailed information concerning the main characteristics of the included studies is presented in Table 1. The scores for included study quality ranged from 5 to 7 according to the NOS (Table 2).

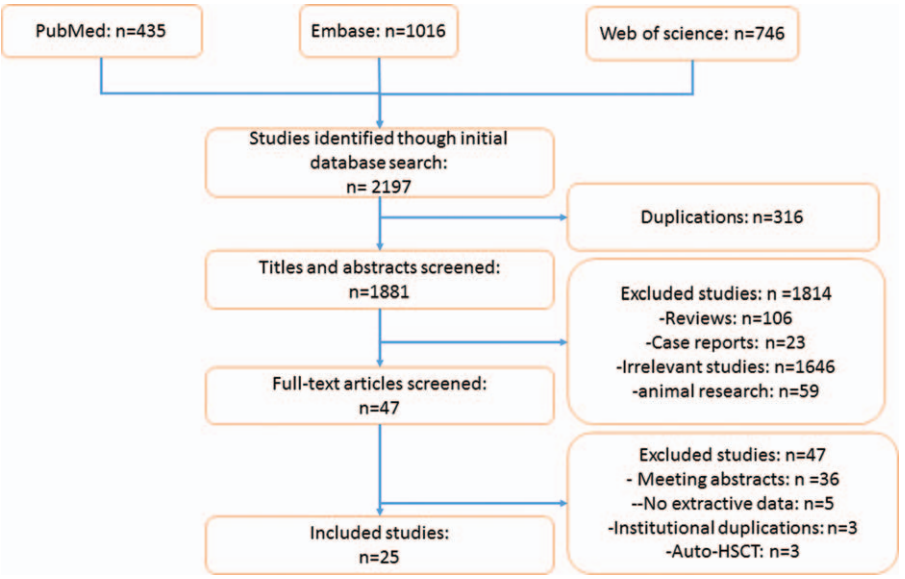

Figure 1. The study flow of study selection process.

3.2. The prognostic significance of high SF in overall survival

Twenty-four studies analyzed the relationship between SF and OS.[4–18,23–29,31,32] Considering the severe heterogeneity (I^2 = 85.1%, $P < .001$), we calculated the HR and 95% CI using a random-effects model. The result from our meta-analysis showed that high SF was significantly related to worse OS (HR = 1.82; 95% CI: 1.47–2.26; $P < .001$) (Fig. 2). Furthermore, we performed stratified analyses to investigate the possible sources of heterogeneity according to region, cut-off value, hematological malignancy type, sample size, and variable type. The results of subgroup analyses indicated that the HR for the association between high SF with OS did not alter significantly in any of the following subgroups: Asian group (HR = 2.23; 95% CI: 1.73–2.87; $P = .08$), American group (HR = 1.71; 95% CI: 1.24–2.37; $P = .09$), European group (HR = 1.52; 95% CI: 1.11–2.09; $P < .001$), Oceania group (HR = 167; 95% CI: 1.25–2.23; $P = .79$), cut-off values (SF = 1000 or 2500 ng/mL; HR = 1.77; 95% CI: 1.49–2.10; $P = .42$ or HR = 1.65; 95% CI:.93–2.92; $P = .11$), malignancy type (MDS, HR = 1.72; 95% CI: 1.27–2.33; $P < .001$), sample size (<100 or ≥100; HR = 2.43; 95% CI: 1.92–3.08; $P = .82$ or HR = 1.62; 95% CI: 1.27–2.06; $P < .001$), or variable type (univariate analysis or multivariate analysis; HR = 1.57; 95% CI: 1.08–2.26; $P < .05$ or HR = 1.88; 95% CI: 1.57–2.25; $P < .01$) (Table 3).

3.3. The prognostic significance of high SF in progression-free survival

The relationship between high SF and PFS was mentioned in 12 studies.[6,7,9,10,14–18,25,27,29] The random-effects model was used to calculate the pooled HR with 95% CI due to obvious heterogeneity. The results indicated that there was an obvious connection between high SF and worse PFS (HR = 1.72; 95% CI: 1.27–2.33, $P < .001$) (Fig. 3). In order to explore the roots of heterogeneity, we performed subgroup analyses by region, cut-off value, sample size, and variable type. From the results, we observed no significant alterations of the pooled HR in any of the following subgroups: Asian group (HR = 1.82; 95% CI: 1.34–2.47; $P = .19$), American group (HR = 1.85; 95% CI: 1.34–2.55, $P = .56$), European group (HR = 1.59; 95% CI:.92–2.75; $P < .001$), Oceania group (HR = 1.84; 95% CI:.57–5.96), cut-off value (SF = 1000, HR = 1.90; 95% CI: 1.48–2.45; $P = .69$), sample size (<100 or ≥100; HR = 1.78; 95% CI: 1.24–2.57; $P = .58$ or HR = 1.70; 95% CI: 1.16–2.48; $P < .001$), or variable type (univariate analysis or multivariate analysis; HR = 1.00; 95% CI: 1.00–1.01; $P = .48$ or HR = 1.92; 95% CI: 1.62–2.27; $P = .45$) (Table 4).

3.4. The prognostic significance of high SF in nonrelapse mortality

A total of 13 studies reported about NRM.[5,7–10,12–16,24,29,31] The pooled HR and 95% CI was calculated using a random-effects model due to severe heterogeneity. The results showed that patients with high SF experienced higher NRM (HR = 2.28; 95% CI: 1.79–2.89; $P < .001$) (Fig. 4). Furthermore, to investigate the roots of heterogeneity, we performed subgroup analyses by region, cut-off value, sample size, and variable type. From the results, no significant alterations of the pooled HR were observed in any of the following subgroups: Asian group (HR = 2.34; 95% CI: 1.62–3.37; $P = .03$), America, group (HR = 1.72; 95% CI: 1.10–2.70; $P = .52$), European group (HR = 2.78; 95% CI: 1.33–5.81; $P = .78$), cut-off value (SF = 1000 or 2500 ng/mL; HR = 3.51; 95% CI: 2.34–5.24; $P = .29$ or HR = 1.87; 95% CI: 1.48–2.37; $P = .29$), sample size (<100 or ≥100; HR = 3.27; 95% CI: 1.71–6.24; $P = .11$ or HR = 2.01; 95% CI: 1.61–2.50; $P = .69$), variable type (univariate analysis or multivariate analysis; HR = 1.95; 95% CI: 0.94–4.06; $P = .73$ or HR = 2.30; 95% CI: 1.76–3.01; $P = .08$) (Table 5).

3.5. The association of high SF with acute/chronic graft versus host disease

The relationship between SF and aGVHD/cGVHD was reported in 9 studies.[5,7,9,11,13–15,17,31] The pooled analysis of our meta-analysis showed that high SF was markedly related to cGVHD (OR = 0.74, 95% CI: 0.58–0.96; $P < .05$) (Fig. 5), but no

Table 1

The main characteristics of the included studies.

Authors	Country	Study design	Recruitment time	No. of patients	Age, median (range)	Disease type	Cut-off, ng/mL	(HR, 95% CI) OS/PFS/NRM/BSI	GVHD			
									High SF		Low SF	
									Total	Case	Total	Case
Aki et al[16]	Turkey	R	2003–2010	106	29 (15–55)	AML (59.4%) ALL (40.6%)	1500	OS, 1.35 (0.81–2.27)[M] PFS, 1.10 (0.57–2.13)[M] NRM, 1.56 (0.77–3.23)[M]	NA	NA	NA	NA
Armand et al[23]	USA	R	1997–2005	45	46 (18–63)	AML (58%) ALL (24%) MDS (18%)	2500	OS, 2.59 (0.87–7.69)[U] NRM, 1.88 (-0.02–3.78)[M]	NA	NA	NA	NA
Artz et al[24]	USA	R	2008–2010	784	50 (18–78)	AML (80%) MDS (20%)	2500	OS, 1.15 (0.86–1.54)[M] NRM, 1.26 (0.84–1.88)[M]	NA	NA	NA	NA
Boehm et al[25]	Austria	R	1988–2010	60	44 (18–68)	AML (47%) MDS (53%)	1000	OS, 2.04 (0.45–9.26)[U] DFS, 1.84 (0.57–5.98)[U]	NA	NA	NA	NA
Chee et al[8]	Australia	R	2000–2013	602	49 (36–62)	AML (37%) ALL (14.8%) CLL (5.6%) CML (5.8%) MDS (1.3%) LYM (20.2%)	1000	OS, 1.66 (1.24–2.23)[M] NRM, 2.82 (1.33–5.96)[M]	NA	NA	NA	NA
Cremers et al[26]	Netherlands	R	2001–2005	62	49 (18–70)	MDS	1000	OS, 1.59 (0.78–3.25)[U]	NA	NA	NA	NA
Emilio Paolo et al[34]	Italy	R	1997–2007	57	49 (18–72)	MDS	1000	OS, 2.24 (1.04–4.83)[U]	NA	NA	NA	NA
Jacobi and Herich[6]	Canada	R	1994–2010	142	54.5 (5.6–75)	AML (26.8%) MDS (15.5%)	1000	OS, 2.058 (1.056–4.008)[M] PFS, 2.15 (1.15–4.10)[U]	NA	NA	NA	NA
Jang et al[27]	Korea	R	2006–2012	74	35 (15–59)	AML	1400	OS, 1.88 (0.88–4.01)[M] PFS, 1.99 (0.97–4.07)[M]	NA	NA	NA	NA
Kanda et al[33]	Japan	R	2004–2009	96	47 (18–66)	AML (41.1%) ALL (9.8%) MDS (14.3%) CML (3.6%) LYM (17%)	700	OS, 3.60 (2.07–5.13)[M] NRM, 5.21 (2.62–7.80)[M]	NA	NA	NA	NA
Kataoka et al[5]	Japan	R	1996–2006	272	40 (16–66)	AML (30%) ALL (23%) MDS (13%) CML (19%) LYM (13%)	599	OS, 3.38 (1.93–4.83)[M] NRM, 3.38 (1.54–5.22)[M]	132	57[c]	132	53[c]
									132	48[a]	132	55[a]
Kim et al[17]	Korea	R	2000–2006	38	42.5 (16–55)	AML (84%) MDS (16%)	1000	OS, 2.68 (0.92–7.84)[U] PFS, 2.89 (0.89–9.34)[U]	16	6[c]	22	7[c]
Lim et al[7]	UK	R	2001–2006	99	51.1 (19–72)	AML (37.5%) MDS (62.5%)	1500	OS, 2.00 (0.97–3.57)[M] PFS, 1.3 (0.59–2.86)[M] NRM,1.79 (0.75–4.35)[M]	53	12[c]	46	10[c]
									53	12[a]	46	9[a]
Mahindra et al[15]	USA	R	2000–2006	222	42 (18–62)	AML (47.3%) ALL (19.8%) MDS (8.6%)	1910	OS,1.82 (1.23–2.67)[M] PFS,1.75 (1.20–2.54)[M] NRM,1.57 (0.69–2.45)[M]	75	10[c]	147	38[c]

(*continued*)

Table 1
(continued).

Authors	Country	Study design	Recruitment time	No. of patients	Age, median (range)	Disease type	Cut-off, ng/mL	(HR, 95% CI) OS/PFS/NRM/BSI	GVHD			
									High SF		Low SF	
									Total	Case	Total	Case
						CML (11.3%) LYM (8.0%)						
									NA	NA	NA	NA
Platzbecker et al[28]	Germany	R	NA	172	51 (10–68)	MDS	1000	OS,0.67 (0.33–1.35)[M]	NA	NA	NA	NA
Pullarkat et al[13]	USA	R	2005–2006	190	46.4 (19.6–68.5)	LYM/MYE (76%) ALL/AML (24%)	1000	OS, 2.28 (1.29–4.02)[M] NRM, 2.53 (0.81–4.25)[M] BSI, 1.99 (1.06–3.75)[M]	84	52[a]	106	45[a]
Sakamoto et al[14]	Japan	R	2000–2010	211	48 (17–69)	AML/CML (54.5%) ALL/CLL (41.7%)	880	OS, 2.16 (1.34–3.48)[M] PFS, 2.83 (1.74–4.59)[M] NRM, 2.19 (1.01–4.75)[M]	71	23[c]	140	69[c]
									71	23[a]	140	53[a]
Sivgin et al[11]	Turkey	R	2004–2010	84	28 (15–56)	AML (44.1%) ALL (19.1%) CML (2.3%) LYM (5.8%)	1000	OS, 2.46 (1.10–5.52)[M] PFS,2.96 (1.32–6.62)[M]	51	15[c]	33	13[c]
									51	13[a]	33	5[a]
Sivgin et al[18]	Turkey	R	NA	125	NA	ALL (66.4%) LYM (16.0%)	NA	OS, 1.00 (0.99–1.01)[U] PFS, 1.00 (1.00–1.01)[U]	NA	NA	NA	NA
Sucak et al[29]	Turkey	R	2003–2008	142	27.5 (16–64)	AML (37.8%) ALL (20.3%) MDS (3.4%) CML (6.1%) LYM (12.8%)	500	OS, 1.43 (0.84–2.45)[U] TRM, 2.38 (1.00–14.29)[U]	NA	NA	NA	NA
Tachibana et al[9]	Japan	R	2000–2008	261	43 (17–64)	AML (61%) ALL (25%) MDS (14%)	1000	OS, 1.87 (1.05–2.47)[M] PFS, 1.83 (1.32–2.54)[M] NRM, 1.83 (1.16–2.89)[M]	87	40[c]	109	61[c]
									122	49[a]	127	58[a]
Tachibana et al[30]	Japan	R	2000–2008	114	25 (0.3–117)	NA	1000	BSI, 2.84 (1.18–6.86)[M]	NA	NA	NA	NA
Tanaka et al[31]	Japan	P	2010–2012	190	48 (20–69)	AML (59.8%) ALL (23.3%) MDS (16.9)	1000	OS, 1.79 (1.11–2.89)[M] NRM, 1.60 (0.83–3.09)[M] BSI, 1.04 (0.64–1.69)[M]	79	28[c]	111	45[c]
									79	43[a]	111	39[a]
Wahlin et al[10]	Sweden	R	1998–2005	309	47 (16–68)	AML (30.7%) ALL (10.4%) MDS (8.1%) CML (19.4%) CLL (3.9%) LYM (9.4%)	400	OS, 1.79 (1.13–2.83)[M] PFS, 2.08 (1.31–3.30)[M]	NA	NA	NA	NA
Wermke et al[32]	Germany	R	NA	88	58	AML (72.7%) MDS (27.3%)	2500	OS, 2.32 (1.05–4.80)[M] NRM, 2.98 (1.23–7.22)[M]	NA	NA	NA	NA

a = acute GVHD, ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, c = chronic GVHD, CCL = chronic lymphoblastic leukemia, CML = chronic myeloid leukemia, LYM = lymphoma (LYM), M = multivariate analysis, MDS = myelodysplastic syndromes, MYE = myeloma, NA = not available, NRM = no-relapse mortality, OS = overall survival, PFS = progression-free survival, U = Univariate analysis.

Table 2

The Newcastle–Ottawa Scale (NOS) quality assessment of the included studies.

	Selection					Outcome			
Study	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest	Comparability	Assessment of outcome	Length of follow-up	Adequacy of follow-up	Total score
Aki et al[16]	★	★	★	★	★	★	★	☆	7
Armand et al[23]	★	★	★	★	★	★	★	☆	7
Artz et al[24]	★	★	★	★	★	★	★	☆	7
Boehm et al[25]	★	★	★	★	☆	★	★	☆	6
Chee et al[8]	★	★	★	★	★	★	★	☆	7
Cremers et al[26]	★	★	★	★	★	★	★	☆	7
Emilio Paolo et al[34]	★	★	★	★	☆	★	★	☆	6
Jacobi and Herich[6]	★	★	★	★	☆	★	☆	☆	5
Jang et al[27]	★	★	★	★	★	★	★	☆	7
Kanda et al[33]	★	★	★	★	★	★	★	☆	7
Kataoka et al[5]	★	★	★	★	☆	★	★	☆	6
Kim et al[17]	★	★	★	★	★	★	★	☆	7
Lim et al[7]	★	★	★	★	★	★	★	☆	7
Mahindra et al[15]	★	★	★	★	★	★	★	☆	7
Platzbecker et al[28]	★	★	★	★	☆	★	★	☆	6
Pullarkat et al[13]	★	★	★	★	☆	★	★	☆	6
Sakamoto et al[14]	★	★	★	★	★	★	★	☆	7
Sivgin et al[11]	★	★	★	★	★	★	★	☆	7
Sivgin et al[18]	★	★	★	★	★	★	★	☆	7
Sucak et al[29]	★	★	★	★	☆	★	★	☆	6
Tachibana et al[9]	★	★	★	★	★	★	★	☆	7
Tachibana et al[30]	★	★	★	★	★	★	★	☆	7
Tanaka et al[31]	★	★	★	★	☆	★	★	☆	6
Wahlin et al[10]	★	★	★	★	★	★	★	☆	7
Wermke et al[32]	☆	☆	★	★	★	★	★	☆	5

★: A score is given; ☆: Zero score is given.

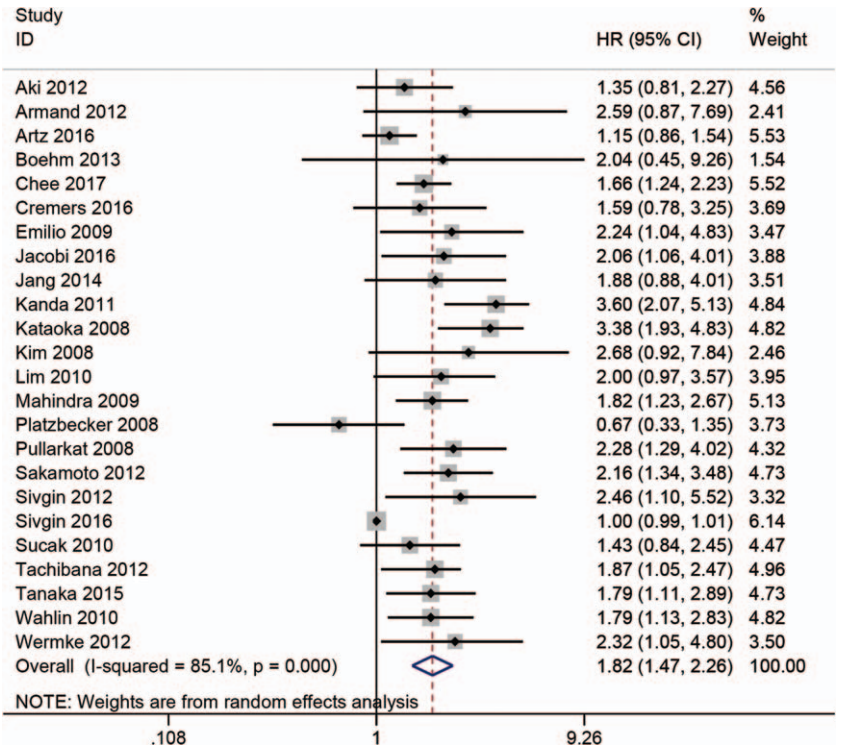

Figure 2. Meta-analysis of the prognostic significance of serum ferritin in overall survival.

Table 3

Results of stratified analysis for the impact of SF on overall survival.

Subgroup	No. of studies	Pooled hazards ratio (95% CI)	*P* for heterogeneity	I^2 (%)
Country				
Asian	8	2.23 (1.73–2.87)	.076	45.6%
America	5	1.71 (1.24–2.37)	.091	50.0%
Europe	9	1.52 (1.11–2.09)	<.001	72.2%
Oceania	2	1.67 (1.25–2.23)	.793	0
Cut-off, ng/mL				
SF = 1000	11	1.77 (1.49–2.1)	.422	2.1%
SF = 2500	3	1.65 (0.93–2.92)	.108	55.0%
Malignancy type				
MDS	3	1.72 (1.27–2.33)	<.001	83.6%
Sample size				
<100	10	2.43 (1.92–3.08)	.819	0
≥100	14	1.62 (1.27–2.06)	.000	86.3%
Variable type				
Univariate analysis	7	1.57 (1.08–2.28)	.024	58.9%
Multivariate analysis	17	1.88 (1.57–2.25)	.002	56.6%

95% CI = 95% confidence interval, SF = serum ferritin.

significance was detected in aGVHD (OR = 1.08, 95% CI: 0.72–1.62; *P* = .70) (Fig. 6).

3.6. The association of high SF with blood stream infections

Only 3 studies mentioned the association of high SF with BSI.[13,30,31] The results of our meta-analysis showed that high SF was significantly associated with a higher incidence of BSI (OR = 1.67, 95% CI: 0.93–3.01; *P* = .09) (Fig. 7).

3.7. Sensitivity analysis

The sensitivity analyses were performed by omitting a single study per step to investigate the influence of individual studies on the pooled HRs of OS, PFS, and NRM. The results showed that the HR in each step did not alter substantially (Fig. 8A–C), indicating that our pooled results of OS, PFS, and NRM were robust to a degree.

3.8. Publication bias

Egger and Begg tests with funnel plots were performed to assess potential publication bias in our meta-analysis. The results of Egger and Begg test with funnel plots showed that that there was no obvious publication bias for NRM (Begg test: *P* = .95; Egger test: *P* = .62; Fig. 8D), but significant publication bias was observed for OS (Begg test: *P* = .08; Egger test: *P* < .001; Fig. 9A) and PFS (Begg test: *P* = .41; Egger test: *P* < .001; Fig. 9B).

To explore whether the publication bias for OS and PFS substantially affected the stability of the pooled HRs in our

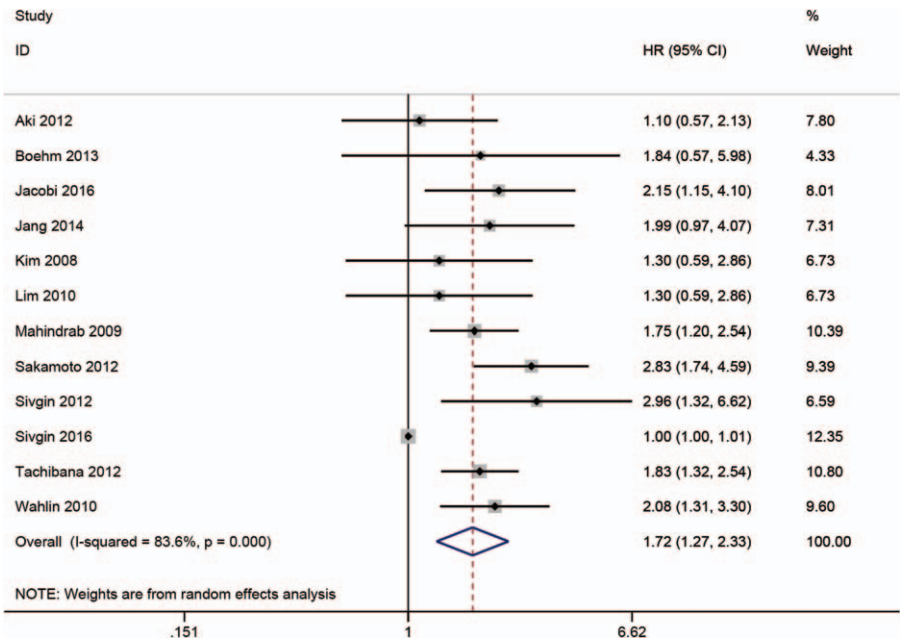

Figure 3. Meta-analysis of the prognostic significance of SF in progression-free survival.

Table 4

Results of stratified analysis for impact of SF on progression-free survival.

Subgroup	No. of studies	Pooled hazards ratio (95%CI)	*P* for heterogeneity	I^2 (%)
Country				
Asian	5	1.82 (1.34–2.47)	.188	35.0%
America	2	1.85 (1.34–2.55)	.585	0
Europe	4	1.59 (0.92–2.75)	.001	82.4%
Cut-off, ng/mL				
SF = 1000	2	2.41 (1.72–3.36)	.368	0
SF = 2500	10	1.58 (1.17–2.13)	.000	77.3%
Sample size				
<100	5	1.78 (1.24–2.57)	.584	0
≥100	7	1.70 (1.16–2.48)	.000	89.0%
Variable type				
Univariate analysis	3	1.00 (1.00–1.01)	.482	0
Multivariate analysis	9	1.92 (1.62–2.27)	.452	0

95% CI = 95% confidence interval, SF = serum ferritin.

meta-analysis, we further performed a trim-and-fill analysis. The results showed that the reasonable number of included studies should be 31 when adding 7 missing studies for OS, and 13 with 1 missing study for PFS; the updated pooled funnel plots for publication bias concerning the association of SF with OS (Fig. 9C) and PFS (Fig. 9D) were relatively symmetrical. More importantly, the updated pooled HRs also did not change significantly (HR = 1.566, 95% CI: 1.307–1.876; $P < .001$) and (HR = 1.657, 95% CI: 1.242–2.209; $P < .001$), suggesting that the pooled HRs of OS and PFS in our meta-analysis were still stable, although the publication bias for the association of SF with OS and PFS was significant in our meta-analysis.

4. Discussion

Consistent with the results of a previous meta-analysis,[19] the results of our study showed that elevated pre-transplantation SF was closely associated with worse OS and a higher incidence of NRM. In addition, we found that there was a substantial relationship between elevated pre-transplantation SF and worse PFS and a higher risk of BSI. Paradoxically, our meta-analysis showed that there was a significant association between high pre-transplantation SF and a lower incidence of cGVHD.

Currently, improving the OS and PFS of patients who undergo allogeneic HSCT is one of leading aims of hematologists. Considering the positive association of high pre-transplantation SF level with worse OS and PFS, pre-transplantation SF might be incorporated in prognostic models to guide physicians to make reasonable decisions about whether to treat individual patients with allogeneic HSCT, and decreasing the pre-transplantation SF level might be an effective strategy to improve OS and PFS. For instance, it has been reported that some drugs targeting mitigating iron overload were able to improve the outcomes in patients who underwent allogeneic HSCT.[33] However, the exact

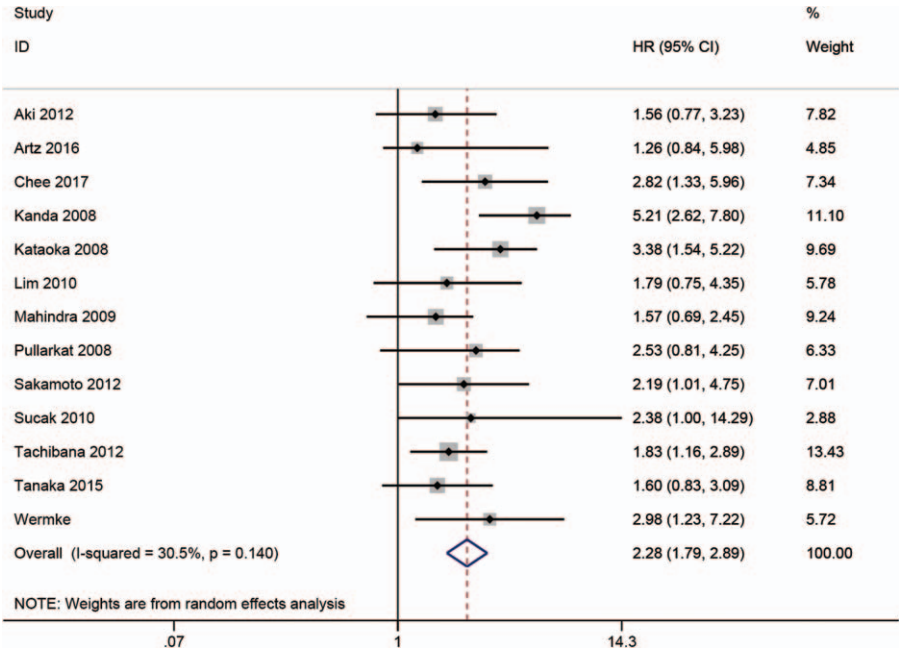

Figure 4. Meta-analysis of the prognostic significance of SF in nonrelapse mortality.

Table 5

Results of stratified analysis for impact of SF on nonrelapse mortality.

Subgroup	No. of studies	Pooled hazards ratio (95%CI)	*P* for heterogeneity	I^2 (%)
Country				
Asian	7	2.34 (1.62–3.37)	.034	56.0%
America	3	1.72 (1.10–2.70)	.522	0
Europe	2	2.78 (1.33–5.81)	.783	0
Cut-off, ng/mL				
SF = 1000	4	3.51 (2.34–5.24)	.288	20.2%
SF = 2500	9	1.87 (1.48–2.37)	.846	0
Sample size				
<100	3	3.27 (1.71–6.24)	.113	54.1%
≥100	10	2.01 (1.61–2.50)	.686	0
Variable type				
Univariate analysis	2	1.95 (0.94–4.06)	.726	0
Multivariate analysis	11	2.30 (1.76–3.01)	.076	40.9%

95% CI = 95% confidence interval, SF = serum ferritin.

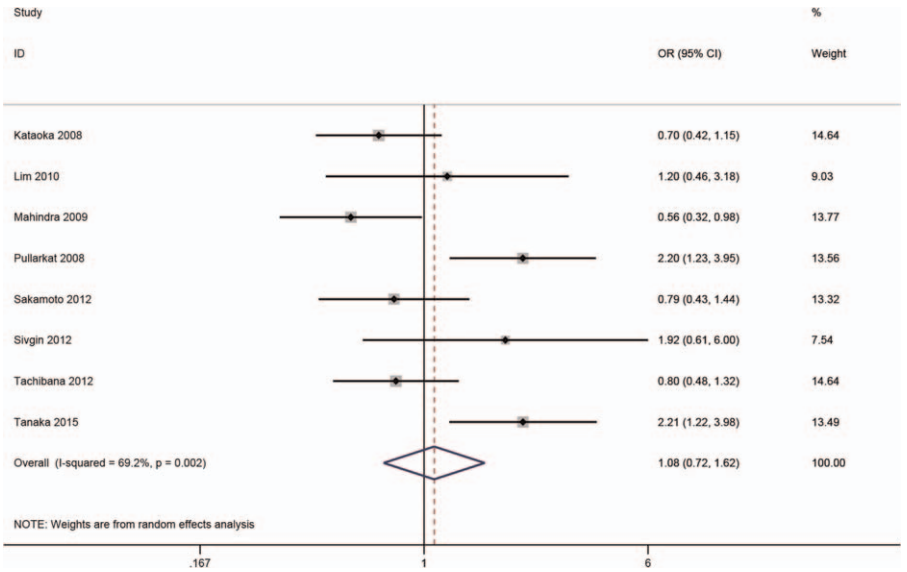

Figure 5. Meta-analysis of the association of SF with chronic graft versus host disease.

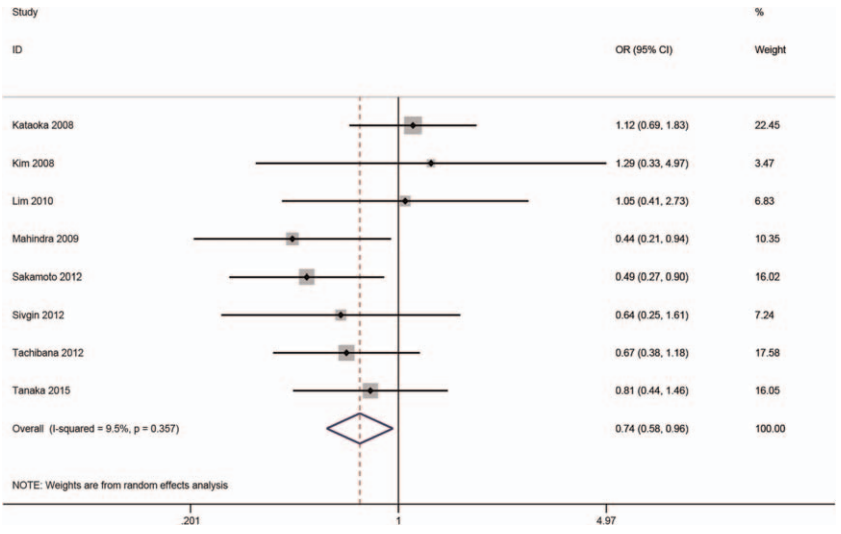

Figure 6. Meta-analysis of the association of SF with acute graft versus host disease.

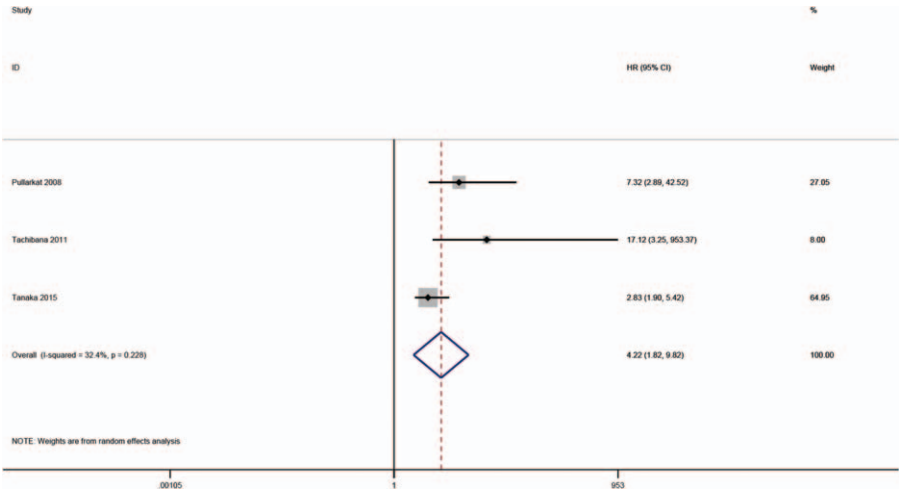

Figure 7. Meta-analysis of the association of SF with blood stream infections.

mechanisms underlying the relationship between SF and long-term survival have not been fully elucidated. It has been hypothesized that elevated pre-transplantation SF might negatively affect pro-oxidative/antioxidative homeostasis, which probably worsens the long-term survival of patients undergoing allogeneic HSCT.[35] Mortality not related relapse is also a serious issue for hematologists, and infection and GVHD are the 2 most common causes of NRM. The application of allogeneic HSCT is in part limited by the high mortality related to the procedure. In particular, it is often difficult for family members to understand and accept when a patient who undergoes HSCT succumbs to NRM. Hence, reducing the NRM rate is another leading goal of hematologists. Inconsistent results were reported in all 13 publications included in our meta-analysis.[7,8,12–16,24,29–32] Although some studies indicated that elevated pre-transplantation SF level was not related to a higher

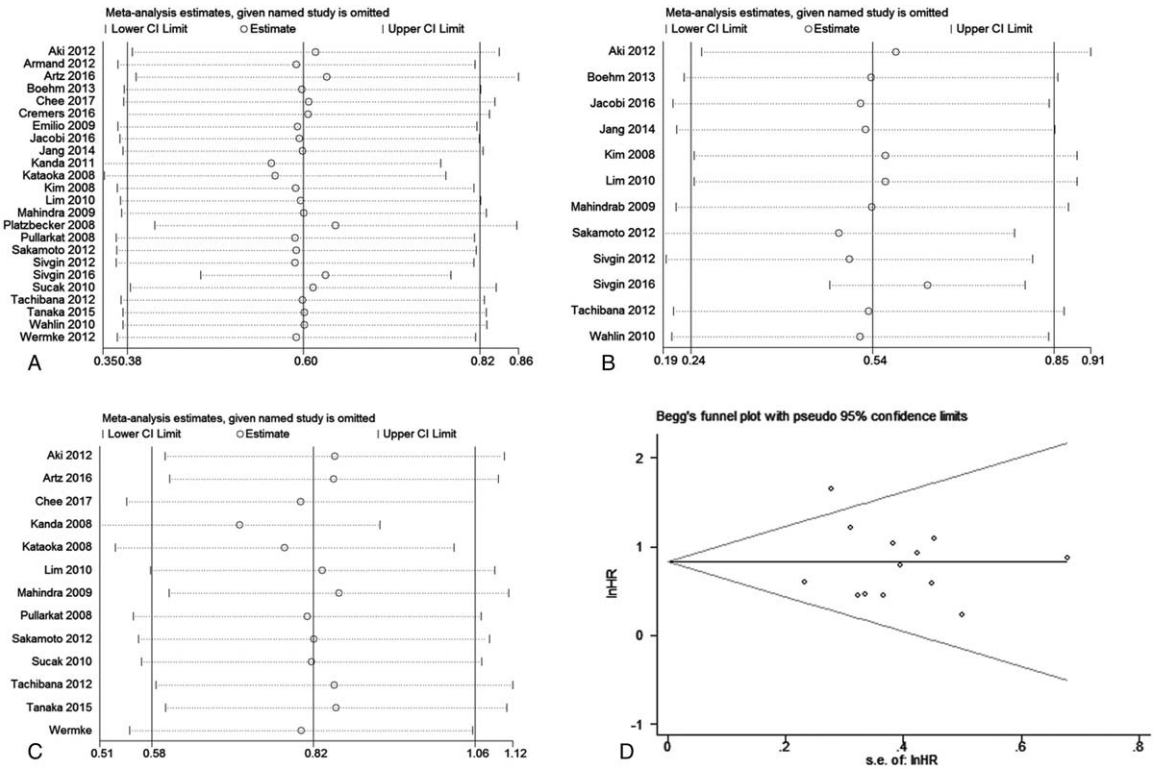

Figure 8. The sensitivity analyses for the pooled HRs of overall survival (A), progression-free survival (B), and nonrelapse mortality (C). The funnel plot for publication bias about the correlation serum ferritin with nonrelapse mortality (D).

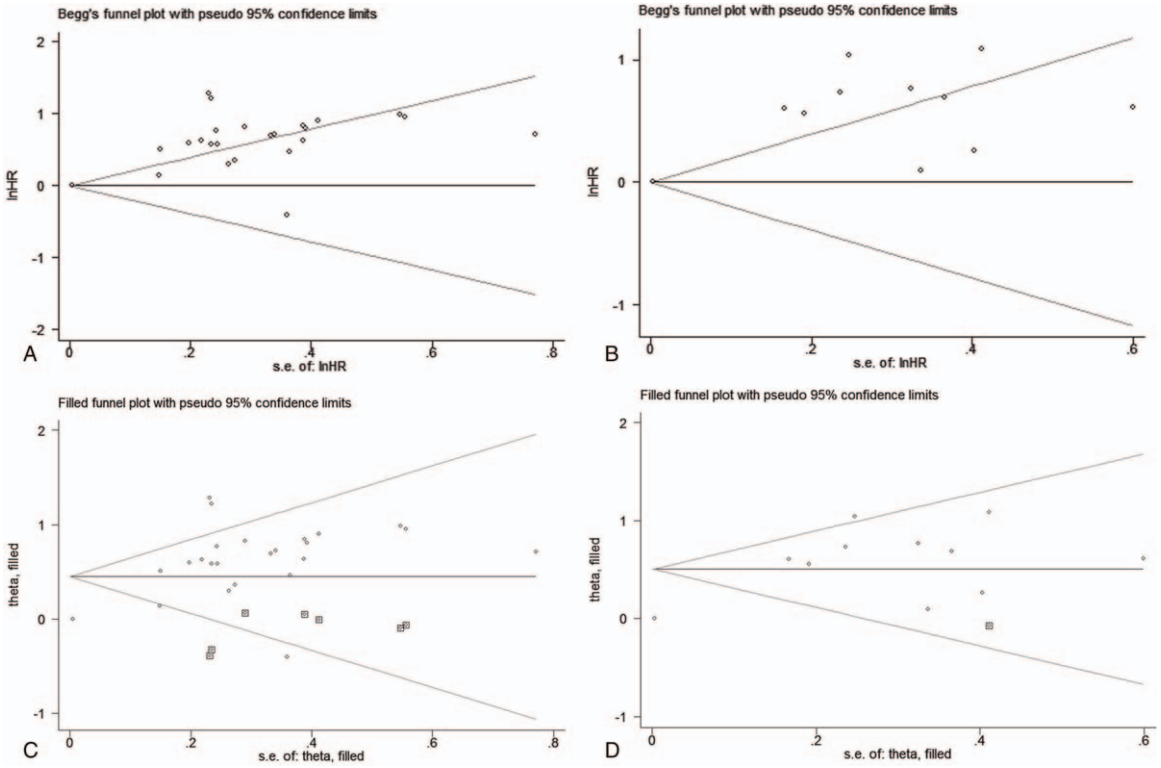

Figure 9. The funnel plots for publication bias about the correlation of SF with overall survival (A) and progression-free survival (B). The updated funnel plots for publication bias after trim-and-fill analysis about the correlation of SF with OS (C) and progression-free survival (D).

risk of NRM,[7,15,16,24,31] in our meta-analysis, the pooled HR suggested that elevated pre-transplantation SF level substantially increase the incidence of NRM. Therefore, decreasing pre-transplantation SF levels might help reduce the incidence of NRM. Similarly, our meta-analysis indicated that elevated pre-transplantation SF level was significantly related to BSI, which might partly explain the effect of elevated pre-transplantation SF on NRM. Some possible mechanisms responsible for the association between elevated pre-transplantation SF level and infection have been suggested. It was hypothesized that high SF levels could damage cellular immunity by affecting phagocytosis of immune cells.[36,37] In addition, the high SF might provide an advantageous environment for the growth of some opportunistic bacteria and fungi that are closely dependent on free iron.[36,37]

As mentioned above, our meta-analysis indicated that elevated pre-transplantation SF level impaired OS and PFS. However, a paradoxical result was found that elevated pre-transplantation SF level was associated with a lower incidence of cGVHD in patients undergoing allogeneic HSCT for hematological malignancies. Several relevant mechanisms might be in place to account for the superficially paradoxical results regarding long-term survival and cGVHD. It was reported that ferritin could play immunosuppressive roles in vitro and in vivo, and ferritin receptors were expressed on both T and B cells.[38,39] In addition, heavy chain ferritin could inhibit the proliferation of T cells in response to mitogen[40] and might play a critical role in immune-related diseases.[41] Thus, on the one hand, high ferritin levels might decrease the incidence of cGVHD via an immunosuppressive effect. On the other hand, in turn, an immunosuppressive effect from high SF might contribute to disease relapse and impairing OS and PFS in patients who undergo allogeneic HSCT for hematological malignancies. Regarding aGVHD, it has been reported that the decrease in aGVHD obtained by comprehensive preventive strategies was not able to reduce incidence of cGVHD in patients with allogeneic HSCT,[42,43] which might suggest that there is no association between aGVHD and c GVHD. In accordance with that, our meta-analysis showed that elevated pre-transplantation SF did not affect the incidence of aGVHD, but it still significantly decreased the incidence of cGVHD. Chronic GVHD is recognized as an immune-mediated syndrome, and its clinical manifestation is often similar to that of autoimmune disorders, but the pathophysiological mechanism responsible for cGVHD remains poorly elucidated. As to the pathophysiological mechanism underlying aGVHD, it has been hypothesized that a group of proinflammatory cytokines and chemokines released from damaged host tissues could activate host antigen-presenting cells, which are capable of promoting the proliferation and differentiation of infused donor T lymphocytes, causing target tissue destruction.[44] Thus, the difference between the pathophysiological mechanisms of acute and chronic GVHD might be an explanation for the results of our meta-analysis, which showed that pre-transplantation SF level exerted no substantial effect on the development of aGVHD, but decreased the incidence of cGVHD.

To the best of our knowledge, the present study is the most comprehensive meta-analysis investigating the effect of pre-transplantation SF on outcomes in patients undergoing allogeneic HSCT. However, our results should be interpreted with caution, considering that there are several potential limitations in our meta-analysis. First, the most important limitation is that the robustness of our conclusions might be challenged by the sound publication bias, although our trim-and-fill analysis and

sensitivity analysis in this meta-analysis showed that the pooled results did not change significantly. Second, the level of SF is highly correlated with the inflammatory state of the patients. Therefore, when our conclusions are applied to clinical practice, the clinicians should exclude the influence of inflammatory state of patients on the level of SF. Third, only studies published in English were included, and some high-quality articles published in other languages might have been excluded, which would increase the publication bias. Fourth, other than the separate investigation of patients with MDS, patients with different kinds of hematological malignancies were mixed in our study for the combined analysis, which might introduce substantial heterogeneity and a degree of distrust in our results. Fifth, the majority of the included studies in our meta-analysis were retrospective in design, which inevitably increases the risk of bias and affects the reliability of the combined results. Sixth, the cut-offs for SF were not consistent among the included studies, which might also introduce significant heterogeneity. Furthermore, the pooled results of studies with different cut-offs limited this study's reliability and the practicability of clinical guidance. At last, the duration of follow-up in the included studies differed considerably, which might affect the reliability of the pooled HRs for OS and PFS.

In conclusion, in patients undergoing allogenic HSCT for hematological malignancies, elevated pre-transplantation SF was significantly associated with worse OS and PFS, a higher incidence of NRM and BSI, and a lower incidence of cGVHD, but it had no effect on aGVHD. Considering the above limitations, more prospective and homogeneous clinical studies are demanded to further confirm our findings.

Acknowledgment

We sincerely thank the Editage for helping us edit our manuscript professionally.

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