Meta-Analysis of Observational Studies in Epidemiology

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The impact of iron chelation therapy on patients with lower/intermediate IPSS MDS and the prognostic role of elevated serum ferritin in patients with MDS and AML

A meta-analysis

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Abstract

Serum ferritin (SF) has been identified as a potential prognostic factor for patients undergoing stem cell transplantation, but the prognostic value of SF in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) patients and the impact of iron chelation therapy (ICT) on MDS patients are controversial. The present meta-analysis aimed to better elucidate these relationships.

Three electronic databases were searched systematically to identify reports on the prognostic role of SF in MDS and AML patients, and those investigating the impact of ICT on prognosis of MDS patients. The hazard ratios (HRs) and its 95% confidence interval (95%CI) were extracted from the identified studies using Cox proportional hazard regression model for overall survival (OS) and progression of MDS to AML.

Twenty reports including 1066 AML patients and 4054 MDS patients were included in present study. The overall pooled HRs for OS of AML and MDS patients with elevated SF prior to transplantation was 1.73 (1.40–2.14), subgroup analyses stratified by the cut-off value of SF ≥1400/1000 ng/mL showed that the pooled HRs were 1.45 (0.98–2.15) and 1.65 (1.30–2.10), respectively. The pooled HRs for ICT in MDS patients was 0.30 (0.23–0.40). For ICT, the pooled HRs for the progression of MDS to AML was 0.84 (0.61–1.61).

SF has a negative impact on the OS of AML and MDS patients when it is higher than 1000 ng/mL. ICT can improve the OS of MDS patients with iron overload but it is not associated with the progression of MDS to AML.

Abbreviations: 95%CI = 95% confidence interval, AML = acute myeloid leukemia, HR = hazard ratio, HSCT = allogeneic hematopoietic stem cell transplantation, ICT = iron chelation therapy, IPSS = international prognostic scoring system, MDS = myelodysplastic syndromes, OS = overall survival, SF = serum ferritin.

Keywords: acute myeloid leukemia, iron chelation therapy, iron overload, myelodysplastic syndromes, serum ferritin

1. Introduction

Myelodysplastic syndromes (MDS), a heterogenous group of hematopoietic stem cell malignance, is characterized by peripheral cytopenias and has a high tendency to transform into acute myeloid leukemia (AML).[1,2] AML is a type of malignant hematologic disorder which is manifested with infiltration of the bone marrow, blood, and other tissues by proliferating, clonal, abnormally differentiated, and occasionally poorly differentiated cells of the hematopoietic system.[3] Long-term survival for AML patients after undergoing standard chemotherapy is only achieved in 35% to 45% of such patients, especially those younger than 60 years, and 10% to 15% of those aged 60 years and older.[4]

Iron overload can lead to liver dysfunction, hepatic sinusoidal obstruction syndrome and other problems, which substantially influencing mortality and long-term survival of patients.[5–7] Liver biopsy is the gold standard for evaluating iron overload, and serum ferritin (SF) is a commonly utilized surrogate index of body iron stores due to its easy availability and it avoids the procedural risks associated with liver biopsy.[8] However, elevated SF has low specificity as a predictor of elevated liver-iron content, and SF level can be affected by circulating iron levels, inflammatory status, and cellular apoptosis.[1,9,10]

Chronic blood transfusion is used to improve anemia and to increase the quality of life and decrease the probability of non-

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YY and ZT contributed equally to this work.

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leukemic death in MDS patients. However, it is associated with iron overload.[1] Iron chelation therapy (ICT) is commonly for patients with transfusional iron overload due to chronic transfusion-dependent anemias, such as sickle cell disease or β-thalassemia, and is also used in some patients with MDS.[11–13]

Several clinical studies, using different cut-off values of SF ranging from 300 ng/mL to 2500 ng/mL, have found that elevated SF prior to transplantation may be associated with the poor prognosis in patients with hematological malignancies.[14–19] In addition, a previously published meta-analysis, which had significant publication bias, reported that elevated pre-transplantation SF has a negative prognostic role in patients with hematological malignancies.[20] However, authors did not perform subgroup analyses stratified by the cut-off value of SF for AML and MDS patients to provide a reliable result. In addition, a meta-analysis[21] with a small sample size including MDS patients concluded that a SF of more than 500 ng/mL had a negative impact on OS at the pre-transplantation stage yet, a significant heterogeneity was found in the pooled analysis of this meta-analysis, which may could introduce bias in the pooled results.

There are controversies concerning the prognostic value of SF in AML and MDS patients, and the impact of ICT on prognosis of MDS patients. We therefore performed this meta-analysis to better elucidate the association between elevated SF and overall survival (OS) of MDS and AML patients, as well as investigate the impact of ICT on OS of MDS patients and the progression of MDS to AML.

2. Materials and methods

2.1. Search strategy

In November 12, 2018, we performed a comprehensive literature search on PubMed, China National Knowledge Infrastructure and Web of Science, aiming to identify all original reports that investigated whether elevated SF are associated with a worse OS of patients with MDS and AML, or studies that examined the impact ICT on OS of MDS patients and the progression of MDS to AML. The publication language was restricted to articles published in English or Chinese. The following search keywords were used: ("Serum ferritin" OR "Ferritin" OR " Iron overload" OR " Iron Chelation") AND ("MDS" OR " Myelodysplastic Syndrome" OR "Acute myeloid leukemia" OR "AML") AND (" Survival" OR "prognoses" OR "Prognosis"). Furthermore, we scrutinized the reference lists of the identified reports, meta-analyses, reviews, and other relevant publications to identify additional studies on the topic. This study did not require ethical approval as all the data used have been published previously, and hence are already in the public domain.

2.2. Eligibility criteria

Published studies were included if they met the following criteria:

(1) studies including patients diagnosed with AML or MDS;
(2) the serum SF and/or ICT were reported;
(3) a multivariate analysis of therapy outcome was performed to find the risk factors associated with the prognosis of AML and/or MDS patients;
(4) the hazard ratios (HRs) with its 95% confidence interval (95%CI) and the corresponding *P* value associated with SF and/or ICT in multivariate Cox models can be extracted.

Studies were excluded based on following criteria:

(1) animal studies;
(2) review articles or case reports;
(3) duplicate publication;
(4) non-English or non-Chinese papers; and
(5) studies that included other hematologic malignancies (primary myelofibrosis, non-Hodgkin lymphoma, chronic myelomonocytic leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, etc); and
(6) studies that provided only data on HRs and its 95%CI for univariate analysis but not for multivariate analysis models.

2.3. Data extraction

Data extraction was carried out by 2 investigators independently (Yuan Yang and Zengwei Tang). If discrepancies occurred, they were resolved through consensus. Data related to the study characteristics were extracted including the following variables: the first author of the study, study design and duration, year of publication, number of participants in each study with mean age and gender, the SF level prior to chemotherapy/transplantation therapy, the type of ICT, the independent risk factor of OS, the value of HRs and their 95% CI for each clinicopathological factor associated with the prognosis of MDS and/or AML patients, and the number of cases progressing from MDS to AML. For 2 studies[19,37] that did not provide the value of HRs and 95% CI, we digitized and extracted the data from the Kaplan–Meier curve using the software designed by Jayne F Tierney and Matthew R Sydes.[22]

2.4. Quality assessment across studies

Quality assessment of the studies included was performed by the modified risk of bias tool recommended by the Cochrane Collaboration as described previously.[23,24] Moreover, 7 of the best differentiating items were selected from the QUADAS checklists.

2.5. Statistical analysis

All the statistical analyses were performed according to the guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology group (MOOSE).[25] The pooled HRs with its 95% CI were calculated with a random-effect model according to the DerSimonian-Laird method to determine the association of elevated SF or ICT with a worse OS of patients with MDS and/or AML.[26] Moreover, the pooled risk ratio (RR) with its 95% CI was calculated to investigate the impact of ICT on the progression of MDS to AML, using the Mantel–Haenszel method. The heterogeneity among included studies was measured using the Q tests and I^2 statistic to assess the extent of the inconsistency.[27] A probability value of $P < .1$ and $I^2 > 50\%$ indicated the existence of significant heterogeneity.[26] A funnel plot and the Egger linear regression test were applied to evaluate potential publication bias among eligible studies using OS as the endpoint.[28] Moreover, a $P < .01$ for Egger test was considered statistically significant. All statistical analyses were performed with Stata/MP 14.0 (StataCorp, Parallel Edition).

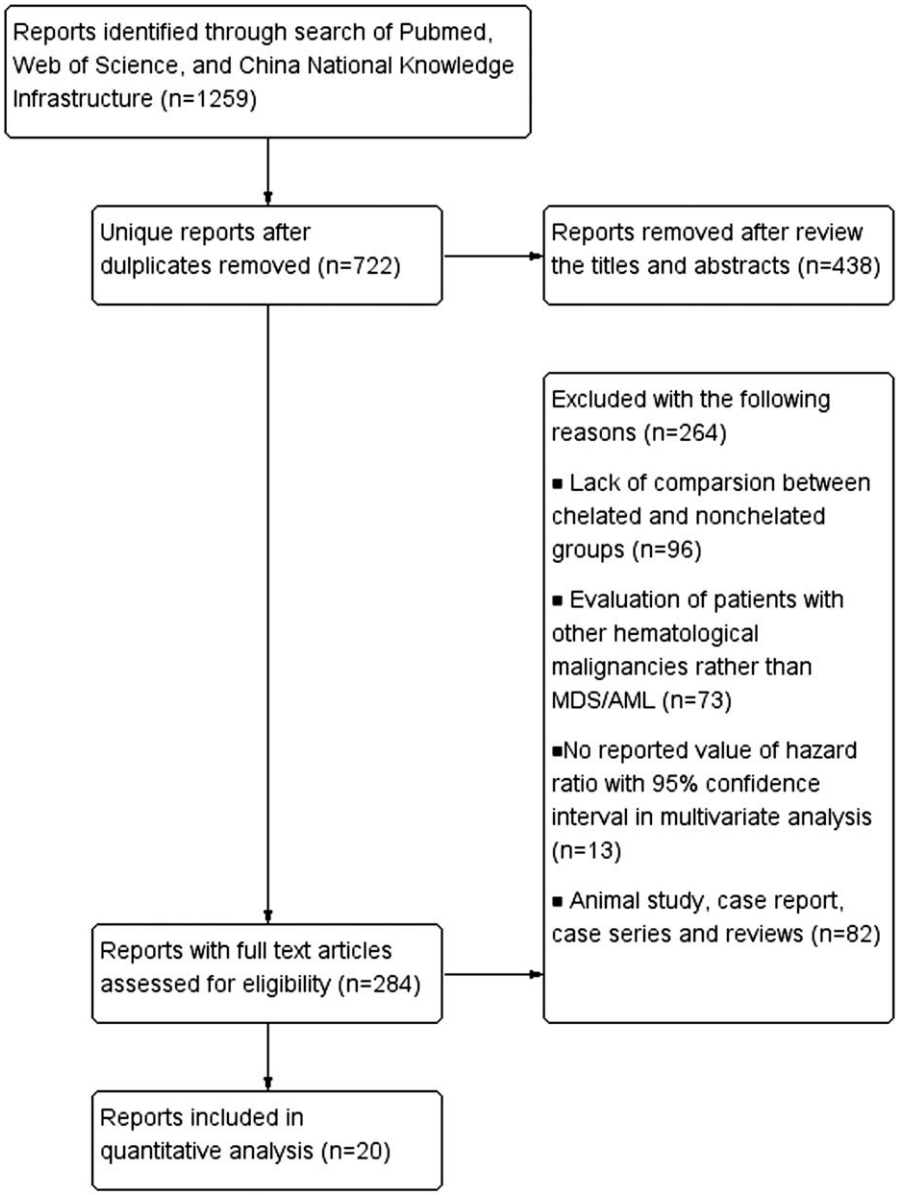

Figure 1. Diagram showing the literature searching work flow.

3. Results

3.1. Study selection

The initial literature research yielded 1259 articles from the three primary electronic databases, of which 284 papers were selected for full-text review. The remaining 438 publications were excluded after reviewing the titles and abstracts. Among the publications selected for full-text reviewing, according to the inclusion and exclusion criteria, 20 articles[5,14,15,17–19,21,29–41] were eligible for this meta-analysis. The detailed screening process is depicted in Figure 1.

3.2. Study and participants characteristics

A total of 20 observational studies,[5,14,15,17–19,21,29–41] investigating the prognostic survival factors for AML and/or MDS patients, including 5 prospective cohorts[17–19,29,40] and 15 retrospective cohort studies[5,14,15,21,30–39,41] met the inclusion criteria. Of the publications, 10 reports[5,14,21,29–35] investigated the prognostic role of SF prior to transplantation for AML and MDS patients; 7 studies[15,17,37–41] investigated the impact of ICT on OS of MDS patients, and 7 studies[17–19,36–38,40] reported the impact of ICT on the progression of MDS to AML. The sample size, mean age, and the level of SF in included studies varied greatly, ranging from 38 to 784, from 35 to 77 years, from 500 ng/mL to 2500 ng/mL, respectively. The detailed characteristics of eligible studies included in this meta-analysis are presented in Tables 1 and 2.

3.3. The impact of SF level prior to transplantation on OS of MDS and AML patients

Ten eligible reports[5,14,21,29–35] including 2651 patients analyzed the relationship between SF prior to transplantation and OS of MDS and AML patients. As shown in Figure 2A, in the initial

Table 1

Characteristics of studies investigating the impact of pre-transplantation SF on prognosis of MDS and AML patients.

Author	Year	Disease (patients)	Study period	Study design	Male/ Female	Median age (year)	The cut-off value of pre-transplantation SF (ng/mL)	HR (95%CI) for OS	Follow-up time (years)
Artz et al	2016	AML(626) MDS (158)	2000-2010	P	402/382	50 (18–78)	2500	1.15 (0.86–1.54)	≥4
Tachibana et al	2013	AML (118) MDS (35)	2000-2010	R	96/57	46 (18–63)	1000	1.79 (1.11–2.91)	>7
Tachibana et al	2011	AML (99) MDS (20)	2000-2008	R	64/55	41 (18–63)	1000	3.25 (1.71–6.17)	>5
Boehm et al	2014	MDS (60)	1988-2010	R	33/27	44 (18–68)	1000	1.93 (1.06–4.15)	>10
Lim et al	2009	AML (36) MDS (63)	2000-2006	R	51/48	51 (19–72)	1500	2.00 (0.97–3.57)	>10
Jang et al	2015	AML (74)	2006-2012	R	34/40	35 (15–59)	1400	1.88 (0.88–4.01)	NR
Alessandrino et al	2009	MDS (244) AML (113)	1997-2007	R	95/162	49 (18–72)	1000	1.40 (1.09–1.81)	>10
Li et al	2013	MDS (191)	2005-2010	R	119/72	50 (12–83)	500	3.53 (1.90–6.60)	>5
Komrokji et al	2012	MDS (767)	2001-2009	R	NR	69 (NR)	1000	1.40 (1.10–1.90)	>5
Kikuchi et al	2009	MDS (47)	1993-2001	R	28/19	65 (27–74)	500	1.90 (1.03–3.50)	>4

AML = acute myeloid leukemian, MDS = myelodysplastic syndromes, NR = not report, OS = overall survival, P = prospective, R = retrospective, SF = serum ferritin.

pooled analysis, the overall pooled HRs was 1.73 (1.40–2.14), indicating that elevated SF prior to transplantation was a negative factor for OS of MDS and AML patients, but heterogeneity tests showed a high heterogeneity among the studies ($I^2 = 52.7\%$; $P = .025$). Furthermore we performed subgroup analyses stratified by the cut-off value of SF prior to transplantation, as Figure 2A shows, the pooled HRs of studies using SF of more than 1400 ng/mL as a cut-off value was 1.45 (0.98–2.15), with a lower heterogeneity among the studies ($I^2 = 38.6\%$; $P = .196$). For studies with a cut-off value of pre-transplantation SF level of more than 1000 ng/mL, the pooled HRs was 1.65 (1.30–2.10), with a lower heterogeneity among the studies ($I^2 = 42.9\%$; $P = .136$). Among studies with cut-off value of pre-transplantation SF level of more than 500 ng/ml, the pooled HRs with its 95%CI was 2.58 (1.41–4.74), and heterogeneity testing showed a lower heterogeneity among these studies ($I^2 = 48.4\%$; $P = .164$).

To reduce the high heterogeneity and obtain more reliable results, we excluded 2 studies reported by Li et al[32] and Tachibana et al[34] from the initial pooled analysis. As Figure 2B shows, the overall pooled HRs was 1.44 (1.26–1.65), and heterogeneity tests showed no heterogeneity among the remaining studies ($I^2 = 0.0\%$, $P = .527$). In addition, we performed subgroup analyses stratified by the cut-off value of SF prior to transplantation. As shown in Figure 2B, the pooled HRs of studies using the level of SF more than 1000 ng/mL as a cut-off value point was 1.47 (1.24–1.74), and no heterogeneity was found among these studies ($I^2 = 0\%$; $P = .678$). Pooled HRs for studies using the level of SFof more than 1400 ng/mL as a cut-off value was 1.45 (0.98–2.15), with a lower heterogeneity ($I^2 = 38.6\%$; $P = .196$).

The subgroup analyses indicated that pre-transplantation SF level of more than 1000 ng/mL was a negative factor for OS of AML and MDS patients, but pre-transplantation SF has no significant impact on OS of MDS and AML patients when it is higher than 1400 ng/mL.

3.4. The prognostic role of ICT in MDS patients

Seven reports[15,17,37–41] including a total of 1174 MDS patients, analyzed the relationship between ICT and OS of MDS patients.

Table 2

Characteristics of studies focusing on investigating the effect of ICT on the prognosis of the low/int-1MDS patients.

Author	Years	Study period	The intervention SF level (ng/ml)	The agent of ICT	Risk of IPSS	Sample size		Study design	HR with 95%CI For ICT	Follow-up time (years)
						ICT	Non-ICT			
Raptis et al	2010	1998–2007	≥1000	Deferasiro deferoxamine	Low	32	46	R	1.07 (0.26–4.49)	>7
Rose et al	2010	2005–2007	NR	Deferoxamine;deferasirox;deferiprone	Low/Int-1	53	44	P	0.57 (0.27–1.20)	>10
Neukirchen et al	2012	1975–2008	≥1000	Deferoxamine;deferasirox	MDS	94	94	R	0.93 (0.45–1.95)	>10
Komrokji et al	2011	2001–2009	≥1000	Deferasirox and deferoxamine	Low/Int-1	45	52	R	0.77 (0.32–1.85)	>5
Wong et al	2018	1980–2017	>1000	Deferasirox; deferoxamine	Low	63	119	R	0.30 (0.10–0.80)	>6
Delforge et al	2014	2008–2010	≥1000	Deferoxamine or deferasirox	Low/Int-1	80	47	R	0.22 (0.12–0.41)	>15
Lyons et al	2014	2010–2012	≥1000	Deferasirox;deferoxamine	Low/Int-1	270	329	P	0.53 (0.28–1.02)	>20
Remacha et al	2015	2010–2011	NR	Deferasirox;deferoxamine	Low/Int-1	146	117	R	0.36 (0.16–0.82)	>10
Leitch et al	2017	2006–2016	NR	Deferasirox;deferoxamine	Low/Int-1	83	156	P	0.50 (0.26–0.91)	>10
Lyons et al	2017	NR	≥1000	Deferasirox; deferoxamine	Low/Int-1	270	329	P	0.91 (0.78–1.06)	>15

95%CI = 95% confidence interval, HR = hazard ratio, ICT = iron chelation therapy, IPSS = International Prognostic Scoring System, NR = not report, P = prospective, R = retrospective, SF = serum ferritin.

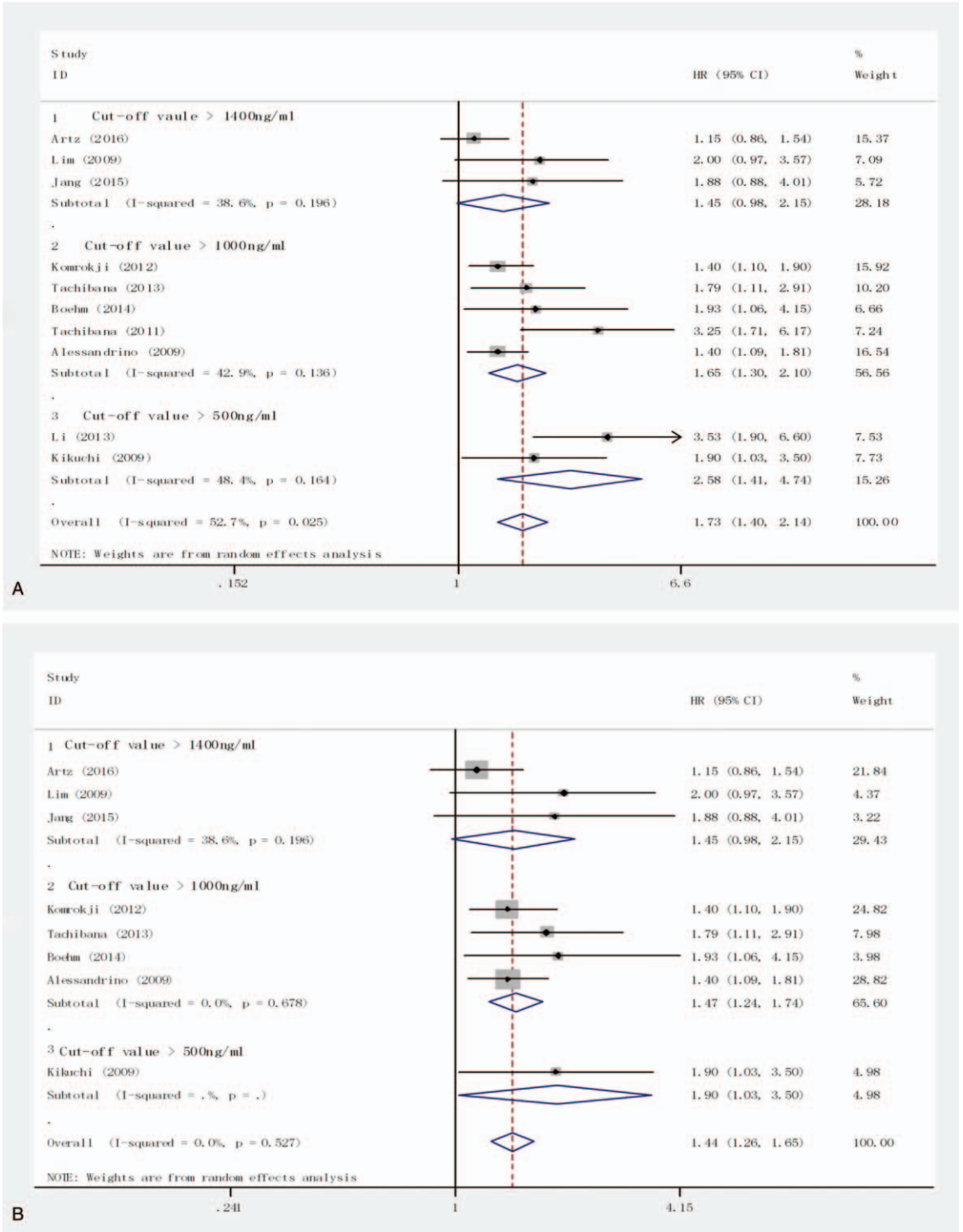

Figure 2. The forest for the pooled analysis the impact of pre-transplantation SF level on the impact on overall survival of MDS and AML patients. A. The initial pooled analysis with subgroup analyses stratified by the cut-off value of SF. B. The final pooled analysis with subgroup analyses stratified by the cut-off value of SF (after 2 studies excluded).

The HR and its 95% CI for each study and the pooled HRs are shown in Figure 3A. The overall pooled HRs was 0.30 (0.23–0.40). And heterogeneity tests showed no heterogeneity among the studies (I^2=0.0%; P=.554).

In subgroup analyses stratified by the International Prognostic Scoring System (IPSS) of MDS, the pooled HRs of studies that included lower IPSS MDS patients was 0.35 (0.21–0.59), the heterogeneity tests showed no heterogeneity among the eligible studies (I^2=0.0%; P=.948) as shown in Figure 3B. For studies with low/int IPSS MDS, the pooled HR was 0.32 (0.20–0.51), with a lower heterogeneity among the studies (I^2=41.4%; P=.182). Both the overall and subgroup analyses results showed

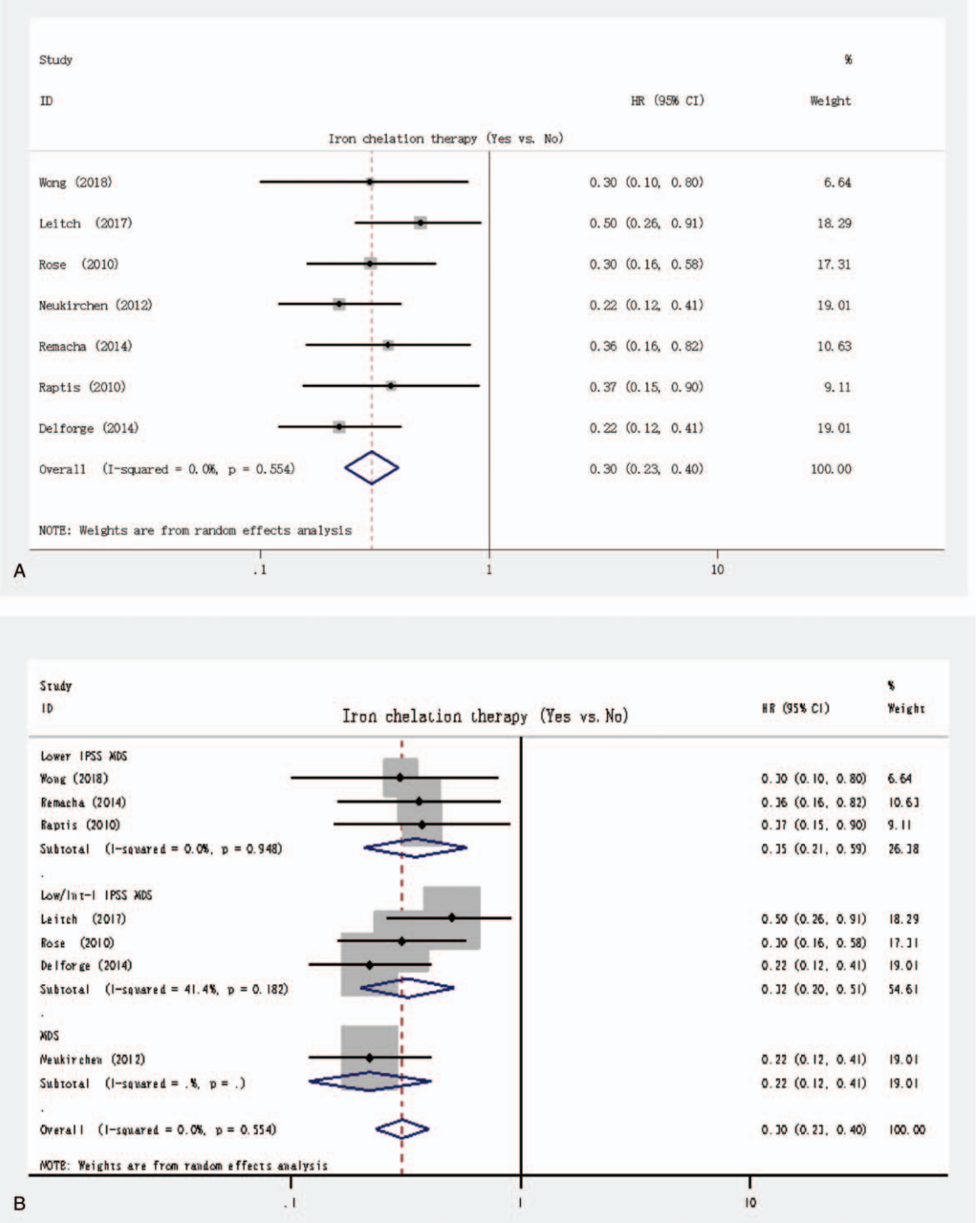

Figure 3. Forest plot for the pooled analysis the impact of ICT on overall survival of patients with lower/intermediate IPSS MDS. A. The overall pooled analysis. B. The subgroup analysis stratified by the risk degree of IPSS in MDS patients.

that ICT was a positive factor for OS of low/*int* IPSS MDS patients.

3.5. The incidence of progression of MDS to AML

Seven reports[17–19,36–38,40] including 1897 patients, analyzed the relationship between ICT and the incidence of the progression of MDS to AML. As Figure 4 shows, the pooled RR was 0.84 (0.61–1.16), and no heterogeneity was found among the studies (I^2 = 0.0%; P = .449). This result showed that there was no significant difference in the incidence of the progression of MDS to AML.

3.6. Additional analyses

In the initial pooled analysis of the prognostic role of SF prior to transplantation for MDS and AML patients, we found a significant result (the overall pooled HRs = 1.73 (1.40–2.41) as

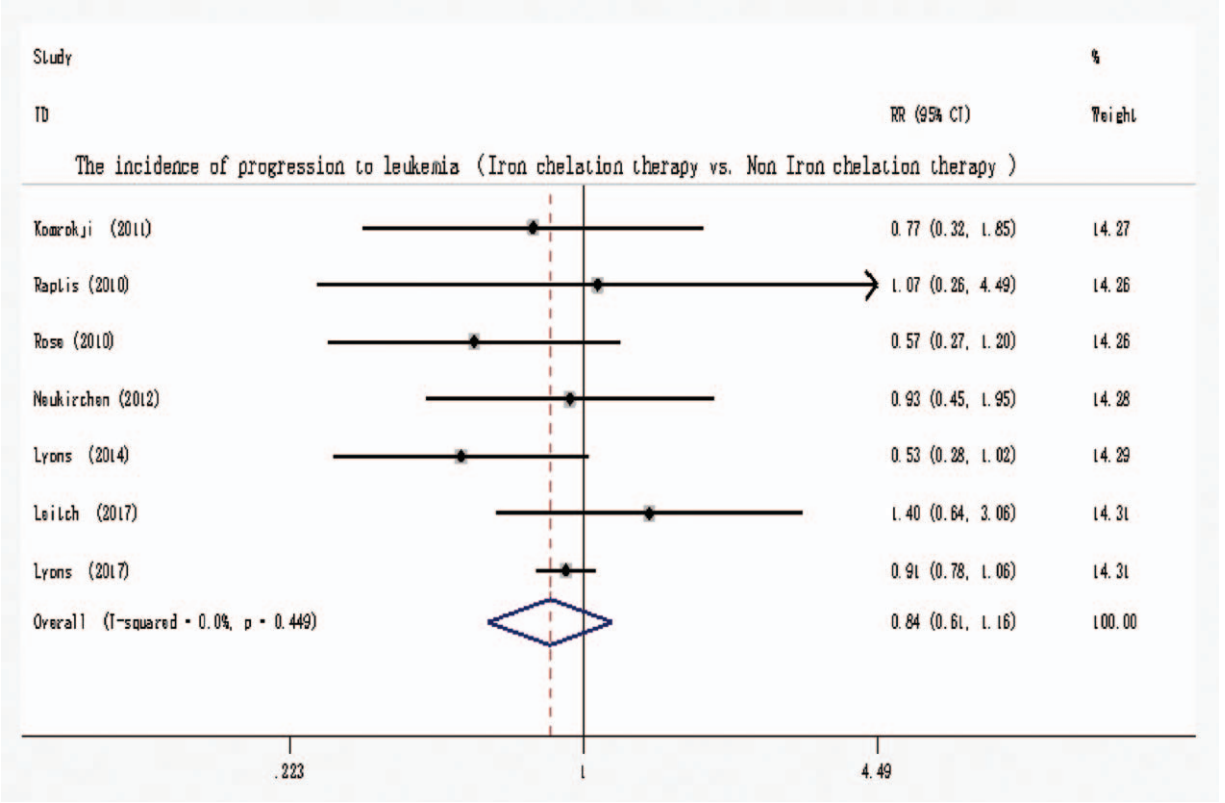

Figure 4. The forest plot for the pooled analysis the impact of iron chelation therapy on the progression of myelodysplastic syndromes to acute myeloid leukemia.

shown in Figure 2A. However, due to the significant heterogeneity (I^2 = 52.7%; P = .025) and publication bias (Egger t value = 0.575; P = .005) among the eligible studies, 2 studies were removed[32,34] from the initial pooled analysis (Fig. 2B). This led to no heterogeneity (I^2 = 0.0%; P = .527) and publication bias were found (Egger t value = 0.721; P = .011) among the remaining eligible studies. The exact cause of the significant heterogeneity caused by the 2 studies reported by Li et al[32] and Tachibana et al[34] was not clear, but we suspect that it might be due to the differences among the subjects included in the 2 studies. Compared with other eligible studies, the age of subjects reported by Tachibana et al[34] was younger (median = 41 years), and the study by Li et al[32] included patients classified as int-1 IPSS.

3.7. Risk of bias among studies

Assessment of risk of bias for each study showed that 4 studies[5,31,37,39] had unclear risk, 14 studies[5,14,17–19,21,32–36,38,40,41] had a low risk and 2 studies[15,29] had a high risk of bias, as depicted in Supplementary Table 1, http://links.lww.com/MD/D263. In the initial pooled analysis of the impact of pre-transplantation SF on OS of MDS and AML patients, the funnel plot displayed significant asymmetry, and the Egger test showed a significant publication bias (Egger t value = 0.575; P = .005) as shown in Figure 5A. After exclusion of 2 studies from the initial pooled analysis, the funnel plot showed no noticeable asymmetry, and no significant publication bias was found among the remaining eligible studies (Egger t value = 0.721; P = .011) (Fig. 5B).

In the pooled analysis of the effect of ICT on the OS of MDS patients, there was no noticeable asymmetry, and the Egger test showed no significant publication bias (Egger t value = 0.081; P = .610) among the eligible studies (Fig. 5C).

In the pooled analysis of the effect of ICT on the prognosis of MDS to AML, the funnel plots (Fig. 5D) showed no noticeable asymmetry, and the Egger test (Egger t value = 0.000; P = .786) indicated that there was no significant publication bias among the included studies.

3.8. Sensitivity analyses

To test the stability of the pooled results of the impact of SF prior to transplantation on OS of MDS and AML patients, we performed a sensitivity analysis by sequentially removing each eligible study. As shown in Figure 6A and B, a plot of the analyses showed that there was no undue influence of any single study.

4. Discussion

In the present prognostic meta-analysis, we first performed pooled analyses with subgroup analyses to investigate the impact of pre-transplantation elevated SF on OS of MDS and AML patients. The pooled results showed that the pooled HRs was 1.44 (1.26–1.65) (Fig. 2B) suggesting that pre-transplantation SF level was a negative predictor for OS of patients with MDS and AML when the cut-off value of SF was more than 1000 ng/mL, and there was no significant difference between the OS and pre-transplantation SF when the cut-off value was more than 1400 ng/mL.

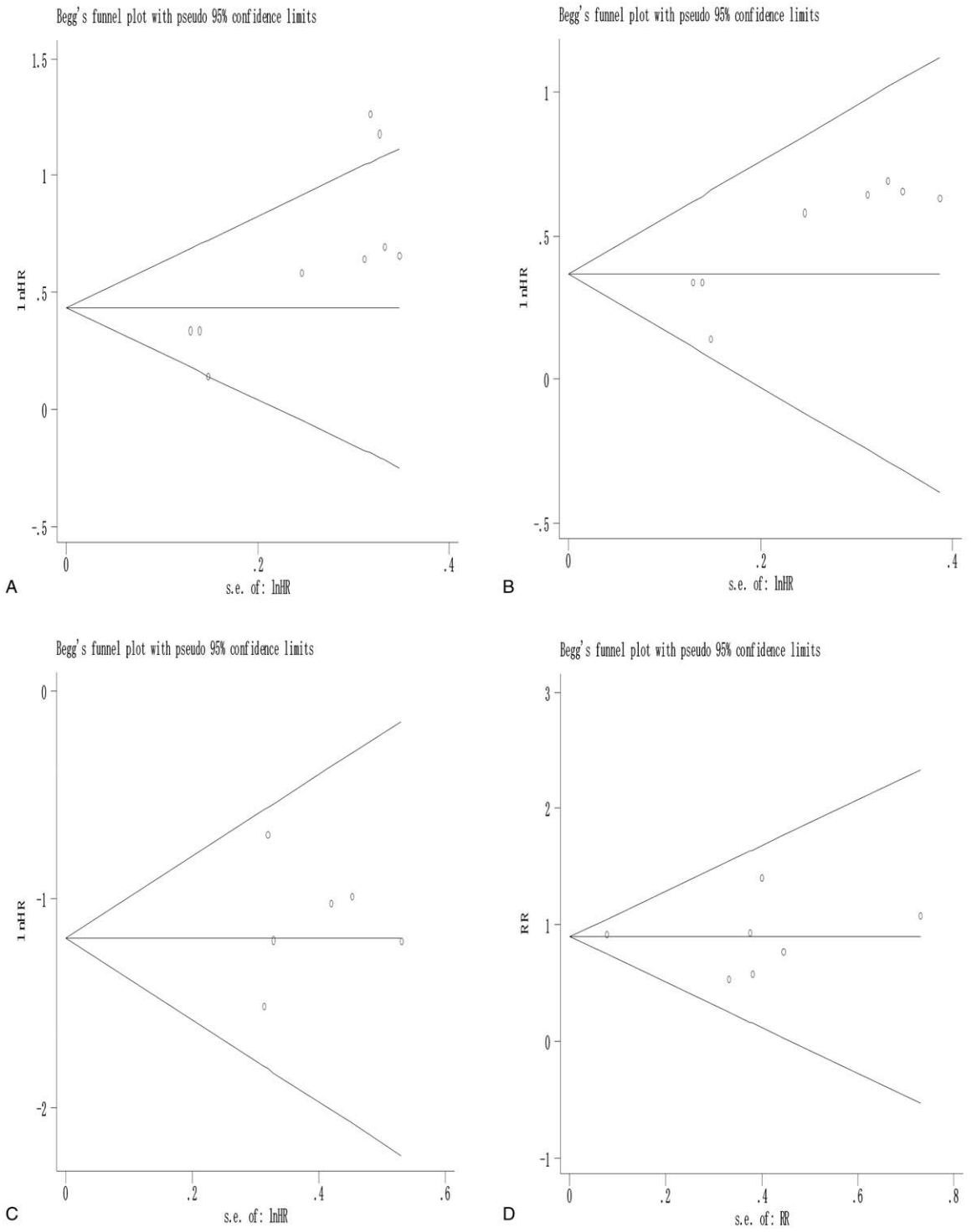

Figure 5. The funnel plots for the initial (A) and final (B) pooled analysis of the impact of pre-transplantation serum ferritin on overall survival of MDS and AML patients, for the pooled analysis the effect of ICT on overall survival of lower/intermediate IPSS MDS patients (C), and for the final pooled analysis the effect of ICT on the progression of lower/intermediate IPSS MDS to AML (D). AML = acute myeloid leukemia, ICT = iron chelation therapy, IPSS = international prognostic scoring system, MDS = myelodysplastic syndromes.

Since only 1 study[21] including 47 MDS patients was included in the final pooled analysis of the impact of pre-transplantation SF level (more than 500 ng/mL) on OS of MDS patients (Fig. 2B), we could not obtain more reliable results about the association between the prognosis of MDS patients and SF. In a previous meta-analysis,[42] a subgroup analysis including 2 studies concluded that SF level of more than 500 ng/mL had a negative impact on OS of MDS patients, but there was medium heterogeneity among the 2 studies reported by Li et al[32] and Kikuchi et al[21] and a significantly high heterogeneity in their

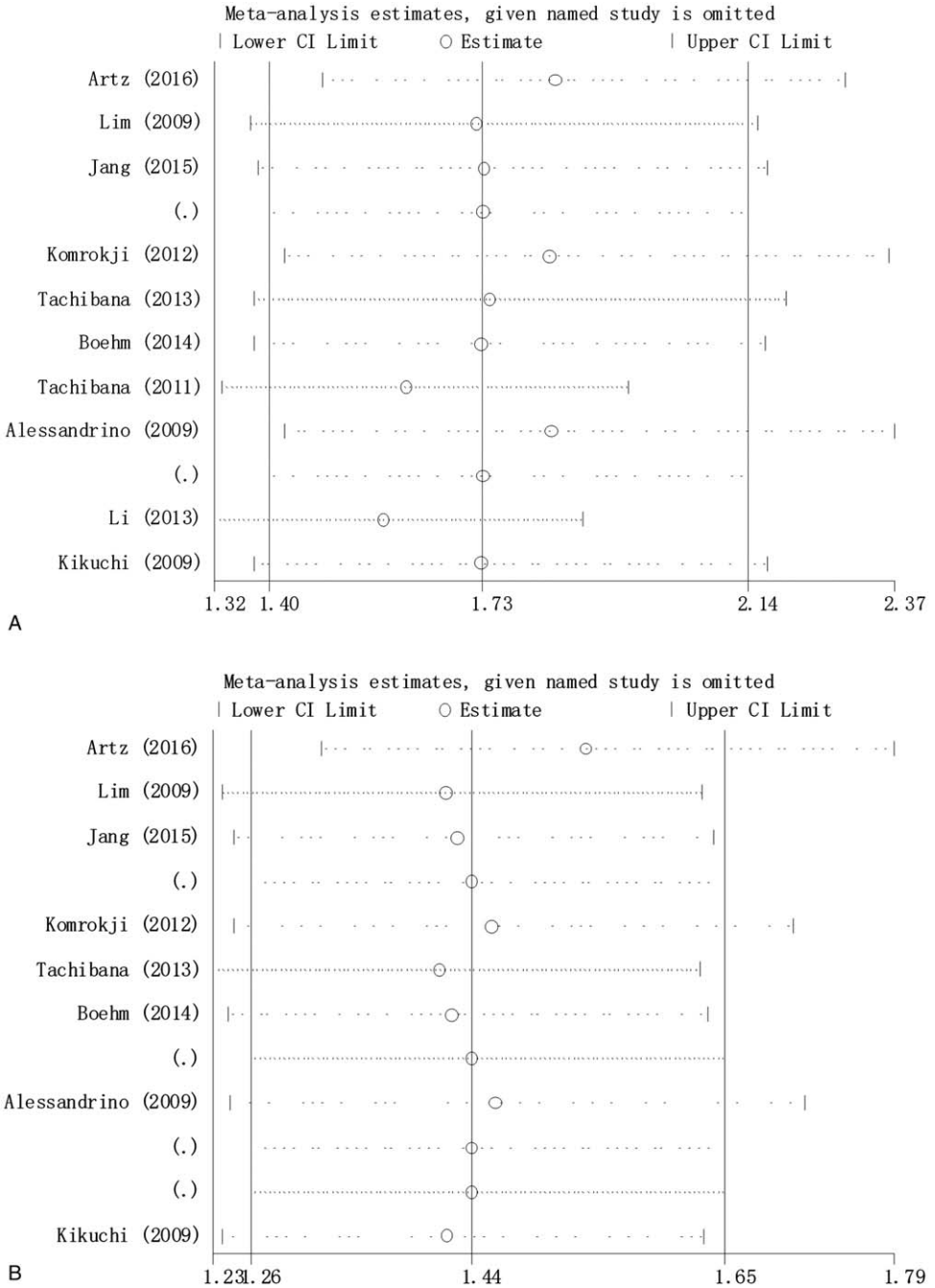

Figure 6. The sensitivity analysis of the initial (A) and final (B) pooled analysis the impact of pre-transplantation serum ferritin on overall survival of myelodysplastic syndromes and acute myeloid leukemia patients.

initial overall pooled analysis. Furthermore, they did not assess the publication bias among the eligible studies. In our initial analysis, we found a significant publication bias and high heterogeneity caused by the publications reported by Li et al[32] and Tachibana et al.[34] When these 2 studies were excluded from the pooled analysis, we obtained a stable pooled result with no heterogeneity (Fig. 2B: $I^2 = 0.0\%$; $P = .527$) and no significant publication bias was found (Egger t value = 0.721; $P = .011$).

Furthermore, in our pooled analysis of the impact of ICT on OS of the lower/int IPSS MDS patients with iron overload, as well as of the impact of ICT on the progression of MDS to AML, we found that adequate ICT can improve the OS of MDS patients with iron overload (Fig. 3A: the pooled HRs = 0.35 (0.21–0.59), but is not associated with the progression of MDS to AML (Fig. 4: the pooled RR = 0.84 (0.61–1.16)). In addition, our subgroup analyses showed that adequate ICT was associated with an improved OS for both lower (the pooled HRs = 0.35 (0.21–0.59)) and Low/Int-1 (the pooled HRs = 0.32 (0.20–0.51)) IPSS MDS patients. This finding is consistent with a previously published meta-analysis[43] which only included lower IPSS MDS patients.

Few previous publications[29,44–47] have found that elevated C-reactive protein, elevated SF, and lower albumin prior to

allogeneic hematopoietic stem cell transplantation are independent risk factors for OS of MDS and/or AML patients, but the threshold of these biomarkers differs greatly. So far, except elevated SF prior to allogeneic HCT, there is limited evidence on the appropriate threshold for other biomarkers associated with the poor prognosis of MDS and/or AML patients. Genomic, epigenetic, molecular, and clinicopathological characterization of AML and/or MDS in individual patients might provide valuable information on pathogenesis, prognosis, and chemosensitivity, and thus reveal the optimal therapeutic options for each patient. ICT has been widely used for MDS and AML patients with iron overload,[1] but the appropriate timing and the optimal agent of ICT are still unclear. Further, studies are required to provide more compelling results on this topic.

4.1. The strengths and limitations of this study

To our knowledge, the present study provides the most comprehensive meta-analysis of whether elevated SF levels are associated with a worse OS among patients with MDS and AML. Sensitivity analysis and subgroup analyses stratified by the cut-off value of pre-transplantation SF level were performed to increase the stability of the results. Moreover, by excluding 2 studies which caused a significant heterogeneity and publication bias, a stable pooled result with no heterogeneity (Fig. 2B: $I^2=0.0\%$; $P=.527$) and no significant publication bias (Egger t value = 0.721; $P=.011$) was obtained in the final pooled analysis of the impact of elevated SF prior to transplantation on OS of MDS and AML patients. In addition, in our pooled analysis of the impact of ICT on the OS of Low/Int-1 IPSS MDS patients, heterogeneity tests showed no heterogeneity (Fig. 3B: $I^2=0.0\%$; $P=.554$), and no significant publication bias (Egger t value = 0.081; $P=.610$) among the eligible studies. Subgroup analyses stratified by the risk level of IPSS were performed which improved the reliability and stability of the pooled result.

Despite these strengths, there are some limitations in our study that should not be underestimated. First, this is a prognostic meta-analysis based on observational studies, and hence some heterogeneity arising from factors, such as differences in the follow-up time, strategies of chemotherapy, sample size, median degree of iron overloaded, type of ICT, timing and duration of ICT etc may introduce some bias in the results. Secondly given that the majority of included studies comprised both MDS and AML patients, we did not perform analysis to investigate the impact of pre-transplantation SF level on the OS of AML patients, thus the existence of selection bias in our pooled analysis for the impact of pre-transplantation SF level on the OS of MDS and AML patients cannot be ruled out.

In conclusion, elevated SF prior to transplantation was found to be a negative predictor of OS for AML and MDS patients when it is higher than 1000 ng/mL. ICT can improve the OS of Low/Int-1 MDS patients with iron overload but is not associated with the progression of MDS to AML.

Author contributions

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