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Review

RAS mutations in acute myeloid leukaemia patients: A review and meta-analysis

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ABSTRACT

RAS oncogene mutations frequently occur in acute myeloid leukaemia (AML), but the prognostic significance of *RAS* mutations in AML is inconclusive. We searched the databases of PubMed, Web of Science, EMBASE, and Cochrane from 1990 to 2018. In this study, 24 eligible studies were included, and the meta-analysis was conducted with the Comprehensive Meta-Analysis Version 2 software program. The row hazard ratio (HR) was adjusted and re-evaluated when publication bias existed after detecting all the heterogeneities.

A combined analysis showed that *RAS* mutations were not associated with a poor prognosis in general AML patients (HR: 0.96, 95% CI: 0.78–1.19, $p = 0.70$). To further verify the results, a subgroup analysis was conducted. Interestingly, in the analysis of age bracket, children with *RAS* mutations had an unfavourable survival (HR: 1.35, 95% CI: 1.05–1.75, $p = 0.02$) of AML, but the adults did not (HR: 0.87, 95% CI: 0.70–1.09, $p = 0.21$). Further analysis of the subgroup of children indicated that patients with *NRAS* mutations had an adverse prognosis (HR: 1.55, 95% CI: 1.13–2.12, $p = 0.007$), but not those with *KRAS* mutations (HR: 1.51, 95% CI: 0.34–6.73, $p = 0.59$).

In conclusion, this study revealed that *RAS* mutations did not influence the over survival for adults with AML. However, *NRAS* mutations may be a key prognostic marker related with poor survival for children with AML.

1. Introduction

Acute myeloid leukaemia (AML) is the most frequent acute leukaemia, accounting for 75–80% of the cases and the largest number of annual deaths from leukaemia [1,2]. Despite improvements in diagnosis and therapy, AML is still a disease with a variable prognosis, a high mortality rate, and a five-year survival rate of < 50% [3,4]. AML affects both adults and children and has a higher incidence in adults (54% of the patients were diagnosed at ≥65 years of age) [5]. The incidence rate of paediatric AML (pAML) is lower, but the relapse rate remains high [6,7]. In addition to different clinical outcomes, notable differences in the genomic landscape were noted between pAML and adult AML [8].

The RAS protein is a key protein in many signalling pathways and regulates normal cell growth and malignant transformation. Nearly 40 years after its discovery showed that *RAS* was an activated oncogene in human tumours. *RAS* oncogenes, by encoding a family of guanine nucleotide-binding proteins, play important roles in tumorigenesis and progression [9–12] and are regarded as an important therapeutic target. The RAS family consists of three small GTP proteins (HRAS, NRAS, and KRAS). *NRAS* mutations occur more frequently than *KRAS* mutations, and *HRAS* mutations rarely happen (< 1%) [13]. *RAS* mutations have been generally considered as oncogenic events and are thought to be associated with prognosis in solid tumours and haematologic malignancies, including AML [14–17].

In AML, *RAS* mutations are one of the most common genetic alterations, with a frequency of 15–40% [18–21]. However, the prognostic role of *RAS* mutations in AML is inconclusive. Whereas some studies demonstrated a poor survival in patients with *RAS* mutations [22–24], others reached a different conclusion [25–27]. In this study an integrated meta-analysis was performed to evaluate the role of *RAS* mutations in the overall survival of adults and children with AML.

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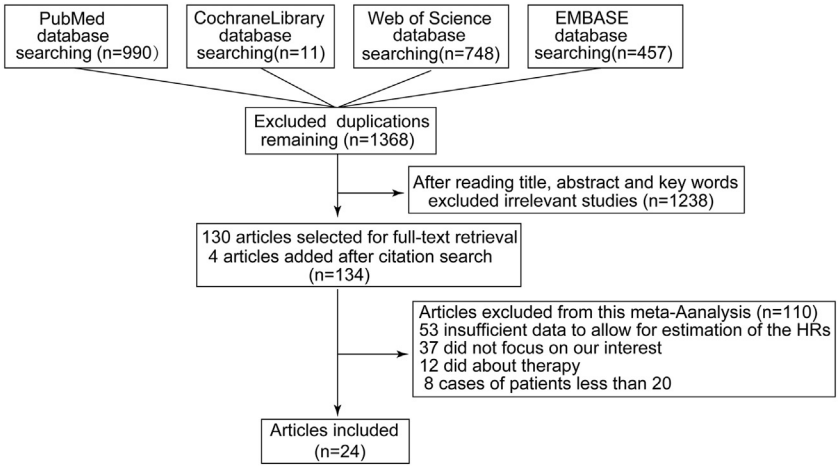

Fig. 1. A flowchart of the article search.

2. Methods

2.1. Literature search and selection reasons

The systematic literature review was performed by two independent researchers (XL and PBZ) in the PubMed, Web of Science, EMBASE and Cochrane Library databases to search for papers online from 1990 to 2017. The following terms were used in the search: AML, acute myeloid leukaemia, *RAS* or *KRAS* or *K-RAS* or *NRAS* or *N-RAS* or *HRAS* or *H-RAS*, and prognosis or prognostic or survival. In addition, the cited references in the eligible studies were also reviewed, and the literature search was completed.

The literature search and eligible criteria were listed as follows: (1) The research was a prospective or retrospective study; (2) The study goal was to research the relationship between *NRAS* or *KRAS* mutation and the prognostic survival of AML; (3) The study included > 20 cases of patients; (4) The hazard ratio and 95% CI (HRs) of overall survival was reported or could be calculated from the study; (5) Studies were published in English. Two researchers (QY and XPZ) decided the ultimate eligible studies independently, and disagreements were resolved by consulting a third researcher (RQL).

2.2. Data extraction and quality evaluation

Three researchers (XL, SL and XLZ) perused the full-text of the article independently and extracted data from each study, including the name of the first author, country of studies, year of publication, age of patients, sample sizes, mutation points, and univariate and multivariate analysis. Moreover, two reviewers (XLZ and PBZ) independently read and scored each study according to the Newcastle Ottawa Scale (NOS) [28]. NOS scores of 1–3, 4–6, and 7–9 were considered to indicate low, medium and high quality, respectively.

2.3. Statistical analysis

A $p < 0.05$ meant that there was a significant prognostic relationship for the statistical test comparing the groups with and without mutations of *RAS* in AML patients. If $p \geq 0.05$ in the research studies, we observed no statistically significant difference.

The HRs were used to evaluate the overall survival effect and were obtained using a method based on the outcomes reported in eligible articles [29,30]. When articles did not provide the HRs, we calculated the accurate HRs by the O-E value (observed value minus expected value), the 95% CI or the log rank *p* value. If the total number of cases, the number in each group, and the log rank *p* value were reported, we could calculate approximate HRs [29]. In addition, if the effective data were provided in the form of survival curves, the data from Kaplan-Meier survival curves could be extracted by the Engauge Digitizer software, and HRs could be calculated by the Parmar's method [31].

With respect to the quality assessment, mean and standard deviation were given in each group. Q statistic and I^2 statistics were used to detect the statistical heterogeneity in studies (If $I^2 \leq 50\%$ identified lower heterogeneity, the fixed-effects model was selected; If $I^2 > 50\%$ identified higher heterogeneity, the random-effects model was selected) [32]. Subsequently, the publication bias was detected by the Egger's method and observed in the form of a funnel plot [33]. If publication bias was detected, then Duval and Tweedie's trim-and-fill method was used to adjust the HRs [30] and the adjusted HRs were the final outcome.

3. Results

3.1. Study selection and characteristics

Two reviewers perused 134 studies independently and excluded 110 articles. Finally, 24 articles [13,20–24,27,34–50] were selected for this meta-analysis. All included studies were published from 1990 to 2017. The details of the excluded articles are shown as follows: 37 articles were not related to this analysis; 12 articles were focused in therapy; 53 articles lacked HRs or the HRs were unable to be calculated; and 8 articles reported < 20 cases of patients. Our search process is shown in Fig. 1.

The main features of the included articles are shown in Table 1. According to the age bracket, 19 studies were for adults and 5 studies were for children. The division criterion for adults and children was age (children population: ≤18 years old, adult population: > 18 years old). In addition, univariate and multivariate analyses in each study are listed separately. Seven studies were conducted by multivariate analysis, and 17 studies were conducted by univariate analysis.

3.2. Quality evaluation

The data were extracted from all the included studies. According to the Newcastle-Ottawa Scale quality assessment system, 12 studies were of high quality (NOS score ≥ 7), 11 studies were of medium quality (4 ≤ NOS score ≤ 6) and 1 study was of low quality (NOS = 3). Overall, the average score of all included studies was 6.54.

3.3. Meta-analysis

The 24 studies (761 *RAS* mutations cases in 5647 AML patients) were systematically analysed in this meta-analysis. As shown in Fig. 2,

Table 1
Characteristics of the included studies.

Study	Year	Country	Age (years)	No. of Pts	Mutation cases	Mutation types	Mutations point	U&M analysis	HR (95% CI)	NOS
Zhou	2017	China	Median 54 (10–93)	143	12	N	12, 13, 61	U	1.61 (0.67–3.85)	8
					6	K	12, 13, 61	U	5.23 (1.53–18.48)	
Bachas	2015	Netherland	Median 10.2 (0.4–19.5)	198	15	N	12, 13	U	1.17 (0.63–2.18)	6
					5	N	61	U	2.46 (0.91–6.67)	
					16	K	12, 13, 61	U	0.74 (0.36–1.51)	
Reuter	2014	Sweden	Median 46 (17–60)	204	25	N&K	12, 13, 61	U	1.20 (0.68–2.10)	7
Kao	2014	China	Median 49 (0.3–97.9)	65	8	N&K	12, 13, 61	M	1.73 (0.50–5.98)	8
Park	2013	Korea	20–88	123	7	K	12, 13, 61	U	1.12 (0.22–5.58)	6
Yang	2013	China	Median 44 (16–83)	504	64	N&K	12, 13, 61	M	1.45 (0.62–3.40)	7
Kadia	2012	USA	17–88	609	66	N&K	12, 13, 61	U	0.93 (0.71–1.20)	7
Zuo	2012	USA	Median 64 (18–89)	83	4	N&K	12, 13, 61	M	0.78 (0.42–1.45)	8
Sano	2012	Japan	Mean 6 (0–15)	157	29	N&K	12, 13, 61	U	2.33 (0.76–7.18)	5
Aly	2011	Egypt	Median 7.4 (5.6–13)	39	6	N	12, 13, 61	M	3.61 (1.53–8.52)	9
Ahmad	2011	Egypt	Median 37 (21–59)	71	23	K	12, 13	U	1.76 (0.73–4.21)	6
Preston	2010	Germany	Mean 50.9 (25.9–73)	31	9	K	12	U	0.85 (0.08–9.50)	6
Elghannam	2009	Egypt	Median 55(19–74)	150	19	N	12,13	M	0.17 (0.09–0.32)	8
Kong	2007	China	Mean 8.6 (0.8–13)	27	12	N	12, 13, 61	U	2.33 (1.01–5.37)	5
Bacher	2006	Germany	Mean 63.4 (18.3–91.8)	1560	160	N	12, 13, 61	U	0.89 (0.72–1.11)	5
Nakamura	2004	Japan	Mean54 (34–78)	24	12	N	12, 13	U	1.22 (0.44–3.40)	6
Bowen	2005	UK	≤60	1106	126	N	12, 13	U	1.01 (0.80–1.28)	7
					39	K	12, 13	U	0.96 (0.63–1.46)	
Meshinchi	2003	USA	< 18	61	12	N	12, 13	U	1.70 (0.76–3.83)	7
					7	K	12, 13	U	3.40 (1.21–9.53)	
Nakano	1999	Japan	15–76	28	8	N	12, 13, 61	U	1.09 (0.49–2.45)	6
Kiyoi	1999	Japan	Mean 49 (15–85)	201	28	N	12, 13, 61	M	1.70 (0.92–3.14)	8
De Melo	1997	Brazil	≥25	40	8	N	12, 13, 61	U	3.08 (1.51–6.29)	5
Neubauer	1994	USA	Mean 48 (21–75)	99	18	N&K	12, 13. 61	M	1.94 (1.01–3.76)	8
Casey	1993	Australia	≥18	69	9	N	12, 13, 61	U	0.94 (0.35–2.50)	3
Radich	1990	USA	17–64	55	8	N	12, 13, 60, 61	U	0.96 (0.54–1.71)	6

Abbreviations: No. of Pts = number of patients; HR = hazard ratio; CI = confidence interval; U&M Analysis = univariate & multivariate analysis.

the pooled adjusted HR for *RAS* was 0.96 (0.78–1.19, $p = 0.70$), showing high heterogeneity ($I^2 = 66.89$, $p < 0.001$). As publication bias was observed, the raw HRs were adjusted and re-evaluated. The results indicated that *RAS* mutations were not associated with the prognosis of AML patients. Subsequently, we conducted subgroup analyses in AML groups according to univariate and multivariate analyses, NOS score evaluation and age bracket. The results are shown in Table 2. *RAS* mutations had no significant prognostic values in the subgroups of univariate and multivariate analyses and NOS score evaluation. However, in the age bracket groups we found a poor prognosis in children population with *RAS* mutations, and the pooled HR was 1.72 (95% CI: 1.28–2.31, $p < 0.001$). After adjusting for the publication bias, the pooled HR was 1.35 (95% CI: 1.05–1.750, $p = 0.02$).

To further confirm the role of *RAS* mutations in AML, subtypes of *RAS,* including *KRAS* and *NRAS,* were conducted separately and the results are shown in Figs. 3 and 4, respectively. *KRAS* mutations did not affect the prognosis of adults and children with AML (Table 3). In addition, *NRAS* mutations were significantly prognostic in children (HR: 1.55, 95% CI: 1.13–2.12, $p = 0.007$), but not in the adult population (HR: 0.80, 95% CI: 0.57–1.13, $p = 0.20$). The results are shown in Table 4 and Fig. 5.

To further confirm the role of *NRAS* mutations in pAML, univariate

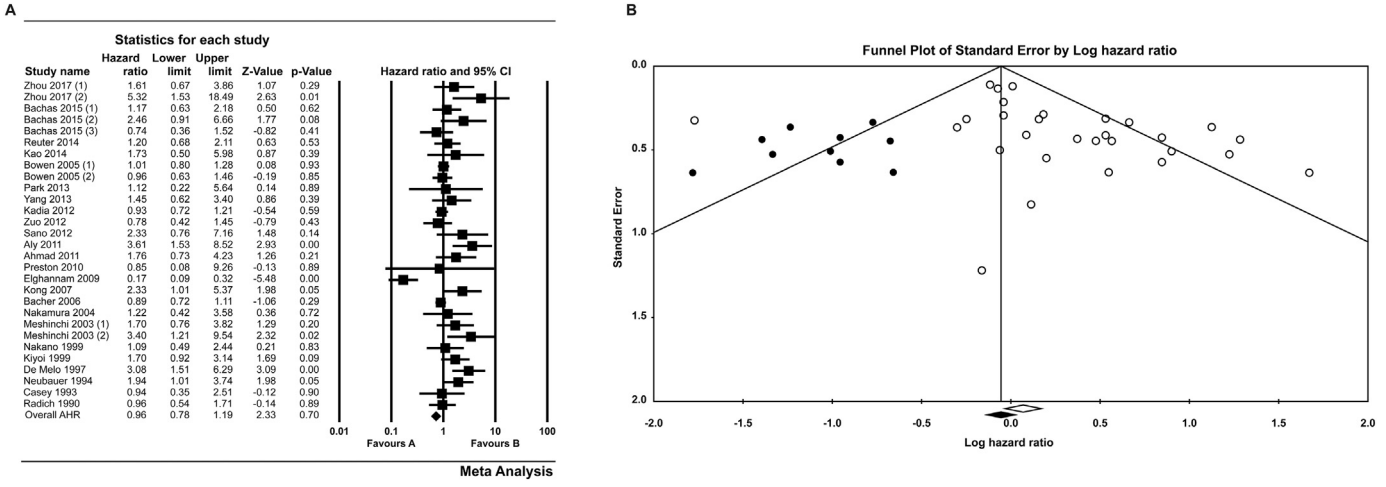

Fig. 2. Meta-analysis evaluating the prognosis of AML with *RAS* oncogene mutations. (A) The forest plot for evaluating all included studies. $I^2 = 66.89\%$ was identified as a higher heterogeneity, and the random-effects model was used. A publication bias was found, and Duval and Tweedie's trim-and-fill method was used to adjust HRs (AHRs). (B) The Funnel plot for detecting the publication bias. The white circles represent observed studies and black circles represent possibly missed studies imputed using Duval and Tweedie's trim-and-fill method. White and black rhombuses represent the observed and theoretical combined effect size, respectively.

Table 2
The prognosis of AML patients with *RAS* mutations.

Studies (n)	HR (95% CI)	*p value*	Heterogeneity I^2(%) *p*		*p* for Begg (2-tailed)	*p* for Egger (2-tailed)	Pub. bias	[a]AHR (95%CI)	*p value*
All studies (24)	1.28 (1.04–1.57)	0.02	66.89	< 0.001	0.02	0.01	Yes	0.96 (0.78–1.19)	0.70
U&M analysis									
Univariate (17)	1.08 (0.97–1.20)	0.16	42.83	0.02	0.01	0.001	Yes	0.97 (0.87–1.08)	0.58
Multivariate (7)	1.19 (0.54–2.60)	0.67	87.34	< 0.001	0.45	0.43	Yes	0.81 (0.39–1.71)	0.57
[b]NOS score									
High (12)	1.28 (0.93–1.75)	0.13	77.58	< 0.001	0.02	0.13	Yes	0.97 (0.71–1.32)	0.85
Medium (11)	1.09 (0.93–1.28)	0.30	44.46	0.04	0.54	0.04	Yes	0.92 (0.79–1.07)	0.28
Low (1)	0.94 (0.35–2.50)	0.90	–	–	–	–	–	–	–
Age bracket									
Adults (19)	1.12 (0.90–1.41)	0.31	66.75	< 0.001	0.10	0.18	Yes	0.87 (0.70–1.09)	0.21
Children (5)	1.72 (1.28–2.31)	< 0.001	44.54	0.08	0.14	0.04	Yes	1.35 (1.05–1.75)	0.02

Abbreviations: HR = hazard ratio; CI = confidence interval; Pub. bias = publication bias, AHR = adjust HR, U&M analysis = univariate & multivariate analysis.
[a] AHR: If a publication bias was found, the HRs would be adjusted and re-evaluated; if the number of combined studies is no > 3, the publication bias cannot be analysed.
[b] NOS Score: NOS Score was used to evaluate the quality of included studies and NOS scores of 1–3, 4–6, and 7–9 were considered to indicate low, medium and high quality, respectively.

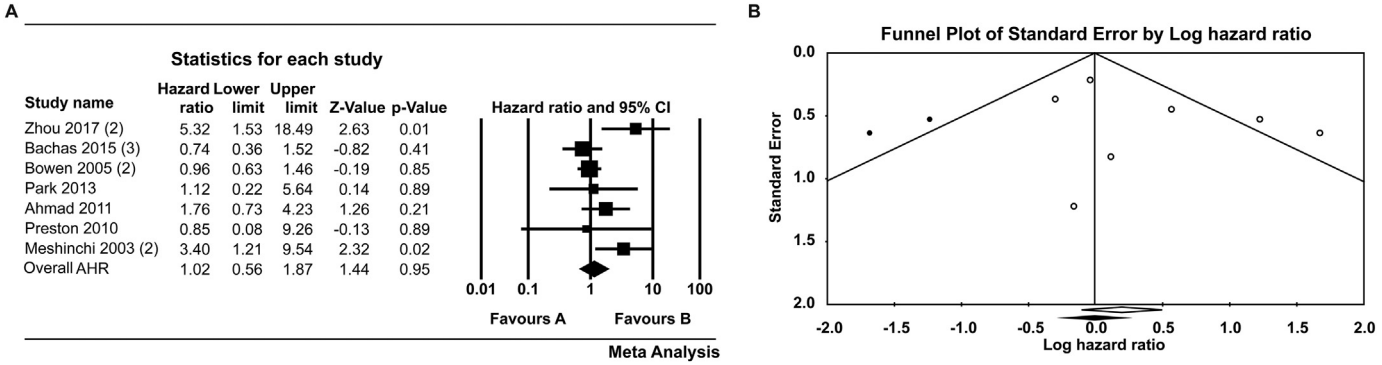

Fig. 3. Meta-analysis evaluating the prognosis of AML with *KRAS* oncogene mutations. (A) The forest plot for evaluating all included studies. I^2 = 54.01% was identified as a higher heterogeneity, and the random-effects model was used. A publication bias was found, and Duval and Tweedie's trim-and-fill method was used to adjust HRs (AHRs). (B) The Funnel plot for detecting the publication bias. The white circles represent observed studies and black circles represent possibly missed studies imputed using Duval and Tweedie's trim-and-fill method. White and black rhombuses represent the observed and theoretical combined effect size, respectively.

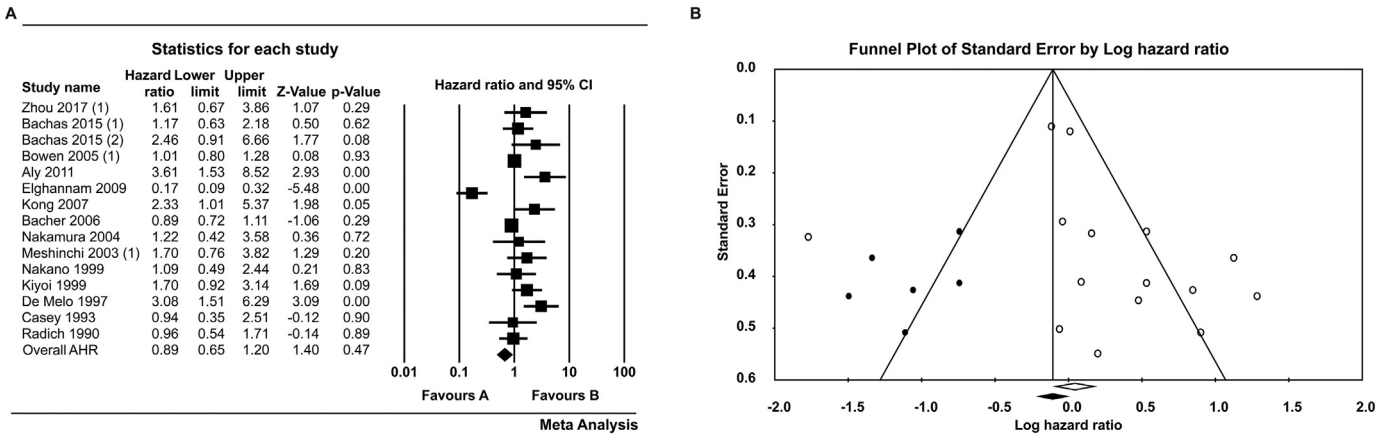

Fig. 4. Meta-analysis evaluating the prognosis of AML with *NRAS* oncogene mutations. (A) The forest plot for evaluating all included studies. I^2 = 77.41% was identified as a higher heterogeneity, and the random-effects model was used. A publication bias was found, and the method of Duval and Tweedie's trim-and-fill was used to adjust HRs (AHRs). (B) The Funnel plot for detecting the publication bias. The white circles represent observed studies and black circles represent possibly missed studies imputed using Duval and Tweedie's trim-and-fill method. White and black rhombuses represent the observed and theoretical combined effect size, respectively.

and multivariate analyses and NOS score evaluation were conducted separately, and the results are shown in Table 5. The combined analysis showed that *NRAS* mutations have significant prognostic value in pAML: univariate analysis (HR: 1.34, 95% CI: 1.08–1.66, p = 0.008), multivariate analysis (HR: 3.61, 95% CI: 1.53–8.52, p = 0.003) and NOS score evaluation (High: 3.61, 95% CI: 1.53–8.52, p = 0.003; Medium: 1.65, 95% CI: 1.06–2.58, p = 0.027). The adult group was likewise analysed and the results indicated that *RAS* mutations were not

Table 3
The prognosis in AML with *KRAS* mutations.

Studies (n)	HR (95% CI)	*p value*	Heterogeneity I^2(%) *p*		*p* for Begg (2-tailed)	*p* for Egger (2-tailed)	Pub. bias	[a]AHR (95%CI)	*p value*
All studies (7)	1.48 (0.87–2.53)	0.15	54.01	0.04	0.29	0.26	Yes	1.02 (0.56–1.87)	0.95
Age bracket									
Adults (5)	1.22 (0.86–1.73)	0.27	45.86	0.12	1.00	0.39	Yes	1.07 (0.77–1.50)	0.69
Children (2)	1.51 (0.34–6.73)	0.59	82.32	0.02	–	–	–	–	–
U&M analysis									
Univariate (7)	1.48 (0.87–2.53)	0.15	54.01	0.04	0.29	0.26	Yes	1.02 (0.56–1.87)	0.95
[b]NOS score									
High (3)	2.32 (0.74–7.34)	0.15	80.48	0.01	0.12	0.001	Yes	0.96 (0.34–2.75)	0.94
Medium (4)	1.04 (0.63–1.74)	0.87	0	0.52	1.00	0.88	No	–	–

Abbreviations: HR = hazard ratio; CI = confidence interval; Pub. bias = publication bias, AHR = adjust HR, U&M analysis = univariate & multivariate analysis.
[a] AHR: If a publication bias was found, the HRs would be adjusted and re-evaluated; if the number of combined studies is no > 3, the publication bias cannot be analysed.
[b] NOS Score: NOS Score was used to evaluate the quality of included studies and NOS scores of 1–3, 4–6, and 7–9 were considered to indicate low, medium and high quality, respectively.

Table 4
The prognosis in AML with *NRAS* mutations.

Studies (n)	HR (95% CI)	*p value*	Heterogeneity I^2(%) *p*		*p* for Begg (2-tailed)	*p* for Egger (2-tailed)	Pub. bias	[a]AHR (95%CI)	*p value*
All studies (14)	1.25 (0.91–1.72)	0.16	77.41	< 0.001	0.13	0.18	YES	0.89 (0.65–1.20)	0.47
Age bracket									
Adults (10)	1.02 (0.70–1.47)	0.94	79.77	< 0.001	0.65	0.74	YES	0.80 (0.57–1.13)	0.20
Children (4)	1.90 (1.33–2.71)	< 0.001	20.81	0.28	0.05	0.09	YES	1.55 (1.13–2.12)	0.007
U&M analysis									
Univariate (11)	1.07 (0.94–1.23)	0.30	44.74	0.05	0.10	0.01	YES	0.96 (0.85–1.09)	0.51
Multivariate (3)	1.00 (0.17–6.05)	1.00	95.06	< 0.001	0.60	0.65	NO	–	–
[b]NOS score									
High (6)	1.16 (0.56–2.38)	0.70	88.69	< 0.001	0.57	0.77	YES	0.86 (0.46–1.63)	0.64
Medium (7)	1.37 (0.96–1.96)	0.08	60.01	0.01	0.22	0.04	YES	0.96 (0.66–1.40)	0.83
Low (1)	0.94 (0.35–2.51)	0.90	0	1.00	–	–	–	–	–

Abbreviations: HR = hazard ratio; CI = confidence interval; Pub. bias = publication bias, AHR = adjust HR, U&M analysis = univariate & multivariate analysis.
[a] AHR: If a publication bias was found, the HRs would be adjusted and re-evaluated; if the number of combined studies is no > 3, the publication bias cannot be analysed.
[b] NOS Score: NOS Score was used to evaluate the quality of included studies and NOS scores of 1–3, 4–6, and 7–9 were considered to indicate low, medium and high quality, respectively.

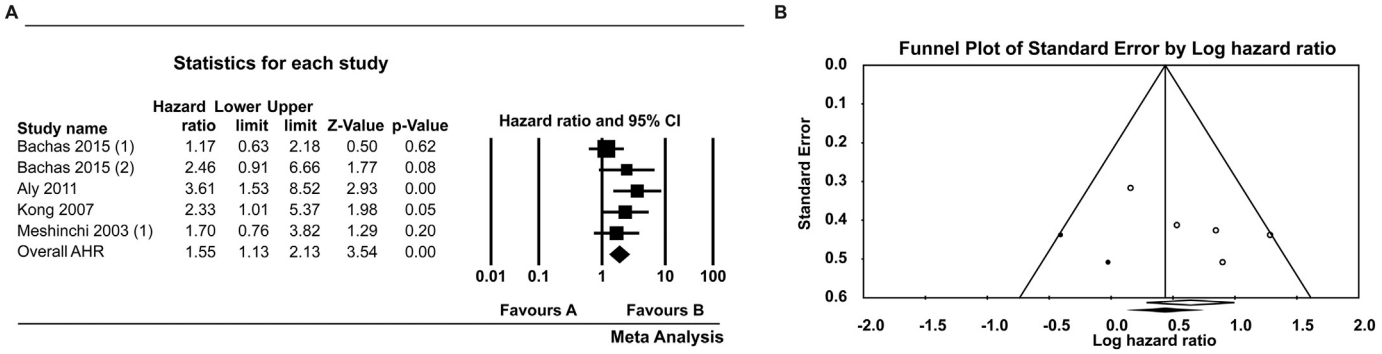

Fig. 5. Meta-analysis evaluating the prognosis of pAML with *NRAS* oncogene mutations. (A) The forest plot for evaluating all included studies. I^2 = 20.81% was identified as lower heterogeneity and the fixed-effects model was used. A publication bias was found and Duval and Tweedie's trim-and-fill method was used to adjust HRs (AHRs). (B) The Funnel plot for detecting the publication bias. The white circles represent observed studies and black circles represent possibly missed studies imputed using Duval and Tweedie's trim-and-fill method. White and black rhombuses represent the observed and theoretical combined effect size, respectively.

significantly prognostic in adults with AML (Table 3 and 4).

4. Discussions

High frequencies of *RAS* oncogene mutations had been found in AML patients. However, the prognostic effect in AML patients remained inconclusive. In the present meta-analysis, 24 eligible studies were included. The combined analysis showed that *RAS* mutations were not significantly prognostic in patients with AML, which was in accordance with previous papers [13,46]. Bowen et al. and Bacher et al. conducted large cohort studies about the role of *RAS* mutations in AML, and both of their studies indicated that *RAS* mutations in AML did not influence the prognosis of patients. A previous meta-analysis conducted by Cheng et al suggested that *RAS* oncogene mutations were not correlated with the prognosis of patients with AML. However, age bracket had not been deliberately regarded as an important factor in these papers. As

Table 5
The prognosis in Children group with *NRAS* mutations.

Studies (n)	HR (95% CI)	*p value*	Heterogeneity I^2(%) *p*		*p* for Begg (2-tailed)	*p* for Egger (2-tailed)	Pub. bias	[a]AHR (95%CI)	*p value*
All studies (4)	1.90 (1.33–2.71)	< 0.001	20.81	0.28	0.05	0.09	YES	1.55 (1.13–2.13)	0.007
U&M analysis									
Univariate (3)	1.66 (1.13–2.46)	0.01	< 0.001	0.48	0.17	0.06	YES	1.34 (1.08–1.66)	0.008
Multivariate (1)	3.61 (1.53–8.52)	0.003	–	–	–	–	–	–	–
[b]NOS score									
High (2)	2.42 (1.34–4.36)	0.003	0.21	36.15	–	–	–	–	–
Medium (2)	1.65 (1.06–2.58)	0.027	0.29	18.42	–	–	–	–	–

Abbreviations: HR = hazard ratio; CI = confidence interval; Pub. bias = publication bias, AHR = adjust HR, U&M analysis = univariate & multivariate analysis.
[a] AHR: If a publication bias was found, the HRs would be adjusted and re-evaluated; if the number of combined studies is no > 3, publication bias cannot be analysed.
[b] NOS Score: NOS Score was used to evaluate the quality of included studies and NOS scores of 1–3, 4–6, and 7–9 were considered to indicate low, medium and high quality, respectively.

reported, adults and children with AML have different clinical outcomes and genomic landscapes [5].

Univariate and multivariate analysis, NOS score evaluation, age bracket and subtypes of *RAS* were conducted detail by detail in this meta-analysis. Interestingly, in age brackets, we found that *RAS* mutations were significantly prognostic in children (HR: 1.35, 95% CI: 1.05–1.75, $p = 0.02$), but not in adults (HR: 0.87, 95% CI: 0.70–1.09, $p = 0.21$). To further confirm the role of *RAS* mutations in AML, subtypes of *RAS,* including *NRAS* and *KRAS,* were conducted separately. As expected, the prognosis of adults with AML was not connected with *NRAS* or *KRAS* mutations. However, *NRAS* mutations were significantly prognostic in children (HR: 1.55, 95% CI: 1.13–2.12, $p = 0.007$). Univariate and multivariate analyses and NOS score evaluation further confirmed that *NRAS* mutations were a significant prognostic marker in pAML.

This meta-analysis indicated that the prognostic values of *RAS* mutations were different in different age brackets. AML affects both adults and children and is of higher incidence in adults [5], but the relapse and death rates of pAML remain high, especially in undeveloped countries [6,7]. Different cytogenetics and molecular genetics in paediatric AML patients and adult patients [51] may cause different prognostic markers and different therapies. We demonstrated that the *RAS* mutations were a significant prognostic marker in pAML, but not in adult AML. Recently, published papers showed a higher frequency of *NRAS* mutations in children with AML than in adults [8] and age or ageing needs to be considered in AMLs involving *RAS* [52–55].

There were several limitations to this meta-analysis. First, several studies did not distinguish the age brackets of AML patients, such as Zhou et al. [34] (patients age: median 54, from 10 to 93), Kao *et al* [39] (patients age: median 49, from 0.3 to 97.9) and Bowen *et al* [46] (patients age: younger than 60 years), and the study groups in these studies were assigned to the adults group. Second, some studies did not distinguish the subtype of *RAS* mutations, such as Reuter *et al* [38], Kadia *et al* [36], Zuo *et al* [41] and Sano *et al* [42], and these studies were not included in the analyses of *NRAS* and *KRAS* mutations. Third, only studies written in English were selected for this analysis. This limitation comes from the fact that researchers prefer to publish the positive results in English and the negative outcomes in native languages [49]. Last, the studies of pAML harbouring *RAS* mutations are rarely reported, especially studies on pAML with *KRAS* mutations.

In conclusion, this study revealed that *RAS* mutations did not influence clinical outcomes (overall survival) in adults with AML. However, we found *NRAS* mutations were a prognostic factor related with poor survival in children with AML. Targeted therapy may improve the outcomes of children harbouring *NRAS* mutations. Nevertheless, more large-scale and well-designed studies are required to update and confirm our findings in the future.

Conflicts of interest

The authors have declared no conflicts of interest.

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