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REVIEW ARTICLE

Iron chelation therapy for myelodysplastic syndrome: a systematic review and meta-analysis

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Abstract

Iron overload remains a concern in myelodysplastic syndrome (MDS) patients especially those requiring recurrent blood transfusions. Whether iron chelating therapy (ICT) is beneficial to the long-term survival of myelodysplastic syndrome is still a controversial issue. Therefore, we conducted a systematic review and meta-analysis to clarify the relationship between ICT and long-term survival in patients with MDS. A total of 14 studies involving 7242 participants were identified; the outcomes revealed that for patients with MDS, ICT resulted in a lower risk of mortality compared to those with no ICT (HR 0.57; 95% CI 0.44–0.70; $P < 0.001$); what is more, ICT led to a lower risk of leukemia transformation (HR 0.70; 95% CI 0.52–0.93; $P = 0.016$). Results of subgroup analyses based on adequate ICT or any ICT, low/int-1 IPSS or unclassified IPSS and study types indicated that the ICT had a beneficial role in all these groups of patients.

Keywords Iron overload · Iron chelation therapy · Myelodysplastic syndrome · Overall survival · Leukemia-free survival

Introduction

Myelodysplastic syndrome (MDS) is a group of refractory heterogeneous diseases originating from hematopoietic stem cells and characterized by pathological hematopoiesis and enhanced risk of transformation to acute myeloid leukemia (AML) [1, 2]. Anemia is the most frequent cytopenia diagnosed in patients with MDS [3], and the majority of the patients will require red blood transfusion therapy when anemia appears through the disease course. The short-term benefit of red blood cell (RBC) transfusion is that it can rapidly improve anemia symptoms and life quality of patients [3]. However, iron overload often occurs as an iatrogenic consequence of RBC transfusions in some patients [4]. What is worse, because of ineffective erythropoiesis and consequently unrestrained intestinal iron uptake, iron overload in MDS often appears before patients become transfusion-dependent and the clinical consequences of iron overload include cardiac and/or hepatic failure, endocrinopathies and infection risk [5]. MDS patients showed increased levels of oxidative stress, which was further aggravated by iron overload [6–8]. A meta-analysis including 1855 participants underlined worse survival in patients with MDS who had higher SF levels [9].

Iron chelation therapy (ICT) was commonly used in patients with transfusional iron overload in chronic transfusion-dependent anemia, such as sickle cell disease or β-thalassemia, and is also used in some patients with MDS [10–14]. No validated threshold has been established for SF levels, but experts have recommended 1000–2500 ng/mL [15]. ICT was usually recommended for managing iron overload in MDS patients with low/int-1 IPSS score when serum ferritin (SF) levels are above 1000 ng/mL, but the data indicate that SF levels between the upper limit of normal and 1000 ng/mL adversely affect genetic stability [16, 17]. However, these treatment suggestions for ICT in MDS patients are not based on clinical outcomes from prospective randomized trials, and there are different opinions among experts on whether to choose ICT or not for MDS patients with iron overload [18]. In addition, ICT in MDS is sometimes terminated due to adverse events (AEs), and the overall annual discontinuation rates for MDS patients in these trials ranged approximately 40–50% [19–22]. In a previous meta-analysis concerning ICT for MDS conducted by Mainous et al. in 2014, eight observational studies were included; finally, they concluded that the use of ICT in patients with MDS is associated with a greater median survival time than their counterparts who

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did not receive ICT [23]. However, only 1562 participants were included in their study and these studies were focused on patients with low IPSS score. In recent years, several new studies with larger sample size and better design have been reported; therefore, a new meta-analysis is needed to evaluate the application value of ICT in MDS, including high IPSS score [23]. To further illustrate whether ICT is beneficial to overall survival (OS) and/or leukemia-free survival (LFS), we performed a new systematic review and meta-analysis of studies focused on the relationship between ICT and OS and/or the rates of transformation to AML.

Materials and methods

Study identification

PubMed, EMBASE, Web of Science and Cochrane Library electronic databases were searched with no language restriction from inception through January 18, 2019, with search terms (MDS OR Myelodysplastic syndrome) AND (iron chelation OR iron chelating) AND (overall survival OR OS). The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [24, 25]. References from the above-selected reports were accordingly searched to include any additional publications. Published abstracts were permitted if the primary outcomes of interest were reported. If the publications were reported from the same cohort, those with the longer follow-up or larger samples were included.

The potentially relevant studies were downloaded and reviewed for the following exclusion criteria: (1) not a clinical study, (2) not reporting data for leukemia-free survival (LFS) and/or overall survival (OS), (3) not reporting original data, (4) the objectives investigated had multiple hematological malignancies including MDS and (5) studies not focused on relationship between ferritin and OS.

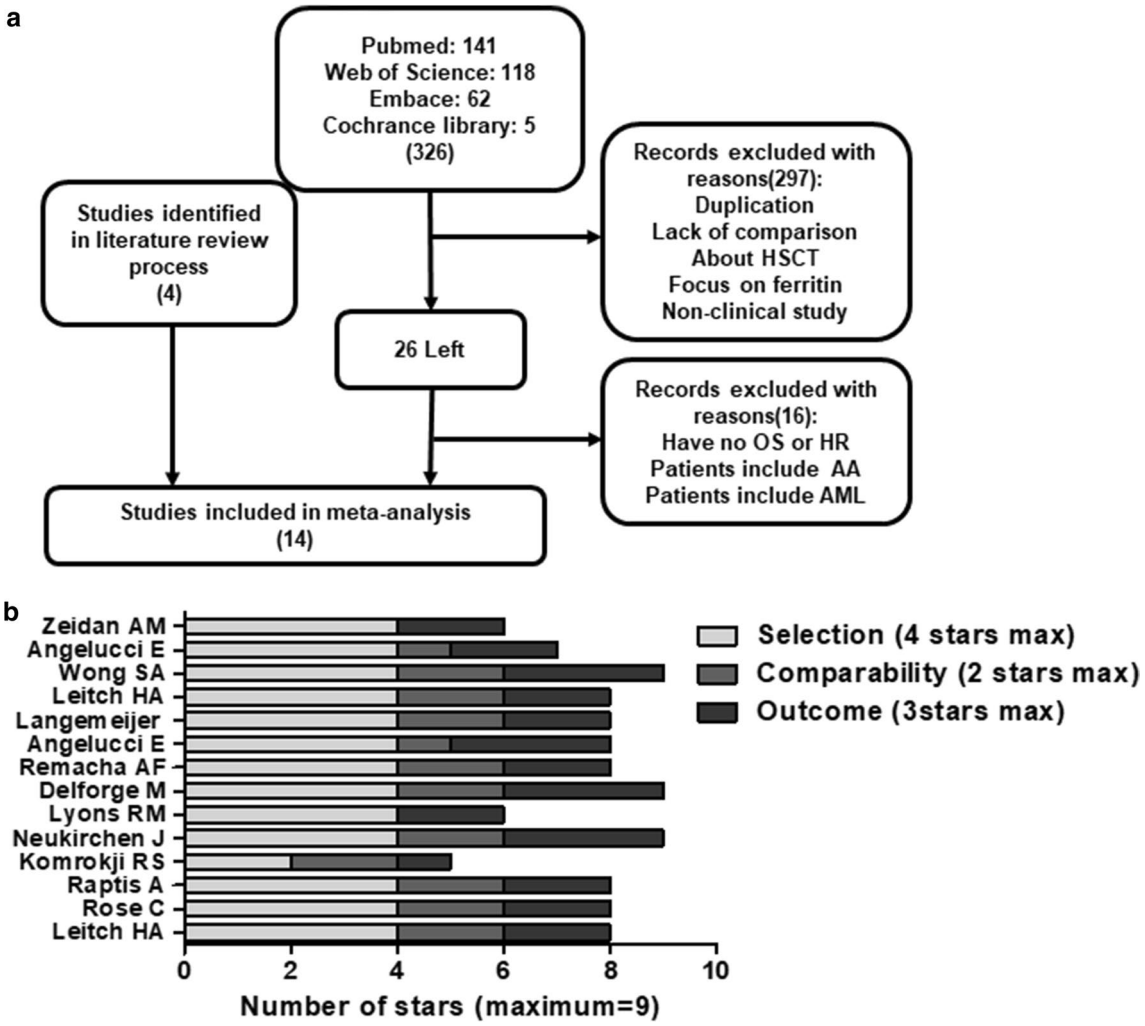

Fig. 1 **a** PRISMA flow diagram; **b** quality assessment of included studies as evaluated using the Newcastle–Ottawa Scale

Data extraction

The data included in this meta-analysis were extracted from publicly available published articles and were independently extracted from published articles by Hailing Liu and Nan Yang. PRISMA flow diagram is shown in Fig. 1a. We collected key study characteristics, including study design, treatment strategy, sample size, median LFS, median OS and hazard ratios (HRs) with confidence intervals for LFS and OS. This present meta-analysis included 14 studies that fulfilled our eligibility criteria; in total, 7242 patients were included; of these studies, six studies were prospective (one RCT included) and eight studies were retrospective. The main sample characteristics are presented in Table 1.

Study quality

We judged the quality of studies included in the present meta-analysis using Newcastle–Ottawa Scale (NOS) as shown in Fig. 1b. Publication bias of the included literature was assessed with Egger's regression intercept, as shown in Fig. 2a; there were some elements with the appearance of publication bias ($P < 0.001$), with smaller studies not being symmetrical around the mean effect size, which suggested that studies with much larger effect size were more likely to be published.

Sensitivity analysis

We performed sensitivity analysis with a pre-planned sensitivity analysis by removing each study and then re-conducted the meta-analysis for the remaining studies to determine the stability of the results (shown in Fig. 2b). The results suggested that the two studies conducted by Zeidan et al. [38] and Angelucci et al. [22] had a great influence on the final results. Subsequently, we further analyzed the reasons why these two studies brought such obvious heterogeneity to this meta-analysis.

Table 1 Basic characteristic of studies included in the present meta-analysis

Author	Year	Country	Mean age (years)	Male/Female	Sample size (ICT and non-ICT)	Study types	IPSS (low/int/high/unclassified)
Leitch [26]	2008	Canada	69	105/73	178(18/160)	Retro	44/72/17/45
Rose [27]	2010	France	72	55/42	97 (53/44)	Pro	45/52/0/0
Raptis [28]	2010	USA	71.4	116/167	283 (128/155)	Retro	142/0/38/84
Komrokji [29]	2011	USA	67/65.5	NA	97 (45/52)	Retro	24/173/0/0
Neukirchen [30]	2012	Germany	64/67.5	98/90	188 (94/94)	Retro	138/28/22/0
Lyons [31]	2014	USA	75/72	347/253	600 (263/337)	Pro	112/181/0/0
Delforge [32]	2014	USA	71/73	56/71	127 (80/47)	Retro	54/73/0/0
Remacha [33]	2015	Spain	72	150/107	263 (146/117)	Retro	218/0/0/45
Angelucci [22]	2014	Italy	72	96/56	159 (152/7)	Pro	61/89/0/0
Langemeijer [34]	2016	European	69/73	NA	678 (195/573)	Pro	NA
Leitch [35]	2017	Canada	71/76	141/97	239 (83/156)	Retro	118/83/38/0
Wong [36]	2018	Canada	67/74	106/75	182 (63/119)	Pro	76/96/0/10
Angelucci [37]	2018	Italy	61	137/88	225 (149/76)	RCT*	62/163/0/0
Zeidan [38]	2015	USA	NA	1785/2141	3926 (398/3528)	Retro	NA

ICT Iron chelation therapy, *IPSS* international prognostic scoring system, Pro prospective study, Retro retrospective study, *NA* not available
RCT* randomized placebo-controlled phase II clinical trial

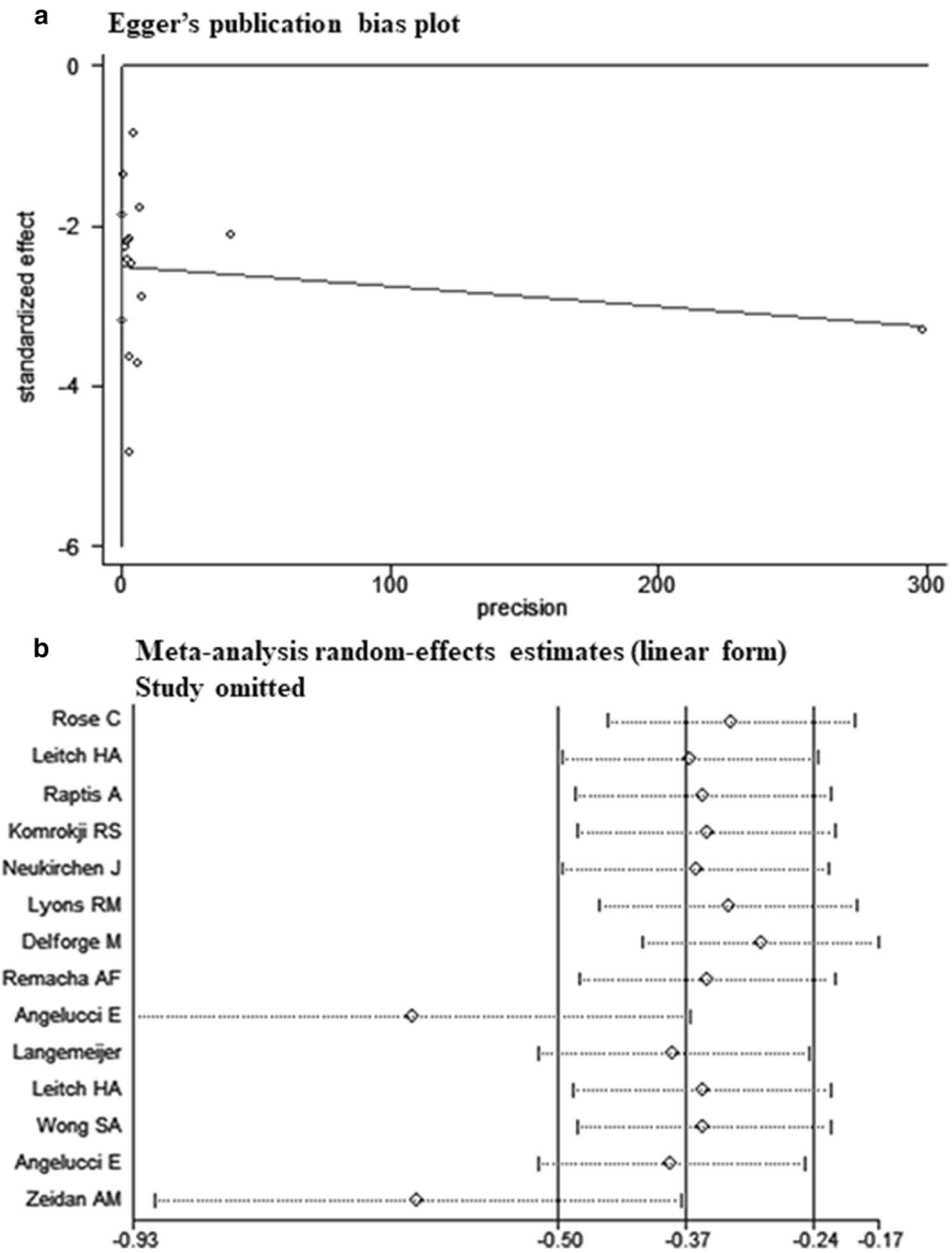

Fig. 2 **a** Egger's funnel plot of publication bias; **b** sensitivity analysis of HR for OS

Results

Some studies had tolerability or adverse events (AEs) as their primary end points, and ten included studies reported data on HRs of LFS and OS, while the median OS was not yet reached for several studies. The treatment effect sizes were little greater for OS (HR 0.57; 95% confidence interval (CI) 0.44–0.70; $P<0.001$) (Fig. 3) in the ICT group than for LFS (HR 0.70; 95% CI 0.52–0.93; $P=0.016$) (Fig. 4).

We conducted subgroup analysis based on adequate ICT or any ICT (Fig. 5a, b), low/int-1 IPSS or unclassified IPSS (Fig. 6a, b) and study type (Fig. 7a, b). The results indicated that ICT exerted a better effect on the OS for different groups of patients with MDS compared to those without ICT treatment.

Discussion

A total of 14 prospective and retrospective studies focusing on ICT and OS and/or LFS of patients with MDS were included in this meta-analysis, and the results indicated ICT was associated with both prolonged OS (HR 0.57; 95% CI 0.44–0.70; $P<0.001$) and LFS (HR 0.70; 95% CI 0.52–0.93; $P=0.016$). The conclusions were consistent with previous studies of ICT in MDS [23, 39, 40]. There was no statistical

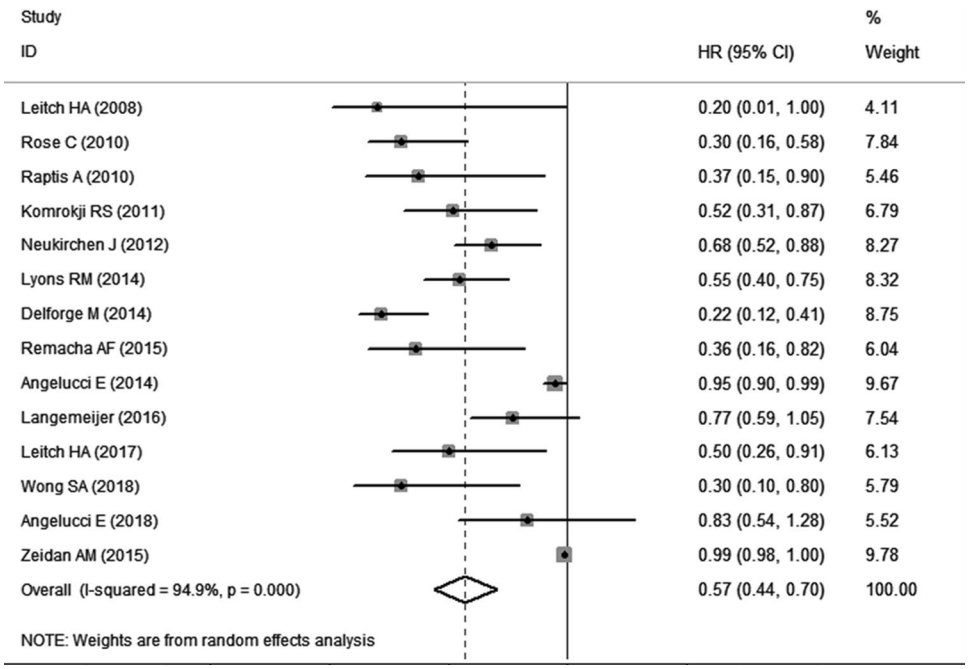

Fig. 3 ICT was associated with an overall lower risk of mortality (HR 0.57; 95% CI 0.44–0.70; $P<0.001$, $n=14$)

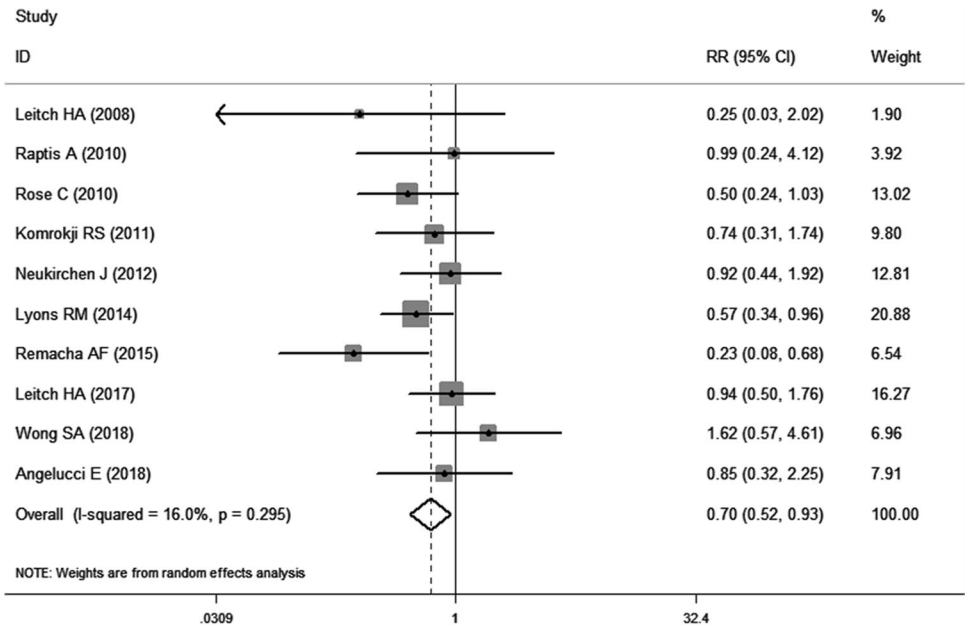

Fig. 4 ICT was associated with a decreased risk of progression to leukemia (HR 0.70; 95% CI 0.52–0.93; $P=0.016$, $n=10$)

difference between two studies regarding the benefits of ICT compared with no ICT for OS of MDS [34, 37]. The study conducted by Angelucci et al. was a randomized placebo-controlled phase II clinical trial, reporting a median OS of 1907 days (95% CI: 1440—not estimable) with ICT and 1509 days (95% CI 1095–1804) with placebo, HR 0.832 (95% CI 0.54–1.28, $P=0.20$). A potential OS difference was thought to be diluted because of the young age of the patients and the fact that half of placebo patients dropped out and subsequently received chelation, in addition to the fact that the patient numbers were reduced by two-thirds due to poor enrollment [37]. Clinical practice of ICT in MDS varied fairly in the European countries registered in the EUMDS. Deferasirox was most frequently used in MDS with iron overload, and the frequency ranged from 0 to 25% per country. OS was significantly better when compared with a large control group; besides, OS was longer after treatment with deferasirox than deferoxamine [34].

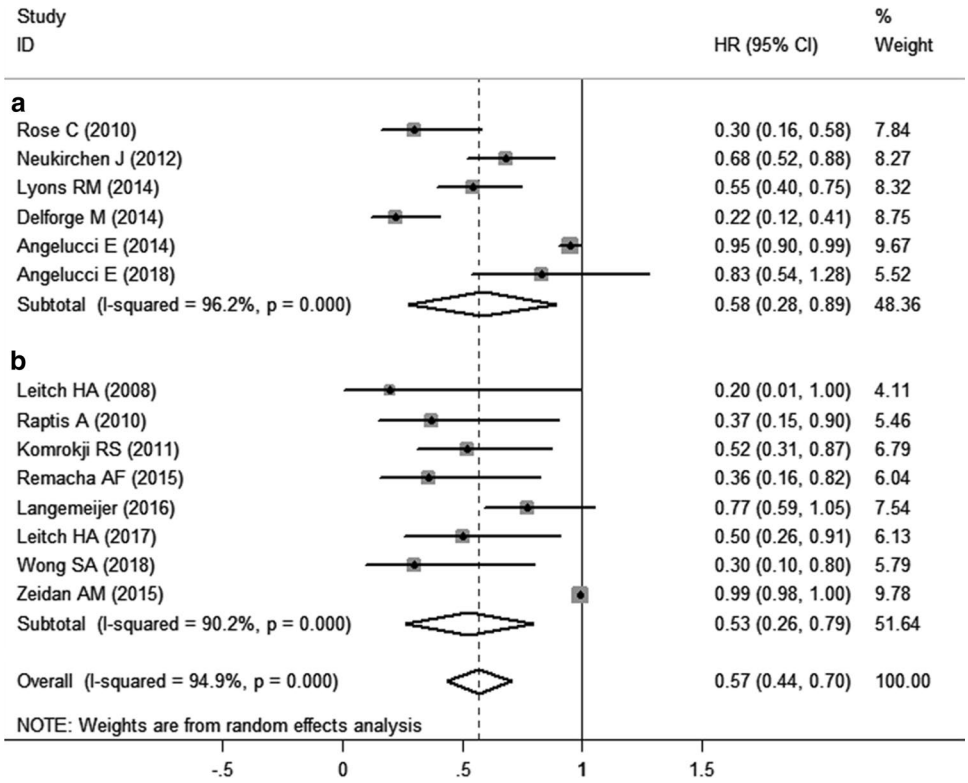

Fig. 5 Random-effects model of OS, in patients treated with: **a** adequate ICT and **b** any ICT

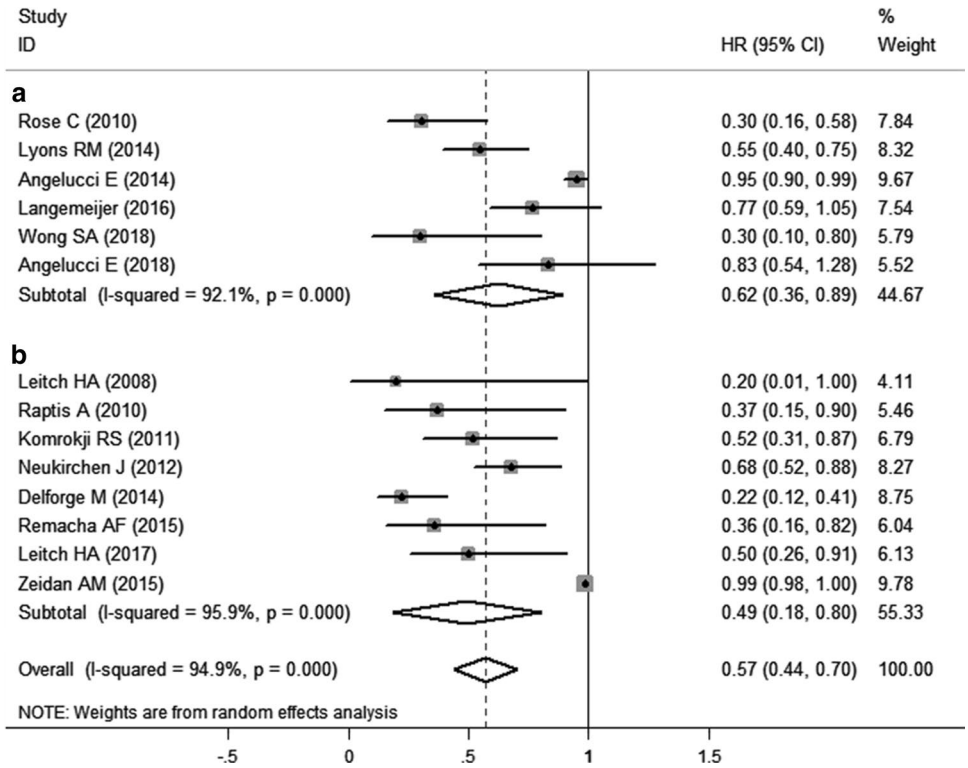

Fig. 6 Random-effects model of OS, in patients treated with ICT in different study types: **a** prospective and **b** retrospective

Sensitivity analysis indicated that the stability of meta-analysis results was greatly affected by two included studies [22, 38]. Small size of the control compared to the ICT group (7 vs. 152) might be one of the factors influencing the final OS [22]. The study conducted by Zeidan A et al. [38] included a large proportion of patients with intermediate

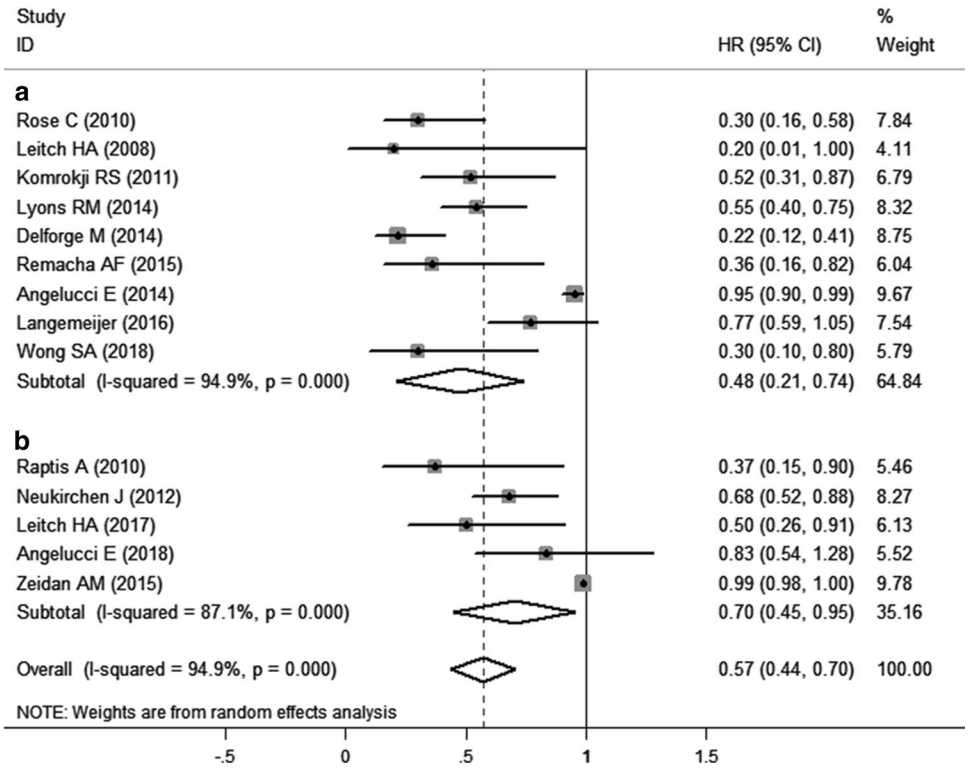

Fig. 7 Random-effects model, of OS following treatment with ICT in MDS patients with: **a** low/int-1 risk and **b** unclassified risk

IPSS score, so the final treatment effect may also be less significant compared those including a large proportion of low-IPSS patients.

Poor patient adherence to therapy was also a common problem in ICT treatment. High trial discontinuation rates of patients with MDS likely reflected the poor physique with insufficient motivation with regard to the disease and the expected benefits of ICT. Patients with longer duration of disease were more likely to complete the trial, which potentially implied improved patient education and cognition of the disease progression. The advanced age and poor physical condition of patients with MDS may also explain the high incidence of non-treatment-related AEs reported in a previous study. However, no treatment-related deaths, treatment-related grade 4 AEs or dose-limiting toxic effects were observed in the whole study, and the majority of treatment-related AEs were minor [22]. Another study reported a rate of AEs of 47.5% among patients, mainly gastrointestinal and renal toxicity [41]. Nevertheless, ICT is an effective measure in MDS patients with iron overload, even at an earlier stage of the disease. The threshold of ferritin for starting ICT is expected to be explored in future studies.

The studies included in the present meta-analysis did not limit the IPSS risk of patients; therefore, it explored universal applicability of ICT in MDS. We found that although ICT was beneficial to OS (HR 0.57; 95% CI 0.44–0.70; $P < 0.001$) of patients with any IPSS risk, it was more effective in patients with low/int-1 IPSS (HR 0.48; 95% CI 0.21–0.74; $P < 0.001$). Therefore, ICT should be recommended in more MDS patients with iron overload. Besides, MDS patients with iron overload receiving deferasirox resulted in increased hemoglobin level from 6 to 44.5%, increased platelet count from 13 to 61% and neutrophil count from 3 to 76% [17, 20, 22, 42, 43], which might be another underlying mechanism to reduce the risk of death by preventing patients from hemorrhage and infection. Hypermethylation of tumor suppresser genes occurs frequently in MDS patients, and these epigenetic abnormalities have been confirmed to be associated with MDS progression and transformation to leukemia. Besides, oxidative stress was correlated with tumor suppressor genes methylation, and iron chelators may reverse tumor suppressor genes hypermethylation by reducing oxidative stress, thereby reducing disease progression and leukemia transformation [44]. Of course, avoiding unnecessary blood transfusion is an important means to reduce iron overload. It has been reported that cyclosporine therapy can make patients achieve blood transfusion independence [45].

Our meta-analysis included only one randomized clinical study, in which the HR (0.832; 95% CI 0.54–1.28; $P = 0.20$) of ICT for OS seems to have little effect, though this study has limitations as discussed above. Therefore, more well-designed randomized clinical trials are expected to confirm the current results, and further seek measures to reduce treatment-related adverse reactions and explore the threshold of SF for initiating ICT.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

Ethical approval The study was approved by the Second Affiliated Hospital of Xi'an Jiaotong University.

Informed consent Informed consent was obtained from all individual participants included in this study in their original studies.

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