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REVIEW ARTICLE

Prognostic significance of the EVI1 gene expression in patients with acute myeloid leukemia: a meta-analysis

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Abstract

Ecotropic virus integration site-1 (EVI1) is frequently expressed in patients with acute myeloid leukemia (AML). Many studies have reported the potential poor prognostic impact of EVI1 higher expression ($EVI1^H$) in the AML patients; however, the conclusions previously reported have not been fully assessed and are still controversial. Therefore, we performed a meta-analysis to evaluate the prognostic significance of $EVI1^H$ in patients with AML. The primary endpoint was overall survival (OS), and the event-free survival (EFS) was selected as the secondary endpoint. We extracted the hazard ratio (HR) and their 95% confidence interval (CI) for the OS and EFS from the multivariate COX proportional hazard models. A total of 4767 AML patients from 11 studies up to 23 February 2019 were subjected to our meta-analysis. Pooled HRs suggested that $EVI1^H$ had an adverse impact on OS (HR = 1.52, 95%CI 1.24–1.86) and EFS (HR = 1.41, 95%CI 1.14–1.74) in AML patients. $EVI1^H$ was also associated with a shorter OS (HR = 1.73, 95%CI 1.43–2.11) and EFS (HR = 1.17, 95%CI 1.05–1.31) in AML patients with the intermediate cytogenetic risk (ICR) according to the National Comprehensive Cancer Network (NCCN), European leukemia network (ELN), or International System for Human Cytogenetic Nomenclature (ISCN). Furthermore, $EVI1^H$ appeared to be a poor prognosis indicator in patients with normal cytogenetics (NC) (HR for OS:2.01, 95%CI 1.32–3.05; HR for EFS 1.54, 95%CI 1.09–2.17) and young patients (HR for OS 1.30, 95%CI 1.09–1.55), respectively. This meta-analysis indicates $EVI1^H$ has an independent and significantly adverse prognostic impact on AML patients in the entire population, and this conclusion same applies to some subgroups like AML patients with ICR, NC, and young AML patients.

Keywords EVI1 · Expression · Acute myeloid leukemia · Prognosis · Meta-analysis

Introduction

Acute myeloid leukemia (AML) is a common malignant disorder of hematology characterized by the aberrant growth and differentiation of hematopoietic stem cells (HSCs), which results in the presence of cytopenia in the peripheral blood (PB) [1]. Due to the further understanding of AML and improvement of the detecting techniques, cytogenetic and molecular analysis has been incorporated into the National Comprehensive Cancer Network (NCCN) or European Leukemia Net (ELN) risk stratification of AML, which significantly contributes a physician to diagnose and predict the prognosis more accurately and protocol more appropriate therapeutic regimens for patients with AML [2, 3]. The molecular genetic abnormalities include gene mutations like common *FLT3*, *NPM1*, *DNMT3A*, and *TP53*; the inappropriate gene expression of EVI1, MN1, and BAALC and the aberrance of chromosomes, all of these are critical to diagnose, predict the prognosis, and make therapy protocols for patients with AML [4].

Ecotropic virus integration site-1 (EVI1), a transcription factor locusing on chromosome 3(3q26.2), firstly recognized in a mice model of AML 20 years ago, has stem cell-specific expression pattern and is pivotal for the regulation of HSC proliferation and differentiation [5–7]. Aberrant expression of EVI1 plays an essential role in the hematological malignances including AML, myelodysplatic syndrome (MDS), and chronic myeloid leukemia (CML) [8] . Given locating

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on the chromosome 3 (3q26.2), EVI1 abnormal expression frequently follows the 3q26 rearrangements, but also found in the patients without any 3q aberrations [9]. Some studies reported the higher EVI1 expressions were significantly associated with the adverse survival in patients with AML [10–12]; nevertheless, others did not confirm the unfavorable prognostic impact of $EVI1^H$ in AML patients [13–16]. Ya-Zhen Qin et al. (2018) and Genki Yamato et al. (2017) reported that the $EVI1^H$ was an independently unfavorable prognosis factor in the AML patients with intermediate cytogenetic risk and in de novo AML patients, respectively [17, 18].While, Langabeer SE et al. (2003) reported that there was no evidence that $EVI1^H$ predicted an adverse prognosis in AML patients with intermediate and favorable cytogenetic risk [19]. Haas, K et al. (2008) showed that there were no significant effects of $EVI1^H$ for OS and EFS in AML patients without the 3q aberrances [15]. Stefan Groschel et al. (2010) revealed that the presence of higher expression of EVI1 independently predicted inferior EFS and lower complete remission (CR), but not OS in young AML patients whether 3q abnormalities or not [14]. Stefan Groschel et al. (2013) even reported that AML patients with $EVI1^H$ MLL-rearranged seem to benefit from allogeneic transplantation in first complete remission (CR) [12]. Addition, BV Balgobind (2010) reported that the overexpression of EVI1 in children was not independently related to the inferior OS and EFS in the multivariate analysis (HR for OS 1.0, $P = 0.97$; for EFS 1.2, $P = 0.67$) [20]. In consideration of the inconsistent conclusion, the aim of the present meta-analysis on related data from all eligible studies is to get insight into the association between the EVI1 expression and prognosis in AML patients.

Materials and methods

Literature search and search strategy

Literature search was conducted in several main databases without any restriction, including PubMed, Embase (OVID), and Web of Science (up to 23 February 2019). The main MESH terms, used to search the eligible studies, were as follows: "EVI1," "Ecotropic virus integration site-1," "MECOM," "PRDM3," "EVI1c," "EVI1b," "EVI1a," "MDS1 and EVI1 complex locus protein," "acute myeloid leukemia," and "AML."

The review protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42019134411).

Selection criteria

Studies were kept in the meta-analysis if they met the following criteria: (1) article was published up to 23 February 2019 focusing on the prognostic impacts of EVI1 expression in AML patients, including de novo AML, secondary AML (sAML), and therapy-related AML (tAML); (2) the study offered overall survival (OS) and/or event-free survival (EFS) information of patients with EVI1 higher expression; (3) the study was published as original articles written in English. Review articles, case reports, letters/reports, conference abstracts, laboratory studies, and studies only for the children were all excluded. The presence of the same data or overlapping data in multiple studies, only the latest or the highest quality study were incorporated in our meta-analysis.

Two investigators (Xia Wu and Jili Deng) search and screen the studies independently. The divergence between them were solved by discussing, or if necessary, the third investigator (Xue Zheng) was involved in solving the disagreement.

Data extraction

Two reviewers (Xia Wu and HuiFang Wang) screened all of the included articles that met all the inclusion criteria and extracted the relevant data from them, independently. The following data extracted from the articles including: the first author's name, year of publication, country of origin, total patients, age and gender distribution of patients, number of patients of EVI1 expression distribution, French-America-British (FAB) classification, cytogenetics analysis, and direct method. We selected the OS as the primary endpoint and EFS as the secondary endpoint. Overall survival meaning dead or alive at last follow-up is distinct from EFS linked to events in life from any cause. Hazard ratio (HRs) and 95% confidence intervals (CIs) for OS and EFS from COX multivariable models were used to calculate the estimated effect to assess the prognostic impact of EVI1 higher expression in patients with AML. If the necessary data for analysis were not provided in the published articles, we contacted with the corresponding author to obtain the insufficient or missing data. Divergences between two reviewers in the progress were solved by discussion until obtaining a consensus.

Quality assessment

Two reviewers (Xia Wu and HuiFang Wang) independently assessed the methodological quality of each eligible study with Newcastle-Ottawa quality assessment scale (NOS) for cohort studies. NOS covers nine items divided into three broad perspectives: selection including four items, comparability including two items, and exposure or outcome including three items [21]. The overall quality score ranges from one to nine points, and study can have one star (*) for meeting each criterion except that comparability (design or

analysis) can have a maximum of two stars (**). Cohort studies with six or more scores were considered as high quality [21]. Discrepancies between two reviewers were resolved by discussion.

Statistical analysis

Stata ver.12 software (College Station, TX, USA) was used to perform all statistical analyses to evaluate the total survival impact of EVI higher expression in AML patients. The HRs and their 95% CIs for the OS and EFS were extracted from the eligible papers and calculated by the Stata ver.12 software with the inverse variance method in the total population and subgroups. The pooled HRs and their 95% CIs were used to assess the survival prognostic implication of EVI1 higher expression in patients with AML. The final result indicated statistical significance when the pooled 95% CIs did not overlap 1. In addition, compared to the patients with EVI1 no/lower expression, the EVI1 higher expression suggested poor prognosis effect when the HR is > 1. The heterogeneity of the included studies was evaluated by chi-square test with a significance level at $P < 0.1$. The I^2 was used for the quantitative assessment of heterogeneity with four classifications: $I^2 = 0–25\%$: no observed heterogeneity; $I^2 = 25\%–50\%$: moderate heterogeneity; $I^2 = 50\%–75\%$: large heterogeneity; $I^2 = 75–100\%$: extremely heterogeneity) [22]. The fixed-effect model was applied when the heterogeneity was moderate or lower; if not, a random model was used. We employed the meta-regression to explore the heterogeneity between studies.

Sensitivity analysis and publication biases

Sensitivity analysis was used to assess the effect of each included study on the stability of the pooled results by sequentially omitting one study each time. We evaluated the potential publication biases of included studies through Begg's test [23] and Egger's test [24]. All the relevant calculations were implemented in Stata version 12.0 software (Stata Corp, College Station, TX, USA) with a *P* value less than 0.05 being considered significant.

Results

Study identification and selection

As shown in Fig. 1, the initial search included 1227 studies. After exclusion of 462 studies for duplication, the rest of the 765 records were screened further in titles and abstracts to exclude 691 records for irrelevant subject or improper types of articles. A total of 74 citations were needed to be reviewed in full text. After being further screened, 15 studies without sufficient data or interest, 22 letters or reports, 13 studies of children, four studies published in Chinese and nine studies with published data were all excluded. Eleven studies covering 4501 patients were finally kept in our meta-analysis [10–18, 25, 26]. The selection process was documented in a flow chart recommended by the PRISMA (Fig. 1).

Characteristic of selected studies

Eleven included studies, published between 2003 and 2018, were all cohort studies (Table 1). Four studies originated from Asia, six from Europe, and one from Austria. A total of 4767 patients were included from 11 eligible studies, among them, 853 patients with EVI1 higher expression ($EVI1^H$) and 3727 patients with EVI1 no/lower expression ($EVI1^{N/L}$) (12 patients missing, 175 patients without EVI1 expression information offered were excluded).

Quality assessment of included studies

The NOS was used to assess the quality of the included studies in the meta-analysis. The mean overall score of the total 11 eligible studies was 7.8 (6–9), suggesting that the quality of included studies was high (Table 1) (Supplement Fig. 1).

Clinical characteristics of AML patients with EVI1 higher expression

No significant differences in age, sex, and WBC counts were presented between $EVI1^H$ and $EVI1^{N/L}$ patients with AML [10, 14, 17, 18], but the $EVI1^H$ frequently implicated with the MLL aberrances or 3q abnormalities [10–14, 18, 25]. Additionally, $EVI1^H$ had an inverse association with *NPM1* mutation, *FLT3-ITD*, and *DNMT3A* mutation, respectively [10, 12, 14, 17, 18]. And among included studies, one reported that $EVI1^H$ had a lower occurrence in patients with normal cytogenetics [25].

Analysis of outcomes

As shown in Fig. 2, the pooled HR for OS from 11 eligible studies was used to evaluate the prognosis effect of EVI1 higher expression in patients with AML, which suggested $EVI1^H$ was an independently adverse prognostic factor for OS (HR = 1.52, 95%CI 1.24–1.86, $P < 0.0001$) with a large heterogeneity (I = 73%) in the random-effects model (Fig. 2a). To avoid the heterogeneity of studies, we performed a subgroup analysis for OS (HR = 1.43, 95%CI 1.25–1.64, $P < 0.0001$, $I^2 = 19.9\%$) (Fig. 2b). Meanwhile, the summary HR for the EFS from seven studies covering 3702 patients indicated an inferior prognostic impact of $EVI1^H$ on AML patients (HR = 1.41, 95% CI 1.14–1.78, $P = 0.001$), with a

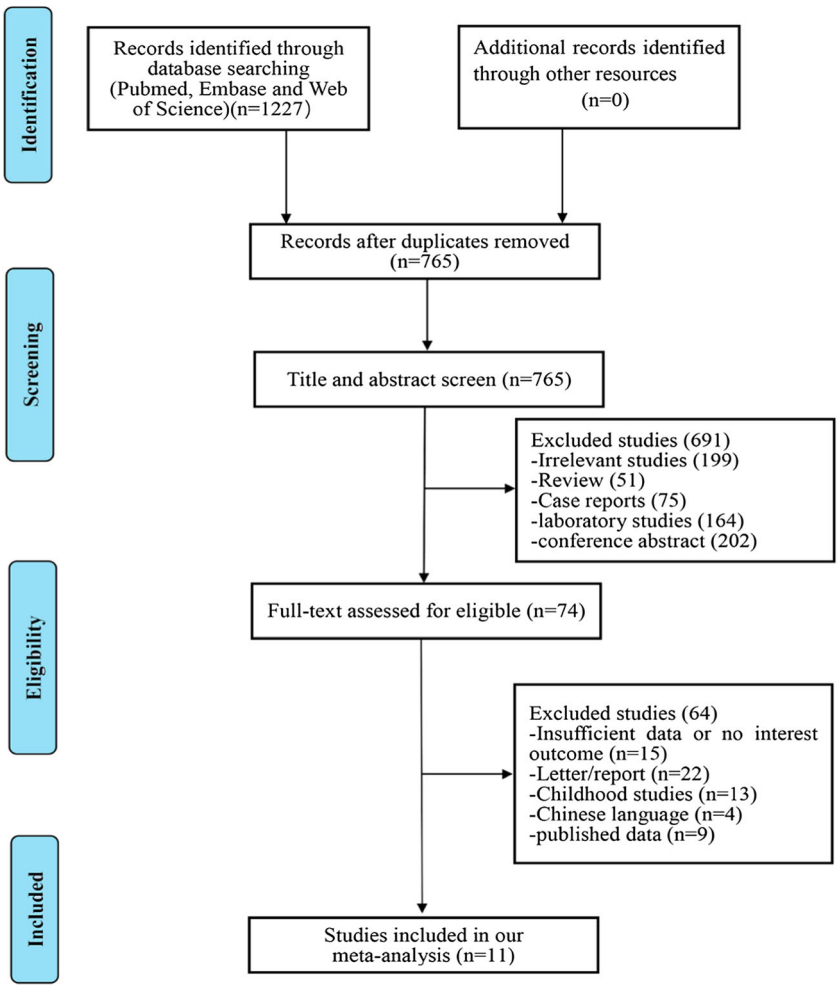


Fig. 1 Flow diagram of study selection

large heterogeneity (I^2 = 67.9%) in the random-effects model (Fig. 2c).

Among the 11 included studies, five studies also focused on patients with EVI1 higher expression classified into intermediate cytogenetic risk (ICR) and two studies for cytogenetic normal (CN). The pooled HR for OS (HR = 1.73, 95% CI 1.43–2.11, $P < 0.0001$) and EFS (HR = 1.17, 95% CI 1.05–1.31, $P = 0.004$) both revealed an unfavorable prognosis influence of the EVI1 higher expression in ICR patients, with a moderated heterogeneity (I^2 = 33.7%) and a large heterogeneity (I^2 = 67.8%), respectively (Fig. 3). The presence of higher EVI1 expression was also associated with the inferior survival in patients with the cytogenetics normal, resulting in patients with the shorter OS (HR = 2.01, 95% CI 1.32–3.05, $P = 0.001$, I^2 = 0%) and EFS (HR = 1.54, 95% CI 1.09–2.17, $P = 0.014$, I^2 = 7.5%), compared with the those with EVI1 no/lower expression (Fig. 4). In addition, the analysis of young patients with EVI1 higher expression in our meta-analysis showed that $EVI1^H$ was also associated with poor OS (HR = 1.30, 95%CI 1.09–1.55, with a value of $P = 0.004$) with no heterogeneity (I^2 = 13.1%) (Fig. 5).

Meta-regression analysis, sensitivity analysis, and publication biases

Given the limitation of data for EFS, we employed the meta-regression to explore the possible source of heterogeneity only in OS of the entire population. Four factors were calculated in the meta-regression analysis, including the publication year, population, median age of patients, and the number of patients, and none of them were showed to be significantly related to the heterogeneity (Table 2).

We carried out a sensitivity analysis by sequentially deleting one study at a time to assess the effect of each study on the pooled HR for OS, not for EFS due to limitation of data for EFS. The results revealed that one study had no evident effect on the combined HR for the OS of the total population in a random-effects model, but significantly in the fixed effects (Fig. 6). Although no significant publication bias was detected in Begg's test ($P = 0.276$) for the OS in entire population of the 11 included studies, but in Egger's test ($P = 0.003$) (Supplement Fig. 1). For this discrepancy, we took the results based on the Egger's test,

Table 1 Data of 11 included studies in the meta-analysis

First author	Year	Population	Patients (*n*)	Median age, year (range)	Median follow-up, month (range)	Male/ Female	$EVI1^{H}$/ $EVI1^{N/L}$	FAB classification	Cytogenetics risk FCR/ICR/ ACR	Direct method
Sahar Barjesteh	2003	Holland	319	45.1(15.2–76.8)	NR(NR-60)	167/152	32/287	M0-M6[a]	57/212/50/6[f]	qRT-PCR
Katja Haas	2008	Austria	266	59(16–93)	NR	130/136	41/225	M0-M7[a]	28/156/42/40[f]	RQ-PCR
Sanne Lugthart	2008	Holland	534	NR (15–77)	NR(NR-60)	267/267	41/493	M0-M6[a]	90/364/80	RQ-PCR
Stefan Groschel	2010	German	1382	NR (15–60)	58.9 (1.2–224.4)	697/685	148/1234	M0-M7[a]	263/836/191/92	RQ-PCR
Veronika Rockova	2011	Holland	439	43(15–60)	NR	220/219	39/400	M0-M7[a]	0/439/0	NR
Iria Vazquez	2011	Spanish	476(213[d])	58(16–83)	39.75(6-N)	110/103	92/384	M0-M7[b]	55/269/152	qRT-PCR
Elias Bou Samra	2012	French	163	58(17–83)	30(1.6–79)	75/88	57/106	M0-M6[b]	0/163[e]/0	Microarrays
Stefan Groschel	2013	German	286(177[g])	NR (15–78)	65.1/N	132/154	81/96	M0-M7[a]	NR	qRT-PCR
Genki Yamato	2017	Japan	151	61(17–88)	34(1.4–60)	87/64	25/126	M0-M7[b]	21/105/25	qRT-PCR
Yong-Mei Zhu	2017	China	560	NR (1–83)	NR	320/240	274/274/12[c]	M0-M7[b]	89/401/55/15[f]	TaqMan gene expression assay
Ya-Zhen Qin	2018	China	191	43 (17–65)	13 (2–91)	106/85	23/168	M0-M6[b]	0/191/0	qRT-PCR

FAB French American British classification, *RQ-PCR* real-time quantitative polymerase chain reaction, *qRT-PCR* quantitative real-time polymerase chain reaction, *FCR* favorable cytogenetic risk, *ICR* intermediate cytogenetic risk, *ACR* adverse cytogenetic risk, *n* number of patients in total, *NR* not reported or provided; *NOS* Newcastle-Ottawa quality assessment scale

[a] FAB classification includes the M3

[b] FAB classification excludes the M3

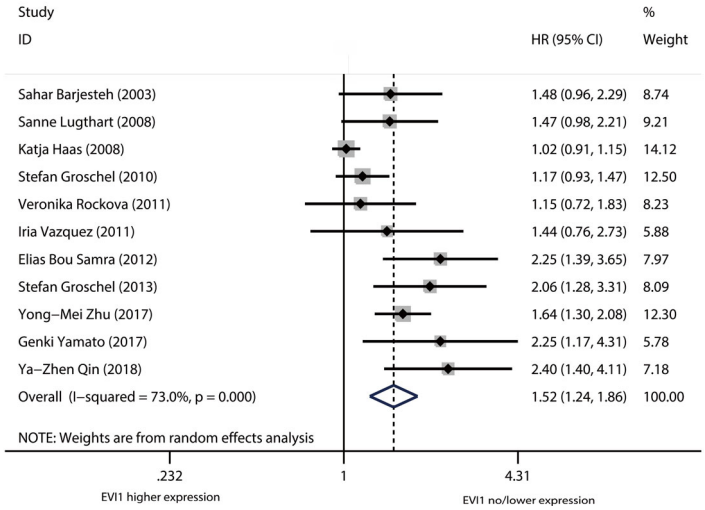
[c] Missing patients

[d] Survival analysis was performed in the 213 AML patients

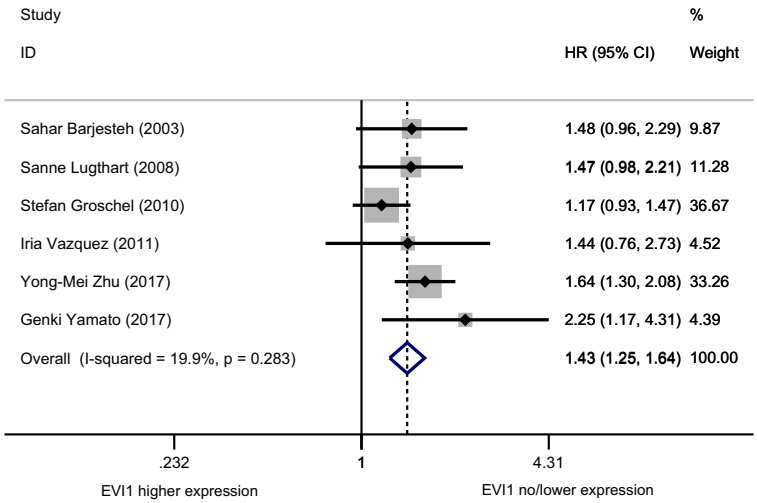
[e] The 163 patients in this study all harbored normal cytogenetics

[f] No cytogenetic information was available at diagnosis

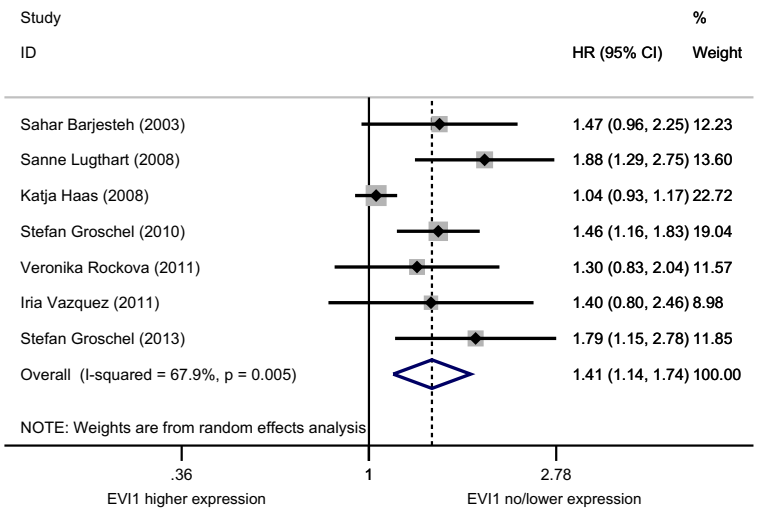
[g] Only the 177 AML patients with available material for EVI1 analysis



a Forest plots of the HRs for the OS in total population in a random-effects model



b Forest plots of HRs for the OS in AML patients from six studies including with and without 3q abnormalities in a fixed-effects model

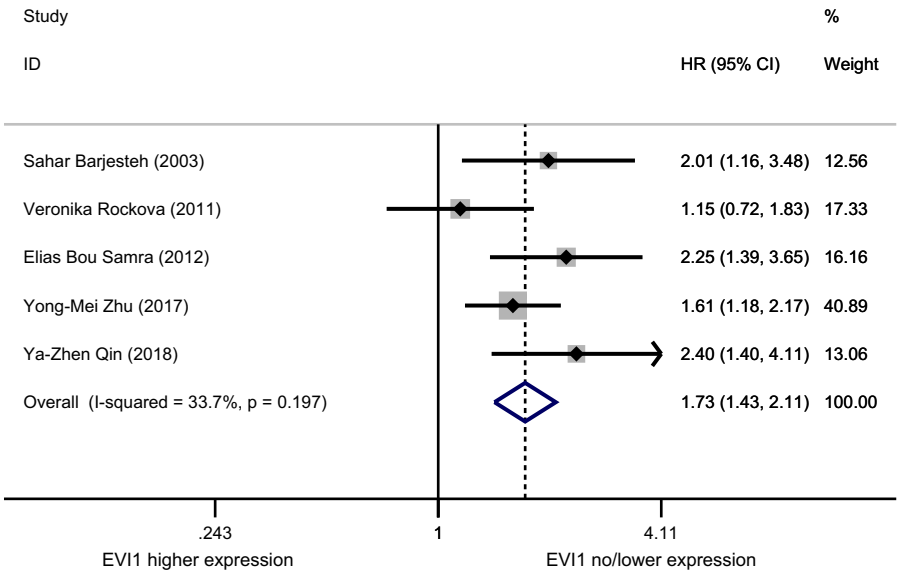


c Forest plots of the HRs for the EFS of AML patients from seven studies in a random-effects model

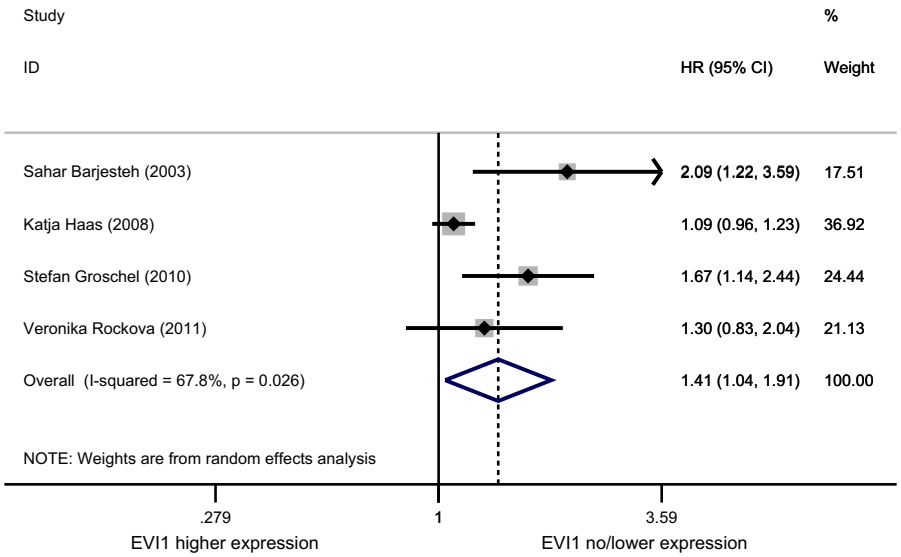
◀ **Fig. 2** Forest plots of the pooled HRs and 95% CIs for the OS and EFS assessing the prognostic value of EVI1 higher expression in the patients with AML. The size of the blocks or diamonds represents the weight for the random-effects model in the meta-analysis. **a** Forest plots of the HRs for the OS in total population in a random-effects model. **b** Forest plots of HRs for the OS in AML patients from six studies including with and without 3q abnormalities in a fixed-effects model. **c** Forest plots of the HRs for the EFS of AML patients from seven studies in a random-effects model

which is more powerful than the rank correlation test of Begg's test [24]. This study also had a significant effect on the EFS of AML patients with ICR, resulting in the pooled HR from 1.17 (95%CI 1.05–1.31) changing to 1.62 (95%CI 1.25–2.09); meanwhile, the I^2 decreased from 67.8% (0.026) to 0% ($P = 0.407$). The results described above indicated that this study may be the source of the heterogeneity. Therefore, we performed a subgroup analysis of six studies including patients with and without 3q abnormalities to avoid the heterogeneity, which made the I^2 decrease from 73 to 19.9% and the pooled HR change from 1.52 (95%CI 1.24–1.86, $P < 0.0001$) to 1.43 (95%CI 1.25–1.64, $P < 0.0001$).

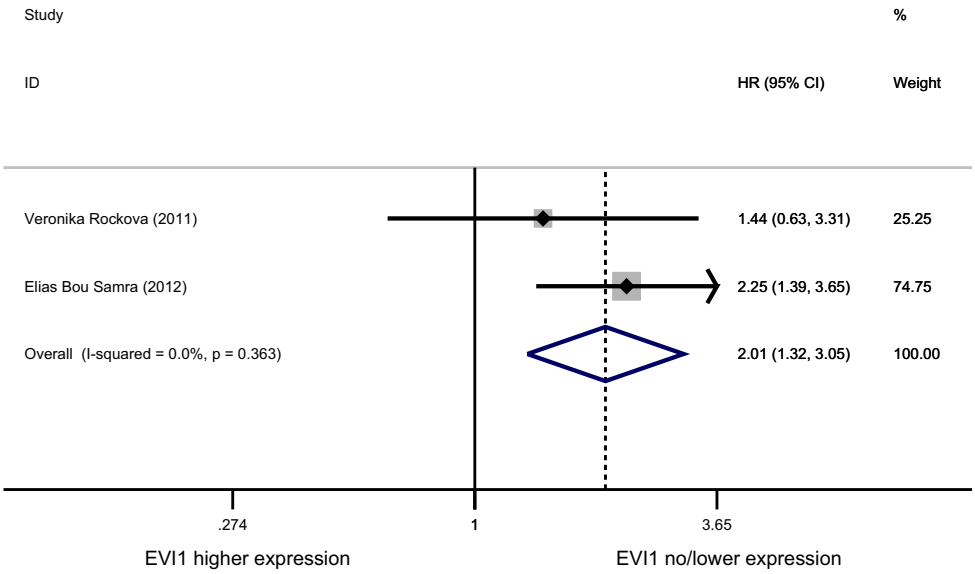
Fig. 3 Forest plots of the pooled HRs and 95% CIs for OS and EFS assessing the prognostic value of EVI1 higher expression in the AML patients with intermediate cytogenetic risk (ICR). The size of the blocks or diamonds represents the weight for the fixed-effects model or random-effect model in the meta-analysis (**a** for OS, **b** for EFS). **a** Forest plots of the HRs for OS in AML patients with intermediate cytogenetic risk in a fixed-effects model. **b** Forest plots of the HRs for EFS in AML patients with intermediate cytogenetic risk in a random-effects model



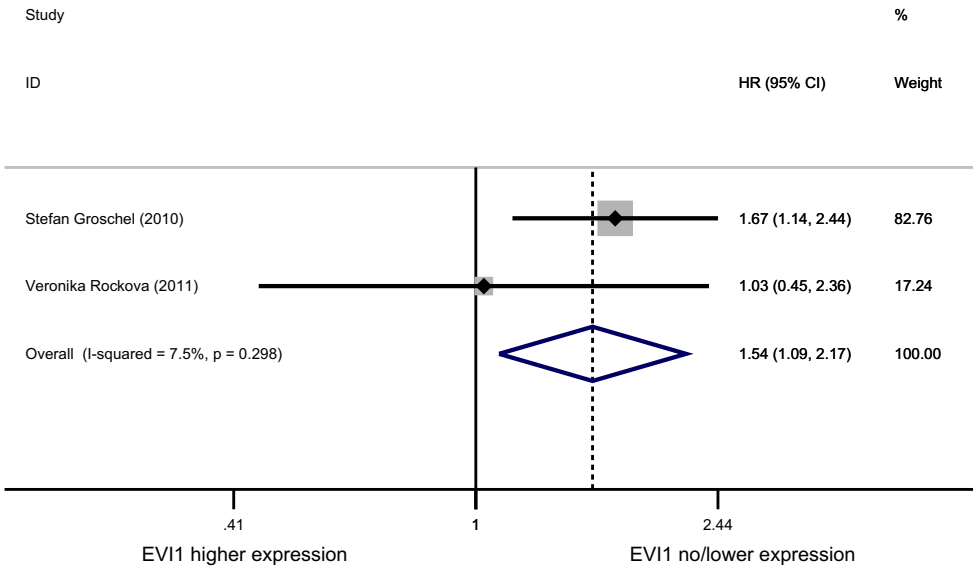
a Forest plots of the HRs for OS in AML patients with intermediate cytogenetic risk in a fixed-effects model



b Forest plots of the HRs for EFS in AML patients with intermediate cytogenetic risk in a random-effects model



a Forest plots of HRs and 95% CIs for OS in patients with CN



b Forest plots of HRs and 95% CIs for EFS in patients with CN

Fig. 4 Forest plots of the pooled HRs and 95% CIs for OS and EFS assessing the prognostic value of EVI1 higher expression in the AML patients with cytogenetics normal (CN). The size of the blocks or diamonds represents the weight for the fixed-effects model in the meta-analysis (**a** for OS, **b** for EFS). **a** Forest plots of HRs and 95% CIs for OS in patients with CN. **b** Forest plots of HRs and 95% CIs for EFS in patients with CN

Discussion

As a malignant disorder in hematology usually with a poor prognosis, AML needs an accurate prediction of prognosis to indicate protocoling the appropriate therapy regimens for patients hoping for survival improvement. Molecular markers increasingly play an utmost significant role in the diagnosis and risk stratification of AML. As one of the cytogenetic aberrances, EVI1 inappropriate expression plays a critical role in the AML risk stratification and guides to make the corresponding therapy protocols. Although many studies have assessed the prognostic effect of EVI1 higher expression in patients with AML [10–19, 25, 26], the conclusions among these studies are still inconsistent. Thus, the aim of the present meta-analysis is to further identify and understand the role of EVI1 aberrant expression in AML patients. EVI1 (also named MECOM), a transcription factor encoding a unique zine-finger protein of 145 kDa binding with DNA, was regarded to be involved in the differentiation and proliferation of hematopoietic stem cells, such as interfering with granulocytic and erythroid differentiation, or promoting megakaryocytic breakdown [27, 28]. Several putative target genes of EVI1 has been

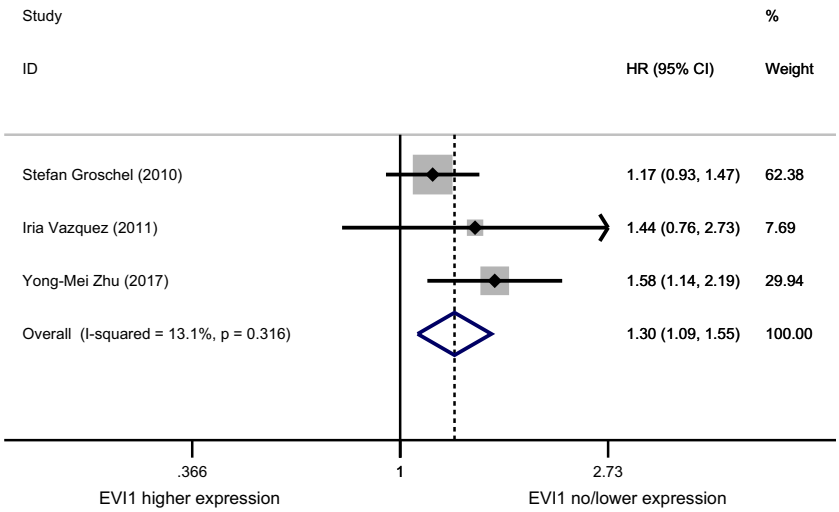


Fig. 5 Forest plots of HRs and 95% CIs for OS in young AML patients in a fixed-effects model. The size of the blocks or diamonds represents the weight for the fixed-effects model in the meta-analysis

proposed, including genes involved in stem cell maintenance and leukaemogenesis, like the tumor suppressor gene *Phosphatase and Tensin Homolog* (*PTEN*) [29] and the transcription factor *Pre-B Cell leukemia Homeobox 1* (*PBX1*) [30], *GATA2* [31]; however, none of these have been identified as the key in EVI1-deregulated human AML [32].

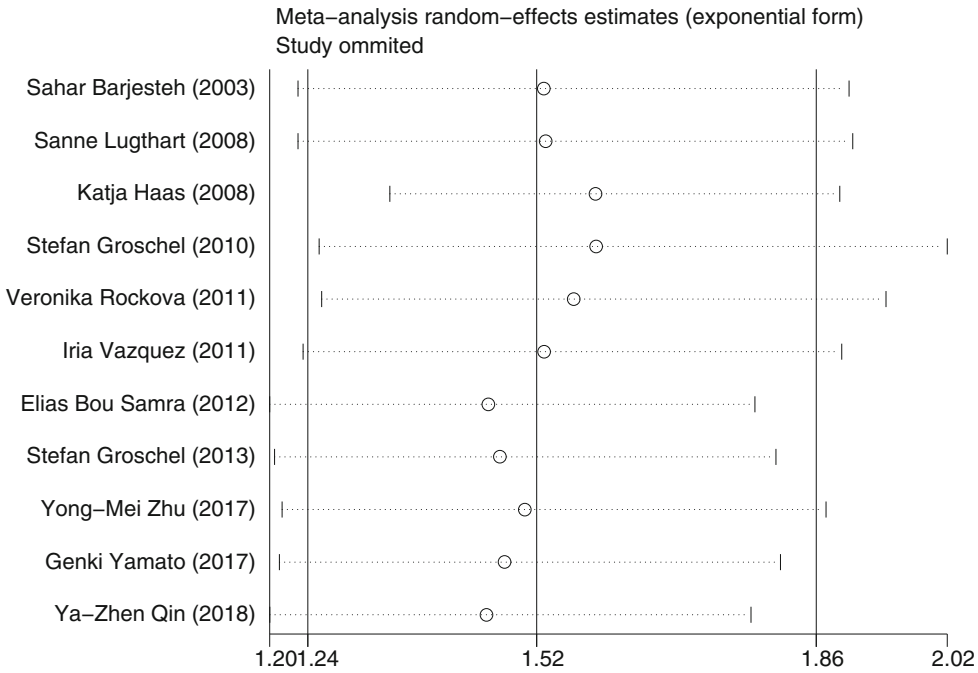
The pooled HR for the OS of the total population in our present meta-analysis confirmed the view that EVI1 higher expression was an independent risk factor for an adverse prognosis in patients with AML, and also with a shorter EFS, compared to those with no or lower EVI1 expression. In addition, AML patients with $EVI1^{H}$ classified into intermediate cytogenetic risk, cytogenetic normal, or young patients also harbored inferior OS and EFS than patients with $EVI1^{N/L}$. Despite that there is no significant difference between the $EVI1^{H}$ and $EVI1^{N/L}$ AML patients regarding the sex, age, and WBC counts, $EVI1^{H}$ was rarely associated with *NPM1* mutation ($P < 0.05$) and *FLT3-ITD* and *DNMT3A*, respectively, which may deserve us to further explore the correlation between the EVI1 aberrant expression and any other gene mutations. As the heterogeneity in entire AML patients for OS is considerable, we used the meta-regression including four factors described previously to explore the heterogeneity, but none of them was shown to be the possible source of heterogeneity. The sensitive analysis indicated that one study (Haas, K et al (2008)) (HR for OS 1.02, $P = 0.793$; for EFS 1.04, $P = 0.496$) had a significant effect on the pooled HR for OS of total population in the fixed-effects model, but not in the random-effects model. In fact, no publication biases were detected in the Begg's test ($P = 0.276$) but in Egger's test ($P = 0.003$). We speculated this study excluding the patients without the 3q aberrances may be the factor resulting in the large heterogeneity, so we performed a subgroup analysis of six studies including patients with and without 3q defects to avoid the heterogeneity, and the heterogeneity decreased from 73% to 19.9%.

Table 2 Results of meta-regression analysis for heterogeneity for OS of total population

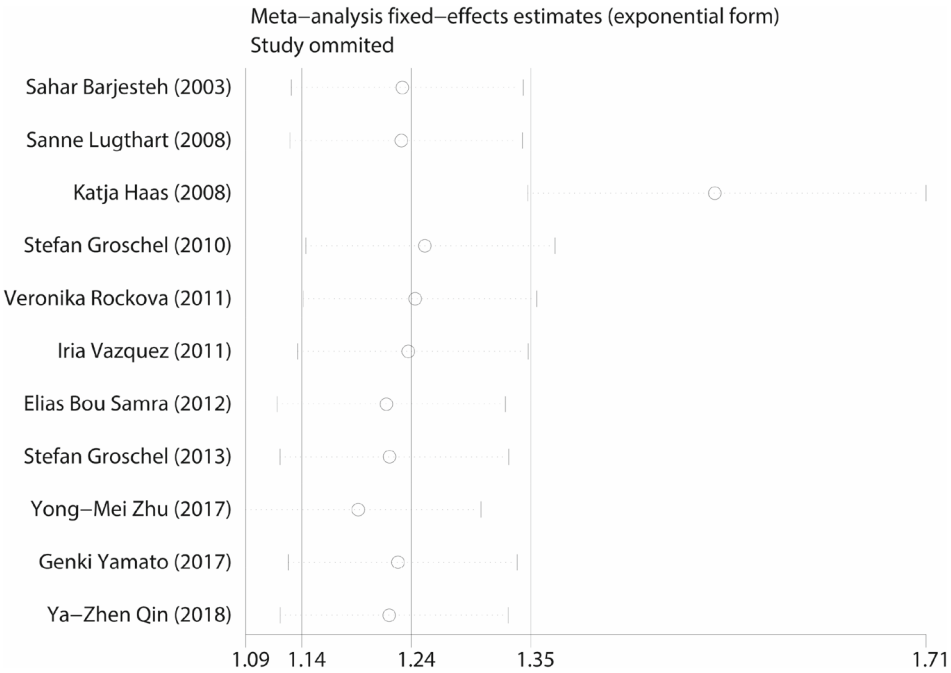
	Overall survival			95%CI	
	exp(b)	SE	*P* value	LL	UL
Publish year	1.412	0.286	0.123	0.89	2.23
Population	1.412	0.286	0.123	0.89	2.23
Median age	1.07	0.183	0.698	0.73	1.58
Number of patients	0.99966	0.000262	0.229	0.99907	1.000254

Although our paper is the first meta-analysis regarding the prognosis implication of EVI1 higher expression in AML, several limitations existing in our meta-analysis should not be neglected. Firstly, our meta-analysis was mainly based on observational studies rather than the random control trails (RCT). Secondly, our meta-analysis covered a small percentage of tAML and sAML patients with an inherently worse prognosis, which might potentially affect our results in some degree. Thirdly, except for the heterogeneity possibly from one study (Haas, K et al (2008)), there was still much clinical heterogeneity among studies, such as age and gender distribution of patients, cytogenetic and molecular aberrances, cytogenetic risk classification, exact definition of EVI1 higher expression, time of follow-up, and diverse treatment regimens, which may be the potential factors to influence the clinical outcomes. Thirdly, we did not make a subgroup analysis of patients without the 3q abnormalities because of limited information for OS. Finally, publication biases were detected by Egger's test in our meta-analysis, and other potential publication biases could exist in our meta-analysis, since our eligible data were only from published articles and we did not get contact successfully with several authors for the missing or unpublished data.

Despite that subgroup analysis for patients without the 3q aberrances was not presented in our meta-analysis, we should not ignore these special patients being a large number of



a Sensitivity analysis in a random-effects model for the OS in the total publication



b Sensitivity analysis in a fixed-effects model for the OS in the total publication

Fig. 6 Sensitivity analysis for the OS in the total publication. **a** Sensitivity analysis in a random-effects model for the OS in the total publication. **b** Sensitivity analysis in a fixed-effects model for the OS in the total publication

patients in AML. Whether EVI1 higher expression has an adverse prognosis value in the AML patients with or without the cytogenetics aberrance involving 3q is still a controversial conclusion existing in the previously reported studies. Langabeer, S. E et al. (2003) detected the higher expression of EVI1 in AML cases with 3q defects (70%) but did not reveal the prognosis value of $EVI1^{H}$ in de novo AML patients classified into favorable or intermediate cytogenetic risk [19]. Meanwhile, they also showed that higher expression of EVI1 is relatively frequent event in AML patients with the absence

of 3q abnormalities. Lugthart, S. et al (2008) reported the prediction value of EVI1 as an inferior prognosis indicator in AML patients no matter 3q abnormalities or not [10]. With respect to the significant difference among the previous study, large-scale clinical researches need to take place to identify the potential value of EVI1 higher expression in patients without chromosome defects.

In conclusion, results of our meta-analysis including 11 studies reveal that EVI1 higher expression is an independent adverse prognosis predictor for OS and EFS in patients with AML. And this conclusion same applies to the subgroup of patients with intermediate cytogenetic risk (ICR) or normal cytogenetic (NC), and the young patients (< 60 years). This result may somehow be conductive to the risk stratification and therapy decision of patients with AML, especially for the NC patients accounting most patients of AML. Albeit, EVI1 aberrant expression usually accompanying the cytogenetic abnormalities involving 3q, but also in patients with the normal 3q. Hence, whether the EVI1 higher expression is an independent poor prognostic predictor in AML patients without 3q abnormalities or any other chromosome aberrances should be further explored and confirmed. Furthermore, the impacts of EVI1 higher expression for different subgroups of AML patients and the association with other gene mutations also need to be further studied, which is of utmost significance for clinical physicians.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics statement This article does not contain any studies with human participants or animals performed by any of the authors.

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