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Original Article

Prognostic significance of IDH1 mutations in acute myeloid leukemia: a meta-analysis

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Abstract: Isocitrate dehydrogenase 1 (IDH1) gene aberrations have recently been reported in acute myeloid leukemia (AML). To evaluate the prognostic significance of IDH1 mutations in AML, we performed a meta-analysis. Fifteen studies covering a total of 8121 subjects were included in this analysis. The frequency of IDH1 R132 mutations were 4.4–9.3% for AML patients and 10.9–16.0% for cytogenetically normal (CN)-AML patients. The IDH1 mutations were associated with NPM1 mutations in 6 studies and normal cytogenetics in 5 studies. AML patients with IDH1 mutations had inferior overall survival compared to patients without the mutations (hazard ratio 1.17, 95% CI: 1.02–1.36). Additionally, in CN-AML patients, IDH1 mutations were associated with a lower complete remission rate (risk ratio 1.30, 95% CI: 1.04–1.63). Although the available literature is limited to observational studies, these results may justify the risk-adapted therapeutic strategies for AML according to the IDH1 status.

Keywords: Acute myeloid leukemia, IDH1, mutation, prognosis, meta-analysis

Introduction

Acute myeloid leukemia (AML) is a group of heterogeneous diseases with respect to its underlying cellular and molecular biology, acquired genetic profiles, and associated clinical responses to treatment [1, 2]. To date, cytogenetic aberrations provide the most important prognostic information of this heterogeneous disease [3, 4]. Furthermore, the molecular genetic alterations have been reported with prognostic significance. The increasing number of genetic alterations discovered in AML has additionally contributed to our understanding of mechanisms of leukemogenesis, to an improvement of individual risk assessment, and eventually to the development of risk stratification and molecularly based therapies [5].

Among these genetic alterations, recurrent somatic mutations in nicotinamide adenine dinucleotide phosphate (NADPH)-dependent isocitrate dehydrogenase 1 (IDH1) gene affecting codon R132 [6] are special in that the gene is involved in metabolism [7, 8], rather than signaling pathways or transcription factors. IDH1, a citric acid cycle enzyme encoded by the IDH1 gene, converts isocitrate to α-ketoglutarate in an $NADP^+$-dependent manner and is supposed to control redox status in cells [9, 10]. Mutations of IDH1 were found to cause dominant-negative inhibition of normal enzymatic function and gain the neomorphic enzyme activity and, ultimately, catalyze the NADPH-dependent reduction of α-ketoglutarate to 2-hydroxyglutarate (2-HG) [8, 11]. It is thought that consumption of NADPH and production of 2-HG could contribute to leukemogenesis [8, 11, 12], which might be due to the damage of DNA via the elevated levels of reactive oxygen species [9, 11] and/or the induction of DNA hypermethylation via the disruption of TET2 function [13]. IDH1 mutations have been reported in 4.4% to 9.6% of patients with AML [6, 14-18]. However, the prognostic implications of IDH1 mutations are less clear and wildly variable among different institutions [14, 16-20]. A recent meta-analysis conducted by Zhou et al. including 11 studies suggested subtle but significant inferior event-free survival (EFS) and possible adverse overall survival (OS) for AML patients with IDH1 mutations [21]. However, only the studies dealing with non-promyelocytic AML were considered eligible for inclusion in the Zhou study, while

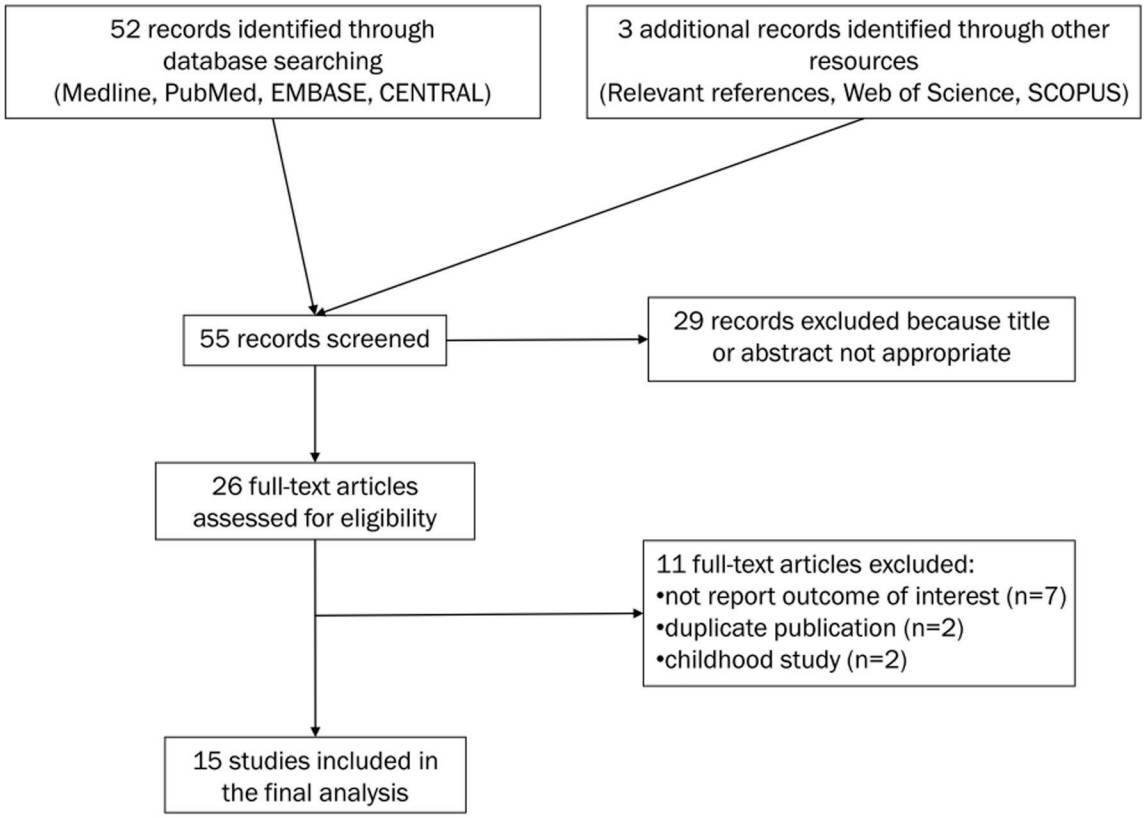

Figure 1. Flow diagram showing the process of identifying and selecting relevant studies.

some current studies focus on cytogenetically normal (CN)-AML or all AML subtypes. Therefore, in order to gain a full insight into the prognostic value of IDH1 mutations in patients with AML, we conducted an updated meta-analysis, including all available clinical evidences to date.

Materials and methods

Selection of studies

Studies were eligible for inclusion in the meta-analysis if they met all of the following criteria. (1) published up to October 2012 as original articles, (2) dealt only with untreated AML patients, (3) offered survival information based on the IDH1 status: IDH1 mutations and wild type, and (4) described survival information (overall survival (OS)) and/or response to induction therapy (complete remission (CR)). Studies were excluded if they focused exclusively on children or on acute promyelocytic leukemia.

A computerized literature search of Medline, PubMed, EMBASE and The Cochrane Central Register of Controlled Trials (CENTRAL) was conducted by using the free text search term *AML* AND *isocitrate dehydrogenase* AND *survival*, with the publication period limited to before October 2012. The search was restricted to human studies with no language limitations. The initial database search yielded 52 citations. Three studies were found through other resources (Relevant references, Web of Science and SCOPUS). Abstracts of the 55 papers were reviewed, resulting in 29 of them being excluded, and leaving 26 as candidate articles. Of these, 15 studies satisfied eligibility criteria and were included in the meta-analysis (**Table 1**). The reasons for excluding 11 articles are shown in **Figure 1** [22-32].

Data extraction and quality assessment

To avoid bias in the data abstraction process, the two reviewers (J.-H.F and Y.-M.T) independently abstracted the data from the articles and subsequently compared the results. All data were checked for internal consistency, and disagreements were resolved by discus-

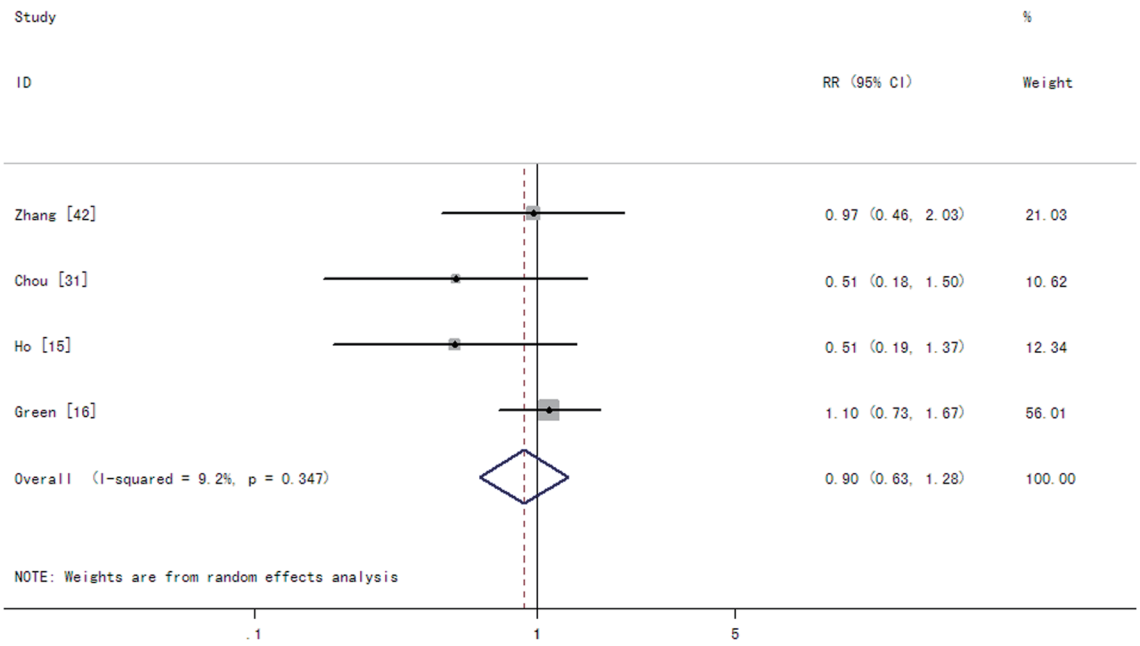

Figure 2. Forest plots of the risk ratios (RRs) and 95% confidence intervals for complete remission in AML patients. The size of the blocks or diamonds represents the weight for the random-effect model in the meta-analysis. A RR higher than one would indicate that the presence of IDH1 mutations is associated with a lower CR rate.

sion. Characteristics abstracted from the articles included the name of the first author, year of publication, location of the study, number of subjects, mean or median values of age and initial white blood cell (WBC) counts, the incidence of IDH1 mutations, incidence of NPM1 mutations, incidence of FLT3-ITD and percentage of cases with normal cytogenetics, and outcomes including hematologic complete remission (CR) rate and hazard ratio (HR) for OS according to the IDH1 status based on multivariate analysis. When the data required for the analysis could not be abstracted, attempts were made to contact the investigators who conducted the studies.

The quality of evidence and the strength of recommendations were evaluated by GRADE profiler (version 3.2) [33]. Any discrepancies in quality assessments were resolved by consensus amongst authors. The overall quality of the evidences was graded as moderate.

Quantitative data synthesis

HR was used to assess the survival effect of IDH1 mutations compared with wild type. The natural logarithm of a crude HR and its variance within the study was calculated by using the abstracted survival probabilities at each time point with the methods proposed by Parmar et al. [34] and described elsewhere [35]. HR was calculated to show how many times higher the probability of the survival failure was for patients with IDH1 mutations than for those with wild type, as an HR higher than unity indicates that IDH1 mutations yield a worse survival rate than wild type.

Risk ratio (RR) was calculated to describe the probability of response failure to induction treatment based on IDH1 mutation status. RR greater than one indicates that the patients with IDH1 mutations are associated with a worse outcome as compared to those without the mutations.

A Der-Simonian Laird random method was used to calculate summary HRs or RRs and their 95% confidence intervals (CI). Begg's funnel plots [36] and Egger's test [37] were used to detect possible publication bias. We also calculated the between-study variation (τ^2) from the Q statistic [38]. All statistical analyses were conducted with Stata ver. 12 software (College Station, TX, USA). We defined a *P*-value of less than 0.05 as a statistically significant test result for a summary HR or RR.

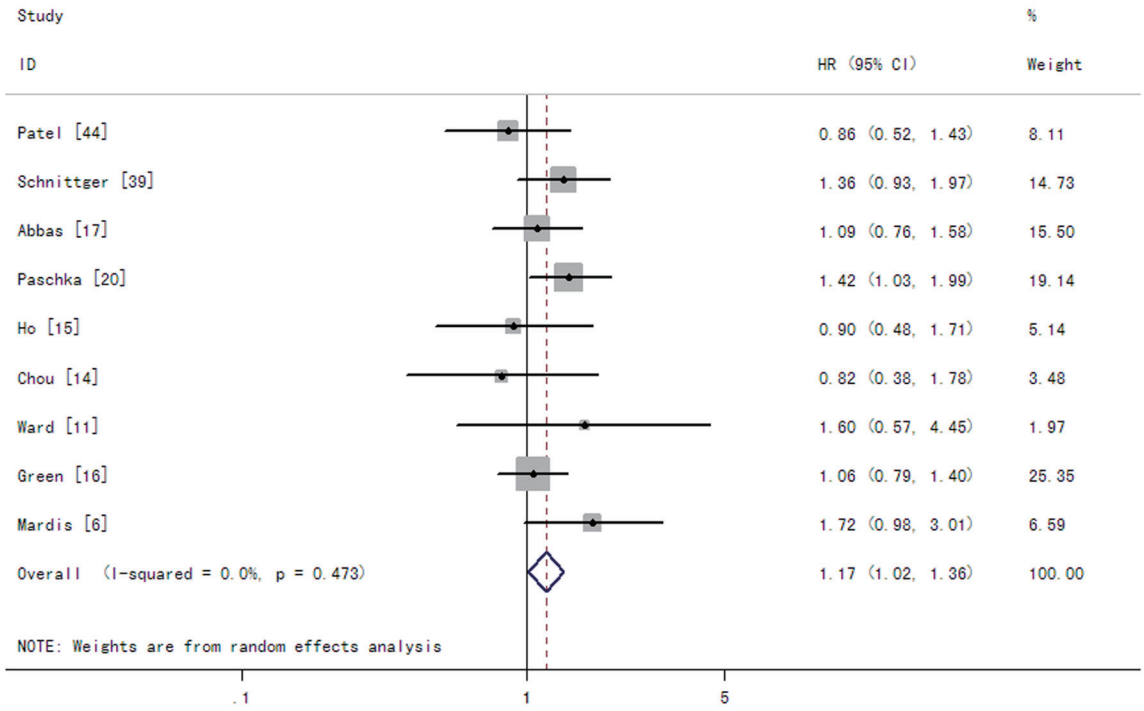

Figure 3. Forest plots of the hazard ratios (HRs) and 95% confidence intervals for overall survival in AML patients. The size of the blocks or diamonds represents the weight for the random-effect model in the meta-analysis. A HR higher than one indicates that the presence of IDH1 mutations is associated with a worse prognosis.

Results

Study characteristics

As shown in **Table 1**, 15 studies with a total of 8121 subjects were included in the meta-analysis. Six studies originated from Europe [16-18, 20, 39, 40], three from Asia [14, 41, 42] and six from the United States [6, 11, 15, 19, 43, 44]. The frequency of IDH1 R132 mutations varied between 4.4–9.3% for AML patients and 10.9–16.0% for CN-AML patients.

IDH1 mutations were associated with a higher frequency of NPM1 mutations in six studies [14, 16-18, 39, 43]. No significant correlation was reported between IDH1 mutations and FLT-ITD although one study showed that IDH1 mutations were associated with a lower frequency of FLT-ITD [19]. The frequency of normal cytogenetics was higher among IDH1 mutant patients in 5 studies (**Table 2**) [6, 14, 16, 17, 39]. We find no evidence of publication bias for either CR or OS.

Treatment outcomes

Table 3 and **Table 4** show CR rate and HR for OS among AML and CN-AML patients with IDH1 mutations compared to patients without the mutations in individual studies.

In patients with AML, the summary RRs for CR in the IDH1 mutant group were 0.90 (95% CI: 0.63–1.28 with a *P*-value of 0.559) (**Figure 2**). The summary HRs for OS were 1.17 (95% CI: 1.02–1.36 with a *P*-value of 0.029) for patients with the IDH1 mutations compared to those without the mutations (**Figure 3**). The test for heterogeneity, which evaluates variation in study outcomes between studies in a meta-analysis, showed no significant heterogeneity among studies included in OS analysis ($Q = 7.61$, $df = 8$, $P = 0.473$, $\tau^2 = 0$).

Among CN-AML patients, the summary RRs for CR of IDH1 mutations were 1.30 (95% CI: 1.04–1.63 with a *P*-value of 0.021) (**Figure 4**). The summary HRs for OS were 1.09 (95% CI: 0.91–1.30 with a *P*-value of 0.373) in patients with the IDH1 mutations compared to those without the mutations (**Figure 5**). The test for heterogeneity for OS between studies showed no evidence of heterogeneity related to IDH1 status ($Q = 2.65$, $df = 6$, $P = 0.852$, $\tau^2 = 0$).

Furthermore, we conducted a sensitivity test during the process of meta-analysis. Exclusion

Table 1. List of studies included in the meta-analysis

Author [ref.]	Publication year	Region	N	Age (years)	Tumor types	IDH1 R132 mutation (%)
Ravandi [43]	2012	USA	170	53 (17–73)	AML	7.1%
Patel [44]	2012	USA	657	48 (17–60)	AML	7%
Shen [41]	2011	China	605	43 (18–86)	AML[a]	9.3%
Zhang [42]	2011	China	365	39 (15–74)	AML	6.3%
Schnittger [39]	2010	Germany	1414	66 (17–93)	AML	6.6%
Abbas [17]	2010	Netherlands	893	46 (15–77)	AML	6.2%
Paschka [20]	2010	Germany	805	NA (16–60)	AML	7.2%
Ho [15]	2010	USA	274	63 (18–88)	AML	4.4%
Chou [14]	2010	Taiwan	493	53 (18–90)	AML	5.5%
Ward [11]	2010	USA	78	61 (6–91)	AML	7.7%
Green [16]	2010	England	1333	43 (15–68)	AML	8.0%
Mardis[b] [6]	2009	USA	188	47 (16–81)	AML	8.5%
Boissel [18]	2010	France	213	48 (17–70)	CN-AML	16.0%
Marcucci [19]	2010	USA	358	61 (19–83)	CN-AML	13.1%
Wagner [40]	2010	Germany	275	47 (17–60)	CN-AML	10.9%

Ref, reference; AML, acute myeloid leukemia; CN-AML, cytogenetically normal AML; —, not applicable; NA, not assessed. [a]Only including AML without prognostic cytogenetic markers. [b]Including 30 AML patients (16%) who underwent transplantation.

Table 2. Diagnostic characteristics according to the IDH1 status in the patients with AML and CN-AML

Author [ref.]	IDH1 status	N	Age (years)	Initial WBC count (10^9/L)	NPM1 mutation (%)	FLT3-ITD (%)	Normal cytogenetics (%)
Ravandi [43]	IDH1 wild type	158	53 (17–72)	4.9 (0.3–161.5)	24%*	20%	59%
	IDH1 Mutation	12	53 (36–73)	8.8 (0.6–50.7)	67%	33%	92%
Shen [41]	IDH1 wild type	585	38±19*	7.8 (0.3–453)	NR	NR	NR
	IDH1 Mutation	34	48±18	10.1 (0.6–255)	NR	NR	NR
Zhang [42]	IDH1 wild type	342	39 (15–74)	38.3 (0.5–443)	NR	NR	36.1%
	IDH1 mutation	23	44 (16–67)	28.0 (1.0–127)	NR	NR	33.3%
Schnittger [39]	IDH1 wild type	1321	66 (17–93)	8.6 (0.4–600)	25%*	18%	45.9%*
	IDH1 Mutation	93	67 (22–86)	5.0 (0.3–255)	47%	19%	72.0%
Abbas [17]	IDH wild type	743	45 (15–77)	46 (0–510)	26%*	23.82%	38.1%*
	IDH1 Mutation	55	50 (20–71)	48 (1–400)	64%	27.27%	71.0%
Ho [15]	IDH1 wild type	262	63 (18–88)	29.1 (0.7–298)	NR	34%	41%
	IDH1 Mutation	12	61 (34–81)	59.2 (1.2–98.2)	NR	50%	60%
Chou [14]	IDH1 wild type	466	38.41% > =60 years	NA	19%*	23%	46.0%*
	IDH1 mutation	27	44.44% > =60 years	NA	56%	37%	76.9%
Ward [11]	IDH wild type	60	58 (6–86)	NR	7%	NA	86.3%
	IDH1 Mutation	6	70 (51–91)	NR	17%	NA	100%
Green [16]	IDH1 wild type	1226	42 (15-68)	22.9 (0.4–480)	36%*	26%	47%*
	IDH1 mutation	107	49 (16-67)	22.5 (0.4–502)	65%	25%	74%
Mardis [6]	IDH1 wild type	172	46.3±15.8	NR	21%	21%	39%*
	IDH1 mutation	16	48.9±15.4	NR	44%	25%	81%
Boissel [18]	IDH1 wild type	179	48 (17–70)	12 (0.5–250)	37%*	20%	—
	IDH1 mutation	34	54 (19–70)	20 (0.8–120)	62%	18%	—
Marcucci [19]	IDH wild type	240	60 (19–81)	28.4 (0.9–450)	60%	38%*	—
	IDH1 Mutation	49	62 (21–82)	24.6 (0.9–152)	71%	20%	—
Wagner [40]	IDH1 wild type	245	47 (17–60)	23.2 (0.5–328.2)	55%	32%	—
	IDH1 mutation	30	50 (33–60)	21.1 (0.65–192.0)	57%	13%	—

WBC, white blood cell; NR, not reported; NA, not assessed; —, not applicable. *Statistically significant difference ($P < 0.05$).

Table 3. IDH1 mutations and outcomes in acute myeloid leukemia

Author [ref.]	IDH1 status	N	CR (%)	*P*-value	HR for OS	95% CI for OS
Patel [44]	IDH1 wild type	372	NR		1.00	Reference
	IDH1 mutation	23	NR		0.86	0.52–1.43
Zhang [42]	IDH1 wild type	194	65.5%	NS	NR	NR
	IDH1 mutation	15	66.70%		NR	NR
Chou[a] [31]	IDH1 wild type	287	73.60%	NR	NR	NR
	IDH1 mutation	22	86.44%		NR	NR
Schnittger [39]	IDH1 wild type	717	NR		1.00	Reference
	IDH1 mutation	52	NR		1.36	0.93–1.97
Abbas [17]	IDH wild type	694	NR		1.00	Reference
	IDH1 mutation	49	NR		1.09	0.76–1.58
Paschka [20]	IDH wild type	607	NR		1.00	Reference
	IDH1 Mutation	NA	NR		1.42	1.03–1.99
Ho [15]	IDH1 wild type	262	51%	0.14	1.00	Reference
	IDH1 Mutation	12	75%		0.90	0.48–1.71
Chou [14]	IDH1 wild type	466	NR		1.00	Reference
	IDH1 mutation	27	NR		0.82	0.38–1.78
Ward [11]	IDH1 wild type	72	NR		1.00	Reference
	IDH1 mutation	6	NR		1.60	0.57–4.45
Green [16]	IDH1 wild type	1226	83%	NR	1.00	Reference
	IDH1 mutation	107	81%		1.06	0.79–1.40
Mardis [6]	IDH1 wild type	172	NR		1.00	Reference
	IDH1 mutation	16	NR		1.72	0.98–3.01

CR, complete remission; HR, hazard ratio; 95% CI, 95% confidence interval; OS, overall survival; NS, not significant; NA, not assessed; NR, not reported. For the Abbas and Paschka studies, AML patients younger than 60 years were used for survival analysis.

Table 4. IDH1 mutations and outcomes in cytogenetically normal acute myeloid leukemia

Author [ref.]	IDH1 status	N	CR (%)	*P*-value	HR for OS	95% CI for OS
Ravandi [43]	IDH1 wild type	93	NR		1.00	Reference
	IDH1 mutation	11	NR		0.59	0.24–1.44
Shen [41]	IDH1 wild type	506	61.30%	0.223	NR	NR
	IDH1 mutation	52	51.90%		NR	NR
Abbas [17]	IDH wild type	268	NR		1.00	Reference
	IDH1 mutation	35	NR		1.19	0.64–2.22
Green [16]	IDH wild type	468	NR		1.00	Reference
	IDH1 mutation	60	NR		1.06	0.75–1.49
Boissel [18]	IDH1 wild type	179	86%	0.19	1.00	Reference
	IDH1 mutation	34	76%		0.95	0.58–1.54
Marcucci [19]	IDH wild type	240	75%	0.86	1.00	Reference
	IDH1 Mutation	49	73%		1.20	0.83–1.73
Wagner [40]	IDH1 wild type	245	80%	0.097	1.00	Reference
	IDH1 mutation	30	67%		1.19	0.72–1.96
Mardis [6]	IDH1 wild type	67	NR		1.00	Reference
	IDH1 mutation	13	NR		1.18	0.61–2.27

CR, complete remission; HR, hazard ratio; 95% CI, 95% confidence interval; OS, overall survival; NR, not reported.

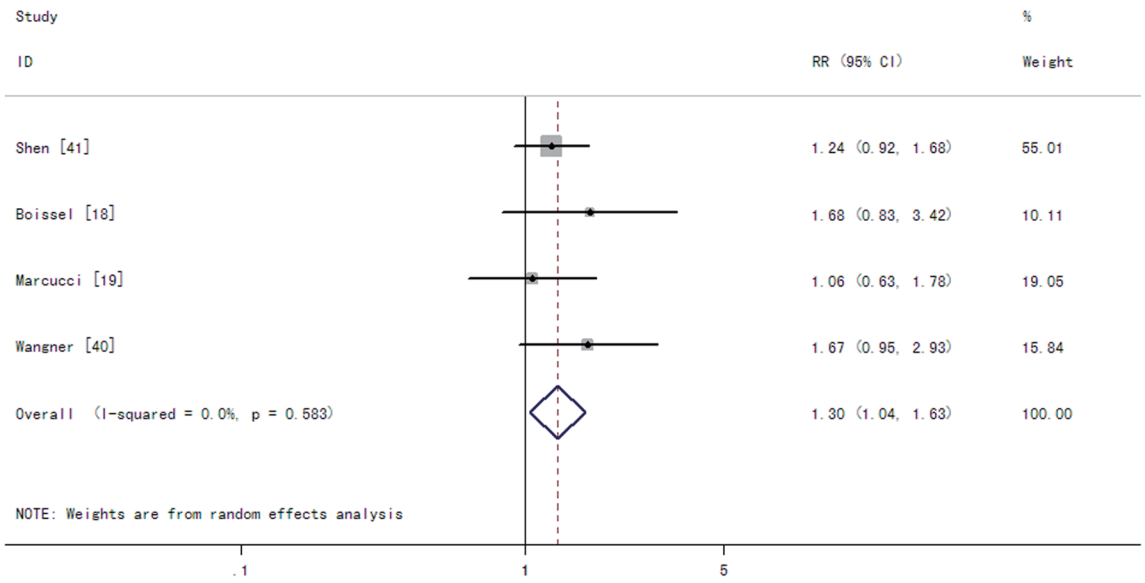

Figure 4. Forest plots of the risk ratios (RRs) and 95% confidence intervals for complete remission in CN-AML patients. The size of the blocks or diamonds represents the weight for the random-effect model in the meta-analysis. A RR higher than one would indicate that the presence of IDH1 mutations is associated with a lower CR rate.

of any single study did not change the overall results in any way.

Discussion

While the prognostic implication of IDH1 mutation status in patients with gliomas is well described [45, 46], its importance in AML remains a matter of discussion. There have been several studies investigating the prognostic significance of IDH1 mutation status in AML patients, some of which demonstrated the negative prognostic effect of IDH1 mutations [16-20, 39, 42], whereas others found no clinical outcome difference between patients with and without IDH1 mutations [14, 15, 40, 41]. The aim of the present meta-analysis was to clarify the prognostic significance of IDH1 mutation status in AML patients. Our study is a recent update on the prior meta-analysis by Zhou et al. [21] with the largest sample size and power. Also, it includes studies focusing on CN-AML and all AML subtypes, which reflects a real-world scenario. Meta-analysis is a useful statistical method for integrating results from independent studies for a specified outcome. Combining the relevant studies increases statistical power, and makes it possible to detect effects that may be missed by individual studies.

The meta-analysis reported here suggests that IDH1 mutations are associated with a higher frequency of NPM1 mutations and normal cytogenetics and with poor OS in AML patients. Interestingly, the presence of IDH1 mutations did not impact CR rates in AML patients, suggesting that the poor survival is not likely due to death during induction or induction failure. Another interesting observation of our study is that, unlike the situation in AML patients, IDH1 mutations were found to be associated with a lower CR rate in CN-AML patients, thereby supporting the notion that the clinical importance of molecular aberrations may vary according to distinct biologic and/or therapeutic contexts in which they are evaluated.

Notably, when the prognostic significance of IDH1 mutations were analyzed in CN-AML patients, the OS difference was weakened to become insignificant. This finding suggests that the issue surrounding IDH1 mutations is far more complicated than the simple presence or absence of the mutations, and needs to be put in the context of other collaborating factors. Several recurrent transcription factor aberrations such as *AML1/ETO*, *PML/RARα* and *CBFβ/MYH11* were recently showed co-existence with IDH1 mutations in AML [42]. The co-existence implicates that IDH1 mutations may cooperate with these fusion genes in leukemogenesis and impact the outcome of AML with abnormal cytogenetics, which may be one of the reasons why the poor prognostic effect of

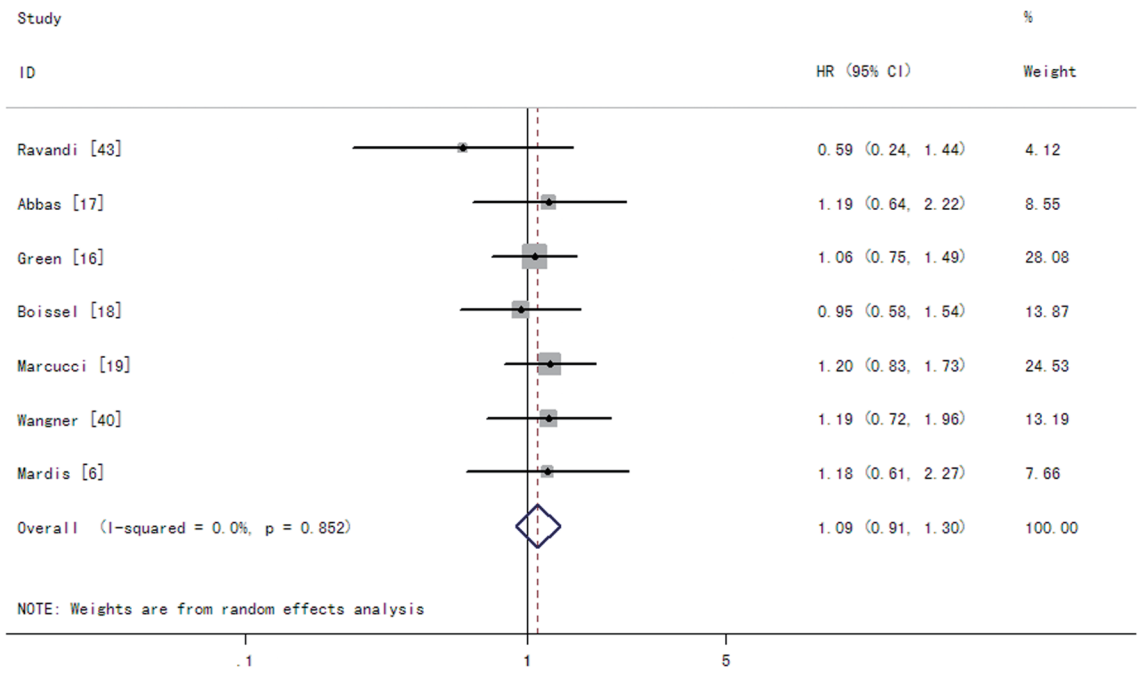

Figure 5. Forest plots of the hazard ratios (HRs) and 95% confidence intervals for overall survival in CN-AML patients. The size of the blocks or diamonds represents the weight for the random-effect model in the meta-analysis. A HR higher than one indicates that the presence of IDH1 mutations is associated with a worse prognosis.

IDH1 mutations is not evident in CN-AML, but only in genetically heterogeneous series of AML.

Our study has several limitations. The first problem is that the analyses were based on observational studies rather than prospective controlled studies or randomized trials. Secondly, we used abstracted data, while an individual patient data-based meta-analysis would have provided a more robust estimate of the association. The results reported here should therefore be interpreted carefully by clinical physicians. Thirdly, as is often the case with meta-analysis, there was some heterogeneity among studies in terms of diagnostic characteristics such as WBC count at the time of diagnosis as well as other confounding factors such as differences in treatment and distinct cytogenetic categories, which were not examined in our analysis. Finally, publication bias is also possible and we do not have information about studies that were not reported or published.

Although these limitations need to be borne in mind, our meta-analysis showed that IDH1 mutations have an unfavorable impact on OS for AML. Additionally, in CN-AML patients, IDH1 mutations can predict a decreased CR rate. These findings may make it advisable to distinguish AML with IDH1 mutations from AML without mutations and justify the risk-adapted therapeutic strategy for AML based on the IDH1 status. However, these conclusions should be verified in prospective clinical trials with a large number of patients. Furthermore, comprehensive functional studies are needed to understand the biologic role of the mutations in leukemogenesis.

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Conflict of interest statement

The authors declare no conflict of interest.

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