Clinical Cancer Research

Correlation Between Isocitrate Dehydrogenase Gene Aberrations and Prognosis of Patients with Acute Myeloid Leukemia: A Systematic Review and Meta-Analysis

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Abstract

Purpose: Whether isocitrate dehydrogenase (*IDH*) gene aberrations affected prognosis of patients with acute myeloid leukemia (AML) was controversial. Here, we conducted a meta-analysis to evaluate their prognostic value.

Experimental Design: PubMed, Embase, Cochrane, and Chinese databases were searched to identify studies exploring how *IDH* gene aberrations affected AML outcome. Pooled HRs and relative risks (RR) were calculated, along with 95% confidence intervals (CI).

Results: Thirty-three reports were included. *IDH* mutations seemed not to affect overall survival (OS: HR, 1.05; 95% CI, 0.89–1.23) and event-free survival (EFS: HR, 0.97; 95% CI, 0.80–1.18) when considered as a single factor, but improved accumulative incidence of relapse (CIR: HR, 1.44; 95% CI, 1.18–1.76) in patients with intermediate-risk karyotypes (IR-AML). However, *IDH1* mutation conferred worse OS (HR, 1.17; 95% CI, 1.05–1.31) and EFS (HR, 1.29; 95% CI, 1.07–1.56), especially in patients with normal cytogenetics (OS: HR, 1.21; 95% CI, 1.01–1.46; EFS: HR, 1.56; 95% CI, 1.23–1.98). Prognosis of the *IDH1* single-nucleotide polymorphism rs11554137 was also poor (OS: HR, 1.34; 95% CI, 1.03–1.75). *IDH2* mutation improved OS (HR, 0.78; 95% CI, 0.66–0.93), particularly in IR-AML patients (OS: HR, 0.65; 95% CI, 0.49–0.86). The *IDH2 (R140)* mutation was associated with better OS among younger cases (HR, 0.64; 95% CI, 0.49–0.82). Treatment outcome was poor [RR for complete remission rates in *IDH1* mutation: 1.21; 95% CI, 1.02–1.44; *IDH2* (*R172*) mutation: 2.14; 95% CI, 1.61–2.85].

Conclusions: Various subtypes of *IDH* mutations might contribute to different prognosis and be allowed to stratify IR-AML further. *Clin Cancer Res; 23(15); 4511–22. ©2017 AACR.*

Introduction

The development of effective therapies for most subtypes of acute myeloid leukemia (AML) has remained sluggish for decades. Among the many reasons, an essential one is the substantial heterogeneity of this malignancy (1). Prognosis of AML can be divided into three risk stratifications according to cytogenetic karyotypes reported in National Comprehensive Cancer Network (NCCN) guidelines: favorable, intermediate, and unfavorable risk. Although clinical outcome in most AML patients with favorable or poor karyotypes could be predicted (2), those with intermediate-risk karyotypes (IR-AML) need more molecular markers to determine their prognosis and guide personalized therapies. Fortunately, next-generation sequencing (NGS) techniques provided new opportunities for discovering more mutational profiles in AML genomes, such as the genes encoding DNA methyltransferase 3A (*DNMT3A*), isocitrate dehydrogenase 1 and 2 (*IDH1/2*), as well as Tet oncogene family member 2 (*TET2*; ref.3), which are the key for the modification of DNA methylation and involved in the pathogenesis of leukemia (4, 5).

Several studies and reviews have reported poor prognosis of patients with *DNMT3A* (6) and *TET2* (7) mutation. However, prognostic assessment of *IDH* mutations was still controversial and needs to be further evaluated. Notably, a meta-analysis performed by Feng and colleagues (8) containing 15 studies indicated that mutant *IDH1* was significantly related to shorter overall survival (OS), whereas in a study from Zhou and colleagues (9) including 13 studies, the *IDH2* mutation was observed to improve OS. Besides, *IDH* mutations are particularly common in cytogenetically normal AML patients (CN-AML; ref. 9). For these reasons, prognostic availability of *IDH* mutations in IR-AML patients should be further explored. In addition, several studies, including the one by Wagner and colleagues (10), reported the association of the *IDH1* single-nucleotide polymorphism (SNP) rs11554137 with noticeably poor prognosis in CN-AML patients. In addition, a large sample study by Papaemmanuil and colleagues (11) systematically perfected existing molecular classification system and especially pointed out that *IDH2* (*R172*) but not *IDH2* (*R140*) mutation was related to favorable prognosis in AML patients. Therefore, it is necessary to further assess *IDH1* SNP rs11554137 and different subtypes of *IDH2* mutation in AML.

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Translational Relevance

With advent of prognostic heterogeneity in isocitrate dehydrogenase (*IDH*) gene aberrations in acute myeloid leukemia (AML) patients, it is necessary to determine what prognostic differences are between various subtypes of *IDH* aberrations, especially in cases with intermediate-risk karyotype who were harboring higher frequency of *IDH* mutations. In this meta-analysis including 33 reports, the authors eventually identified the diverged impact of *IDH1* and *IDH2* mutations on survival. Mutant *IDH1* and *IDH1* single-nucleotide polymorphism (SNP) rs11554137 might contribute to adverse prognosis, whereas *IDH2* mutation should be related to better survival, particularly for *IDH2 (R140)* mutation among younger cohorts, all of which were allowed to perform more accurate molecular risk stratification of IR-AML in details and eventually direct personalized medicine in the future.

In the other side, *IDH* mutations conferred a new enzymatic function, resulting in accumulation of 2-hydroxyglutarate (2-HG), which plays a vital role in changing DNA methylation of cells, impairing cell differentiation and probably contributing to aberrantly epigenetic mechanism of pathogenesis in AML (1). On the basis of the mechanism of *IDH* mutations, there have been 3 types of target drugs (IDH305 to *IDH1R132* mutation, clinicaltrials.gov NCT02381886; AG-120 to *IDH1* mutation, clinicaltrials.gov NCT02074839, NCT02632708, NCT02677922 and AG-221 to *IDH2* mutation, clinicaltrials.gov NCT01915498, NCT02632708) generated and undergoing clinical trials (12–14). However, due to controversial prognosis of *IDH* mutations, it is crucial to determine a clear insight of prognostic value of each subtype in these mutations, which will contribute to more accurate and personalized medicine.

In this study, we identified whether each subtype of *IDH* mutations [*IDH1*, *IDH2* (*R140*) and *R* (*172*)] could influence prognosis of AML patients.

Materials and Methods

Inclusion and exclusion criteria

Eligible studies have these criteria: (i) cohort studies published in English or Chinese, (ii) restricted to human studies mainly reporting the prognostic impact of *IDH* mutations on adult AML patients, (iii) included information in terms of survival and treatment outcome, and (iv) simultaneously described prognosis-related details comparing characteristics between patients harboring *IDH* mutations or not. Studies were excluded if they: (i) only emphasized on pediatric leukemia, (ii) reported data which were unavailable or insufficient, (iii) were reviews, case reports, editorials and letters, and (iv) had overlapping cohorts.

Literature review

We performed a literature search without limitation in regions. The primary sources were the electronic databases of PubMed, Embase, and Cochrane as well as Chinese databases including WanFang Database and China National Knowledge Internet (CNKI), with the publication date from January 1, 2010 to June 26, 2016. The terms included "AML," "acute myeloid leukemia," "*IDH*," "*IDH1*," "*IDH2*," "*IDH1/2*," " isocitrate dehydrogenase" and "*IDH1* SNP." In addition, manual searches of reference list were also performed.

The titles and abstracts of all potential studies were initially browsed independently by two reviewers (Q.Y. Xu and Y. Li) to screen and narrow down the studies according to inclusion and exclusion criteria. Any discrepancy was resolved by discussion or consultation with another investigator not involved in the initial procedure. After candidate studies were selected, full-length articles were reviewed to identify eligible studies and the ultimately identified studies were determined by quality assessment.

Quality assessment of primary studies

The methodologic quality of primary manuscripts was evaluated separately by two reviewers (Q.Y. Xu and Y. Li), according to the Newcastle-Ottawa-Scale (NOS; ref. 15), which is used for quality assessment of cohort studies and case–control studies. Studies scoring six or more were considered to be with high quality. Any disparities between investigators were addressed by discussion.

Data extraction

Related information from the identified studies were extracted and summarized independently by two of the authors (Q.Y. Xu and Y. Li). Any disagreement was solved by discussion or consultation with a third reviewer.

The extracted data contained the first author, study characteristics (including NOS scores, publication year, journal, region, sample size, age, tumor types, incidence of different *IDH* gene aberrations, mutation detection therapies, therapeutic regimens and data types; Table 1) and participant characteristics [including sex ratio, laboratory examination results, French-American-British (FAB) classification, cytogenetic risk categories, sample size with normal karyotype, incidence of mutant nucleophosmin 1 gene (*NPM1*) and fms-like tyrosine kinase 3-internal tandem duplication gene (*FLT3-ITD*; Supplementary Table S1)].

Furthermore, survival and treatment outcome information was also incorporated into this meta-analysis, including relative risk (RR) for complete remission (CR) rates as defined according to recommended criteria (16) and HR for overall survival (OS, defined from diagnosis or the date of entry onto the studies to death or alive at last follow-up; refs. 10, 17), event-free survival (EFS, defined from diagnosis or the date of entry onto the studies to treatment failure, relapse, death or last follow-up in CR; refs. 17, 18), as well as cumulative incidence of risk (CIR; ref. 19). Data were preferentially extracted from multivariate analyses. However, in some studies without multivariate results provided, data were obtained from univariate analyses, or calculated from numeric reports or Kaplan–Meier survival curves using the methods previously proposed by Tierney and colleagues (20).

Statistical analysis

The Stata 12.0 statistical software was used for the meta-analysis. Pooled RRs or HRs less than 1.00 indicated a better therapeutic effect or prognosis in AML patients with *IDH* gene aberrations, compared with those harboring wild-type *IDH* gene, and it would be considered statistically significant that 95% CIs did not cover 1. A *P* value less than 0.05 also meant statistical significance.

The heterogeneity among primary studies was evaluated by using the *Q* test. A *P* value greater than 0.10 was considered to be without heterogeneity or with slight heterogeneity, whereas

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

Author	NOS	Publication year	Journal	Region	N	Age (years)	Tumor types	IDHm	IDH1m	IDH1 (R132)m	IDH2m	IDH2 (R140)m	IDH2 (R172)m	IDH1 SNP rs11554137	Mutation directing methods	Therapy	Data type
Abbas	9	2010	Blood	Netherlands	893	46 (15–77)	AML	150	55	55	97	74	23	—	Direct sequencing	unknown	Others[b]
Boissel	9	2010	Journal of Clinical Oncology	France	213	48 (17–70)	CN-AML	—	34	—	12	—	—	—	Direct sequencing	1.Arac+daunorubicin/idarubicin; MTX+Arac+Anthracycline (resistant)/Arac+Anthracycline (CR);2.MTX+DNR+Arac; Arac+amsacrine(resistant)/ MTX+etoposide+Arac(CR).3.4 (DNR+Arac);high-dose Ara-c	Multivariate and others
Chou	9	2010	Blood	China	493	53 (18–90)	AML	—	—	27	—	—	—	—	Direct sequencing	Anthracycline-containing regimens	Multivariate
Green	9	2010	Blood	England	1333	43 (15–68)	AML	—	—	132	—	—	—	—	Direct sequencing	Standard or higher dose Arac within a DAT(daunorubicin, Arac, thioguanine);ATRA	Multivariate and others
Ley[a]	9	2010/2013	New England Journal of Medicine	America	281	53.1 (39.4–66.8)	AML	—	—	25	—	18	2	—	Whole-genome sequencing, exome capture and sequencing	Unknown	Multivariate
Marcucci	9	2010	Journal of Clinical Oncology	America	358	61 (19–83)	CN-AML	118	49	47	69	56	13	—	Direct sequencing	1Arac+DAT+etoposide;high dose Arac+etoposide(CR);2.Arac/DTA; Arac;3.Arac+DTA;Arac;4. Arac+DTA;Arac(+MTX). 5. Arac+DTA+etoposide	Others
Paschka	9	2010	Journal of Clinical Oncology	Germany-Austria	805	— (16–60)	AML	129	61	59	70	48	22	—	Direct sequencing	Idarubicin, Arac, etoposide;high-dose Arac(NR/PR)/high-dose Arac and MTX(CR)	Multivariate
Schnittger	9	2010	Blood	Germany	1414	65.8 (17.1–93.3)	AML	—	93	93	—	—	—	—	Direct sequencing	Arac+anthracycline	Others
Thol	9	2010	Blood	Germany	272	— (17–60)	CN-AML	—	—	—	33	30	3	—	Direct sequencing	High-dose cytarabine/daunorubicin (AraC/DNR)	Others
Wanger	9	2010	Journal of Clinical Oncology	Germany	275	47 (17–60)	CN-AML	—	—	30	—	—	—	33	Direct sequencing	High-dose cytarabine/daunorubicin (AraC/DNR)	Multivariate and others
Ho	7	2010	Leukemia	Asia, Africa, America	274	— (18–88)	AML	—	—	12	—	—	—	30	Direct sequencing	Unknown	Others
Chou	9	2011	Leukemia	China	446	53 (18–90)	AML	81	27	—	54	41	13	—	Direct sequencing	Anthracycline-containing regimens	Multivariate and others
Green	9	2011	Blood	England	1473	43 (15–68)	AML	—	—	—	148	119	29	—	Direct sequencing	Standard or higher dose Arac within a DAT(daunorubicin, Arac, thioguanine);ATRA	Others
Rockova	9	2011	Blood	Netherlands	439	43 (15–60)	AML	68	32	—	36	—	—	—	Direct sequencing	Unknown	Multivariate
Shen	9	2011	Blood	China	605	43.2 ± 18.9	AML	—	52	—	53	—	—	—	High-throughput sequencing	Daunorubicin, Arac;high-dose Arac based	Others
Lin	9	2012	Annals of Hematology	China	198	— (16–93)	AML	14	4	4	10	7	3	—	Direct sequencing	Unknown	Multivariate
Xu	6	2012	Blood	China	442	40(16–60)	AML	—	23	—	48	—	—	—	Unknown	The standard induction therapy;4–6 cycles high dose Ara-C	Multivariate
Nomdedéu	9	2012	Leukemia Research	Spanish	275	52 (18–73)	AML	64	36	36	28	18	10	—	Direct sequencing	Idarubicin, Arac, etoposide; MTX+Arac;high-dose Arac	Multivariate and others
JP. Patel	9	2012	New England Journal of Medicine	America	657	48 (17–60)	AML	99	46	—	53	—	—	—	Direct sequencing	Unknown	Others
Ravandi	9	2012	Cancer	America	170	53 (17–73)	AML	52	36	12	24	—	—	24	Direct sequencing	1.Arac+idarubicin;2. Arac+idarubicin+tipifarnib;3. Arac+Idarubicin+Sorafenib; 4. Arac+Idarubicin+Vorinostat	Others

(Continued on the following page)

Table 1. Characteristics of studies included in the meta-analysis (Cont'd)

Author	NOS	Publication year	Journal	Region	N	Age (years)	Tumor types	IDHm	IDH1m	IDH1 (R132)m	IDH2m	IDH2 (R140)m	IDH2 (R172)m	IDH1 SNP rs11554137	Mutation directing methods	Therapy	Data type
Koszarska	9	2013	Leukemia Lymphoma	Hungary	376	48.6(16–93)	AML	60	32	32	28	20	8	—	Direct sequencing	Unknown	Others
DiNardo	9	2014	Leukemia Lymphoma	America	68	72 (60–83)	AML	11	3	3	8	7	1	—	Direct sequencing	1.Decitabine alone; 2. decitabine+valproic acid;3. azacitidine+ATRA+valproic acid;4. azacitidine+vorinostat;5. azacitidine+valproic acid;6. azacitidine+low-dose cytarabine;7. decitabine+vorinostat	Others
Willander	9	2014	Biomarker Research	Swedish	189	64 (19–88)	AML	41	35	15	26	21	5	20	Direct sequencing	1.Daunorubicine and Cytarabine or Daunorubicine, cytarabine and mitoxantrone;2Idarubicine and Cytarabine or Idarubicine, Cytarabine and Etoposide;3. Idarubicine, Cytarabine and Cladribine;4.Mtx, cytarabine and Etoposide or Mtx and Cytarabine;5. Daunorubicine, Cytarabine and 6-Thioguanine	Multivariate
Yamaguchi	9	2014	Haematology	Japan	233	56 (15–86)	AML	39	20	20	19	17	2	—	Direct sequencing	Anthracycline +Arac	Others
DiNardo	9	2015	American Journal of Hematology	America	826	62 (18–92)	AML	167	59	59	106	83	23	—	Direct sequencing	Induction:High-dose Arac based/ 7+3/HMA-based/low-dose Arac based;	Others
Ma	9	2015	International Journal of Cancer	China	320	49 (16–85)	CN-AML	69	31	—	38	—	—	—	High-throughput sequencing	Homoharringtonin, Arac, aclarubicin/ daunorubicin or daunorubicin+Arac or idarubicin+Arac;intermediate-dose Arac based	Multivariate
Wang	9	2015	Plos one	China	364	— (14–82)	AML	85	39	—	48	—	—	—	Direct sequencing	Homoharringtonine combined with cytarabine and aclarubicin; high-dose cytarabine-based chemotherapy	Multivariate
Molenaar	9	2015	Leukemia	America, Japan and Germany	334	—	AML	58	26	—	32	—	—	—	Parallel or captured target sequencing	Unknown	Others
Parkin	9	2015	Clinical Cancer Research	America	103	59 (19–90)	AML	28	8	—	20	—	—	—	Exon sequencing	Anthracyline combined with cytarabine or other cytotoxic agents or high-dose cytarabine or clofarabine alone or combined with other agents or HMA, lenolidamide/ small molecule inhibitors	Others
Wei	9	2015	Journal of Experimental Hematology	China	192	42 (18–80)	AML	—	13	13	—	—	—	—	Direct sequencing	Unknown	Others
BH Wang	8	2016	Oncotarget	China	95	45 (12–88)	Intermediate-risk AML	—	—	—	6	—	—	—	Captured target sequencing	With one of the anthracyclines (idarubicin or doxorubicin)or mitoxantrone or DCAG; Arac and anthracycline or MTX or with middle/high-dose Arac	Others
Papaemmanuil	9	2016	New England Journal of Medicine	Germany-Austria	1540	— (18–84)	AML	—	105	—	146	107	39	—	Exon sequencing	Idarubicin, cytarabine and etoposide	Multivariate

Abbreviations: CN-AML, cytogenetically normal acute myeloid leukemia; *IDH* mutation, isocitrate dehydrogenase gene mutation; m, mutation; N, number of cases; NOS, the Newcastle-Ottawa-Scale.

[a]Ley included 2 manuscripts published in 2010 and 2013, respectively.

[b]Others: Data extracted from reported univariate analyses, or calculated from numeric reports and Kaplan–Meier survival curves.

$P < 0.10$ indicated the existence of significant heterogeneity. Besides, I-square (I^2) < 30%, 30%–50%, 50%–75%, and >75% were defined as low, moderate, substantial, and considerable heterogeneity, respectively (21). The random effect model, which was admitted to be more conservative, was chosen if significant heterogeneity was observed. Otherwise, the fixed-effect model was used. Moreover, to find the source of significant heterogeneity, sensitivity analyses were performed to determine whether an individual study affected the aggregate result. Subgroup analyses were also used for exploring the potential source of significant heterogeneity based on the following aspects: region of subjects, mean or median age, mutation detection therapy, data type, and therapeutic regimens.

Visual inspection of the funnel plot was initially done to assess publication bias. We next used the Egger (22) and Begg tests (23) to further evaluate it. A P value less than 0.05 indicates the existence of publication bias.

All analyses were based on published studies; therefore, no ethical approval and patient consent were required.

Results

Study selection procedure

The procedure of selecting studies was shown in Figure 1. First, 502 studies were retrieved from PubMed, Embase, Cochrane, and Chinese databases (WanFang and CNKI), 197 of which were removed because of overlapping datasets. We screened the remaining 305 studies by browsing their titles and abstracts, excluded 225 studies for no association with our interest and chose 80 reports including articles and conference literatures for further evaluation. Of the 80 full-text studies, 47 were ruled out for the following reasons: 6 studies were only involved in pediatric leukemia; 3 reports were reviews; the data of 35 studies were incomplete or unavailable for analysis; the patient cohorts of 3 literatures overlapped with 3 other articles. The reviewers had perfect agreement in identifying the remaining 33 studies using the aforementioned eligibility criteria and all of identified manuscripts were with high quality (Table 1).

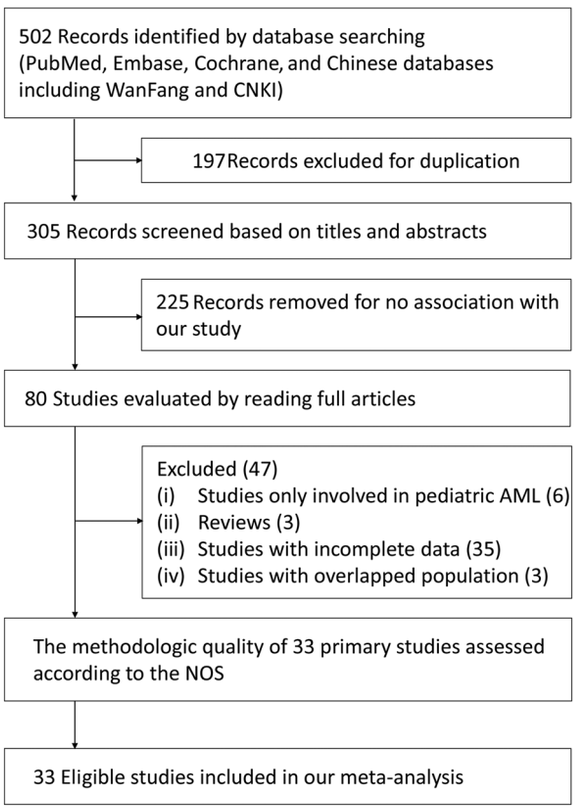

Figure 1.

Flow diagram of the study selection. CNKI, China National Knowledge Internet; AML, acute myeloid leukemia; the NOS: Newcastle-Ottawa-Scale.

Study characteristics

The characteristics of 33 studies were summarized in Table 1 (6, 10, 11, 16–19, 24–49): 13 studies from Europe and Australia, 10 from Asia, 8 from America and 2 collaborated studies from Asia, Africa, and America as well as America, Japan, and Germany, respectively, with a total sample size of 12,747 cases. The frequency of *IDH1* mutation was 2.02%–9.30% in AML patients and 10.91%–15.96 % in CN-AML patients, respectively, whereas the frequency of *IDH2* mutation varied from 5.05% to 14.76% in AML subjects and from 5.85% to 19.27% in CN-AML cases, respectively.

As shown in Supplementary Table S1, *IDH* gene aberrations were closely associated with elderly patients in 12 studies (16, 18, 25, 26, 30, 32, 33, 38, 41–43, 47, 48) and with higher platelet count in 9 studies (16, 18, 26, 27, 29, 36, 38, 42, 43). In addition, in the aspect of FAB classification, patients with M1 harbored higher percentage of *IDH* mutations (6, 17, 18, 24, 25, 29, 30, 39, 42), whereas in cases with M4, lower percentage was observed (17, 24, 29, 47). Besides, the frequency of *IDH* mutations was higher in cases with normal karyotype in 9 studies (6, 16–18, 24, 25, 29, 30, 39, 40, 42, 48). Finally, higher percentage of mutant *NPM1* was always correlated with higher frequency of *IDH* gene aberrations in 14 studies (6, 16–19, 24, 25, 30, 36, 38–40, 42, 43, 47, 48).

Prognosis of AML patients with *IDH* mutation

When mutant *IDH1* and *IDH2* were considered as a single factor - *IDH* mutation, pooled HRs for OS in AML patients were 1.05 (95% CI, 0.89–1.23; $P = 0.5836$; heterogeneity: $I^2 = 65.1\%$, $P = 0.000$; Fig. 2A). Because of significant heterogeneity observed among the selected studies, we conducted a sensitivity test and found that omitting any single study did not influence the result of OS. Hence, subgroup analyses were proposed in Table 2. Among AML patients under 60 years of age, the combined HRs of OS were 0.99 (95% CI, 0.85–1.16, $P = 0.9292$; heterogeneity: $I^2 = 0.0\%$, $P = 0.662$; Fig. 2B). Except for prognostic insignificance for OS, the summary HRs for EFS were 0.97 (95% CI, 0.80–1.18; $P = 0.7713$; heterogeneity: $I^2 = 0.0\%$, $P = 0.674$; Fig. 2C).

For prognostic influence of *IDH* mutation on CN-AML patients, pooled HRs of OS and EFS were 1.09 (95% CI, 0.85–1.40, $P = 0.4944$; heterogeneity: $I^2 = 52.3\%$, $P = 0.078$) and 1.14 (95% CI, 0.69–1.88; $P = 0.6393$; heterogeneity: $I^2 = 67.5\%$, $P = 0.027$) (Supplementary Fig. S1A–S1C), respectively. As heterogeneity was observed, we also performed a similar sensitivity analysis. When the study by Nomdedéu and colleagues (34) was ruled out, the summary HRs of OS and EFS decreased to 1.03 (95% CI, 0.88–1.20, $P = 0.7306$; heterogeneity: $I^2 = 0.0\%$, $P = 0.568$) and 0.91 (95% CI, 0.67–1.23, $P = 0.5460$; heterogeneity: $I^2 = 0.0\%$,

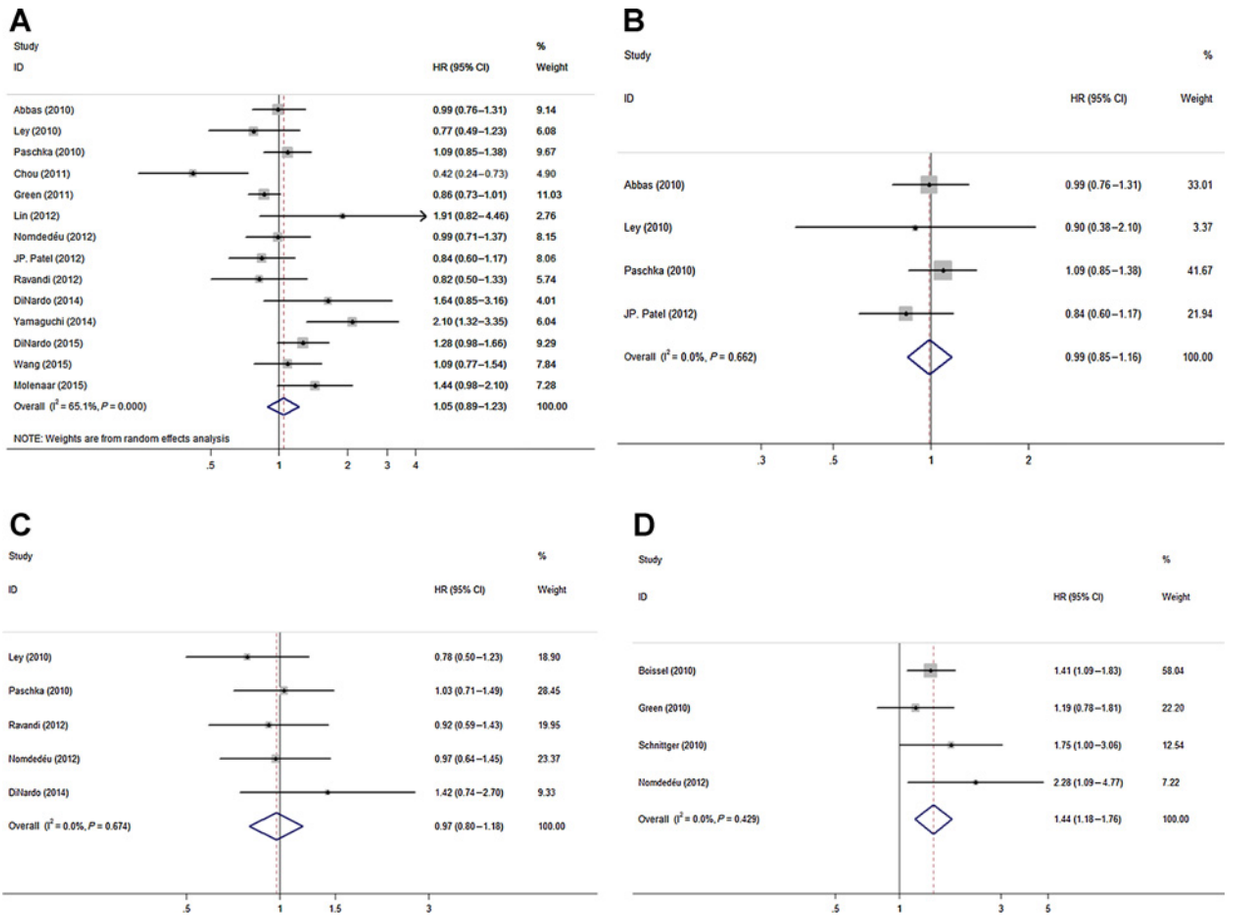

Figure 2.

Prognosis of AML patients with *IDH* mutation. **A,** Pooled HRs and 95% CI for OS (HR 1.05, $P = 0.5836$). **B,** Pooled HRs and 95% CI for OS in patients $\leq$ 60 years (HR 0.99, $P = 0.9292$). **C,** Pooled HRs and 95% CI for EFS (HR 0.97, $P = 0.7713$). **D,** Pooled HRs and 95% CI for CIR in IR-AML patients (HR 1.44, $P = 0.0003$). The diamond represents the pooled HRs and 95% CI. The *P* value less than 0.05 was considered statistically significant.

$P = 0.795$; Supplementary Fig. S1B and S1D), respectively. Therefore, this study might be the source of significant heterogeneity, which needs further discussion.

These pooled HRs of OS and EFS suggested that when *IDH1* and *IDH2* mutation were analyzed together rather than separately, prognostic impact of these mutations were insignificant in AML or CN-AML patients. Interestingly, among IR-AML patients, the combined HRs of CIR was 1.44 (95% CI, 1.18–1.76, $P = 0.0003$; heterogeneity: $I^2 = 0.0\%$, $P = 0.429$; Fig. 2D).

Prognosis of AML patients with *IDH1* mutation and SNP rs11554137

Becasue of prognostic ineffectiveness of *IDH* mutation, it was hypothesized that *IDH1* and *IDH2* mutations might be associated with different prognosis for AML patients. Indeed, patients with mutant *IDH1* had a significant disadvantage of OS (HR: 1.17; 95% CI, 1.05–1.31, $P = 0.0047$; heterogeneity: $I^2 = 0.0\%$, $P = 0.570$; Fig. 3A) and EFS (HR, 1.29; 95% CI 1.07–1.56, $P = 0.0110$; heterogeneity: $I^2 = 2.8\%$, $P = 0.391$; Fig. 3B). Patients with *IDH1* SNP rs11554137 also had shorter OS (HR, 1.34; 95% CI, 1.03–1.75, $P = 0.0294$; heterogeneity: $I^2 = 0.0\%$, $P = 0.396$; Fig. 3C).

Among CN-AML patients, the summary HRs for OS and EFS were 1.21 (95% CI, 1.01–1.46, $P = 0.0388$; heterogeneity: $I^2 = 4.4\%$, $P = 0.393$; Fig. 3D) and 1.56 (95% CI, 1.23–1.98, $P = 0.0002$; heterogeneity: $I^2 = 22.2\%$, $P = 0.273$; Fig. 3E), respectively. Finally, for patients with *IDH1* mutation, the CR rates were also lower (RR, 1.21; 95% CI, 1.02–1.44, $P = 0.0289$; heterogeneity: $I^2 = 0.0\%$, $P = 0.710$; Fig. 3F).

Prognosis of AML patients with *IDH2* mutation

Interestingly, the prognosis of patients with *IDH2* mutation was significantly favorable in OS (HR, 0.78; 95% CI, 0.66–0.93, $P = 0.0053$; heterogeneity: $I^2 = 28.7\%$, $P = 0.199$; Fig. 4A), especially in IR-AML patients (HR, 0.65; 95% CI 0.49–0.86, $P = 0.0026$; heterogeneity: $I^2 = 0.0\%$, $P = 0.950$; Fig. 4B).

However, among CN-AML patients, the combined HRs for OS were 0.99 (95% CI, 0.70–1.42, $P = 0.9867$; heterogeneity: $I^2 = 52.1\%$, $P = 0.051$; Supplementary Fig. S2A) and became 0.85 (95% CI, 0.65–1.10, $P = 0.2114$; heterogeneity: $I^2 = 0.0\%$, $P = 0.608$; Supplementary Fig. S2bB) with the study by Boissel and colleagues (19) excluded. In addition, the summary HRs for EFS in CN-AML cases were 0.89 (95% CI, 0.66–1.21,

Table 2. Subgroup analyses of OS on *IDH* mutation and the *IDH2 (R140)* mutation

	***IDH* mutation (OS)**			***IDH2 (R140)* mutation (OS)**		
Comparison variables	**Number of studies Heterogeneity I^2 %, *p***	**Pooled HRs (95% CI)**	**Interaction (*p*)**	**Number of studies Heterogeneity I^2 %, *p***	**Pooled HRs (95% CI)**	**Interaction (*p*)**
Total	14 (65.1), $P = 0.000$	1.05 (0.89–1.23)		6 (69.0), $P = 0.006$	0.83 (0.60–1.16)	
Region						
Europe and Australia	4 (0.0), $P = 0.421$	0.94 (0.84–1.06)	$P = 0.21$	4 (75.2), $P = 0.007$	0.96 (0.63–1.47)	$P = 0.11$
Asia	4 (85.3), $P = 0.000$	1.14 (0.58–2.24)		—[c]	—	
America	6 (51.6), $P = 0.082$	1.01 (0.77–1.31)		2 (0.0), $P = 0.830$	0.60 (0.41–0.89)	
Others[a]	1 (-)	1.44 (0.98–2.11)		—	—	
Median/mean age						
≤50	4 (0.0), $P = 0.553$	0.91 (0.80–1.02)	$P = 0.005$[d]	3 (0.0), $P = 0.906$	0.64 (0.49–0.82)	$P = 0.02$[d]
>50	7 (74.4), $P = 0.001$	1.00 (0.73–1.37)		2 (84.7), $P = 0.010$	1.11 (0.37–3.33)	
Unknown	3 (0.0), $P = 0.635$	1.36 (1.10–1.68)		1 (-)	1.02 (0.82–1.28)	
Mutation direction methods						
Direct sequencing	11 (69.1), $P = 0.000$	1.04 (0.86–1.25)	$P = 0.79$	4 (74.1), $P = 0.009$	0.82 (0.48–1.41)	$P = 0.85$
NGS	3 (51.6), $P = 0.127$	1.09 (0.79–1.51)		2 (51.7), $P = 0.150$	0.88 (0.57–1.36)	
Unknown	—	—		—	—	
Therapy regimens						
High-dose Ara-c related regimens	4 (0.0), $P = 0.660$	1.12 (0.97–1.29)	$P = 0.54$	—	—	$P = 0.08$
Other Ara-c-related regimens	4 (80.7), $P = 0.001$	1.20 (0.75–1.92)		3 (82.5), $P = 0.003$	1.03 (0.64–1.64)	
Unknown	6 (70.3), $P = 0.005$	0.93 (0.67–1.22)		3 (0.0), $P = 0.977$	0.60 (0.42–0.87)	
Data types						
Multivariate	5 (70.1), $P = 0.010$	0.92 (0.64–1.30)	$P = 0.36$	4 (76.7), $P = 0.005$	0.93 (0.62–1.39)	$P = 0.13$
Others[b]	9 (66.1), $P = 0.003$	1.11 (0.92–1.34)		2 (0.0), $P = 0.955$	0.58 (0.37–0.92)	

Aberrations: *IDH* mutation, isocitrate dehydrogenase gene mutation; NGS: the next generation sequencing.
[a]A study covering America-Japan-Germany cases;
[b]Data obtained from univariate analyses, or calculated from numeric reports and Kaplan–Meier survival curves;
[c]—, Nothing;
[d]The value of $P < 0.05$ indicates statistical significance.

$P = 0.4671$; heterogeneity: I^2=0.00%, $P = 0.933$; Supplementary Fig. S2C).

For patients with the *IDH2* (*R140*) mutation, the combined HRs for OS were 0.83 (95% CI 0.60–1.16, $P = 0.2813$; heterogeneity: I^2= 69.0%, $P = 0.006$; Supplementary Fig. S3). As exclusion of any single study would not alter the aggregate result, subgroup analyses were also performed in Table 2.

For patients harboring the *IDH2 (R172)* mutation, the pooled HRs of OS were 0.72 (95% CI, 0.41–1.27, $P = 0.2579$; heterogeneity: I^2= 64.3%, P= 0.024) and the sensitivity analysis showed that the study by Green and colleagues (30) brought great heterogeneity. After this study was removed, the pooled HRs for OS were 0.59 (95% CI, 0.35–0.99, $P = 0.0457$; heterogeneity: I^2= 30.9%, $P = 0.227$; Supplementary Fig. S4A and S4B).

In the aspect of treatment outcome of patients with mutant *IDH2*, the pooled RRs of CR rates were 1.23 (95% CI, 0.96–1.59, $P = 0.1004$; heterogeneity: I^2= 59.2%, P= 0.023) and were slightly lowered by excluding the study by Boissel and colleagues (ref.19; RR: 1.15; 95% CI, 0.94–1.40, $P = 0.1767$; heterogeneity: I^2= 38.0%, $P = 0.153$; Supplementary Fig. S5A and S5B). Interestingly, the summary RRs of CR rates for the mutant *IDH2 (R172)* were 2.14 (95% CI, 1.61–2.85; $P = 0.0000$; heterogeneity: I^2= 16.4%, $P = 0.302$; Supplementary Fig. S5C).

Sensitivity analyses

In CN-AML patients with *IDH* mutations, sensitivity analysis revealed that the study by Nomdedéu and colleagues (34) was the source of heterogeneity in pooled HRs for OS and EFS. The follow-up period in Nomdedéu and colleagues (34) (12–72 months) was significantly shorter than that of other studies (approximately 10 years), which brought relatively prolonged OS expectancy of patients with wild-type *IDH* gene, leading to outlier HR and generating great heterogeneity.

Among CN-AML cases with mutant *IDH2*, the great heterogeneity was derived from the study by Boissel and colleagues (19) in OS and CR rates analysis due to its lower percentage (5.85%) and fewer samples (12 cases) of *IDH2* mutation than that in the remaining studies, which might be unrepresentative and bring randomness to HR for OS and RR for CR rates.

The prognostic value of *IDH2* (*R172*) mutation was unclear due to significant heterogeneity, which might be from the study of Green and colleagues (30). In fact, the prognostic significance of *IDH2* (*R172*) mutation in this manuscript was really different from four other studies. However, this study could not be excluded for the following two reasons: First, although the frequency of *IDH2* (*R172*) mutation in Green and colleagues (30) was the lowest (2.01%) compared with other studies [Patel and colleagues (35), 2.30%; Koszarska and colleagues (38), 2.65%; Willander and colleagues (41), 2.64%; Papaemmanuil and colleagues (11), 2.53%], the sample size of cases with *IDH2* (*R172*) mutation in this study was large, accounting for 32.22% of the total number of cases with mutant *IDH2 (R172)* in this analysis. Besides, the study by Green and colleagues (30) also had enough cases, accounting for 36.89% of the total. Therefore, the possibility of contingency derived from small samples might be low. Finally, the follow-up period of Green and colleagues (30) was 10 years, which was long enough to minimize bias from shorter duration of follow-up.

Subgroup analyses

With the advent of significant heterogeneity in OS for *IDH* and *IDH2* (*R140*) mutations, we therefore performed subgroup analyses (Table 2). Although the most important source of heterogeneity might be from different prognostic value of subtypes of *IDH* mutations, we did not performed related subgroup analyses for clear prognosis of each mutation has been shown above.

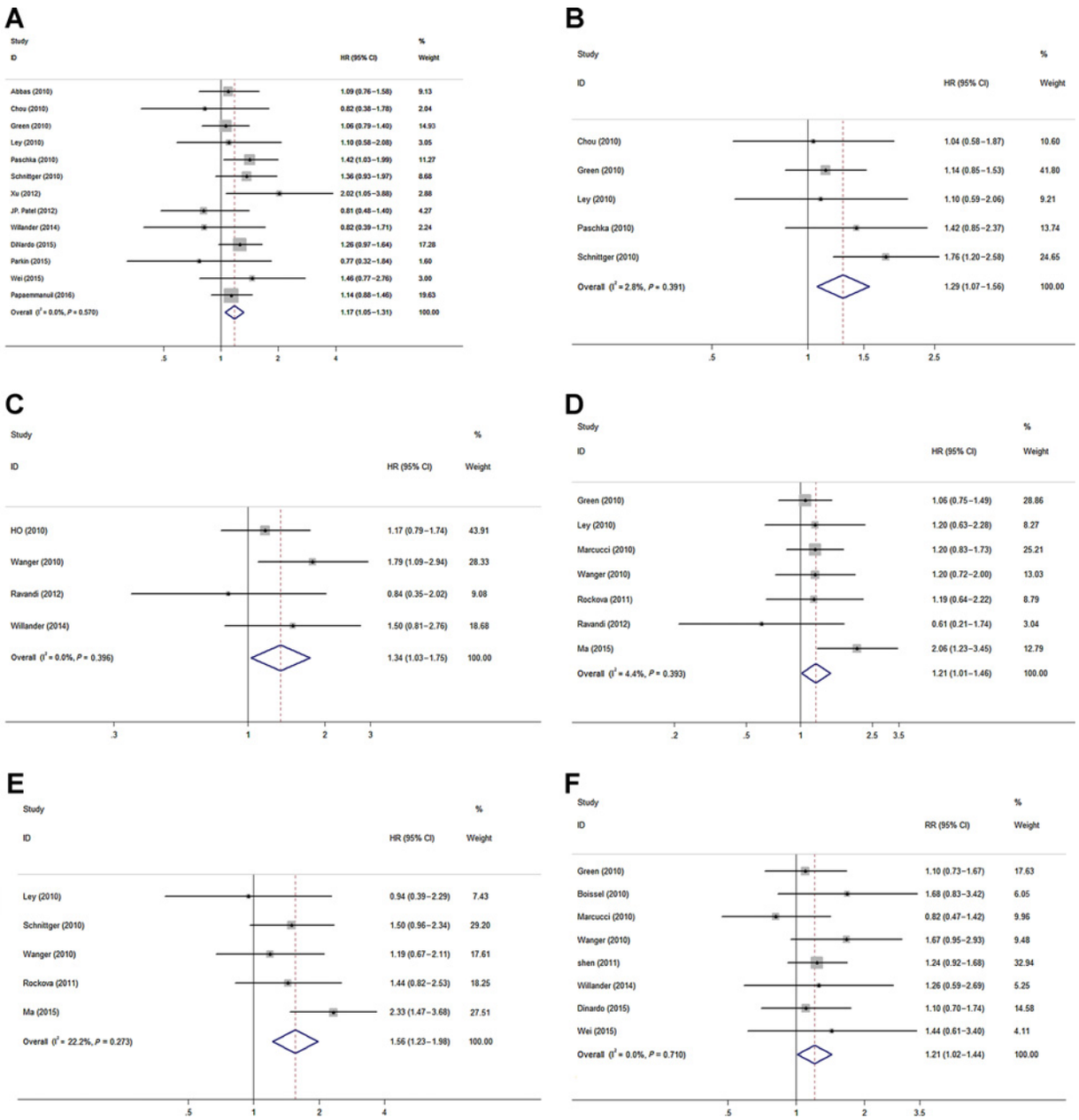

Figure 3.

Survival and treatment outcome of AML patients with *IDH1* mutation. **A,** Pooled HRs and 95% CI for OS (HR 1.17, $P = 0.0047$). **B,** Pooled HRs and 95% CI for EFS (HR 1.29, $P = 0.0110$). **C,** Pooled HRs and 95% CI for OS of *IDH1* SNP rs11554137 (HR 1.34, $P = 0.0294$). **D,** Pooled HRs and 95% CI for OS in CN-AML patients (HR 1.21, $P = 0.0388$). **E,** Pooled HRs and 95% CI for EFS in CN-AML patients (HR 1.56, $P = 0.0002$). **F,** Pooled RRs and 95% CI for CR rates (RR 1.21, $P = 0.0289$). The diamond represents the pooled HRs or RRs and 95% CI. The *P* value less than 0.05 was considered statistically significant.

As shown in Table 2, the original regions of samples, mutation direction methods, therapeutic schedules and data types had no effect on OS for mutant *IDH* and *IDH2* (*R140*). However, in the aspect of mean/median age, younger people (mean/median age $\leq$ 50 years) with *IDH* mutations were with more consistency (HR, 0.91; 95% CI, 0.80–1.02, heterogeneity: I^2= 0.0%, $P = 0.553$) than other age groups (> 50 years, HR, 1.00; 95% CI 0.73–1.37, heterogeneity: I^2= 74.4%, $P = 0.001$, and unknown; HR, 1.36; 95% CI 1.10–1.68, heterogeneity: $I^2 = 0.0\%$, $P = 0.635$; $P = 0.005$). In addition, the *IDH2* (*R140*) mutation was associated with prolonged OS among younger patients (mean/median age $\leq$ 50 years, HR, 0.64; 95% CI, 0.49–0.82, heterogeneity: I^2= 0.0%, $P = 0.906$) when compared with older patients (mean/median age > 50 years, HR, 1.11; 95% CI, 0.37–3.33, heterogeneity: I^2= 84.7%, $P = 0.010$).

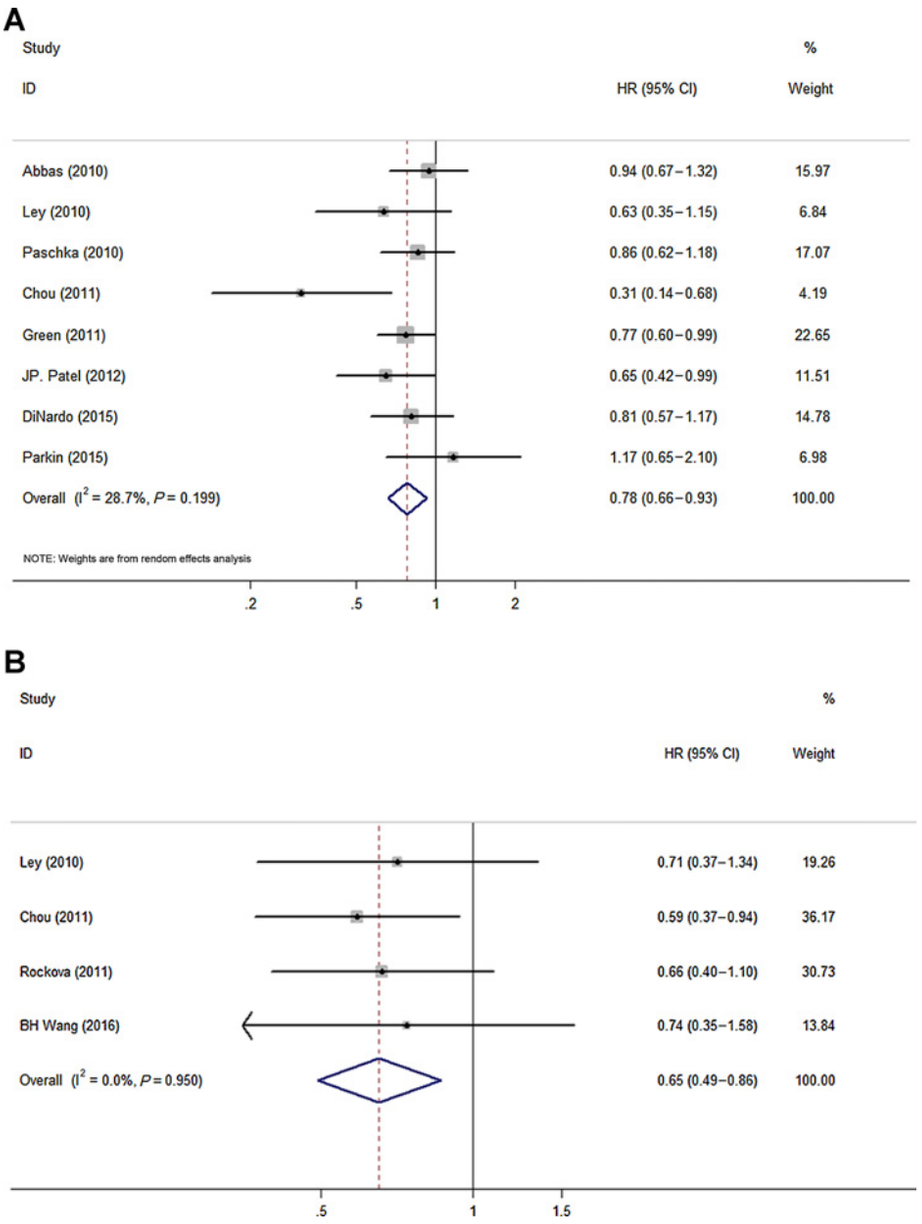

Figure 4.
Survival of AML patients with *IDH2* mutation. **A,** Pooled HRs and 95% CI for OS (HR 0.78, $P = 0.0053$). **B,** Pooled HRs and 95% CI for OS in IR-AML patients (HR 0.65, $P = 0.0026$). The diamond represents the pooled HRs and 95% CI. The *P* value less than 0.05 was considered statistically significant.

Publication bias

Egger and Begg tests were performed to evaluate publication bias and funnel plot symmetry was examined. No evident publication bias was observed based on the visual distribution of funnel plot (Supplementary Fig. S6A–S6C) and *P* values in Egger and Begg tests (Supplementary Table S2).

Comparing results from random effect model with those from fixed effect model

As shown in Supplementary Table S3, the analyses without heterogeneity ($I^2 = 0.00\%$) had the same HRs or RRs and 95% CIs in random effect model and fixed effect model. Additionally, HRs, RRs and 95% CI from the analyses with heterogeneity ($I^2 > 0.00\%$) were slightly changed from random effect model to fixed effect model but it had no impact on prognostic analyses.

Discussion

Major findings

In this study, *IDH* mutations showed obviously different prognostic significance because of various subtypes. When *IDH1* and *IDH2* mutation were analyzed together rather than separately, there was no prognostic availability and great heterogeneity was observed in our analysis, both of which could be explained by the diverged impact of *IDH1* and *IDH2* mutations on survival.

Cases with mutant *IDH1* had reduced OS (HR, 1.17; $P = 0.0047$) and EFS (HR, 1.29; $P = 0.0110$) than those harboring wild type, especially in CN-AML patients (HR for OS: 1.21, $P = 0.0388$; EFS: 1.56, $P = 0.0002$). *IDH1* SNP rs11554137 also conferred shorter OS (HR, 1.34; $P = 0.0294$). Therefore, these results suggested that mutant *IDH1* and *IDH1* SNP rs11554137 might contribute to adverse prognosis, similar to *FLT3-ITD*

mutation (50), and would be allowed to perform more accurate molecular risk stratification of AML.

Likewise, mutant *IDH2* might also be one of prognostic markers for its significant association with better prognosis (HR for OS: 0.78; $P = 0.0053$), especially in the subset of IR-AML cases (HR for OS: 0.65; $P = 0.0026$). Interestingly, among CN-AML patients, mutant *IDH2* had no impact on OS ($P = 0.2114$) and EFS ($P = 0.4671$). The discrepancy of survival between CN-AML and IR-AML cases might originate from cytogenetically abnormal karyotype belonging to intermediate risk, such as isolated trisomy 8, t (9; 11) and some nondefined karyotypes. Abnormal karyotype frequencies were listed as follows: 24.44% versus 28.95% (mutant *IDH2* vs. wild-type *IDH2*) in Chou and colleagues (29) and 31.58% versus 17.81% (mutant *IDH2* vs. wild-type *IDH2*) in Ley and colleagues (6, 39). Notably, trisomy 8 alone was significantly associated with *IDH* mutations (24, 29). However, little is known about survival of patients with the combination of isolated trisomy 8 and *IDH* mutations, and more data are required to distinguish prognostic differences between IR-AML cases with normal and those with abnormal karyotypes when harboring mutant *IDH*. Furthermore, the *IDH2 (R140)* mutation could improve OS among younger patients (mean/median age $\leq$ 50 years, HR: 0.64, $P = 0.0005$) after conducting subgroup analyses. In addition, since several studies have reported favorable prognosis of *IDH2* (*R172*) mutation, particularly in studies by Papaemmanuil and colleagues (11) and by Paschka and colleagues (European Hematology Association, 2016), we conducted a meta-analysis to evaluate prognostic value of this mutation. The impact of *IDH2* (*R172*) mutation on survival had significant heterogeneity, showing it still remains controversial about its prognostic value and more studies are required to clarify its role.

Despite the diverged survival significance between *IDH1* and *IDH2* mutations, CR rates in patients with *IDH* mutations were consistently lower, particularly for those with mutant *IDH1* (RR, 1.21; $P = 0.0289$) and *IDH2* (*R172*; RR, 2.14; $P = 0.0000$). Interestingly, Green and colleagues (30) found that CR rates of the *IDH2* (*R140*) mutation were relatively high (RR, 0.47; $P = 0.0032$). Except for declining CR rates, there was increasing CIR in IR-AML patients with *IDH* mutations (HR, 1.44; $P = 0.0003$).

Our results have identified the prognostic value of each subtype of *IDH* mutations in AML patients, which might contribute to the application and therapeutic evaluation of target drugs in clinic.

Prognosis when combining with other mutations

As mentioned in Supplementary Table S1, *IDH* mutations appear to be notably connected with mutant *NPM1*. Besides, *FLT3-ITD* and *NPM1* mutations have been compiled into the NCCN guidelines. In this regard, it is worth discussing the prognosis of *IDH* mutations in consideration of the other two.

In cases with wild *NPM1*, *IDH1* mutations were related to reduced OS (refs. 6, 39; $P = 0.0030$) and EFS (ref. 17; $P = 0.044$), whereas *IDH2* mutation was associated with prolonged OS (ref. 30; $P = 0.0206$) and EFS (refs. 6, 39; $P = 0.0283$). In the study by Green and colleagues (30), patients with the *IDH2 (R140)* mutation showed a better OS ($P = 0.0002$) when limited to those with wild *FLT3-ITD*. Furthermore, for IR-AML cases with wild-type *NPM1* and *FLT3-ITD*, *IDH1* mutations were also related to remarkably shorter OS ($P < 0.05$) and EFS ($P < 0.05$; refs. 6, 18, 39).

Comparison with other analyses

Our results were consistent with two other studies published previously: a meta-analysis (8) including 15 studies involved in *IDH1* mutation in AML and another one (9) covering 13 studies associated with *IDH1* and *IDH2* mutation in nonpromyelocytic AML. Both found that *IDH1* mutation was correlated with poor prognosis, whereas opposite prognosis was observed in *IDH2* mutation. Our meta-analysis contained 33 publications and included 12,747 cases in total, a larger scale study that could significantly increase the statistical power and accurately assess the prognostic impact of *IDH* mutations on AML patients.

Another significant feature of our research is that the populations included were broadly from Europe, Asia, Australia, and America. Hence, our meta-analysis promised an extensive utilization of *IDH* mutations in the prognosis of AML patients.

More importantly, we investigated more endpoints of survival and treatment outcome. *IDH* mutations had no impact on OS and EFS if integrated as a single factor. For mutant *IDH1*, we not only performed analyses about OS and EFS in AML and CN-AML cases, but also found that *IDH1* SNP rs11554137 was correlated with poor prognosis for AML patients, a finding previously not reported in the two meta-analyses. We also noted that mutant *IDH1* was more unfavorable for OS in CN-AML cases, which was not shown in the two previous analyses. We found that *IDH2* mutation was not only associated with prolonged OS but more linked to favorable prognosis among IR-AML patients, which was also not shown in the two previous articles. We found that mutant *IDH2* (*R140*) but not *IDH2* (*R172*) was correlated with longer OS in subgroup analyses, a novel finding as well. In addition, we found that *IDH* mutations were related to CIR and treatment outcome. In particular, the CR rates were lower for patients with the *IDH2* (*R172*) mutation, a finding not shown before.

We performed in-depth subgroup analyses according to different clinical and methodological features to synthetically estimate the prognostic influence of *IDH* and *IDH2 (R140)* mutations and investigated potential sources of heterogeneity. It was obvious that characteristics of patients (mean/median age $\leq$ 50 years) were more uniform than those older than 50 years and the *IDH2 (R140)* mutation in younger cases was notably related to better OS, reflecting that older age might be a more powerful factor in contributing to poor prognosis than the *IDH2 (R140)* mutation does.

Limitations of our study

Our meta-analysis has several limitations. First, although comprehensive studies were selected from three major databases and Chinese databases, other relevant studies, especially those published in non-English or non-Chinese language or not published in public might be overlooked. Second, our analyses were based on retrospective cohort studies. Therefore, it was difficult to precisely control selection, attrition, information, and confounding bias. Third, some data were obtained from univariate analyses or calculated from Kaplan–Meier survival curves and numeric reports, which might be in slight disparity with the fact. In addition, these results were from univariate analyses and might not be as stable as multifactor-derived data. Finally, although we extracted HRs or RRs from multivariate analyses as many as possible, various confounding factors existed and should be taken into account in different studies, thereby leading to heterogeneity of pooled HRs or RRs to some extent.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Authors' Contributions

Conception and design: Q. Xu, Y. Li, L. Yu
Development of methodology: Q. Xu, Y. Li
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Q. Xu, Y. Li, Y. Xu, Y.Y. Li, W. Li, Z. Yao, X. Chen, S. Huang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Q. Xu, Y. Li
Writing, review, and/or revision of the manuscript: Q. Xu, Y. Li, Y.H. Li, L. Yu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N. Lv, Y. Jing, L.L. Wang
Study supervision : L. Yu

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