Systematic Review and Meta-Analysis

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Incidence and risk of hematologic toxicities with hypomethylating agents in the treatment of myelodysplastic syndromes and acute myeloid leukopenia

A systematic review and meta-analysis

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Abstract

Background: Hypomethylating agents (HMAs) are believed to have reliable efficacy in treating myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Meanwhile, the adverse events of HMAs have become an increasing concern. There is, however, no systematic meta-analysis available to evaluate overall hematologic toxicities for HMAs. In this meta-analysis, we aim to determine the risk of hematologic toxicities in patients treated with HMAs.

Methods: Relevant studies were identified from PubMed, Embase, Cochrane Library, and the Clinical Trials. gov databases incepted to February 2018. All phase II and III trials meeting the inclusion criteria included adequate safety data. We calculated the relative risk (RR) of high-grade hematologic toxicities (HTEs) with corresponding 95% CI using Review Manager. The incidences of HTEs were also evaluated by R. Heterogeneity was calculated and reported mainly via I^2 analyses.

Results: A total of 2337 MDS or AML patients from 14 studies were identified in this meta-analysis. The overall incidences of high-grade hematologic toxicities in patients who received HMAs were: 27% of the patients with anemia, 45% with neutropenia, 38% with thrombocytopenia, and 25% with febrile neutropenia, respectively. There was a significantly increased RR of neutropenia and thrombocytopenia using HMAs, in comparison with conventional care regimens (CCR) based on the drug type (decitabine vs azacitidine).

Conclusions: We conclude that the use of HMAs are associated with an increased risk of neutropenia and thrombocytopenia in MDS or AML patients, and our results also demonstrate that HMAs exposure does not significantly increase the risk of high-grade anemia, leukopenia, or febrile neutropenia compared with CCR.

Abbreviations: 95% CI = 95% confidence interval, AEs = adverse events, Allo-HSCT = allogeneic hematopoietic stem cell transplantation, AML = acute myeloid leukemia, BM = bone marrow, BSC = best supportive care, CCR = conventional care regimens, CR = complete remission, CTCAE = common toxicity criteria of adverse events, DNMT = DNA methyltransferase, ED = early death, FAB = French–American–British, FDA = United States Food and Drug Administration, HMAs = hypomethylating agents, HTEs = hematologic toxicity effects, IC = intensive chemotherapy, LDAC = low-dose cytarabine, MDS = myelodysplastic syndromes, OR = odds ratio, ORR = overall response rate, PR = partial remission, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement, RCT = randomized controlled trial, RR = relative risks, WHO = World Health Organization.

Keywords: acute myeloid leukemia, hematologic toxicities, hypomethylating agents, meta-analysis, myelodysplastic syndromes, systematic review

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CG and JW contribute equally to this article and are listed as the first authors.

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1. Introduction

Myelodysplastic syndromes (MDS) manifest themselves with characteristic clonal hematopoietic stem cell disorders, dyshaematopoiesis of one or more lineage blood cells, ineffective hematopoiesis, and high risk of progression to acute myeloid leukemia (AML).[1] AML is a group of malignant clonal diseases originating from hematopoietic stem cells, leading to a large number of immature hematopoietic cells proliferating and accumulating in the bone marrow and peripheral blood.[2] Although allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is the only curative treatment for high risk MDS and AML,[3,4] it is expensive and difficult to find an appropriate match, and many patients are not eligible for Allo-HSCT. Therefore, there is an urgent need to develop an effective therapeutic approach for these patients who are ineligible for transplantation.

MDS and AML are diseases of disordered differentiation, in which abnormal DNA methylation plays a critical role in their pathogenesis.[5–8] With the breakthrough of molecular biology research on the characteristics and pathogenesis of MDS and AML, hypomethylating agents (HMAs) have become a hot spot for the treatment of MDS and AML. In fact, 2 representative HMAs, azacitidine and decitabine, have been approved by the United States Food and Drug Administration (FDA) for treating MDS and AML. Surprisingly, several previous clinical trials have shown that the efficacy of demethylation therapy, azacitidine and decitabine, is superior to conventional care regimens (CCR).[9–15]

Although the efficacy of HMAs has been recognized, their clinical application is largely limited by the inherent cytotoxicity. In clinical practice, bone marrow suppression is the most common adverse reaction in demethylation therapy, and it is also the main reason for the dose-reduction or discontinuations of therapeutic regimen. Kantarjian found that serious adverse events were experienced by 69% of decitabine patients, and 43 out of 89 patients (48%) received no or only minimal (and possibly ineffective) therapy due to myelosuppression-related side effects.[9] Likely, another study showed that febrile neutropenia was noted in 25% of patients receiving decitabine compared with 7% of patients receiving best supportive care (BSC), and this result was similar to Kantarjian study.[11] Additionally, other studies also found that discontinuations of the treatment before the completion of the study in the HMAs group compared with CCR group were mostly related to myelosuppression, particularly during early treatment.[10,12,13] High concentrations of decitabine inhibit DNA synthesis and induce cell death, resulting in cytotoxic effect. However, low-dose decitabine has the demethylation effect rather than cytotoxic effect,[16,17] which makes it feasible to reduce myelosuppression by decreasing the dosage. In the meantime, the maximal demethylation effect can be achieved through shortening the interval between cycles and prolonging the duration of treatment.

The previous meta-analysis about HMAs mainly focused on the efficacy of drugs, while the studies on drug adverse events were few and not detailed enough. For instance, one meta-analysis involving 7 trials (only 1 randomized controlled trial, RCT) with small sample sizes has evaluated the incidence of developing hematologic toxicity effects (HTEs) with the use of decitabine,[18] however, it did not mention the relative risk (RR) analysis of HMAs. In addition, the other 2 meta-analysis analyzed HTEs as secondary outcomes, but the quality of the included studies was relatively low or too few RCTs included.[19,20] After referring to we found that quite a few RCTs had inconsistent conclusions and their conclusions were not conducive to the use of clinicians. For example, Fenaux research showed that grade 3/4 neutropenia and thrombocytopenia were both more common with azacitidine than with CCR.[10] However, another study demonstrated that azacytidine was generally well-tolerated, and grade 3/4 neutropenia and thrombocytopenia were similar in patients receiving azacytidine and CCR.[13] Up to now, the risk of using HTEs as an index for HMAs is uncertain and clinicians lack the clinical evidence to select specific HMAs. Therefore, the purpose of the current study is to fully assess the incidence and RR of the HTEs associated with HMAs by performing a meta-analysis.

2. Materials and methods

2.1. Data sources

An independent literature search and review of relevant articles were conducted from inception to February 2018 using PubMed, Embase, Cochrane Library, and the Clinical Trials. gov databases. Key words included hypomethylating agents, azacitidine, decitabine, myelodysplastic syndrome, and acute myeloid leukopenia. Additional relevant abstracts were also included from the proceedings of American Society of Hematology, the American Society of Clinical Oncology, and the European Hematology Association. Only the latest updated report was chosen for meta-analysis. Trials were reviewed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA).[21] The detailed search strategies were listed in Supplementary Table 1, http://links.lww.com/MD/C392.

2.2. Study inclusion criteria

Publications that meet the following inclusion criteria were included: Phase II and III trials of adults with morphologically proved diagnosis of AML or MDS, and without previous Allo-HSCT, for RR analysis, data were extracted from RCT, and participants were randomized to treatment with either HMAs (azacitidine or decitabine) or conventional care regimens BSC, low-dose cytarabine (LDAC), or intensive chemotherapy (IC) in a setting of first-line treatment, for incidence analysis, trials that individuals were randomized to HMA monotherapy were included, and sample size and safety events were both available for high grade HTEs. Trial data were used only once in the analysis from the most recent publication.

2.3. Data extraction, clinical end points

Two investigators (JW and CG) independently read and extracted data with a piloted extraction form. Any disagreement between the 2 investigators was resolved by consensus with other co-authors after reviewing of the full text. The following data were extracted from each study: the first author's name, year of publication, phase of trials, underlying disease, population size, median age, French-American-British (FAB) classification, bone marrow (BM) blast count, cytogenetic risk categories, treatment and dosing regimens, median treatment duration, number of patients available for analysis, and adverse events of interest. The main analysis of the following coprimary endpoints included: neutropenia, leukopenia, thrombocytopenia, and anemia and febrile neutropenia. Count data for all HTEs were defined and recorded according to the common toxicity criteria of adverse

events (CTCAE) version 2.0, 3.0 or 4.0 (http://ctep.cancergov/reporting/ctc_archive.html), which had been widely used in clinical trials.

2.4. Assessment of bias risk

We used the Cochrane Handbook for Systematic Reviews of Interventions to assess the risk of bias of each enrolled RCT (for RR analysis).[22] Criteria for evaluation was made separately according to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other source of bias.

2.5. Statistical analysis

Data analyses were carried out using Review Manager (version 5.3; the Nordic Cochrane Centre, Copenhagen, Denmark) and R (version 3.4.2; Comprehensive R Archive Network, TUNA Team, Tsinghua University, Beijing, China). We calculated the RR of high-grade (grade 3–4) hematologic toxicities with corresponding 95% confidence interval (CI). For incidence analysis, the number of HTEs was extracted from the single-arm and selected randomized clinical trials. For the calculation of RR of HTEs, data were extracted from RCT, comparing the HTEs in participants assigned to HMAs versus controls in each trial. Random effects model was calculated for all analyses, and subgroup analyses were performed to explore the source of heterogeneity, as described by DerSimonian and Laird,[23] which consider within-study and between-study variation. The Cochrane Q statistic (χ^2) was used to estimate the heterogeneity and the I^2 test was used to quantify the inconsistency.[24] A two-tailed $P < .05$ was considered statistically significant in all statistical tests.

2.6. Ethics

All the analyses were based on previous published studies. Therefore, ethical approval is not necessary for systematic review and meta-analysis.

3. Results

3.1. Literature search results

We searched a total of 713 potentially relevant articles using the initial search strategy, and detailed selection process was shown in the Flow Diagram. After reviewing of the titles and abstracts, 689 studies were judged as ineligible for inclusion criteria and were therefore excluded. A total of 23 studies were reviewed in full text, of which 9 studies were excluded due to the lack of HTEs data[17,25–32] (Flow Diagram), the remaining 14 trials were identified and included in this meta-analysis, including 8 Phase II trials (n = 468) and 6 Phase III trials (n = 1869).[9–15,33–39]

3.2. Publication characteristics

The yielded 14 studies included 2337 MDS or AML patients meeting our inclusion criteria in this meta-analysis, of which 1421 patients were treated with either azacitidine (n = 616) or decitabine (n = 805), and 916 patients were treated with CCR, including BSC (n = 393), LDAC (n = 439), and IC (n = 84). Currently, decitabine and azacitidine are the only widely used demethylation drugs in clinical practice. In this meta-analysis, 9 studies used decitabine and 5 studies evaluated azacitidine. The HTEs of included trials were assessed according to the National Cancer Institute's CTCAE criteria (http://ctep.cancergov/reporting/ctc_archive.html, version 2.0, 3.0 or 4.0). Nine studies assessed MDS treatment, of which 5 studies used decitabine and 4 studies used azacitidine. Five studies assessed AML treatment, of which 4 studies used decitabine and 1 study used azacitidine. The baselines characteristics of included studies were summarized in Table 1.

3.3. Risk of bias

Bias analysis was shown in Figs. 1 and 2. For RR analysis, all 7 trials were open-labeled RCT.[9–15] One study was not performed adequately in random sequence generation,[15] and 3 studies were not performed adequately in allocation concealment.[11,14,15] The adequacy of blinding of participants and personnel (performance bias) was evaluated by a description of blind methods for researchers and participants in the study, and the adequacy of outcome assessment blinding was judged by whether efficacy of the treatment was assessed by a reviewer who did not know which group the patient belongs to. Three studies performed blinding of participants and personnel.[10,12,13] In one study, treatment response was assessed by a third person who was a specialist in related fields.[9] Randomization, follow-up, and safety analysis about HTEs were well designed and conducted. Thus, attrition bias and reporting bias were unlikely to exist. In 2 studies, too few patients were enrolled to substantiate their results.[14,15]

3.4. Incidence of high-grade hematologic toxicities

For the incidence of HTEs analysis, only monotherapy treatment with decitabine or azacitidine was considered, excluding the arms combined with chemotherapy and/or other treatments with potential hematologic toxicity. A total of 1377 patients from 13 studies who received HMAs were included for the analysis,[9–13,15,33–39]and the random-effect model was applied. The summary including incidences of high-grade anemia, neutropenia, thrombocytopenia, and febrile neutropenia in patients who received HMAs was presented in Supplementary Figure 1, http://links.lww.com/MD/C392, with an RR value of 0.27 (95% CI 0.18–0.38) for anemia, 0.45 (95% CI 0.30–0.61) for neutropenia, 0.38 (95% CI 0.23–0.57) for thrombocytopenia, and 0.25 (95% CI 0.19–0.31) for febrile neutropenia. Further exploratory analysis was performed to assess the incidence of high-grade hematologic toxicities based on specific HMAs (decitabine vs azacitidine). There was no statistically significance in the incidence of anemia, neutropenia, thrombocytopenia, or febrile neutropenia between these subgroups (Supplementary Figure 2, http://links.lww.com/MD/C392).

3.5. RR of high-grade neutropenia

High-grade neutropenia was calculated in 4 involved studies, which contained patients assigned to the HMA group versus control group (Fig. 3). The pooled analysis showed that the administration of HMAs significantly increased the risk of developing high grade neutropenia. The RR of high-grade neutropenia was 1.41 (95% CI 1.18–1.69; $P < .001$, 4 studies, 1474 pts). However, there was heterogeneity in RR of high-grade neutropenia ($I^2 = 66\%$, $P < .05$) analysis across studies.

Table 1

Baseline characteristics of the trials included in the meta-analysis.

Authors/ year/phase	Disease type	Patients enrolled	Median age (range)	FAB classification (%)	Treatment regimens	BM Blast ≥20% (%)	Risk classification† (%)	Median treatment duration	No. for analysis	Reported high-grade (Grade3/4) adverse events (HTEs)
Hagop et al, 2006/III*[24]	MDS	DAC: 89 BSC: 81	70 (65–76) 70 (62–74)	RA: 12 (13), RARS: 7 (8) RAEB: 47 (53), RAEB-t: 17 (19) CMML: 6 (7), RA: 12 (15), RARS: 4 (5) RAEB: 43 (53), RAEB-t: 14 (17) CMML: 8 (10)	DAC:15 mg/m^2 intravenously 3 h, 8 h for 3 d (135 mg/m^2 per course) repeated every 6 wks Best supportive care	14 (16) 17 (21)	Int-1: 28 (31) Int-2: 38 (43) High risk: 23 (26) Int-1: 24 (30) Int-2: 36 (44) High risk: 21 (26)	3 (0–9)‡ NR	89 81	Neutropenia: 87 (98%) Leukopenia: 22 (25%) Thrombocytopenia: 85 (96%) Febrile neutropenia: 23 (26%) Anemia: 12 (15%) Neutropenia: 50 (62%) Leukopenia: 7 (9%) Thrombocytopenia: 43 (53%) Febrile neutropenia: 4 (5%) Anemia: 15 (19%)
Fenaux et al , 2009/III*[25]	MDS	AZA: 179 CCR: 179	69 (42–83) 70 (38–88)	RAEB: 104 (58) RAEB-t: 61 (34) CMML: 6 (3) AML: 1 (1) RAEB: 103 (58) RAEB-t: 62 (35) CMML: 5 (3) AML: 1 (1)	Aza: 75 mg/m^2/d subcutaneously every 28 d at least 6 cycles LDAC: 20 mg/m^2/d subcutaneously for 14 d, every 28 d, at least 4 cycles. IC: cytarabine 100–200 mg/m^2/d continuous intravenous infusion for 7 d plus 3 d of either intravenous daunorubicin 40–65 mg/m^2/d or idarubicin 9–12 mg/m^2/d or mitoxantrone 8–12 mg/m^2/d.	55 (31) 58 (32)	Int-1: 5 (3) Int-2: 76 (43) High risk: 82 (46) Int-1: 13 (7) Int-2: 70 (39) High risk: 85 (48)	Aza: 9 (4–15)‡ LDAC: 4.5 (2–8)‡ IC: 1 (1–3)‡ BSC: 6.2mo (3.6–10.3)	179 49 25 105	Neutropenia: 159 (89%) Thrombocytopenia: 149 (83%) Anemia: 100 (56%) Neutropenia: 39 (80%) Thrombocytopenia: 42 (86%) Anemia: 34 (69%) Neutropenia: 17 (68%) Thrombocytopenia: 18 (72%) Anemia: 11 (44%) Neutropenia: 70 (47%) Thrombocytopenia: 72 (69%) Anemia: 67 (64%)
Michael et al, 2011/III*[26]	MDS	DAC: 119 BSC: 114	69 (60–90) 70 (60–86)	RA: 5 (4.2), RARS: 3 (2.5) RAEB: 61 (51.3) RAEB-t: 40 (33.6) CMML: 10 (8.4), AML: 1 (0.8) RA: 8 (7), RARS: 2 (1.8) RAEB: 64 (56.1), RAEB-t: 35 (30.7) CMML: 4 (3.5) AML: 1 (0.9)	DAC: 15 mg/m^2 in 2 doses, intravenous infusion every 8 h for 3 d. This treatment cycle was repeated every 6 wks Best supportive care	41 (34.4) 36 (31.6)	Int-2: 64 (53.8) High: 46 (38.7) Missing:1 (0.9) Int-1: 8 (7.0) Int-2: 63 (55.3) High: 42 (36.8) Missing:1 (0.8)	4 (0–8)‡ NR	114 114	Febrile neutropenia: 29 (25%) Febrile neutropenia: 8 (7%)
Hagop et al, 2012/III*[27]	AML	DAC: 242 CCR: 243	73 (64–89) 73 (64–91)	AML	DAC: 20 mg/m^2/d intravenous infusion for 5 d. This treatment cycle was repeated every 4 wks. LDAC: 20 mg/m^2/d subcutaneous injection for 10 consecutive days every 4 wks Best supportive care	242 (100) 243 (100)	Intermediate: 152 (63.1) Poor: 87 (36.1) Intermediate: 154 (63.6) Poor: 87 (36.0)	4 (NR)‡ 2 (NR) NR	238 208 29	Neutropenia: 76 (32%) Leukopenia: 47 (20%) Thrombocytopenia: 95 (40%) Febrile neutropenia: 76 (32%) Anemia: 80 (34%) Neutropenia: 41 (20%) Leukopenia: 20 (10%) Thrombocytopenia: 73 (35%) Febrile neutropenia: 51 (25%) Anemia: 56 (27%) Neutropenia: 1 (3%) Leukopenia: 0 (0%) Thrombocytopenia: 4 (14%) Febrile neutropenia: 0 (0%) Anemia: 4 (14%)

(*continued*)

Table 1
(continued).

Authors/ year/phase	Disease type	Patients enrolled	Median age (range)	FAB classification (%)	Treatment regimens	BM Blast ≥20% (%)	Risk classification† (%)	Median treatment duration	No. for analysis	Reported high-grade (Grade3/4) adverse events (HTEs)
Hervé et al, 2015/III*[28]	AML	AZA: 241 CCR: 247	75 (64–91) 75 (65–89)	AML	Aza: 75 mg/m^2/d subcutaneous for 7 d, 28 d cycle. LDAC: 20 mg/m^2 subcutaneous injection twice a day for 10 days with every 28 days cycle. IC: standard 7 + 3 regimen Best supportive care	241 (100) ≥50% 173 (71.8) 247 (100) ≥50% 193 (78.1)	Intermediate: 155 (64.3) Poor: 85 (35.3) Intermediate: 160 (64.5) Poor: 85 (34.4)	6 (1–28)‡ 4 (1–25) 2 (1–3) 65 (6–535)d	236 153 42 40	Neutropenia: 62 (26%) Leukopenia: 16 (7%) Thrombocytopenia: 56 (24%) Febrile neutropenia: 66 (28%) Anemia: 37 (16%) Neutropenia: 38 (25%) Leukopenia: 13 (9%) Thrombocytopenia: 42 (28%) Febrile neutropenia: 46 (30%) Anemia: 35 (23%) Neutropenia: 14 (33%) Leukopenia: 6 (14%) Thrombocytopenia: 9 (21%) Febrile neutropenia: 13 (31%) Anemia: 6 (14%) Neutropenia: 2 (5%) Leukopenia: 0 (0%) Thrombocytopenia: 2 (5%) Febrile neutropenia: 11 (28%) Anemia: 2 (5%)
Raya et al, 2015/II*[29]	AML or MDS	T + D: 17 T + C: 17	70 (60–83)	AML: 29 (85.3) RAEB-2: 5 (14.7)	Tosedostat 120 mg/d, mouth on days 1–21 of each 35-d cycle, combined with either decitabine 20 mg intravenously (IV) daily or cytarabine 1 g IV daily for the first 5 d of each 35-d cycle	15 (88.2) 14 (82.4)	Favorable:1 (3) Intermediate:19 (56) Adverse:14 (41)	3 (NR)	13 13	Febrile neutropenia: 4 (31%) Febrile neutropenia: 9 (69%)
Joaquin et al, 2017/II*[30]	MDS	AZA: 20 BSC: 20	76.1 (50–85) 74.5 (45–90)	NR	Aza: 75 mg/m^2, subcutaneously for 5 days of each 28-day cycle for 9 cycles Best supportive care	0 (0) 0 (0)	IPSS low or Int-1	9 (2–18) mo 3 (NR)‡	18 18	Febrile neutropenia: 2 (11%) Febrile neutropenia: 1 (6%)
By et al , 2000/II*[31]	MDS	DAC: 66	68 (38–84)	RA/RARS: 8 (12.1) RAEB: 29 (43.9), RAEB-t: 20 (30.3) CMML: 9 (13.6)	15 mg/m^2 infused over a 4-hour period every 8 h (45 mg/m^2 per day) for 3 consecutive days, repeated every 6 wks	NR	Int-1: 16 (24.2) Int-2: 25 (37.9) High risk: 25 (37.9)	NR	66	Neutropenia: 8 (12%) Thrombocytopenia: 3 (5%) Anemia: 7 (11%)
Roger M et al, 2009/II*[32]	MDS	AZA 5–2–2:50 AZA 5–2–5:51 AZA 5:50	73 (37–88) 76 (54–91) 76 (47–93)	RA: 65 (43.0) RARS: 21 (13.9) RAEB: 45 (29.8), RAEB-t: 4 (2.6) CMML: 16 (10.6)	AZA5–2–2: 75 mg/m^2/d subcutaneously for 5 d, followed by 2 d no treatment, then 75 mg/m^2/d for 2 d; AZA5–2–5: 50 mg/m^2/d subcutaneously for 5 d, followed by 2 d no treatment, then 50 mg/m^2/d for 5 d; AZA 5: 75 mg/m^2/d subcutaneously for 5 d All patients administered in 28-day cycles for 6 treatment cycles	NR	NR	NR	50 48 50	Neutropenia: 21 (42%) Leukopenia: 7 (14%) Thrombocytopenia: 13 (26%) Febrile neutropenia: 4 (8%) Anemia: 12 (24%) Neutropenia: 15 (31%) Leukopenia: 4 (8%) Thrombocytopenia: 7 (15%) Febrile neutropenia: 4 (8%) Anemia: 7 (15%) Neutropenia: 11 (22%) Leukopenia: 4 (8%)

(*continued*)

Table 1

(continued).

Authors/ year/phase	Disease type	Patients enrolled	Median age (range)	FAB classification (%)	Treatment regimens	BM Blast ≥20% (%)	Risk classification† (%)	Median treatment duration	No. for analysis	Reported high-grade (Grade3/4) adverse events (HTEs)
										Thrombocytopenia: 6 (12%) Febrile neutropenia: 1 (2%) Anemia: 5 (10%)
Mike et al, 2009/II*[33]	MDS	AZA: 25	69.5 (53–79)	RA: 6 (27.3) RAEB: 12 (54.5), RAEB-t: 2 (9.1) CMML: 2 (9.1)	75 mg/m^2/d of azacitidine by 20-min intravenous infusion for 5 d in every 28 d	NR	Low risk: 1 (4.5) Int-1:8 (36.4) Int-2: 7 (31.8) High risk: 6 (27.3)	4.5 (1–20)	22	Neutropenia: 10 (45%) Leukopenia: 8 (36%) Thrombocytopenia: 4 (18%) Febrile neutropenia: 6 (27%) Anemia: 12 (55%)
Amanda et al, 2010/II*[34]	AML	DAC: 55	74 (61–87)	AML	DAC: 20 mg/m^2 intravenously for 5 consecutive days of a 4-week cycle	55 (100)	Intermediate: 29 (52.7) Poor: 25 (45.5) Not available:1 (1.8)	3 (1–25)	55	Neutropenia: 11 (20%) Thrombocytopenia: 12 (22%) Febrile neutropenia: 16 (29%) Anemia: 10 (18%)
Guillermo et al, 2013/IIa[35]	MDS	DAC: 67	67 (NR) 71 (NR)	NR	Schedule A: DAC 20 mg/m^2 SC per d for 3 consecutive d on days 1, 2, and 3 every 28 d Schedule B: DAC 20 mg/m^2 SC per day once every 7 d on days 1, 8, and 15 every 28 d	NR	Int-1: 31 (72) Int-2: NR High risk: NR Int-1: 15 (68) Int-2: NR High risk: NR	7 (1–13) 5.5 (2–16)	43 22	Neutropenia: 12 (28%) Leukopenia: 4 (9%) Thrombocytopenia: 7 (16%) Anemia: 10 (23%) Neutropenia: 8 (36%) Leukopenia: 6 (27%) Thrombocytopenia: 7 (32%) Anemia: 4 (18%)
Linu et al, 2015/II*[36]	AML	DAC: 15 Cytarabine: 15	65 (60–80) 62 (60–73)	AML	DAC: 20 mg/m^2/d intravenous infusion for 5 d. This treatment cycle was repeated every 4 wks. Cytarabine: 20 mg/m^2 once a day subcutaneously for 10 consecutive days every 4 wks	15 (100) 15 (100)	NR	4 (1–7) 4 (1–14)	15 15	Neutropenia: 7 (46.67%) Thrombocytopenia: 8 (53.33%) Febrile neutropenia: 5 (33.33%) Anemia: 8 (53.33%) Neutropenia: 8 (53.33%) Thrombocytopenia: 8 (53.33%) Febrile neutropenia: 5 (33.33%) Anemia: 7 (46.67%)
Depei et al, 2015/IIIb*[37]	MDS	DAC-3 day: 36 DAC-5 day: 99	49.2 (NR) 54.7 (NR)	RA: 11 (30.6), RARS: (0), RAEB: 18 (50.0), RAEB-t: 4 (11.1) CMML: 3 (8.3), RA: 16 (16.2), RARS: 4 (4.0) RAEB: 67 (67.7), RAEB-t: 7 (7.1) CMML: 5 (5.1)	DAC: 3-h intravenous infusion of 15 mg/m^2 given every 8 h for 3 consecutive days/cycle/6 wks DAC: 1-h intravenous infusion of 20 mg/m^2 once daily on days 1–5/cycle/4 wks	NR	Int-1: 18 (50.0) Int-2: 11 (30.6) High risk: 7 (19.4) Int-1: 39 (39.4) Int-2: 47 (47.5) High risk: 13 (13.1)	3 (NR)‡ 4 (NR)‡	132	Neutropenia: 71 (53.8%) Leukopenia: 90 (68.1%) Thrombocytopenia: 81 (61.4%) Anemia: 57 (43.2%)

AML = acute myeloid leukemia with BM blast more than 30%, AML = acute myeloid leukemia, AZA = azacitibine, BM = bone marrow, BSC = best supportive care, CCR = conventional care regimens, CMML = chronic myelomonocytic leukemia, DAC = decitabine, FAB = French–American–British; FAB classification, HTEs = hematologic toxicities, IC = intensive chemotherapy, IPSS = International Prognostic Scoring System, LDAC = low-dose cytarabine, MDS = myelodysplastic syndrome, NR = not report, RA = refractory anemia, RAEB = refractory anemia with excessive blasts, RAEB-t = RAEB in transformation with BM blast (21–30%), RARS = refractory anemia with ring sideroblasts, T + C = tosedostat + cytarabine, T + D = tosedostat + decitabine.

* Open-label.

† Risk classification: IPSS classification (Low risk; Intermediate-1, Int-1; Intermediate-2, Int-2; High risk); Cytogenetics (good, intermediate, poor). According to European LeukaemiaNet criteria (Cheson et al, 2003).

‡ (Range, the number of courses or cycles).

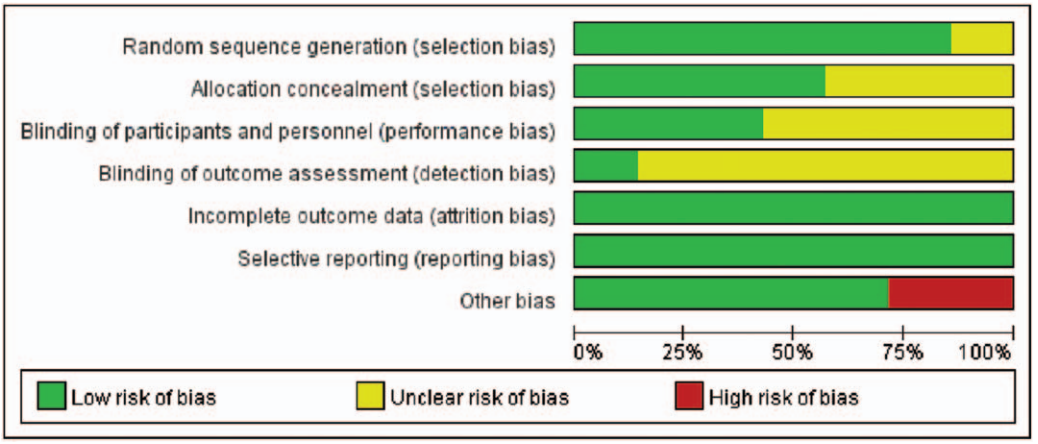

Figure 1. Risk of bias graph in the included RCTs. RCT = randomized controlled trial.

3.6. RR of high-grade thrombocytopenia

For the RR calculation of high-grade thrombocytopenia, 4 trials with patients who received HMAs versus CCR were used for analysis (Fig. 4). Administration of HMAs increased the risk of developing high-grade thrombocytopenia. The RR of high-grade thrombocytopenia was 1.28 (95% CI 1.01–1.62; $P < .05$, 4 studies, 1474 pts). By I^2 statistics, substantial heterogeneity tested was observed ($I^2 = 81\%$, $P < .05$).

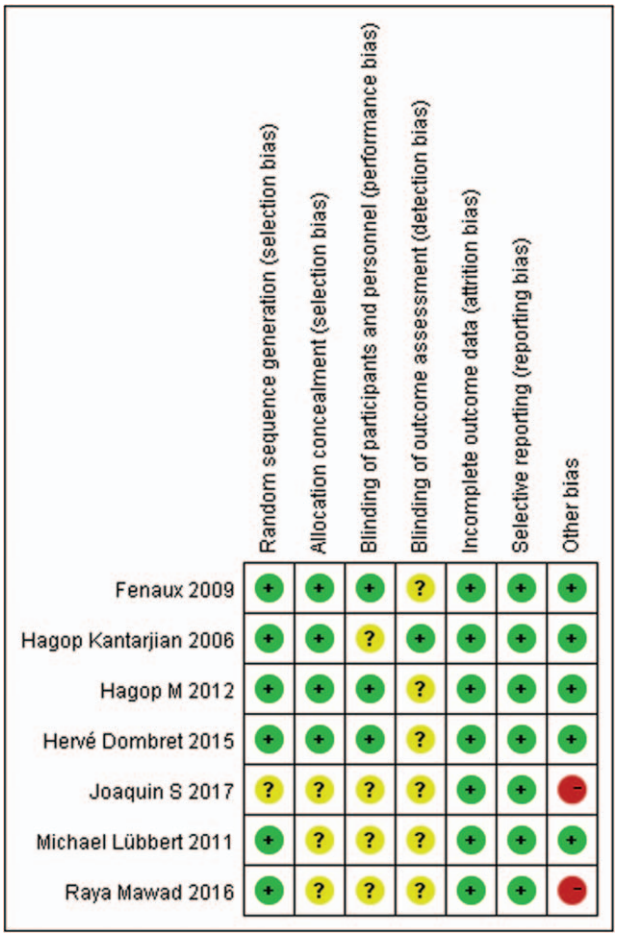

Figure 2. Summary of the risk of bias in the included RCTs. RCT = randomized controlled trial.

3.7. RR of high-grade anemia, leukopenia, and febrile neutropenia

The RR calculation of anemia, leukopenia, and febrile neutropenia was shown in Fig. 5, and 7 randomized trials with patients received HMAs versus CCR were available in this meta-analysis. The RR of high-grade anemia, leukopenia, and febrile neutropenia were 0.98 (95% CI 0.76–1.25; $P > .05$, 4 studies, 1474 pts), 1.76 (95% CI 0.85–3.64; $P > .05$, 3 studies, 1116 pts), and 1.56 (95% CI 0.86–2.75; $P > .05$, 6 studies, 1406 pts), respectively, suggesting that HMAs did not significantly increase the risk of developing any outcomes. There was significant heterogeneity among included studies ($I^2 = 56\%$, $P > .05$), ($I^2 = 75\%$, $P < .05$), ($I^2 = 81\%$, $P < .001$).

3.8. RR of hematologic toxicities by specific HMAs

To investigate the relationship between hematologic toxicities and different HMAs, we performed subgroup analyses based on the drugs used. For high-grade neutropenia, both decitabine treatment (RR = 1.63, 95% CI: 1.40–1.90, $P < .001$) and azacitidine treatment (RR = 1.25, 95% CI: 1.13–1.38, $P < .001$) significantly increased the risk compared with CCR (Fig. 6A), and there was statistical significance between decitabine and azacitidine ($P < .05$). As for the RR of high-grade thrombocytopenia (Fig. 6B), both decitabine group (RR = 1.49, 95% CI: 1.01–2.21, $P < .05$) and azacitidine group (RR = 1.15, 95% CI: 1.04–1.27, $P < .05$) increased the risk of thrombocytopenia compared with CCR; however, no statistical significance was observed among decitabine and azacitidine ($P > .05$). There was no statistical significance in association of anemia (RR = 1.07, 95% CI: 0.61–1.89, $P > .05$) or febrile neutropenia (RR = 0.89, 95% CI: 0.76–1.04, $P > .05$) in groups treated with HMAs compared with CCR (Fig. 7).

3.9. RR of hematologic toxicities by the type of CCR

To further clarify the relationship between HMAs and different CCR in hematologic toxicities, we performed subgroup analysis

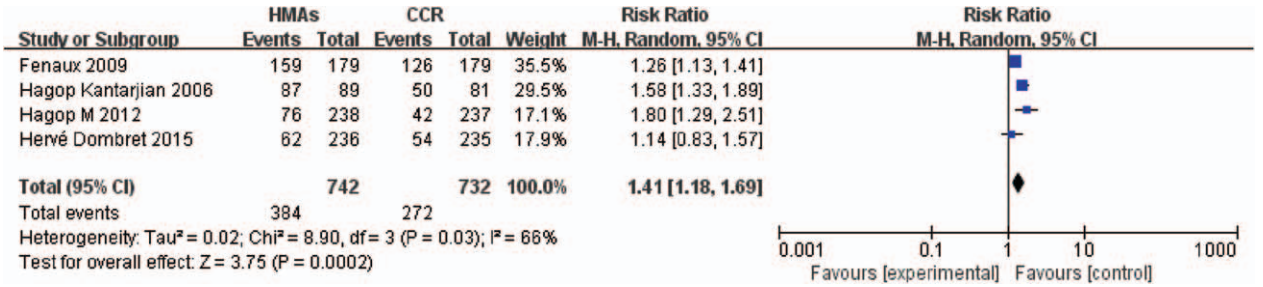

Figure 3. Forest plot of RR of high-grade neutropenia associated with HMAs versus CCR. CCR = conventional care regimens, HMAs = hypomethylating agents, RR = relative risks.

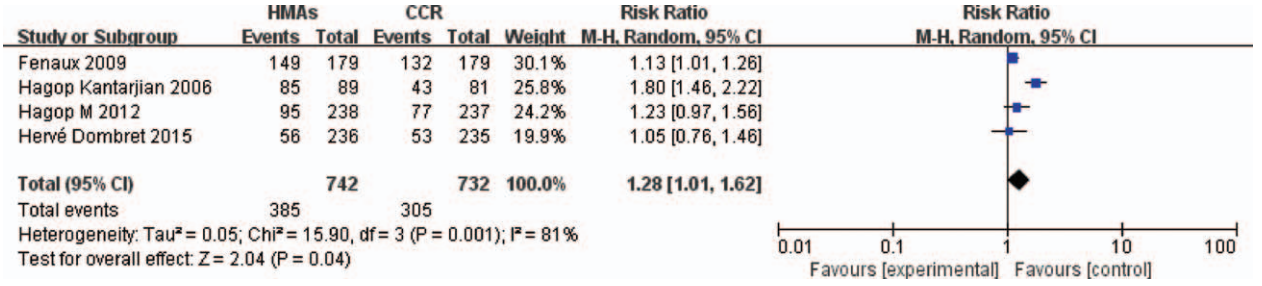

Figure 4. Forest plot of RR of high-grade thrombocytopenia associated with HMAs vs CCR. CCR = conventional care regimens, HMAs = hypomethylating agents, RR = relative risks.

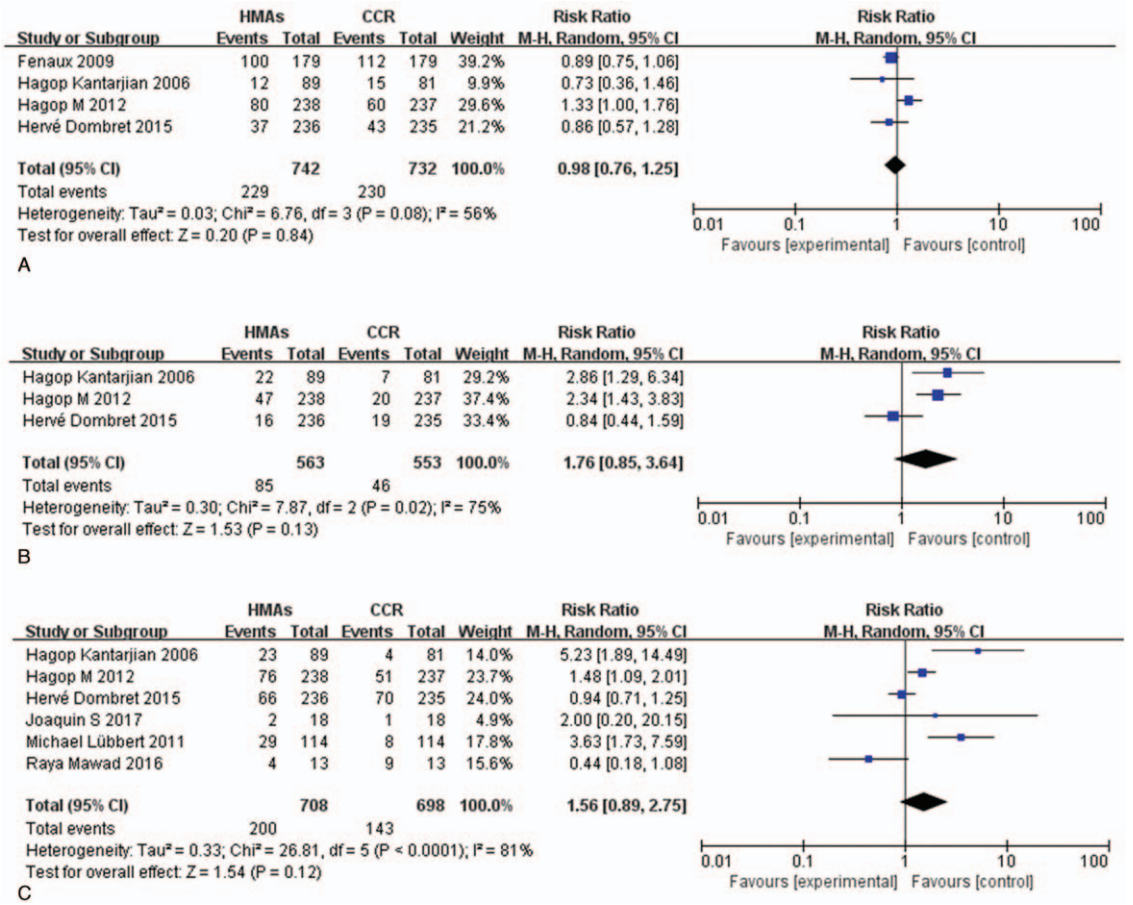

Figure 5. RR of high-grade HTEs in patients associated with HMAs versus CCR. (A) Forest plot of RR of high-grade anemia. (B) Forest plot of RR of high-grade leukopenia. (C) Forest plot of RR of high-grade febrile neutropenia. CCR = conventional care regimens, HMAs = hypomethylating agents, HTEs = hematologic toxicity effects, RR = relative risks.

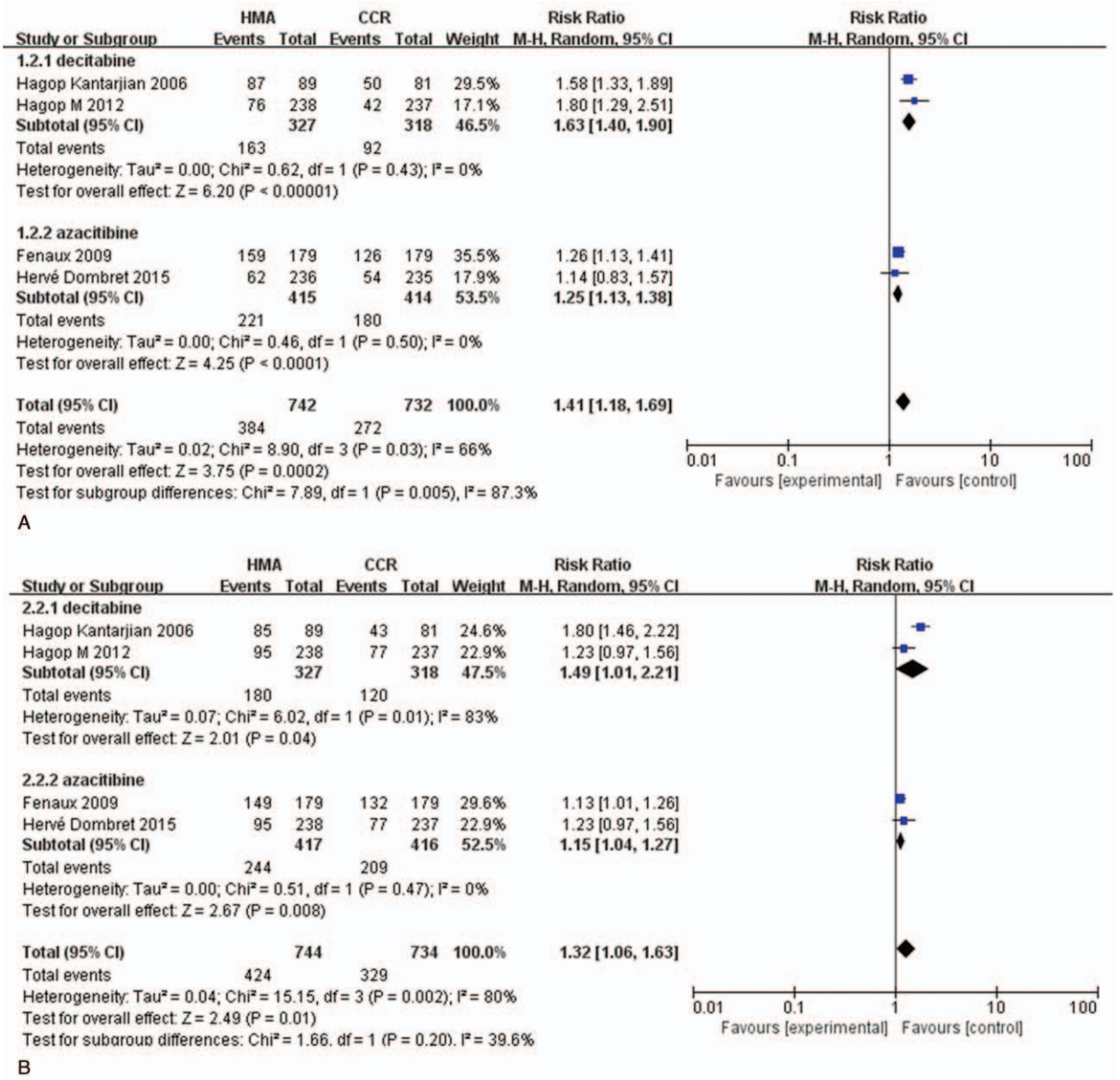

Figure 6. RR of high-grade neutropenia and thrombocytopenia in patients associated with decitabine versus azacitidine. (A) Forest plot of RR of high-grade neutropenia. (B) Forest plot of RR of high-grade thrombocytopenia (sub-grouped by the type of HMAs). HMAs = hypomethylating agents, RR = relative risks.

based on the type of CCR. The RR of high-grade neutropenia, thrombocytopenia, leukopenia febrile neutropenia, and anemia were 2.83 (95% CI 1.17–2.34; $P < .05$, 4 studies, 997 pts), 2.64 (95% CI 1.16–2.72; $P < .01$, 4 studies, 997 pts), 3.19 (95% CI 1.59–6.95; $P < .01$, 3 studies, 713 pts), 2.16 (95% CI 1.11–8.04; $P < .05$, 5 studies, 977 pts), and 0.60 (95% CI 0.64–2.3; $P > .05$, 4 studies, 997 pts), respectively (Fig. 8), suggesting that the HMAs significantly increased the risk compared with BSC except anemia. However, demethylation does not increase the risk of HTEs compared with LDAC or IC (Fig. 8).

4. Discussion

DNA methylation, catalyzed by DNA methyltransferase (DNMT), is one of the most important epigenetic modifications. In normal and cancer cells, DNA methylation regulates gene expression by modifying cytosine, and the silencing of tumor suppressor genes is associated with aberrant promoter DNA methylation.[40–42] Methylation status has been related to the prognosis and pathogenesis of the AML and MDS, with hypermethylation exerting an adverse effect on the results of induction therapy.[43–45] However, DNA methylation can be reversed during DNA synthesis, which makes it a potential therapeutic target. Therefore, demethylation therapy has become a routine treatment in the MDS and AML.

Demethylation therapy has significant overall survival (OS) and complete remission (CR)/partial remission (PR) benefits in comparison to CCR, and it is a preferred therapeutic option especially for the patients not suitable for transplantation and chemotherapy, and for elderly patients with MDS or AML.[18,46] Since HMAs become more commonly used as the routine treatment of MDS or AML, their associated toxicities are being

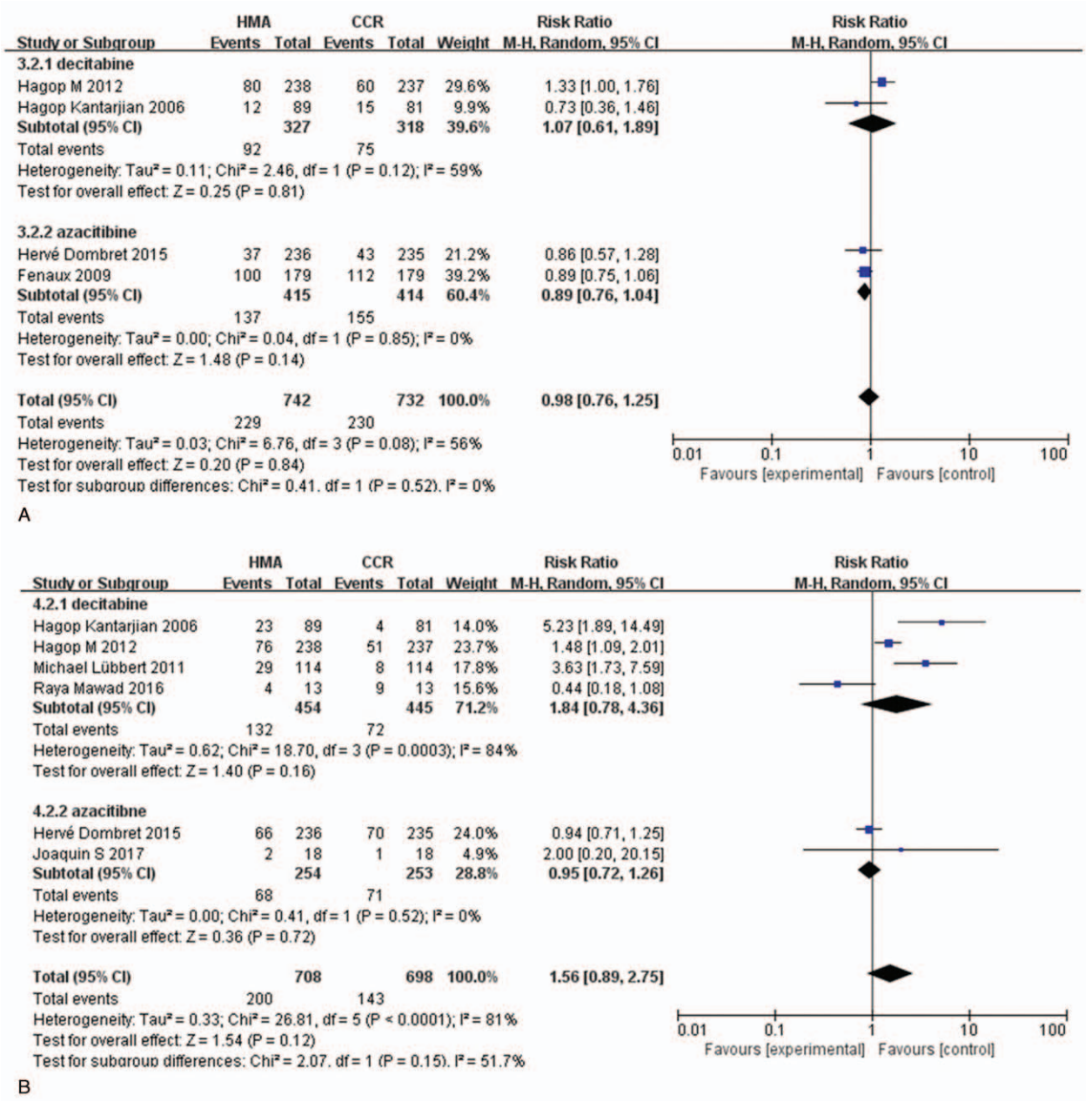

Figure 7. RR of high-grade anemia and febrile neutropenia in patients associated with decitabine versus azacitidine. (A) Forest plot of RR of high-grade anemia. (B) Forest plot of RR of high-grade febrile neutropenia (sub-grouped by the type of HMAs). HMAs = hypomethylating agents, RR = relative risks.

more and more valued in clinical trials. Myelosuppression was the most common adverse effect observed in HMAs treated patients, particularly in early treatment, which frequently led to treatment interruption, discontinuation, disabilities, or deaths.[11,13,26] Intriguingly, the myelosuppression was also the major hematologic adverse effect in clinical trials of HMAs in other diseases.[47,48] Previous studies did not discuss HTEs from using HMAs in detail, and it is difficult for a patient or clinician to judge the risk-benefit balance.

As far as we know, this meta-analysis is among the first to investigate the incidence and risk of HMAs' hematological toxicities in patients with MDS or AML. Our current meta-analysis included 14 studies, of which 7 studies were randomized controlled trials with decitabine or azacitidine. A total of 2337 patients were included in this meta-analysis and all from prospective phase II and phase III trials, representing a comprehensive meta-analysis of HMAs associated HTEs in MDS and AML patients. Therefore, this study has a higher quality of evidence.

For the incidence of high-grade HTEs analysis, they were 27%, 45%, 38%, and 25% for anemia, neutropenia, thrombocytopenia, and febrile neutropenia, respectively. The incidences of neutropenia and thrombocytopenia were among the highest. Interestingly, this result was similar to the RR of hematologic toxicity. The results of this meta-analysis also demonstrated that the RR of high-grade anemia, leukopenia, and febrile neutropenia in comparison with CCR did not significantly increase among patients receiving HMAs. However, there was a significant

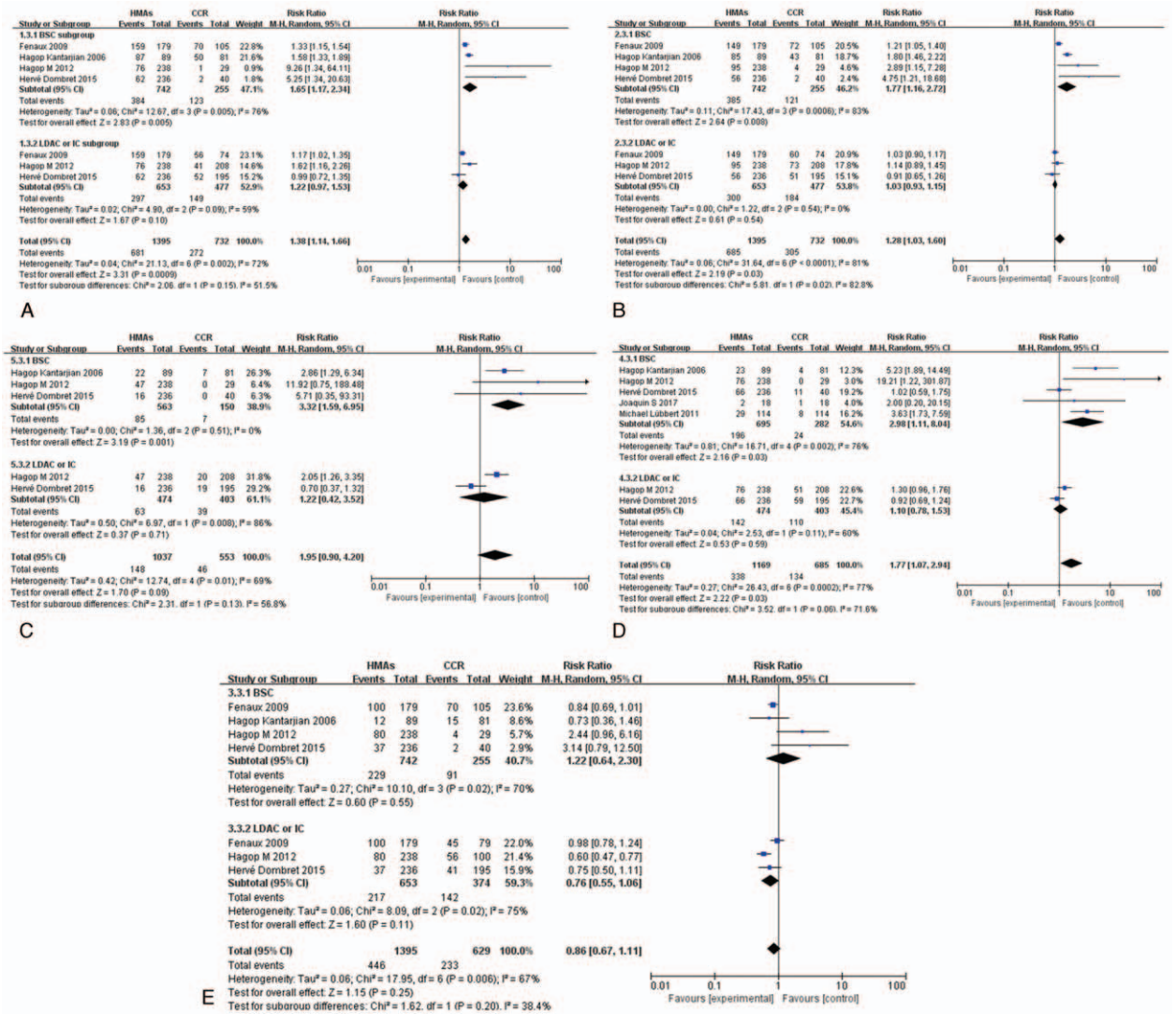

Figure 8. RR of high-grade HTEs in patients associated with HMAs versus CCR (BSC, IC, and LDAC). (A) Forest plot of RR of high-grade neutropenia. (B) Forest plot of RR of high-grade thrombocytopenia. (C) Forest plot of RR of high-grade leukopenia. (D) Forest plot of RR of high-grade febrile neutropenia. (E) Forest plot of RR of high-grade anemia (sub-grouped by the type of CCR). BSC = best supportive care, CCR = conventional care regimens, HMAs = hypomethylating agents, HTEs = hematologic toxicity effects, IC = intensive chemotherapy, LDAC = low-dose cytarabine, RR = relative risks.

difference in the RR of neutropenia and thrombocytopenia between HMAs and CCR ($P < .05$). In order to further investigate the difference in the RR of neutropenia and thrombocytopenia between HMAs and CCR, we performed subgroup analysis between HMAs and different CCR. Our subgroup analysis results demonstrated that HMAs significantly increased the risk of high-grade neutropenia and thrombocytopenia compared with BSC, but there was no significant difference between HMAs and LDAC or IC. However, a retrospective study showed that the efficacy of decitabine alone or using traditional chemotherapy protocols was equivalent in treating MDS, but decitabine alone regimen was safer,[49] which was inconsistent with our meta-analysis.

Decitabine and azacitidine belong to demethylation drugs, with slightly different structures in which decitabine (5-aza-2′-deoxycytidine) is a deoxyribonucleoside whereas azacitidine is a ribose nucleoside.[50] Although both decitabine and azacitidine act via depletion of DNA methyltransferases, these 2 drugs work through 2 distinct mechanisms: azacitidine is modified into a deoxyribonucleoside triphosphate before incorporating into DNA or directly incorporated into RNA, while decitabine is phosphorylated by different kinases and is directly incorporated into DNA.[51] Azacitidine inhibits protein synthesis as an additional function for incorporation into RNA.[52] Because of these 2 distinct mechanisms of action, the hematologic toxicity from these 2 drugs may show differences. Subsequently, we further conducted specific subgroup analyses to explore such differences in the RR of HTEs between azacitidine and decitabine. Our exploratory subgroup analysis demonstrated an increased risk of high-grade neutropenia in patients receiving decitabine compared with azacitidine, which is consistent with other reported studies.[53] However, the other two meta-analysis showed that there were no differences between decitabine and azacitidine regarding grade 3/4 hematological toxicity.[19,20] But, in the 2 meta-analysis, 1 research included only 3 RCTs, while the other contained only 2 RCTs and the rest of the trials were all non-RCTs about the HTEs research. Therefore, the quality of the conclusion of these 2 meta-analysis was not high, and this might be the reason that was inconsistent with our findings.

Previous research showed that more courses (e.g., ≥3) were needed to achieve optimal response to HMAs.[54,55] However, high-grade HTEs of HMAs did not allow patients to receive more courses of treatment in clinical practice. The high-grade HTEs not only caused discontinuation of treatment, but also led to death, as 24% of the deaths were related to the adverse effects of decitabine.[12] Therefore, in order to prevent the occurrence of adverse reactions, selection of optimized treatment plans was advised to achieve better clinical efficacy for demethylation therapy. A meta-analysis suggested that decitabine at 100 mg/m^2/course dosing regimen had a greater clinical benefit in treating MDS than decitabine at 60 to 75 mg/m^2/course and 135 mg/m^2/course regimens.[56]

Several potential limitations should be considered when interpreting the outcomes of this study. In the first place, significant heterogeneity was detected between studies, which was likely caused by the differences of diseases (MDS or AML), types of HMAs, dose schedules, administrations of HMAs (intravenous or subcutaneous injection), primary or secondary disease, and the phase of trials. Random-effects model was used to minimize the influence, and also we conducted a subgroup analysis to explore the feasible reasons for the heterogeneity. However, such subgroup analysis according to disease types, dose schedules, administrations of HMAs, primary or secondary disease, or the phase of trials was not able to achieve due to the limited number of studies included. Secondly, the safety profile was not in detail or classified according to the age of patients, bone marrow blasts, and frequency of transformation of MDS to AML, etc. In addition, the classification of MDS was according to the recognized French–American–British (FAB) classifications, which contained AML patients (World Health Organization [WHO] criteria). Therefore, we could not differentiate the disease types (MDS vs AML), age of patients, and frequency of transformation of MDS to AML. Thirdly, for RR analysis, this meta-analysis only involved 7 RCT, in which 2 studies had <40 subjects, thus serving as an important contributor for the observed heterogeneity. Moreover, some included studies did not report random sequence generation, concealment allocation, blinding of participants, or personnel and evaluator, contributing to bias in analysis.

5. Conclusion

In summary, our results indicate that there are significant differences in the RR of neutropenia and thrombocytopenia in patients receiving HMAs compared with CCR, and an increased risk of high-grade neutropenia in patients receiving decitabine. Early prevention and effective management of HTEs are feasible and crucial for safe use of HMAs in patients with MDS or AML. The findings of this meta-analysis can provide strong evidence for clinicians when assessing the risk-benefit balance of HMAs in clinical practice.

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