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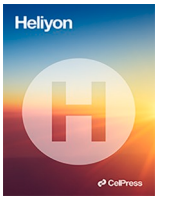

Research article

Association between the pre-transplantation serum ferritin level and outcomes of hematopoietic stem cell transplantation: A systematic review and meta-analysis

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A B S T R A C T

Background: Iron overload, as indicated by evaluated serum ferritin (SF) level, occurs commonly in patients with hematological diseases. To evaluate the association between pre-transplant SF level and outcomes of hematopoietic stem cell transplantation (HSCT), we performed this systematic review and meta-analysis.

Methods: PubMed, Embase, Web of Science and the Cochrane Library electronic database were searched from inception to August 2023, and 56 studies with 14149 patients were found to be eligible.

Results: An elevated pre-transplantation SF level was associated with inferior overall survival (hazard ratio [HR],1.77; 95 % confidence interval [CI],1.61–1.96) and disease-free survival (HR, 1.86; 95 % CI, 1.58–2.19), and increased risk of non-relapse mortality (HR, 1.73; 95 % CI, 1.49–2.02), and relapse (HR, 1.46; 95 % CI, 1.29–1.65). However, no meaningful association was observed between SF levels and acute graft-versus-host disease (GVHD) (risk ratio [RR], 1.09; 95 % CI, 0.96–1.24), or chronic GVHD (RR, 0.95; 95 % CI, 0.79–1.16). Furthermore, an elevated pre-transplantation SF level was associated with a higher risk of fungal infection (RR, 1.56; 95 % CI, 1.16–2.10), but not with bacterial infection (RR, 1.09; 95 % CI, 0.80–1.50). Moreover, an elevated pre-transplantation SF level was related to a higher risk of death due to relapse/disease progression (RR, 1.72; 95 % CI, 1.33–2.23) and infection (RR, 2.21; 95 % CI, 1.55–3.15), but not death due to GVHD (RR, 1.18; 95 % CI, 0.79–1.77).

Conclusions: A higher pre-transplantation SF level was significantly associated with a higher risk of relapse/disease progression and infections, which contributed to worse survival in patients undergoing HSCT. In particular, a higher SF level was related to a higher risk of fungal infection, indicating that patients with a higher pre-transplantation SF level require more attention regarding the risk of fungal infection after HSCT.

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1. Introduction

Iron plays crucial roles in various physiological processes within organisms, including DNA synthesis, energy metabolism, oxygen transportation and storage, as well as electron transfer [1]. However, excess ferrous iron can cause an accumulation of reactive oxygen species (ROS) through the Fenton reaction, ultimately leading to cell damage, cell death, and organ failure [2]. Iron overload is characterized by the serum ferritin (SF) level exceeding the upper limit of the normal range (>150–300 ng/mL), in the absence of acute or chronic infectious/inflammatory conditions [3]. While methods, such as magnetic resonance imaging, liver biopsy, and superconducting quantum interference device susceptometry are available for estimating iron overload [4,5], the SF level remains the most commonly used because of its easy accessibility.

Hematopoietic stem cell transplantation (HSCT) is widely acknowledged as one of the most effective therapeutic interventions for curing hematological diseases. Iron overload commonly occurs in patients with hematological diseases, likely stemming from frequent blood transfusions, reduced iron utilization due to impaired marrow function, and elevated transferrin saturation induced by high-dose chemo-/radiotherapy [6,7]. Some meta-analyses have indicated that an increased pre-transplantation SF level is associated with adverse outcomes following allogeneic HSCT (allo-HSCT) in patients with hematological malignancies (HM) [8–11]. Human leucocyte antigen (HLA)-identical sibling allo-HSCT is also considered a primary curative approach for patients diagnosed with hematological nonmalignant diseases (HNM), such as severe aplastic anemia (SAA) [12]. Patients requiring prolonged blood transfusion support are at a heightened risk of developing iron overload [13]; thus, the influence of the SF level on both HM and HNM should be examined separately. In addition, previous meta-analyses only included studies on allo-HSCT [8,9,14,15], warranting an examination of the correlation between the pre-transplantation SF level and the outcomes of autologous HSCT (auto-HSCT). Iron overload has been linked to an increased risk of hepatic sinusoidal obstruction syndrome (SOS) [16,17], infections [18], mucositis [19], and graft-versus-host disease (GVHD) [20], which can further negatively impact long-term survival after HSCT. However, a previously published meta-analysis failed to include numerous recent studies and did not thoroughly evaluate the association between the SF level and the risk of SOS after HSCT. Furthermore, the relationship of the pre-transplantation SF level to infections and GVHD remains controversial [11]. Therefore, a systematic review and meta-analysis was performed to gain a more thorough understanding of this field.

The primary objective of this review was to determine whether the evaluated pre-transplantation SF level was associated with: (1) overall survival (OS), (2) disease free survival (DFS), (3) non-relapse mortality (NRM), (4) relapse, (5) the risks of grades II-IV acute GVHD (aGVHD), (6) chronic GVHD (cGVHD), (7) SOS, or (8) infections. The secondary objectives were to analyze whether the associations were still significance in different subgroups defined by disease type (HM or HNM) and graft type (allogeneic, autologous HSCT, or umbilical cord blood transplantation).

2. Method

2.1. Registration and protocol

The systematic review protocol was registered on the "International Prospective Register of Systematic Review" with the registration number CRD42023448899. Additionally, this meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [21].

2.2. Eligibility criteria and search strategy

Prospective or retrospective cohort studies, as well as case-cohort studies were incorporated to examine the correlation between the pre-transplantation SF level and clinical outcomes among patients undergoing HSCT. Searches were conducted in PubMed, Embase, Web of Science, and the Cochrane Library database for articles published up to August 1, 2023 (Supplementary Table 1). The inclusion criteria were as follows: (1) assessed the association between SF levels and clinical outcomes in patients undergoing HSCT; (2) reported a hazard ratio (HR) or risk ratio (RR) and 95 % confidential interval (CI) for the associations or Kaplan-Meier plots from which the HR and 95 % CI could be estimated; (3) the number of patients was reported so that the RR could be calculated. Articles were excluded that met the following criteria: (1) non-English written studies, (2) reviews and meta-analyses, (3) case reports, (4) animal studies and *in vitro* studies, (5) book chapters, clinical guidelines, clinician perspectives, editorials, notes, comments, and letters without original studies, (6) SF level was measured post-transplantation, (7) no related outcomes of HSCT involving OS, DFS, NRM, relapse, aGVHD, cGVHD, infection, or SOS. A two-step selection process was employed to identify eligible studies. Three independent investigators (YXY, CHQ, and ZHY) conducted primary screening of all titles or abstracts. Subsequently, they assessed all potentially relevant articles through a comprehensive full-text reviews. Discrepancies were resolved through discussion and, when necessary, through consultation with a third investigator (WSF). This collaborative approach ensured consensus in the decision-making process.

2.3. Data extraction and quality assessment

Data extraction was independently conducted by three authors (WSF, PWJ, and TQP) using a standardized data collection form. The measures of associations were HRs, RRs, and 95 % CIs. Patients were categorized into higher and lower SF groups based on various cut-off values among the included articles. The outcomes of interest include OS, DFS, NRM, relapse, aGVHD, cGVHD, infection, SOS and causes of death (due to infection, progression or relapse, or GVHD). The characteristics recorded from the identified studies

include publication year, primary author, country, study design, cohort sample size, recruitment period, follow-up duration, age at enrollment, graft type, disease subtype, SF cut-off values, and outcome time point. In instances of discrepancies regarding study inclusion or data interpretation, a third investigator (XHW) was consulted to ensure consensus and accuracy.

2.4. Statistical analysis

Review Manager (RevMan) software version 5.4 (Cochrane, Copenhagen, Denmark) was used to analyze the data. A p-value of less than 0.05 was considered statistically significant for the effect of study-level variables. Multivariate-adjusted risk estimates were prioritized if they were reported in the original article; otherwise, unadjusted risk estimates were computed using the original data. In cases where HRs were not directly provided in the articles, Kaplan-Meier curves were analyzed using Engauge Digitizer version 12.1, and HRs along with their corresponding 95 % CIs were estimated using Richard Steven's Excel Workbook [22].

Cochran's Q-test and I^2 statistics were used to assess potential sources of heterogeneity in the included studies. Heterogeneity was considered statistically significant for the p-value <0.1 or I^2> 50 %. In such cases, a random-effect model was used instead of fixed-effect model [23].

Potential publication bias was evaluated using multiple methods, including funnel plots, Egger's linear regression test, and Begg's rank correlation test, with the significance level set at $p < 0.05$ [24]. If a publication bias was indicated, the trim and fill method using STATA version 12.0 (StataCorp LP, College Station, TX, USA) was employed. This method allowed for the estimation of the number of missing studies and recalculates the pooled risk estimate by incorporating these missing studies [25].

3. Results

3.1. Study selection and study characteristics

Among the 6851 records identified in the databases, 4410 titles and abstracts were screened, and 87 manuscripts were assessed for eligibility. Among them, 56 articles [26–81] with 13836 patients, were included in the meta-analysis (Fig. 1). Most of the included studies were retrospective, and only three were prospective. The Trials were performed in Asia (n = 26), Europe (n = 16), North America (n = 12), South America (n = 1) and Oceania (n = 1). Among the included studies, 49 involved patients with allo-HSCT, with three including only patients with umbilical cord blood transplantation (UCBT), six involved patients with auto-HSCT, and one study included patients with either allo- or auto-HSCT. Thirty-four studies recruited patient with hematologic malignancies, three studies enrolled patients with non-hematologic malignancies (severe aplastic anemia), and 19 studies included both hematologic and

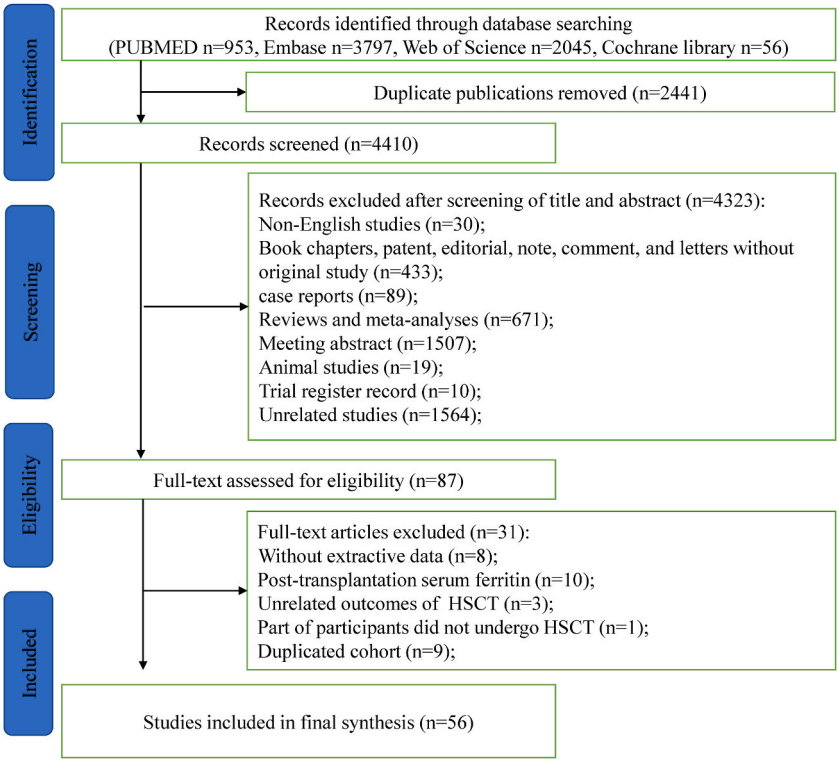


Fig. 1. Preferred reporting Items for systematic reviews and meta-analysis Flow Diagram.

non-hematologic malignancies. The SF cut-off level in the included studies varied greatly, ranging from 250 to 4000 ng/mL. Twenty-six studies employed an SF level threshold of 1000 ng/mL, five used 1500 ng/mL, four used 2500 ng/mL, three used 500 ng/mL, two studies used 2000 ng/mL, and others used independent thresholds. The characteristics of the included studies were summarized in Supplementary Table 2. We assessed study quality using the Newcastle-Ottawa quality assessment scale [82], with an average score of 7.4. Moreover, 54 of the studies achieved a score of six or higher (Supplementary Table 3).

3.2. The impact of pre-transplantation SF level on outcomes

3.2.1. Overall survival (OS)

Data to calculate the impact of the pre-transplantation SF level on OS among patients were available from 47 studies [26–41,43,45–49,51,53–56,58,60,61,63,65–72,74–76,78–80]. A random-effects model was used to calculate the pooled HR with 95 % CI due to moderate heterogeneity ($I^2 = 42$ %; $p = 0.001$). The results showed that OS was significantly poorer in the higher SF group (HR, 1.77; 95 % CI, 1.61–1.96; Fig. 2A). To investigate the origins of the heterogeneity, subgroup analyses were performed based on several parameters, including study location, cut-off value, variable type, disease type, graft type (allogeneic, or autologous HSCT) and outcome time point; However, no factor was identified that significantly altered the HR (Supplementary Table 4).

3.2.2. Disease free survival (DFS)

The relationship between higher pre-transplantation SF level and DFS was reported in 20 studies [26,27,29,34,36,37,39,40,45,46,49,54,61,64,68–70,72,75,78]. Considering the substantial heterogeneity ($I^2 = 52$ %; $p = 0.004$), the HR and 95 % CI were calculated

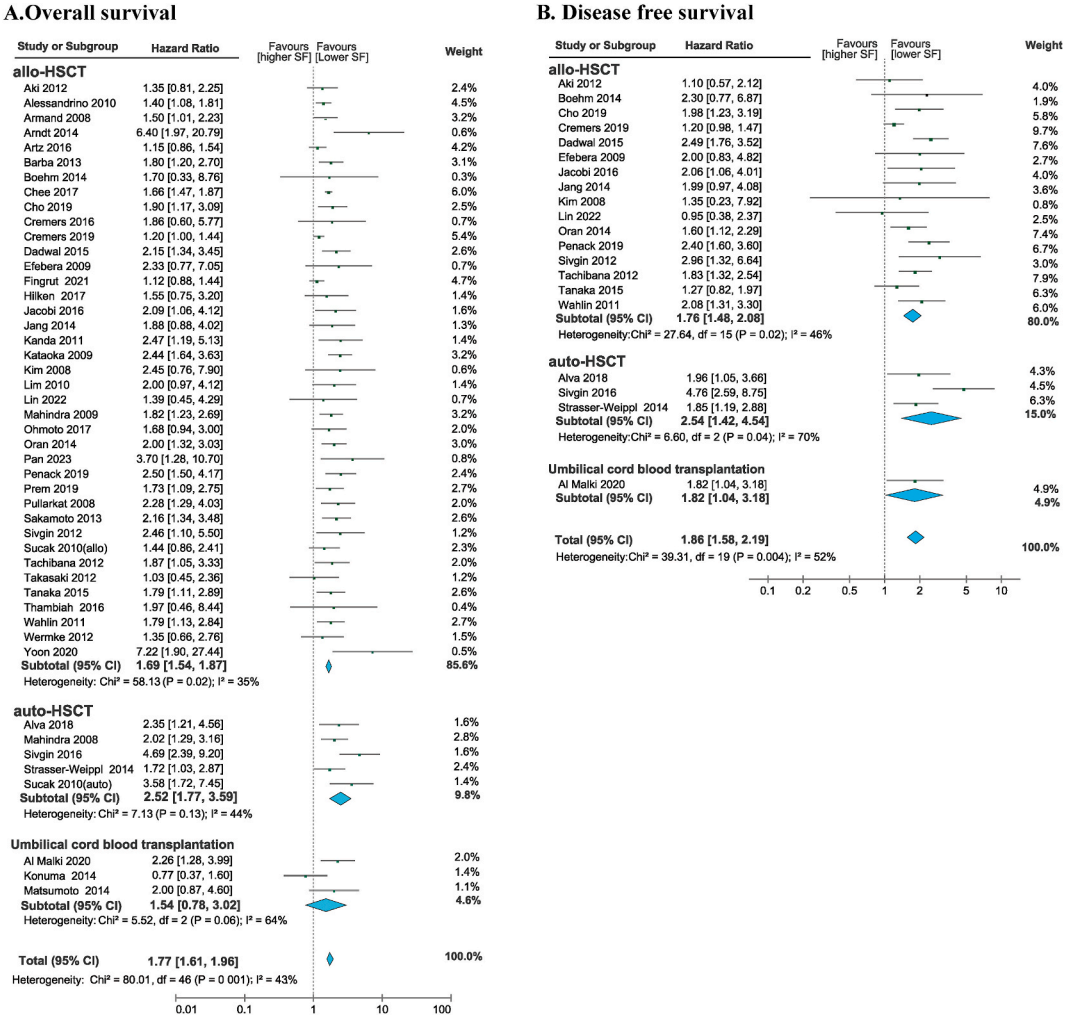


Fig. 2. Forest plots illustrating study specific and pooled hazard ratio (HR) and 95 % confidence interval (CI) for the effect of a higher serum ferritin (SF) level vs a lower SF level. **A:** Overall Survival, grouped by graft type (allogeneic, autologous, or umbilical cord blood transplantation); **B:** Disease-Free Survival, grouped by graft type (allogeneic, autologous, or umbilical cord blood transplantation).

using a random-effects model. The pooled estimate showed a significant association between higher SF level and inferior DFS (HR, 1.86; 95 % CI, 1.58–2.19; Fig. 2B). Additionally, subgroup analyses explored the potential sources of heterogeneity, examining various factors such as: study location, cut-off value, variable type, disease type, graft type, and outcome time point, and no factor was identified that significantly altered the HR (Supplementary Table 5).

3.2.3. Non-relapse mortality (NRM)

Pooled results from 19 studies [27,28,33,35–37,40,41,48,55,56,64,65,72,75,77–80] showed that the NRM was significantly higher in patients with a higher SF level (HR, 1.73; 95 % CI, 1.49–2.02; Fig. 3A) than in those with a lower SF level. Heterogeneity among the studies included in the analysis was moderate ($I^2 = 35$ %; $p = 0.06$). Subgroup analyses revealed that the association between the SF level and NRM remained significant according to study location, cut-off value, variable type, disease type, graft type, and outcome time point (Supplementary Table 6).

3.2.4. Relapse

Sixteen studies [27,33,35–37,41,46,48,53,55,60,64,67,75,78] analyzed the relationship between the SF level and relapse. The risk of relapse was significantly higher in patients with a higher SF level (HR, 1.46; 95 % CI, 1.29–1.65; Fig. 3B) without obvious heterogeneity ($I^2 = 22$ %; $p = 0.20$). The association between higher pre-transplantation SF level and the risk of relapse did not change in the subgroup analysis (Supplementary Table 7).

3.2.5. Grades II-IV aGVHD

Data from twenty-one studies [27,36,39,41,42,48,49,51–54,56,63,66–68,72,75,79–81], involving 3111 patients who underwent allo-HSCT, of whom 1318 developed grades II-IV aGVHD, were used to assess the influence of an elevated SF levels on the cumulative occurrence of grades II-IV aGVHD. Pooled analysis of the risk of grades II-IV aGVHD suggested no significant difference between a higher SF level versus lower SF level (RR, 1.09; 95 % CI, 0.96–1.24; Fig. 4A), with moderate heterogeneity ($I^2 = 52$ %; $p = 0.004$). The pooled RR did not reach significance in the subgroup analysis by study location, cut-off value, variable type, disease type, or graft type (Supplementary Table 8).

3.2.6. Chronic GVHD (cGVHD)

The cumulative incidence of cGVHD was investigated in 18 studies [27,36,40–42,48,49,51–54,56,63,67,68,72,75,81], with a total of 2307 participants and 833 developed cGVHD. The pooled RR showed that a higher SF level had no significant association with the incidence of cGVHD (RR, 0.93; 95 % CI, 0.78–1.12; Fig. 4B), with substantial heterogeneity ($I^2 = 55$ %; $p = 0.003$). The subgroup analysis revealed that patients with SAA with a higher pre-HSCT SF level tended to have a higher incidence of cGVHD (RR, 1.64; 95 % CI, 1.04–2.59; Fig. 4B). The pooled RR in other subgroups did not show significant changes (Supplementary Table 9).

3.2.7. Sinusoidal obstruction syndrome (SOS)

Data to calculate the impact of a higher SF level on the cumulative incidence of SOS among patients were available from eight studies [44,49,50,52,56,57,59,71], with a total of 1318 HSCT patients, of whom 388 patients developed SOS. The pooled RR suggested that patients with a higher SF level have a higher risk of SOS (RR, 2.11; 95 % CI, 1.12–3.98; Fig. 4C) with significant heterogeneity ($I^2 = 88$ %; $p < 0.0001$). The association between higher pre-transplantation SF level and the risk of SOS did not differ substantially in the subgroup analysis, except that elevated pre-transplantation SF level tended to be associated with an increased incidence of SOS in patients with hematologic malignancies (HR, 1.87; 95 % CI, 0.60–2.85; Supplementary Table 10).

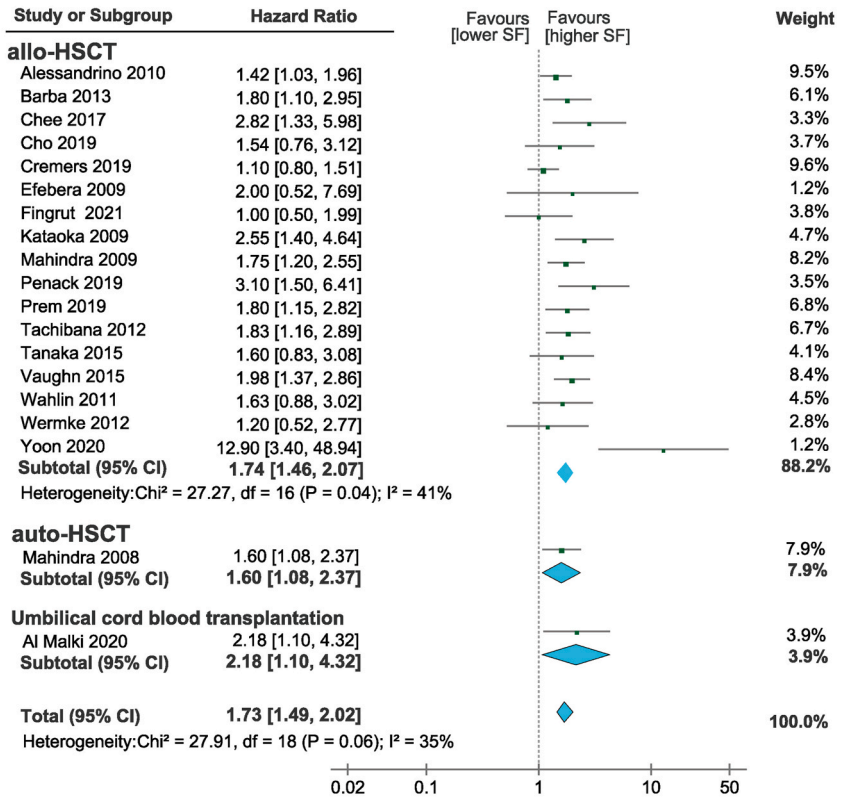
3.2.8. Infections

For extensive infections, data on 643 patients from six articles [27,45,49,52,60,68] were available. The pooled estimate showed a significant association between higher SF level and higher incidence of extensive infection (RR, 1.62; 95 % CI, 1.12–2.36; Fig. 5A) with substantial heterogeneity ($I^2 = 70$ %; $p = 0.005$). For fungal infection, the SF level was examined in six studies [39,62,71,75,79,81] with 1244 participants and 166 fungal infections. The association between higher SF level and higher risk of fungal infection was significant (RR, 1.56; 95 % CI, 1.16–2.10; Fig. 5B) without heterogeneity ($I^2 = 0$ %; $p = 0.78$). However, for bacterial infections, the pooled results from four studies [47,75,79,81] with 470 participants and 208 bacterial infections showed no significant association between the higher SF group (RR, 1.09; 95 % CI, 0.80–1.50; Fig. 5C) and the lower SF group, with substantial heterogeneity ($I^2 = 53$ %; $p = 0.09$).

3.2.9. Cause of death

To examine the correlation between the pre-transplantation SF level and various post-HSCT mortality factors, three primary causes: relapse or disease progression, infections, and GVHD were examined. The pooled results from four studies [35,40,56,64] (1181 participants and 216 deaths due to relapse or disease progression) showed that death due to relapse or disease progression was significantly higher in the higher SF group (RR, 1.72; 95 % CI, 1.33–2.23; Fig. 6A) than in the lower SF group, without heterogeneity ($I^2 = 0$ %; $p = 0.55$). Pooled results from seven studies [35,40,48,56,63,64,75] (1700 participants and 129 deaths due to infection) indicated that death due to infection was also significantly increased in the higher SF group (RR, 2.21; 95 % CI, 1.55–3.15; Fig. 6B) compared to the lower SF group without heterogeneity ($I^2 = 0$ %; $p = 0.65$). the pooled results from seven studies [35,40,48,52,56,63,75] (1462 participants and 92 deaths due to GVHD) suggested that the risk of death due to GVHD was not significantly different between the two groups (RR, 1.18; 95 % CI, 0.79–1.77; Fig. 6C) without heterogeneity ($I^2 = 0$ %; $p = 0.92$).

A. Non-relapse mortality



B. Relapse

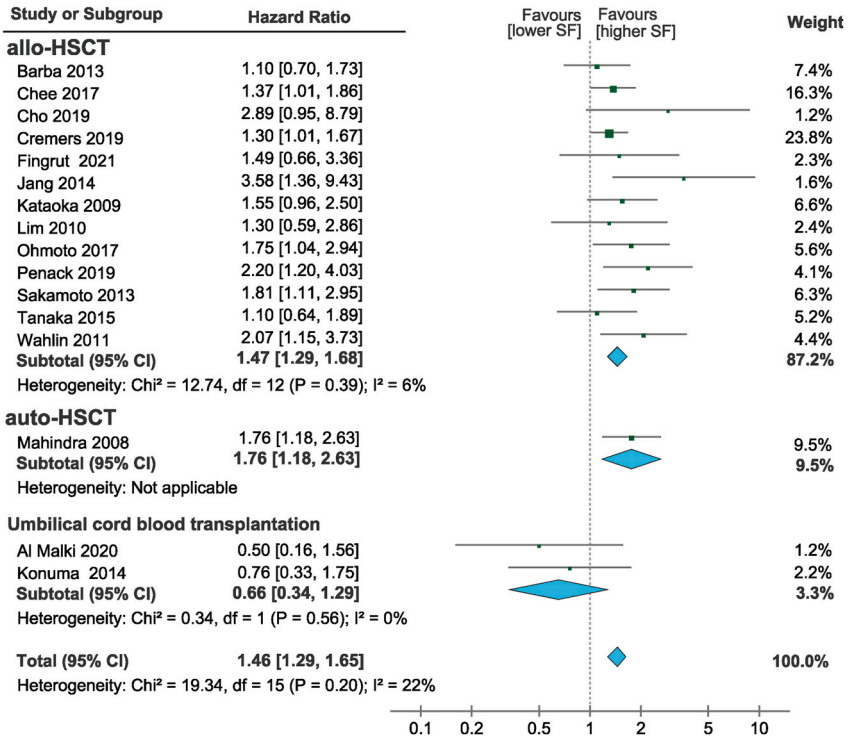


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Fig. 3. Forest plots illustrating study specific and pooled hazard ratio (HR) and 95 % confidence interval (CI) for the effect of a higher serum ferritin (SF) level vs a lower SF level. **A:** Non-Relapse Mortality, grouped by graft type (allogeneic, autologous, or umbilical cord blood transplantation); **B:** Relapse, grouped by graft type (allogeneic, autologous, or umbilical cord blood transplantation).

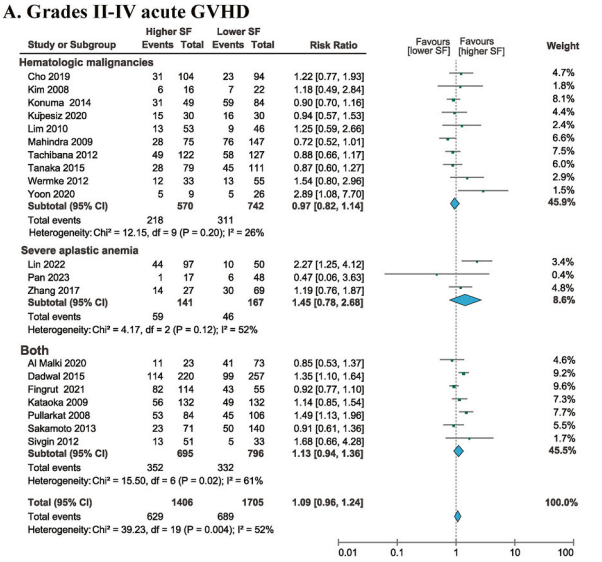

Fig. 4. Forest plots illustrating study specific and pooled risk ratio (RR) and 95 % confidence interval (CI) for the effect of a higher serum ferritin (SF) level vs a lower SF level. **A:** Grade II-IV acute GVHD, grouped by disease type (hematological malignancies, severe aplastic anemia, or both); **B:** chronic GVHD, grouped by grouped by disease type (hematological malignancies, severe aplastic anemia, or both); **C:** hepatic sinusoidal obstruction syndrome.

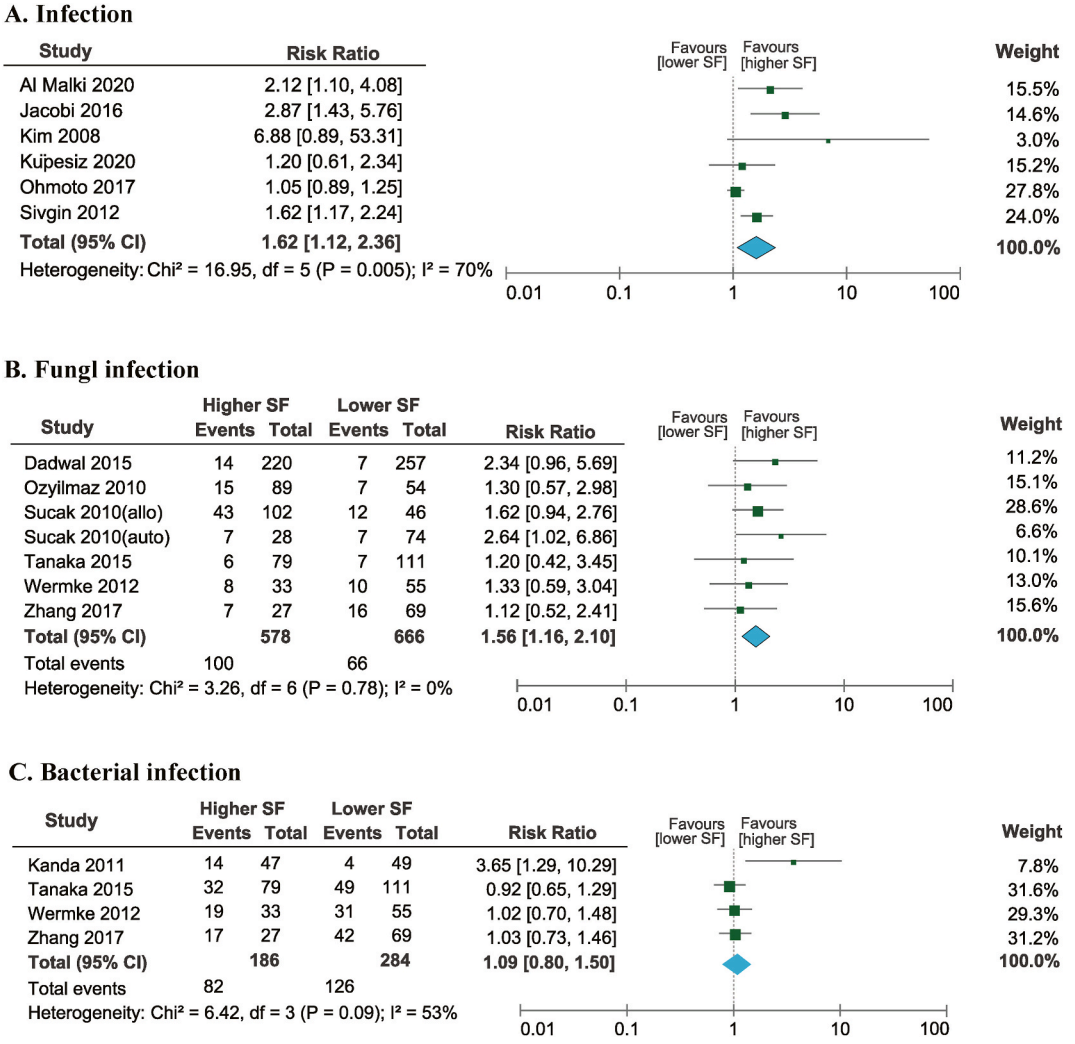

Fig. 5. Forest plots illustrating study specific and pooled risk ratio (RR) and 95 % confidence interval (CI) for the effect of a higher serum ferritin (SF) level vs a lower SF level. **A:** extensive infection; **B:** fungal infection; **C:** bacterial infection.

3.3. Sensitivity analysis and publication bias

To ensure the robustness of our findings for OS, DFS, NRM, relapse rates, aGVHD, cGVHD, infection, and causes of mortality, sensitivity analyses were conducted by omitting one study at each turn. Overall, the sensitivity analyses revealed no alteration in the significance or direction of effect for the association between the pre-transplantation SF level and OS, DFS, NRM, relapse, aGVHD, cGVHD, SOS, infection, or causes of death, suggesting that the overall combined risk estimates were robust.

Egger and Begg tests were conducted along with funnel plots to evaluate potential publication bias in our meta-analysis. Funnel plots indicated no apparent publication bias for DFS (Begg test: $p = 0.974$; Egger test: $p = 0.099$; Supplementary Fig. 1), relapse (Begg test: $p = 0.499$; Egger test: $p = 0.494$; Supplementary Fig. 2), aGVHD (Begg test: $p = 0.112$; Egger test: $p = 0.363$; Supplementary Fig. 3), or cGVHD (Begg test: $p = 0.303$; Egger test: $p = 0.773$; Supplementary Fig. 4); however a significant publication bias was observed for OS (Begg test: $p = 0.150$; Egger test: $p = 0.001$; Supplementary Fig. 5) and NRM (Begg test: $p = 0.234$; Egger test: $p = 0.024$; Supplementary Fig. 6).

A trim-and-fill analysis was conducted to assess the impact of potential publication bias on OS and NRM in our meta-analysis. For OS, adding 17 missing studies led to total of 64 included studies, and for NRM, adding 5 missing studies led to a total of 24 included studies. The updated funnel plots for publication bias regarding the association of the SF level with OS (Supplementary Fig. 7) and NRM (Supplementary Fig. 8) appeared to be relatively symmetrical. Importantly, the updated pooled HRs remained largely unchanged: 1.53 (95 % CI: 1.38–1.69; $p < 0.001$) for OS and 1.555 (95 % CI: 1.309–1.846; $p < 0.001$) for NRM. This suggests that the pooled HRs for OS and NRM in our meta-analysis remained stable.

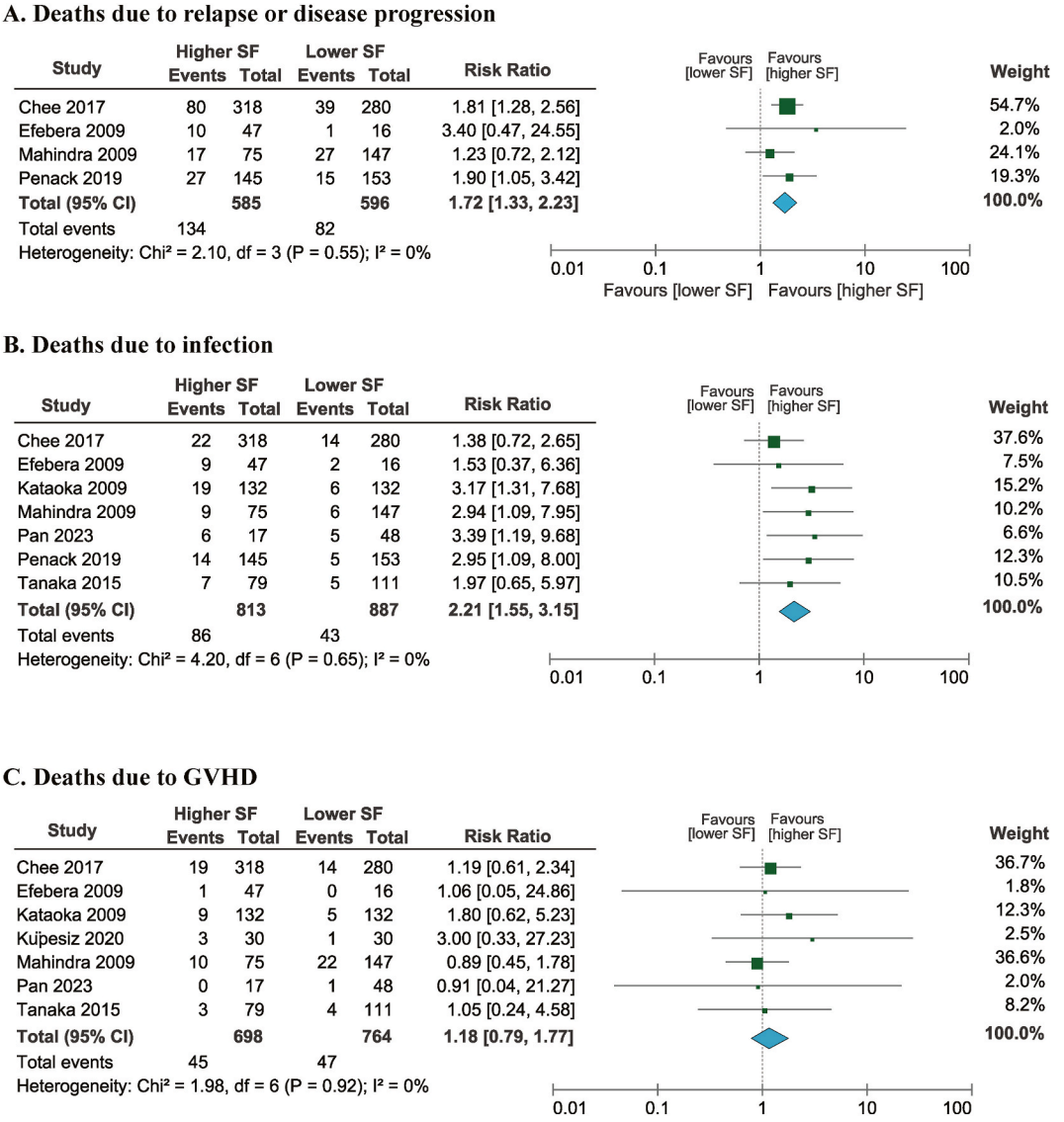

Fig. 6. Forest plots illustrating study specific and pooled risk ratio (RR) and 95 % confidence interval (CI) for the effect of a higher serum ferritin (SF) level vs a lower SF level. **A:** death due to relapse/disease progression; **B:** death due to infection; **C:** death due to GVHD.

4. Discussion

This meta-analysis highlighted that a higher pre-transplantation SF level was associated with inferior OS and DFS, as well as an increased risk of NRM, relapse and SOS. However, no association was found between the SF levels and grades II-IV aGVHD, or cGVHD. In addition, a notable relationship was observed between an elevated pre-transplantation SF level and a higher risk of infections, particularly fungal infection. Furthermore, a higher pre-transplantation SF level was correlated with an increased risk of death due to relapse/disease progression and infection, but not due to GVHD.

4.1. Results in relation to other studies

Although several previous meta-analyses have reported that a higher SF is related to inferior OS and increased NRM [8–11,14], they lack a more comprehensive description of the relationship between the SF levels and other outcomes of HSCT, such as GVHD, SOS, and infection, which increase the risk of transplant-related mortality and long-term survival. Only one meta-analysis conducted by Yan et al. [11] analyzed the relationship between SF level and the multiple outcomes of allo-HSCT. However, they did not include many recently published papers and did not perform sensitivity analysis, subgroup analysis, or publication bias analysis for the association of a higher SF level with acute/chronic GVHD and infection. In our meta-analysis, the association between the SF level and OS, DFS,

NRM, relapse, SOS, aGVHD, and cGVHD were systematically analyzed, and subgroup analyses by study location, cut-off value, variable type, disease type, graft type and outcome time point were performed. Sensitivity analyses indicated that our results for OS, DFS, NRM, relapse, aGVHD, cGVHD, SOS, infection, and causes of death were robust to a degree.

Previous studies focused only on the impact of the SF level on outcomes of allo-HSCT. In our meta-analysis, studies involving allo- and auto-HSCT were included in subgroup analysis. Subgroup analyses showed that an elevated pre-transplantation SF level was significantly associated with inferior OS and DFS, as well as higher risks of NRM and relapse in patients with allo- and auto-HSCT. These results highlight the importance of maintaining the SF level within a reasonable range before transplantation in both allo- and auto-HSCT. Importantly, several studies have demonstrated significant reductions in the SF level and notable improvements in OS and DFS after treatment of iron chelation before or after HSCT [83–86]. Pan et al. [63] suggested that chelating excess iron to an SF level below 1000 ng/mL is necessary and could potentially improve outcomes. However, attempts to reduce pretreatment ferritin levels should not interfere with the timing of transplantation in high-risk acute leukemia patients eligible for allogeneic hematopoietic cell transplantation (HCT).

Graft-versus-host disease, which results from allo-responses triggered by donor T-cells against recipient histocompatibility antigens, poses a significant challenge in patients undergoing allo-HSCT. It is closely linked to adverse outcomes and diminished long-term quality of life [87]. To date, data regarding the role of the pre-transplantation SF level in the pathogenesis of GVHD are controversial and often inconsistent. A previous meta-analysis reported that higher a SF level was strongly related to a lower incidence of cGVHD (OR, 0.74; 95 % CI: 0.58–0.96; $p < 0.05$), but not aGVHD (OR, 1.08; 95 % CI: 0.72–1.62; $p = 0.70$) [11]. In contrast, our meta-analysis indicated that an elevated pre-transplantation SF level was not significantly related to grade II-IV aGVHD (RR, 1.09; 95 % CI, 0.96–1.24), or cGVHD (RR, 0.93; 95 % CI, 0.78–1.12). In addition, our meta-analysis showed that a higher pre-transplantation SF level was significantly associated with a higher risk of death due to relapse/disease progression and infection, which may contribute to worse survival in patients undergoing HSCT, but is not associated with a risk of death due to GVHD. These findings suggest that a higher pre-transplantation SF level is not associated with GVHD.

Hepatic sinusoidal obstruction syndrome, commonly known as veno-occlusive disease of the liver, is an early complication of HSCT. It should be noted that our study was the first meta-analysis to estimate the association between the SF level and the risk of SOS. The pooled RR indicate that the pre-transplantation SF level act as a significant risk factor for developing SOS. An elevated SF level indicates iron overload, which can catalyze the formation of hydroxyl radicals, leading to hepatic tissue injury. Chueh et al. demonstrated that iron-chelating therapy using deferasirox effectively reduced the pre-transplantation SF level and, subsequently decreased the incidence of hepatic SOS following allo-HSCT [88].

In addition to causing oxidative stress, iron also serves as a crucial cofactor in the growth of numerous microbial pathogens [89]. An elevated SF level can create an environment conductive to the proliferation of bacteria and fungi that rely heavily on freely available iron [90]. In addition, iron overload can adversely affect the phagocytosis of immune cells [91], which may damage the immune barrier and lead to infection. Therefore, it is intriguing to speculate on the impact of an elevated SF level in patients with infections who had HSCT. As expected, the pooled results showed that an elevated pre-transplantation SF level was associated with an increased risk of infection. Unexpectedly, an elevated SF level was not significantly related to bacterial infection, but was related to an increased risk of fungal infection. Owing to the use of antibiotics, antibacterial prophylaxis is strongly considered for recipients of HSCT, as infections can be effectively prevented [92]. In a cohort of 112 patients with hematological malignancies who had allo-HSCT without antibacterial prophylaxis, Kanda et al. [47] found that a higher pre-transplantation SF level was a significant risk factor for bacterial infection. However, other cohorts [75,79,81]of patients who received antibacterial prophylaxis, did not show a significant association between the SF level and bacterial infection. Although fluconazole prophylaxis has decreased the occurrence of fungal infections caused by susceptible microorganisms, it has led to a subsequent increase in resistant species [93]. Therefore, patients with a high pre-transplantation SF level need more attention regarding the risk of fungal infection.

Since the course of post-HSCT is quite long, any outcomes can occur immediately after HSCT or can occur even more than one year after HSCT. Long-term outcomes may have been influenced by various factors after HSCT. The occurrence of outcomes such as aGVHD, cGVHD and SOS is defined by specific diagnostic criteria: aGVHD occurs within 100 days after transplantation, cGVHD appears after 100 days, and SOS occurs within 30 days post-transplantation. While, the reported outcome measures (such as OS, DFS, NRM, Relapse) among the included studies span different time points, including 1-year, 2-year, 3-year, 4-year, 5-year and 6-year intervals. In our meta-analysis, we conducted subgroup analyses based on outcome time points, and results indicated that the associations between pre-transplantation SF level and the outcomes (including OS, DFS, NRM, Relapse) were still significant. Subgroup analyses based on variable type (univariate analysis or multivariate analysis) showed that the overall combined risk estimates were not significantly altered. Therefore, we suggested that the impact of pre-transplant SF levels on survival after transplantation is long-term and independent. However, regarding to the occurrence of infections post-transplantation, some of the studies included in our meta-analysis lack specific timing details. Thus, whether elevated pre-transplant SF level affects only early infections after HSCT or has a long-term impact on infections requires further extensive and detailed research to confirm.

4.2. Limitations of the review

In addition to the aforementioned strengths, our meta-analysis has several limitations. First, the cut-off SF level differed among the included studies. Although SF > 1000 ng/mL is commonly regarded as iron-overload, several studies have calculated the impact of the SF level using different thresholds. By subgroup analysis, it was show that SF > 1000 ng/mL was significantly associated with poorer OS and DFS and increased NRM; however, we cannot suggest that 1000 ng/mL is the optimal threshold for iron-overload, which may influence the outcomes of HSCT. Second, the follow-up duration varied considerably among the included studies, which could have

impacted the reliability of the pooled results. Third, the number of studies specific to each subtype of hematological malignancy remains insufficient as most studies have included patients with different types of hematological malignancies. Tachibana et al. [94] indicated that the pre-HSCT serum ferritin level is significantly associated with the outcome of acute myeloid leukemia, but not acute lymphocytic leukemia. These subtypes differ with regard to disease biology; thus, they should be analyzed separately. In this meta-analysis, the association between the SF level and HM and HNM was analyzed separately.

5. Conclusions

This study highlights that a higher pre-transplantation SF level is associated with inferior OS and DFS in both allogeneic and autologous HSCT patients. Our results suggest that there may be an increased risk of relapse and infection in patients with a higher pre-transplantation SF level, which contribute to worse OS. Unexpectedly, a higher SF level was related to a higher risk of fungal infection, but not bacterial infection, indicating that patients with a high pre-transplantation SF level require greater attention paid to the risk of fungal infection after HSCT. Overall, our meta-analysis serves as a valuable resource to inform clinical practice and guide the development of individualized preemptive or therapeutic strategies to enhance HSCT outcomes. Therefore, well-designed prospective studies are necessary to deepen our understanding of this relationship. Crucially, these studies should aim to determine whether early iron chelation therapy can enhance OS following HSCT.

Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SF, Serum ferritin; HSCT, Hematopoietic stem cell transplantation; OS, Overall survival; DFS, Disease-free survival; NRM, Non-relapse mortality; SOS, Sinusoidal obstruction syndrome; ROS, Reactive oxygen species; MRI, Magnetic resonance imaging, SQID, Superconducting quantum interference device; HM, Hematological malignancies; HNM, Hematological non-malignant disease; SAA, Severe aplastic anemia; HR, Hazard ratio; RR, Risk ratio; CI, Confidence intervals; allo-HSCT, allogeneic HSCT; auto-HSCT, autologous HSCT; UCBT, Umbilical cord blood transplantation; VOD, Veno-occlusive disease.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability statement

Data associated with my study has not been deposited into a publicly available repository. All data generated or analyzed during this study are included in this article and its supplementary material files.

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CRediT authorship contribution statement

Wenjue Pan: Writing – original draft, Resources, Investigation, Formal analysis, Data curation, Conceptualization. **Qibei Teng:** Writing – original draft, Resources, Investigation, Formal analysis, Data curation, Conceptualization. **Huiqiao Chen:** Resources, Investigation, Formal analysis. **Liangning Hu:** Resources, Investigation, Formal analysis. **Xiaoyan Yue:** Resources, Investigation, Formal analysis. **Zijun Qian:** Software, Methodology, Formal analysis. **Ruoyu Dong:** Software, Methodology, Conceptualization. **Hongyu Zhou:** Software, Methodology, Formal analysis. **Xiujie Zhao:** Software, Methodology, Formal analysis. **Haowen Xiao:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition. **Shufen Wang:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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