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Prognostic significance of FLT3-ITD in pediatric acute myeloid leukemia: a meta-analysis of cohort studies

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Abstract The purpose of the study was to assess the effect of the internal tandem duplication in FMS-like tyrosine kinase 3 (FLT3-ITD) on the outcome in pediatric acute myeloid leukemia (AML) patients. We identified eligible studies from several databases including PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) (from January 1995 to July 2015). Ten studies of 1661 pediatric patients with AML were included in exploring the relationship between the FLT3-ITD and overall survival (OS)/event free survival (EFS). Pediatric patients with AML with FLT3-ITD had worse OS [HR = 2.19 (1.60–3.01)]/EFS [HR = 1.70 (1.37–2.11)] than those patients without FLT3-ITD. Furthermore, FLT3-ITD had unfavorable effect on OS/EFS in the subgroups of NOS, uni/multivariate model, number of patients, the length of following-up, and patient source. The findings of this meta-analysis indicated that FLT3-ITD had negative impact on pediatric patients with AML.

Keywords Acute myeloid leukemia · FLT3-ITD · Pediatric · Meta-analysis

Introduction

Acute myeloid leukemia (AML) is a group of heterogeneous diseases with respect to biological and clinical outcomes, which have been considered to be related to cytogenetic and gene lesions in hematopoietic stem or progenitor cells [1]. The internal tandem duplication in FMS-like tyrosine kinase 3 (FLT3-ITD) was one of the most common mutations in AML [2]. FLT3-ITD was postulated to cause constitutive phosphorylation of the FLT3 protein thereby impairing normal haematopoiesis and contributing to leukemogenesis [3].

In adult AML, patients with FLT3-ITD have aggressive disease characterized by early relapse and decreased survival [4–6] compared to those with FLT3 wild type (WT). However, the prognosis of FLT3-ITD in pediatric AML was still controversial. Some studies showed that FLT3-ITD had a worse prognostic implication [7–9], whereas others reported no additional prognostic value of FLT3-ITD [10–12]. Thus, it is necessary to perform a meta-analysis to further clarify the relationship between FLT3-ITD and prognosis in pediatric patients with AML.

Materials and methods

Eligibility criteria

Studies were eligible for inclusion in the meta-analysis if they met all the following criteria: (1) Cohort studies were published from January 1995 to July 2015. (2) The patients with AML in the study were diagnosed according to FAB classification [13] or WHO2008 criteria [14]. (3) The age of patients included in the study was under 20. (4) The number of patients with FLT3-ITD and without WT was

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available in the study. (5) They offered the data of overall survival (OS) and/or event free survival (EFS). Studies were excluded if the number of patients with AML in the study was under 50. Multiple reports of a single study were considered as one publication, and only the most complete or recent article was examined.

Information sources and search

Studies were identified by searching electronic databases and scanning reference lists of articles. No limits were applied for language, and foreign papers were translated. This search was applied to PubMed (1995–2015), Embase (1995–2015), and the Cochrane Central Register of Controlled Trials (CENTRAL) (1995–2015). We used the following strategy to search the databases: ("FLT3*" OR "FMS-like tyrosine kinase 3") AND ("Acute Myeloid Leukemia" OR"AML") AND ("pediatric*" OR "paediatric*" OR "child*").

Study collection

Eligibility assessment was performed independently by two investigators. Disagreements between two investigators were resolved by asking the opinion of the third investigator. Endnote 6.0 was used for the managing the articles and removing most of the duplicates. Unrelated articles and remaining duplicates were excluded by reading the abstracts carefully. Then the remaining full-text articles were retrieved and reviewed to identify the eligible studies. The selection process was documented in a flow chart recommended in the PRISMA statement [15] (Fig. 1).

Data collection process

Two reviewers reviewed all of the articles that met the including criteria independently. We abstracted and tabulated the following information for each eligible study: first author, journal, year, location of publication, the number of pediatric patients with AML, and Kaplan–Meier curves. Primary outcome was the OS and secondary outcome was EFS.

Risk of bias in individual studies

Two authors independently assessed the methodological quality of each individual study using the Newcastle-Ottawa quality assessment Scale (NOS) for cohort studies [16]. Any discrepancies were resolved by another reviewer. This scale has nine items classified into three major categories: selection (four items), comparability (two items) and outcome for cohort design (three items). According to the NOS for cohort studies, the qualities of these studies were classified into three groups: high (7–9 points), intermediate (4–6 points), and low (1–3 points).

Summary measures

Hazard ratio (HR) was used to assess the OS or EFS (OS/EFS) between FLT3-ITD and WT in pediatric AML. 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 Tierney et al. [17]. We pooled the HRs for OS/EFS by using fixed and random effect models simultaneously [18]. However, only the estimates from random effect model were selected as the basis of our conclusion, because this approach could provide a more conservative assessment of the average effect size.

Assessment of heterogeneity and subgroup analysis

We assessed statistical heterogeneity of the pooled HRs for OS/EFS by visual inspection of the forests plots and by a formal statistical test using Chi-square test with a significance level at $P < 0.1$. I^2 statistics was also used to quantitatively assess the possible heterogeneity ($I^2 = 0$–30 %: not be important; $I^2 = 30$–50 %: moderate heterogeneity; $I^2 = 50$–75 %: substantial heterogeneity; $I^2 = 75$–100 %: considerable heterogeneity) [19]. We explored the possible causes of heterogeneity for OS/EFS by five subgroups: NOS; uni/multivariate model; number of patients; the length of following-up; patient source.

Assessment of reporting biases

The risk for OS/EFS in pediatric patients with AML was selected to form contour enhanced funnel plots [20]. Contour-enhanced funnel plots display areas of statistical significance on a funnel plot by contour lines representing different levels of statistical significance. If studies seemed to be "missing" in areas of non-significance ($P < 10$ %), the asymmetry of the funnel plot might be due to publication bias, although other explanations should still be considered. In addition, we tried to figure out missing studies and assessed the robustness of pooled HR for OS/EFS in childhood patients with AML by the trim and fill adjustment method [21].

A $P < 0.05$ was considered significant. All calculations were conducted with Stata version 12.0 software (Stata Corp., College Station, TX, USA).

Results

Study selection

As shown in flow diagram (Fig. 1), the initial search yielded a total of 1020 studies and 184 studies were

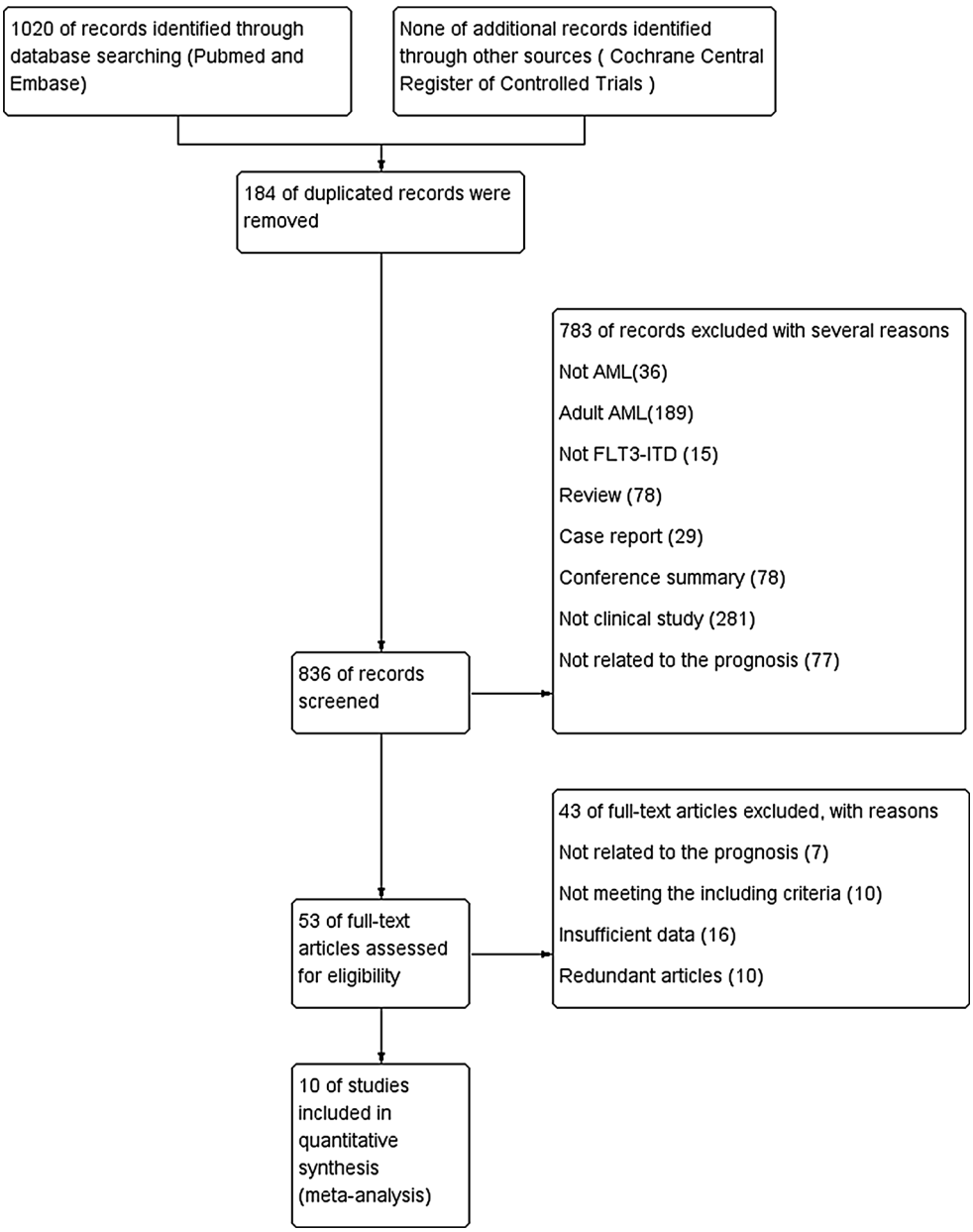

Fig. 1 Flow diagram for study review and inclusion

excluded because of the duplication. Then, 836 studies were reviewed the titles and abstracts and 53 were considered potentially eligible and were retrieved in full text, 10 studies met the inclusion criteria and were included in the meta-analyses.

Study characteristics

As shown in Table 1, 10 studies of 1661 pediatric patients with AML (250 FLT3-ITD and 1411 WT) were included in the meta-analysis. Among these studies, five studies [9, 11, 12, 22, 23] from Asia, three studies [10, 24, 25] form European and two studies from USA [7, 8].

Risk of bias in within studies

The NOS for cohort studies was used for assessing the quality of all 10 studies in this meta-analysis (Table 2). The qualities of seven studies were high (7–9) and the remaining three studies were moderate (4–6). The median overall score was 7, which indicated that the methodological quality was high.

Table 1 Characteristics of 10 studies included in the meta-analysis

Study [reference]	Year	Area (trial or city)	No. of patients (FLT3-ITD/WT)	Age (range, years)	FAB classification	Following-up length (years)	Outcomes, model	NOS
Meshinchi et al. [7]	2001	USA (CCG2891)	91 (15/76)	0.2–18.7	M0–M7	8	OS,M/EFS,M	7
Brown et al. [8]	2007	USA (POG-9421)	281 (53/228)	0–19.5	M0–M7	5	OS,U/EFS,U	7
Balgobind et al. [10]	2011	Europe (DCOG/AML-BFM-SG/CPH/Louis)	372 (67–305)	0–18.8	M0–M7	10	OS,M/EFS,M	9
Leo et al. [11]	2011	Asia (Ma-Spore)	121 (13/108)	0.2–17.4	M0–M7	4	OS,U/EFS,U	6
Ruan et al. [23]	2011	China (Tianjin)	103 (9/94)	1–15	M0–M7	3	OS,U	5
Staffas et al. [25]	2011	Europe (NOHPO-93/2004)	185 (18/167)	0–18	M0–M2, M4–M7	12	OS,M/EFS,M	9
Sano et al. [22]	2013	Japan (AML-99)	130 (17/113)	0–15	M0–M7	3	OS,M	8
Yatsenko et al. [24]	2013	Russia (Moscow)	186 (15/171)	0–17	M0–M7	5	OS,U/EFS,U	6
Kinoshita et al. [9]	2014	Japan (AML-05)	93 (10/83)	0–18	M0–M2, M4–M7	5	OS,M/EFS,M	8
Liu et al. [12]	2014	China (Shanghai)	99 (33/66)	0.3–16.9	M0–M7	10	OS,U/EFS,U	7

No. number, *Ref.* reference, *OS* overall survival, *EFS* event free survival, *U* univariate, *M* multivariate, *NOS* Newcastle-Ottawa quality assessment scale

The impact of FLT3-ITD on the OS and EFS in total population

As shown in Fig. 2, data were extracted from 10 studies, with a total of 1661 pediatric patients with AML, including 250 patients with FLT3-ITD mutation, to analyze the OS. In this population, patients with FLT3-ITD mutation had inferior OS [HR = 2.19 (1.60–3.01), $P < 0.001$] as compared to WT patients. There was substantial heterogeneity by I^2 testing [$I^2 = 40$ %, $P = 0.091$].

As shown in Fig. 3, data were extracted from 8 studies, with a total of 1428 pediatric patients with AML, including 224 patients with FLT3-ITD mutation, to analyze the EFS. In this population, patients with FLT3-ITD mutation had worse EFS [HR = 1.70 (1.37–2.11), $P < 0.001$] as compared to WT patients. The heterogeneity among the studies was not important [$I = 0$ %, $P = 0.472$].

Prognostic impact of FLT3-ITD in different subgroups

We pooled the HRs for OS/EFS in different groups by fixed and random effect models simultaneously, which are shown in Table 3. In the majority of subgroups, FLT3-ITD had an unfavorable impact on the OS/EFS in pediatric patients with AML. Due to the limited studies included, FLT3-ITD might not be associated with worse EFS [HR = 1.63 (0.91–2.86), $P < 0.091$] in the NOS subgroup (middle quality). In pediatric patients with AML from Europe, FLT3-ITD was prone to have adverse effect on the OS [HR = 1.58 (0.97–2.59)] and EFS [HR = 1.92 (0.98–3.75)].

Publication bias

Due to the limited studies included for the EFS, only the data about the OS of total population were utilized to search publication bias. Supplementary Figure 1 demonstrated the distribution of 10 real studies and 3 filled studies in the aspect of OS. The trim and fill method imputed a total of 3 filled studies in a random effects model, which located in the region of statistical non-significance ($P < 10$ %). Thus, the asymmetry of the funnel plot might be due to publication bias, although other explanations should still be considered. After adding the studies to the funnel plot, the pooled fixed effects HR was 1.70 (1.38–2.11), and the pooled random effects HR was 1.73 (1.20–2.51), which implied that FLT3-ITD was associated with shorter OS in pediatric patients with AML.

Discussion

We have performed a meta-analysis to figure out the association between FLT3-ITD and survival in pediatric patients with AML. Ten studies with 1661 patients with AML were included in our meta-analysis. According to the NOS scale, 7 studies belonged to high quality and the others had moderate quality.

Table 2 Assessment of Methodological Quality of Cohort Studies

Study [reference]	Selection				Comparability	Outcome			Score
	Representativeness of exposed cohort	Selection of non exposed cohort	Ascertainment of exposure	Outcome of interest not present at start		Assessment of outcome	Follow-up length	Follow-up adequacy	
Meshinchi et al. [7]	*	*	*	*	*	*	*	–	7
Brown et al. [8]	*	*	*	*	–	*	*	*	7
Balgobind et al. [10]	*	*	*	*	**	*	*	*	9
Leow et al. [11]	*	*	*	*	–	*	–	*	6
Ruan et al. [23]	*	*	*	*	–	*	–	–	5
Staffas et al. [25]	*	*	*	*	**	*	*	*	9
Sano et al. [22]	*	*	*	*	*	*	*	*	8
Yatsenko et al. [24]	*	*	*	*	–	*	*	–	6
Kinoshita et al. [9]	*	*	*	*	*	*	*	*	8
Liu et al. [12]	*	*	*	*	–	*	*	–	7

Newcastle-Ottawa Quality Assessment Scale: study can have one point (*) for meeting each criterion, except that comparability can have a maximum of two points (**)

The primary outcome was OS. FLT3-ITD conferred shorter OS in total population. Moreover, FLT3-ITD had an adverse effect on the OS in subgroups of NOS, uni/multivariate model, number of patients and the length of following-up. The secondary outcome was EFS. FLT3-ITD was associated with poor EFS in the total population. This conclusion was also suitable for the subgroups of uni/multivariate model, number of patients, and the length of following-up.

According to the results described above, we found that FLT3-ITD suggested a significantly negative prognostic effect in pediatric patients with AML, which might help us to justify the risk-adapted management decisions. Furthermore, given the relatively high frequency of FLT3-ITD in pediatric patients with AML, much interest has been generated in whether FLT3 may be potential therapeutic targets. These findings will hopefully yield critical information for further research on the FLT3 inhibitor [26, 27], which may highlight the need to identify FLT3-ITD in the clinical management of patients with AML.

Although our study is the first meta-analysis relating to the controversial prognostic impact of FLT3-ITD in pediatric AML, the result must be viewed cautiously due to its own limitations. First, the analyses were based on cohort studies rather than random controlled trials. Second, we used abstracted data only from publications, because individual patient data could not be obtained, when a meta-analysis based on individual patient data would provide a more robust estimate of the association. Third, we did not assess the potential effects of other factors, such as therapeutic regimens [28, 29], chromosomal aberration [30], and gene lesions. Fourth, we did not consider the impact of FLT3-ITD allelic ratio and their association of outcome. Fifth, due to the limited data, we did not assess the achievement of CR and disease post-induction. A study of children with de novo AML determined that an FLT3-ITD allelic ratio ≥ 0.4 identified the highest risk group with the worse prognosis, whereas children with allelic ratios <0.4 had similar outcomes as children with FLT3-WT.

In conclusion, the findings of this study indicated that FLT3-ITD mutation had negative impact on OS and EFS in pediatric patients with AML and related subgroups. These findings may help to justify risk-adapted therapeutic strategies for pediatric AML based on FLT3-ITD. However, combining other important genetic biomarkers, such as NPM1 [31] and CEBPA [32], FLT3-ITD would contribute to a more precise clinical risk stratification and decision of treatment. More cohort studies concerning FLT3-ITD are needed in an effort to further verify or modify the pooled estimates to a certain extent.

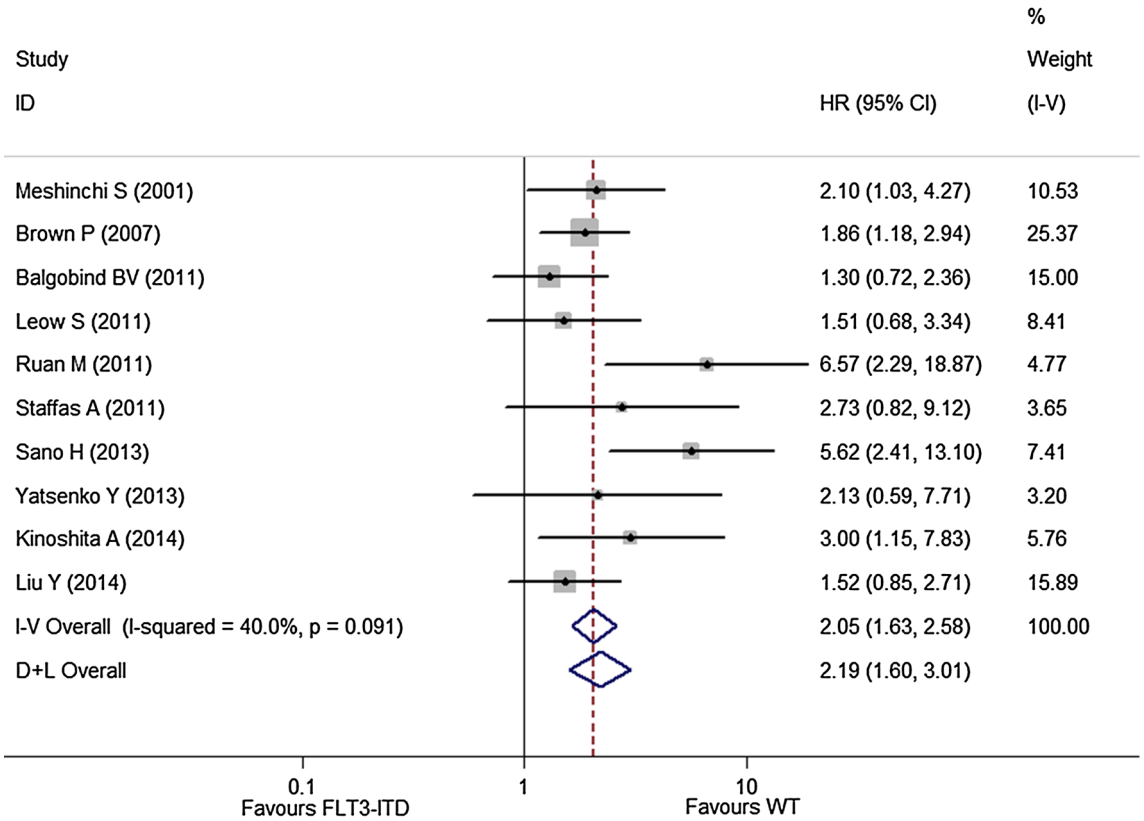

Fig. 2 Forest plots of the HRs for survival between FLT3-ITD and WT for OS in pediatric AML patients

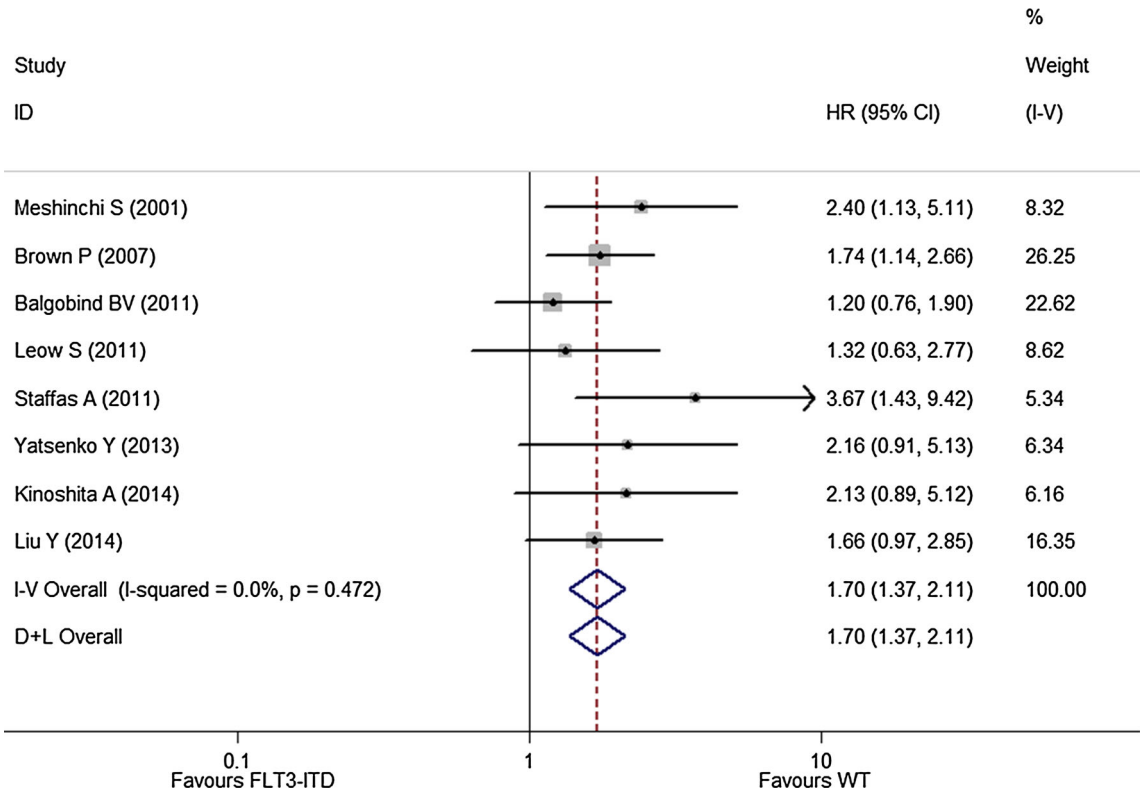

Fig. 3 Forest plots of the HRs for survival between FLT3-ITD and WT for EFS in pediatric AML patients

Table 3 Meta-analysis of association between FLT3-ITD and prognosis of pediatric AML (FLT3-ITD versus WT)

	Overall survival				Event free survival				Effect model
	No. of studies (FLT3-ITD/WT)	HR (95 % CI)	*P* value of HR	I^2 (%)	No. of studies (FLT3-ITD/WT)	HR (95 % CI)	*P* value of HR	I^2 (%)	
Entire group	10 (250/1411)	2.05 (1.63–2.58)	<0.001	40	8 (224/1204)	1.70 (1.37–2.11)	<0.001	0	Fixed
		2.19 (1.60–3.01)	<0.001			1.70 (1.37–2.11)	<0.001		Random
NOS									
High quality (7–9)	7 (213/1038)	1.98 (1.54–2.54)	<0.001	37.8	6 (196/925)	1.71 (1.37–2.11)	<0.001	14.5	Fixed
		2.08 (1.49–2.91)	<0.001			1.74 (1.34–2.27)	<0.001		Random
Middle quality (4–6)	3 (37/373)	2.48 (1.40–4.38)	0.002	58.6	2 (28/279)	1.63 (0.91–2.86)	0.091	0	Fixed
		2.68 (1.06–6.76)	0.036			1.63 (0.93–2.86)	0.091		Random
Uni/multivariate model									
Univariate	5 (123/667)	1.91 (1.41–2.59)	<0.001	35.9	4 (114/573)	1.69 (1.27–2.25)	<0.001	0	Fixed
		2.00 (1.32–3.02)	0.001			1.69 (1.27–2.25)	<0.001		Random
Multivariate	5 (127/744)	2.26 (1.59–3.22)	<0.001	51.5	4 (110/631)	1.72 (1.23–2.40)	0.001	48.5	Fixed
		2.47 (1.46–4.20)	0.001			1.97 (1.18–3.27)	0.009		Random
Number of patients									
≤100	3 (58/225)	1.91 (1.27–2.86)	0.002	0	3 (58/225)	1.93 (1.30–2.85)	0.001	0	Fixed
		1.91 (1.27–2.86)	0.002			1.93 (1.30–2.85)	0.001		Random
>100	7 (192/1186)	2.12 (1.60–2.81)	<0.001	54.9	5 (166/979)	1.61 (1.24–2.09)	<0.001	25.4	Fixed
		2.38 (1.60–3.01)	<0.001			1.65 (1.20–2.27)	0.002		Random
The length of following-up									
≤5	6 (142/915)	2.25 (1.60–3.17)	<0.001	39.4	5 (125/802)	1.77 (1.30–2.42)	<0.001	34	Fixed
		2.41 (1.52–3.81)	<0.001			1.94 (1.29–2.93)	0.001		Random
>5	4 (108/496)	1.90 (1.39–2.59)	<0.001	51.7	3 (99/402)	1.64 (1.21–2.22)	0.002	0	Fixed
		2.02 (1.25–3.28)	0.004			1.64 (1.21–2.22)	0.002		Random
Patient source									
Asia	5 (82/464)	2.47 (1.73–3.52)	<0.001	64.5	3 (56/257)	1.64 (1.11–2.42)	0.013	0	Fixed
		2.83 (1.53–5.26)	0.001			1.64 (1.11–2.42)	0.013		Random
Europe	3 (100/643)	1.58 (0.97–2.59)	0.068	0	3 (100/643)	1.59 (1.10–2.31)	0.014	59.6	Fixed
		1.58 (0.97–2.59)	0.068			1.92 (0.98–3.75)	0.058		Random
USA	2 (68/304)	1.93 (1.31–2.83)	0.001	0	2 (68/304)	1.88 (1.30–2.72)	<0.001	0	Fixed
		1.93 (1.31–2.83)	0.001			1.88 (1.30–2.72)	<0.001		Random

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Compliance with ethical standards

Conflicts of interest All the authors declare that they have no conflict of interest.

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