Association between the Wilms tumor-1 rs16754 polymorphism and acute myeloid leukemia
A MOOSE-compliant meta-analysis

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Abstract

The Wilms tumor-1 (WT1) protein is an important regulator of malignant hematopoiesis and has been implicated in the pathogenesis of acute myeloid leukemia (AML). Recently special attention has been paid to the relationship of the *WT1* single nucleotide polymorphism (SNP) rs16754 with AML risk and outcome, but the conflicting results made it difficult to draw definitive conclusions. In the present study, we systematically reviewed the literature and performed a meta-analysis of existing evidence. We searched Embase, Pubmed, Web of Science, Medline, Cochrane Library, Wanfang, and China National Knowledge Infrastructure databases using predefined search methodology for relevant studies. We pooled odd ratio (OR) with 95% confidence intervals (95% CI) to evaluate the association between SNP rs16754 and AML risk. In addition, we analyzed hazard ratio (HR) with 95% CI for overall survive, relapse-free survival, and disease-free survival. Q-statistic was used to assess the homogeneity and Egger test was used to evaluate publication bias. Eleven studies met the inclusion criteria for analysis. The results of fixed-effect meta-analyses revealed no association between SNP rs16754 and AML risk (AA + GA vs GG: OR = 0.92, 95% CI: 0.71–1.19, $P = .518$; AA vs GA + GG: OR = 1.23, 95% CI: 0.86–1.76, $P = .262$; AA vs GG: OR = 1.05, 95% CI: 0.68–1.63, $P = .820$; AG vs AA: OR = 0.77, 95% CI: 0.53–1.13, $P = .186$; AG vs GG: OR = 0.89, 95% CI: 0.68–1.16, $P = .376$). In subgroup analysis by race, age, and disease type, we did not find any significant association. However, the presence of rs16754 GA/GG genotype was associated with improved overall survive (HR = 0.48, 95% CI: 0.26–0.91, $P = .024$) and relapse-free survival (HR = 0.82, 95% CI: 0.68–1.00, $P = .048$) compared with the rs16754 AA. In summary, the *WT1* SNP rs16754 was not associated with AML risk, but it had a significant impact on clinical outcome in AML patients.

Abbreviations: AML = acute myeloid leukemia, CI = confidence intervals, DFS = disease-free survival, HR = hazard ratio, OR = odd ratio, OS = overall survive, RFS = relapse-free survival, SNP = single nucleotide polymorphism, WT1 = Wilms tumor 1.

Keywords: acute myeloid leukemia, meta-analysis, rs16754, Wilms tumor-1

1. Introduction

Acute myeloid leukemia (AML) is a bone marrow-based hematologic malignancy with widely heterogeneous clinical

outcomes. It is the most commonly occurring acute leukemia in adults and accounts for approximately 18% of childhood leukemia diagnoses. Although there has been considerable progress in the diagnosis and treatment of AML over the past 2 decades, AML remains a difficult-to-treat disease. With a few exceptions, response to treatment is unsatisfactory and prognosis is poor.[1] Thus the identification of novel markers for risk stratification and therapeutic targeting is needed.[2,3]

The Wilms tumor 1 (*WT1*) gene is located at chromosome locus 11p13 and encodes a zinc-finger transcription factor that can either activate or repress genes to regulate cell growth, apoptosis, and differentiation.[4]*WT1* was originally identified as a putative tumor suppressor gene whose inactivation was associated with the development of Wilms' tumor, a kidney neoplasm of childhood.[5] However, subsequent findings suggest that *WT1* has an oncogenic role in leukemogenesis and tumorigenesis. *WT1* expression is detectable in a wide range of leukemias, and *WT1* is overexpressed in the leukemic blasts of a majority of AML patients.[6,7] In myelodysplastic syndromes, *WT1* expression is linked to increased blast counts and reflects disease progression to AML.[8] Several studies have shown that high *WT1* expression in AML is associated with treatment resistance and a worse long-term outcome.[9] In recent years, special attention has been paid to the synonymous single nucleotide polymorphism (SNP) rs16754 of *WT1*. This SNP is located in exon 7, resulting in a change of the nucleotide adenine (A) into guanine (G).[4] Numerous research groups assessed a

probable association of rs16754 with AML susceptibility and clinical outcomes, but the conflicting results made it difficult to draw definitive conclusions. We aim to review the literature and conduct a meta-analysis to provide an overview of the field.

2. Methods

2.1. Information sources and search strategy

The reporting of this meta-analysis adhered to the Meta-analysis of Observational Studies in Epidemiology statement standards. Ethics approval was not required for this meta-analysis because we only analyzed published data. Embase, Pubmed, Web of Science, Medline, Cochrane Library, Wanfang, and China National Knowledge Infrastructure databases were searched. A combination of the following search terms were used: "acute myeloid leukemia," "Wilms tumor 1," "WT1," "rs16754," "polymorphism," "mutation," "genetic variants," "clinical outcomes," "prognosis," and "prognostic factor." In addition, the reference lists of retrieved reports were reviewed. Only papers published in English or Chinese were considered for inclusion. No time period for publication date was specified. Two reviewers (XY and YZ) independently screened the citations and performed full text evaluation using the inclusion criteria. Any disagreements regarding eligibility of an article was discussed.

2.2. Inclusion criteria

Studies were eligible if they met the following inclusion criteria:

(1) original research articles;
(2) case-control or case-only design;
(3) human population;
(4) investigation of the effect of rs16754 on AML susceptibility or clinical outcome; and
(5) sufficient data for calculating pooled effect sizes.

Studies were excluded if:

(1) in vitro experimental studies;
(2) review articles;
(3) editorials;
(4) conference abstracts; and
(5) insufficient data.

2.3. Data extraction

Data extracted included the following: last name of the first author, country, publication of year, ethnicity, study design, number of participants, type of AML, measurement, average age, genotyping distributions, genotyping method, and Hardy–Weinberg equilibrium in controls. One reviewer (XY) extracted the data using a standardized data collection form and the second reviewer (YZ) checked the extracted data.

2.4. Synthesis of results

We pooled odd ratio (OR) with 95% confidence intervals (95% CI) to evaluate the relationship between rs16754 and AML risk. In addition, we analyzed hazard ratio (HR) with 95% CI to assess the association between rs16754 and clinical outcomes of AML. Between-study heterogeneity was calculated according to Cochrane statistic and its related metric I^2 ($I^2 < 50\%$ indicates low to moderate heterogeneity, whereas $I^2 > 50\%$ indicates

moderate to high heterogeneity).[10] A fixed effect model was used unless statistical heterogeneity was significant ($P < .05$).[11] Evidence of publication bias was assessed using the Egger test.[12] All comparisons were conducted using Stata 13.0 (StataCorp LP, College Station TX), and statistical significance was set at $P < .05$.

3. Results

3.1. Study characteristics

Our literature search and study selection process are summarized in Figure 1. The systematic search of databases retrieved 427 citations; manual scanning of reference lists did not identify additional articles. After 168 duplicate records were excluded, 259 references were screened on the basis of title, abstract, or both to determine potential eligibility. Of this, 23 articles underwent full-text screening, and 11 fulfilled the eligibility criteria.[4,9,13–21] Study characteristics are summarized in Table 1. The studies were published between 2010 and 2018 and were performed in different geographical locations: 5 in Asia, 4 in Europe, and 2 in North America. Ten studies were written in the English language and 1 was written in Chinese. Regarding study design, 6 studies were case-only design,[9,13,14,16,19,21] and the remaining were case-control studies. Sample size was largest (790) in the study performed by Ho et al[13] and lowest (66) in the study by Chen et al.[16]

3.2. Data analysis

The association between SNP rs16754 and AML susceptibility was evaluated in 5 case-control studies including a total of 764 AML patients and 525 controls.[4,15,17,18,20] There was no significant heterogeneity among the studies in the included models where the P-value for Q was >.05. The results of fixed-effect meta-analyses revealed no association between rs16754 and AML risk when combining the 5 studies (AA + GA vs GG: OR = 0.92, 95% CI: 0.71–1.19, $P = .518$; AA vs GA + GG: OR = 1.23, 95% CI: 0.86–1.76, $P = .262$; AA vs GG: OR = 1.05, 95% CI: 0.68–1.63, $P = .820$; AG vs AA: OR = 0.77, 95% CI: 0.53–1.13, $P = .186$; AG vs GG: OR = 0.89, 95% CI: 0.68–1.16, $P = .376$) (Fig. 2). In subgroup analysis according to race, the results suggested that SNP rs16754 was not associated with AML risk in Asian populations (AA + GA vs GG: OR = 0.92, 95% CI: 0.71–1.18, $P = .502$; AA vs GA + GG: OR = 1.09, 95% CI: 0.71–1.68, $P = .690$; AA vs GG: OR = 1.04, 95% CI: 0.67–1.63, $P = .863$; AG vs AA: OR = 0.87, 95% CI: 0.55–1.37, $P = .537$; AG vs GG: OR = 0.89, 95% CI: 0.68–1.16, $P = .379$) (Table 2). There was only 1 case-control study conducted in Caucasians, which did not support an association between SNP rs16754 and AML risk (Table 2).[4] When subgroup analysis was performed based on age and disease type, no association with AML was found (Table 2).

To assess the evidence for the association of SNP rs16754 with AML outcomes, 2 studies were excluded because one had an overlapped sample and the other did not report available data.[4,15] Nine studies with a total of 2567 patients were included in the quantitative analysis.[9,13,14,16–21] We analyzed HRs for overall survive (OS), relapse-free survival (RFS), and disease-free survival (DFS). Compared with the rs16754 AA, the presence of rs16754 GA/GG genotype was associated with improved OS (HR = 0.48, 95% CI: 0.26–0.91, $P = .024$) (Table 3 and Fig. 3) and RFS (HR = 0.82, 95% CI: 0.68–1.00, $P = .048$) (Table 3) after adjusting for basic covariates including age, sex,
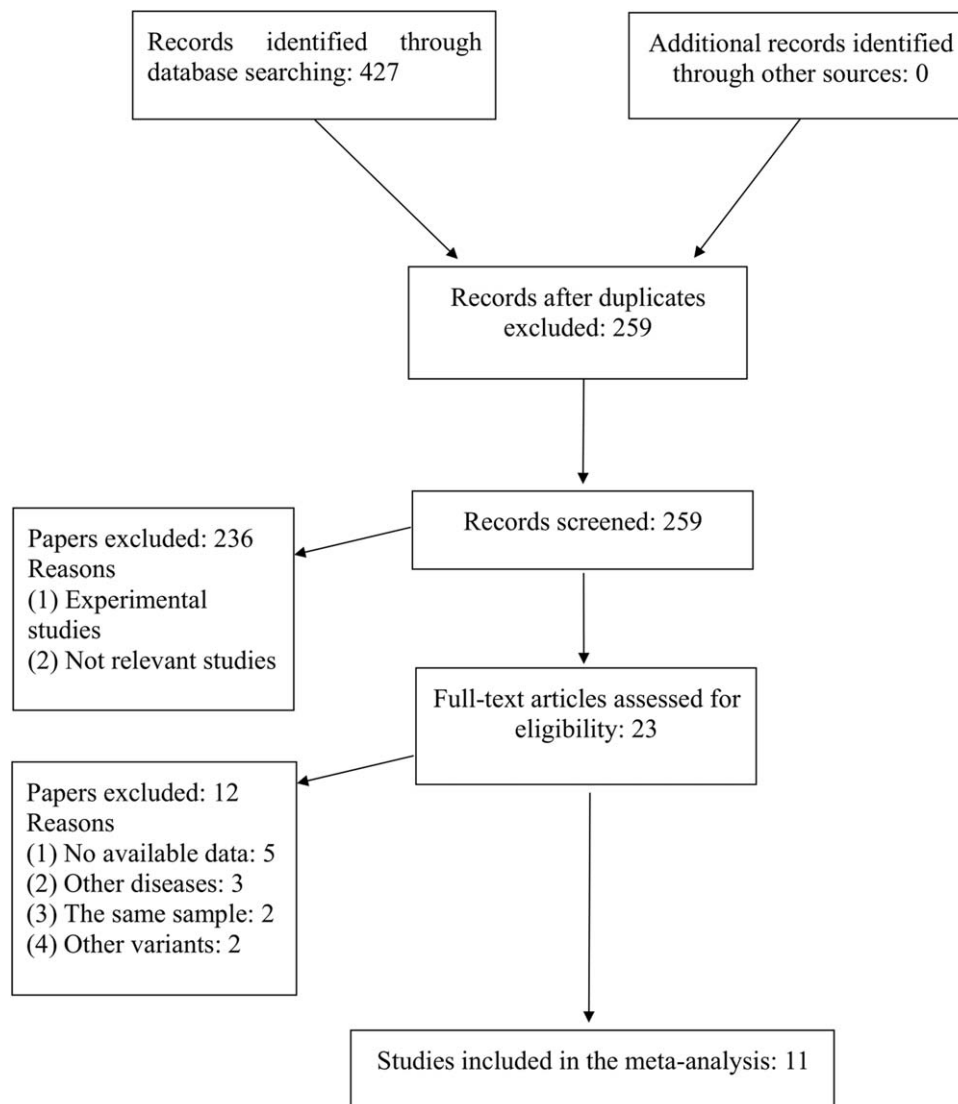
Figure 1. Flow chart of search history and study selection.

white blood cell count, FLT3-ITD, and NPM1 mutations. However, HRs for OS, RFS, and DFS were not statistically different between patients with the GG genotype and those with the GA or AA genotype (Table 3).

3.3. Publication bias

No evidence of publication bias was found based on the results of the Egger test (AA + GA vs GG: $P = .881$; AA vs GA + GG: $P = .213$; AA vs GG: $P = .754$; AG vs AA: $P = .282$; AG vs GG: $P = .651$).

4. Discussion

AML is an aggressive hematological malignancy that affects the myeloid lineage and causes clonal malignant proliferation of white blood cells. AML usually has a rapid onset of symptoms in only a few weeks. Despite the relative success of current front-line cytotoxic chemotherapies, the disease remains lethal to the majority of sufferers. The 5-year survival rate is 17% in the EU

and 26% in the US.[22] This highlights the need for the identification of specific therapeutic targets for developing novel and effective treatments. Over the last 5 years, many molecular biomarkers have been identified in patients with AML; 1 of them is WT1.

Originally named for its role in Wilms' tumor, *WT1* has since been found to be implicated in hematological malignancies including AML. The *WT1* gene product plays multiple and important roles in cell biology, such as proliferation, differentiation, apoptosis, and tissue development. Accumulating evidence suggests that *WT1* possesses both oncogenic and tumor suppressor properties. *WT1* is highly expressed in 85% of AML. Although several reports initially demonstrated that high *WT1* mRNA expression was associated with improved clinical outcomes in AML,[23,24] more recent studies showed that *WT1* expression was not an independent predictive factor for clinical outcome of AML.[7,17] The *WT1* gene is located on chromosome 11p13 and contains 10 exons. Among all the *WT1* polymorphisms evaluated, much attention is paid to the synonymous SNP rs16754. This variant has 2 alleles that differ by harboring the

Characteristics of studies included in the meta-analyses.

Year	Author	Country	Ethnicity	Participants	AML type	Male (%)	Age (yr)	Available parameters for meta-analysis	Adjusted factors for outcome assessment	Median follow-up time
2010	Damn	Germany	Caucasians	249 patients and 50 controls	CN-AML	51.8	17–60	AML risk, OS, and RFS	WBC count, platelet count, age, WT1 expression, NPM1/FLT3 mutation status, and CEBPA mutation	5.3 yr
2010	Wagner	Germany	Caucasians	275 patients	CN-AML	NA	47	OS and RFS	Age, platelets count, NPM1/FLT3 mutation status, and CEBPA mutation	78 mo
2011	Ho	USA	Mix	790 patients	Mix	53.5	0.01–21.63	OS and RFS	WBC count, race, and cytogenetics	5 yr
2011	Becker	USA	Mix	433 patients	CN-AML	49.9	62	DFS and OS	Age	6.5 yr
2012	Choi	Korea	Asians	73 patients, and 50 controls	CN-AML	63.0	42	AML risk, OS, EFS, and RFS	Age and NPM1/FLT3 mutation status	30.8 mo
2012	Chen	China	Asians	66 patients	Mix	NR	4 mo to 15 years	RFS and OS	CEBPA mutation	NR
2014	Luo	China	Asians	122 patients and 60 controls	Mix	41.8	45	AML risk, OS, and DFS	WT1 expression, age, WBC count, and FLT3 mutation	40 mo
2015	Zhang	China	Asians	205 patients and 188 controls	Mix	54.1	40	AML risk, OS, and RFS	WBC count, and LDH count, age, risk stratification, and allo-SCT	458 d
2016	Niavarani	UK	Caucasians	474 patients	NK-AML	NR	45	OS and RFS	Age, sex, WBC, secondary disease, performance status, FLT3-ITD, and NPM1 mutations	10 yr
2016	Xu	China	Asians	115 patients and 177 controls	Mix	57.4	47	AML risk and OS	Age and sex	NR
2018	Petiti	Italy	Caucasians	87 patients	Mix	51.7	NR	OS	Age, sex, therapy, cytogenetic risk, and WT1 expression	NR

AML = acute myeloid leukemia, CEBPA = CCAAT/enhancer binding protein α, CN-AML = cytogenetically normal acute myeloid leukemia, DFS = disease-free survival, FLT3 = FMS-like tyrosine kinase 3, ITD = internal tandem duplication, LDH = lactate dehydrogenase, NK-AML = normal karyotype acute myeloid leukemia, NPM1 = nucleophosmin 1, NR = not reported, OS = overall survive, RFS = relapse-free survival, WBC = white blood cell, WT1 = Wilms tumor-1.
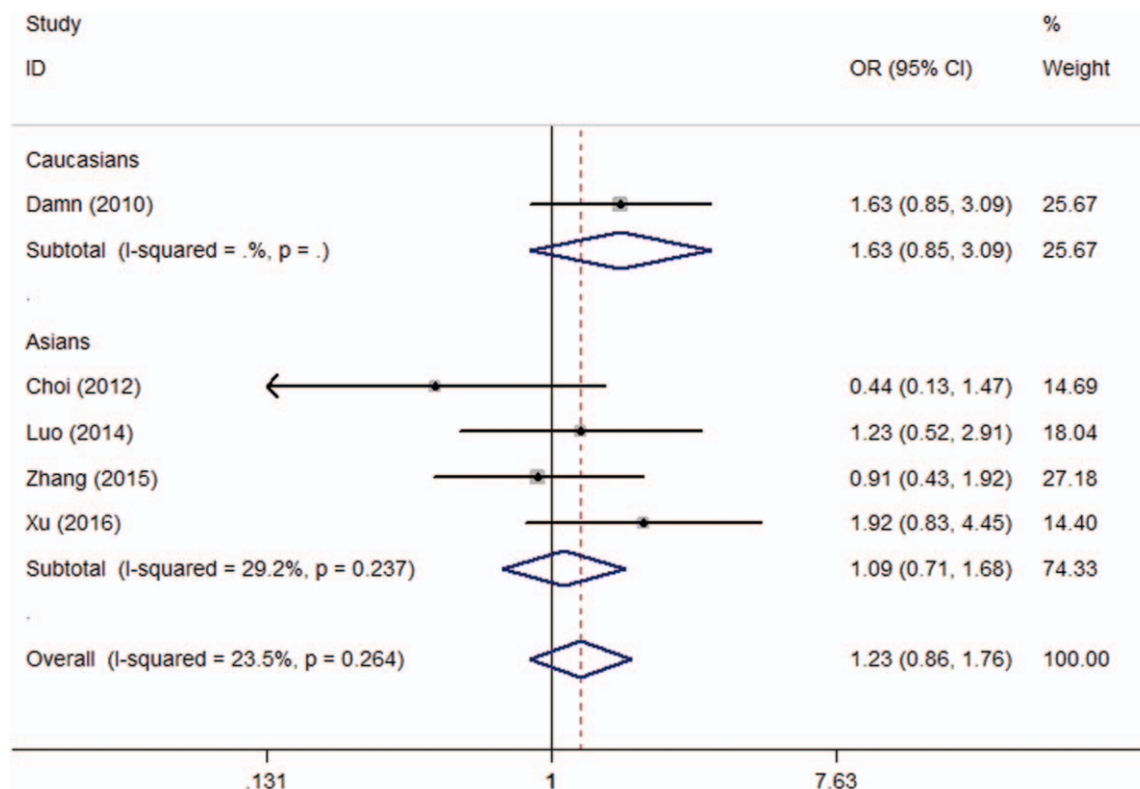

Figure 2. Forest plot of odds ratio for association between SNP rs16754 and AML risk (AA vs GA + GG). AML = acute myeloid leukemia, SNP = single nucleotide polymorphism.

Table 2

Meta-analysis of the relationship between SNP rs16754 and AML risk.

Genetic contrast	Subgroup	Number of studies	Association		Heterogeneity	
			OR (95% CI)	P-value	I^2 (%)	P-value
AA + GA versus GG	All	5	0.92 (0.71–1.19)	.518	0	.626
	Asians	4	0.92 (0.71–1.18)	.502	0	.469
	Caucasians	1	1.25 (0.14–11.43)	.843	NA	NA
	CN-AML	2	0.60 (0.30–1.19)	.145	0	.492
	Adults	2	0.91 (0.61–1.34)	.624	0	.773
	Adults and Children	3	0.93 (0.67–1.30)	.667	20.4	.285
AA versus GA + GG	All	5	1.23 (0.86–1.76)	.262	23.5	.264
	Asians	4	1.09 (0.71–1.68)	.690	29.2	.237
	Caucasians	1	1.63 (0.85–3.10)	.139	NA	NA
	CN-AML	2	1.19 (0.68–2.11)	.540	71.6	.061
	Adults	2	1.26 (0.77–2.05)	.358	25.1	.248
	Adults and Children	3	1.20 (0.70–2.03)	.508	48.4	.144
AA versus GG	All	5	1.05 (0.68–1.63)	.820	21.3	.279
	Asians	4	1.04 (0.67–1.63)	.863	40.1	.171
	Caucasians	1	1.45 (0.16–13.35)	.745	NA	NA
	CN-AML	2	0.49 (0.16–1.51)	.213	15.8	.276
	Adults	2	0.91 (0.44–1.90)	.810	0	.672
	Adults and Children	3	1.14 (0.66–1.97)	.642	57.3	.096
AG versus AA	All	5	0.77 (0.53–1.13)	.186	0	.470
	Asians	4	0.87 (0.55–1.37)	.537	0	.415
	Caucasians	1	0.61 (0.32–1.18)	.141	NA	NA
	CN-AML	2	0.77 (0.43–1.39)	.396	52.8	.146
	Adults	2	0.77 (0.46–1.27)	.304	4.1	.307
	Adults and children	3	0.78 (0.44–1.39)	.404	20.3	.285
AG versus GG	All	5	0.89 (0.68–1.16)	.376	0	.902
	Asians	4	0.89 (0.68–1.16)	.379	0	.789
	Caucasians	1	0.88 (0.09–8.43)	.913	NA	NA
	CN-AML	2	0.64 (0.31–1.32)	.228	0	.767
	Adults	2	0.90 (0.60–1.36)	.623	0	0.984
	Adults and children	3	0.87 (0.61–1.25)	.455	0	.596

CI = confidence interval, CN-AML = cytogenetically normal acute myeloid leukemia, NA = not available, OR = odds ratio, SNP = single nucleotide polymorphism.

nucleotide G or A. Recently, SNP rs16754 was suggested to have a role in the AML risk and prognosis, but the data from different studies still remained confused.

We performed a literature-based meta-analysis to investigate the association of SNP rs16754 with AML risk and clinical outcomes. In the qualitative analysis of the included studies, we did not find any significant association between the SNP rs16754 genotypes and AML risk. However, we found that AML patients with the GA or GG genotype had improved OS and RFS in comparison to those with the AA genotype. To the best of our knowledge, this is the first meta-analysis that specifically looks at the relationship between SNP rs16754 and AML risk. We applied several genetic models for the evaluation, including dominant, recessive, and homozygote models. Besides the overall analysis,

we performed subgroup analysis according to race, disease type, and age. Our data disclosed no evidence of association of SNP rs16754 with AML risk. Two previously published meta-analyses included case-only studies to assess the impact of SNP rs16754 on AML prognosis, but neither of them took the risk of AML into consideration.[25,26] Our results on the relationship between SNP rs16754 and AML prognosis were consistent with those from the meta-analysis by Megías-Vericat et al, which reported a higher OS in AML patients with the G allele of SNP rs16754.[25] However, unlike the Megías-Vericat et al meta-analysis that employed ORs with 95% CI for the pooled analysis, we used different parameters and analyzed HRs for OS, RFS, and DFS. In addition, we performed the analysis based on unadjusted and adjusted data, respectively. We thus

Table 3

Meta-analysis of the association between SNP rs16754 and outcome of AML.

Comparison	Outcome	Unadjusted data			Adjusted data		
		HR (95% CI)	P-value	No. of studies	HR (95% CI)	P-value	No. of studies
GG + AG versus AA	OS	0.70 (0.48–1.03)	.072	3	0.48 (0.26–0.91)	.024	4
	RFS	0.85 (0.71–1.01)	.068	3	0.82 (0.68–1.00)	.048	3
GG versus AA + AG	OS	NA	NA	NA	0.84 (0.43–1.65)	.613	5
	RFS	NA	NA	NA	0.73 (0.13–4.05)	.723	2
	DFS	NA	NA	NA	1.41 (0.20–9.91)	.730	2

CI = confidence interval, CN-AML = cytogenetically normal acute myeloid leukemia, DFS = disease-free survival, HR = hazard ratio, NA = not available, OS = overall survive, RFS = relapse-free survival, SNP = single nucleotide polymorphism.
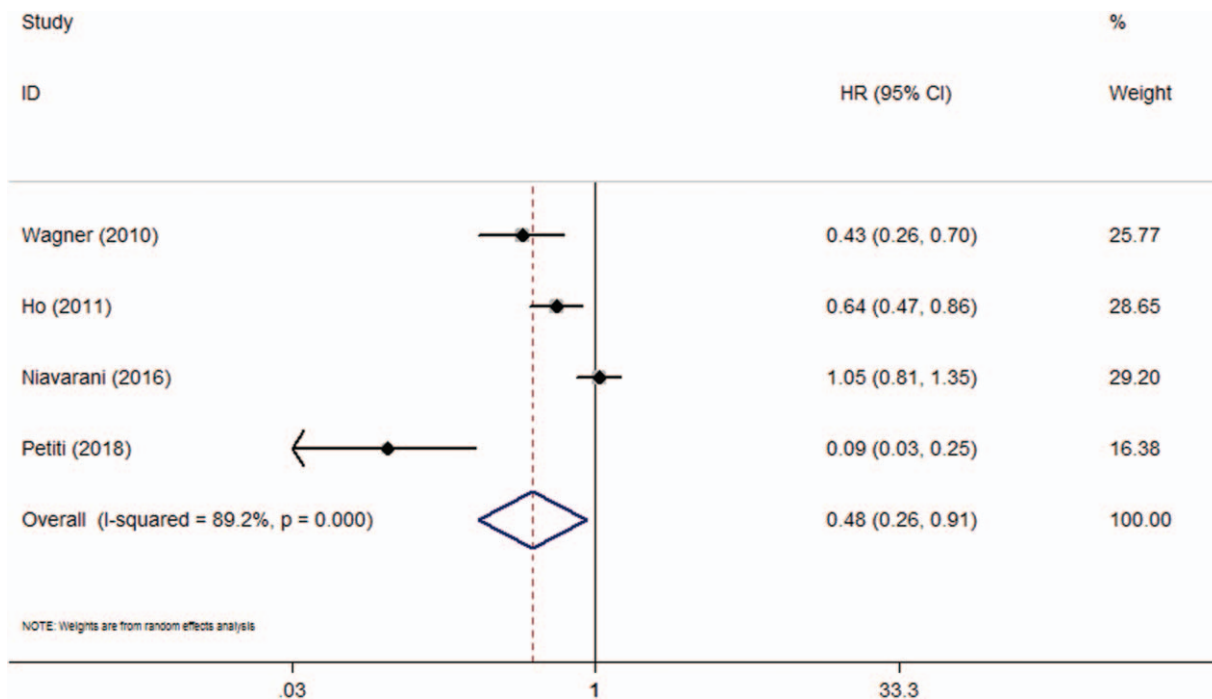
Figure 3. Forest plot of hazard ratio for overall survive in AML patients (GG + AG vs AA). AML = acute myeloid leukemia.

provided additional information on the effect of SNP rs16754 on AML prognosis. The meta-analysis by Long et al also reported an association between SNP rs16754 and better survival of AML, but they did not state the genetic comparison models which they used, making it unclear which rs16754 genotype accounted for the favorable outcome.[26]

The rs16754 polymorphism is a germline, synonymous SNP; the possible mechanisms by which a synonymous SNP contributes to favorable outcome of AML remains poorly understood. SNP rs16754 may be in linkage disequilibrium with other functional polymorphisms that are AML-associated molecular markers. Besides this, several mechanisms such as alternative splicing, alterations in a microRNA binding site, and protein folding are proposed by research groups from the EU and USA.[7,21] Further genetic studies should clarify whether SNP rs16754 is inherited as part of a specific haplotype. In addition, more molecular studies should be conducted to expand our knowledge of the functional effects of this SNP.

Some limitations of the existing literature need to be considered. First, the included case-control studies evaluating the association between SNP rs16754 and AML risk were mainly from Asia, which may prevent us from obtaining robust estimates for the associations. Future data should accumulate in other populations including Caucasians and Africans. Second, the effects of SNP rs16754 on *WT1* expression in pretreatment bone marrow specimens was not studied because of insufficient information. Third, due to relatively small sample sizes, we were unable to investigate the association of SNP rs16754 with de novo and secondary AML, respectively. After more prospective cohort studies are available future meta-analyses can address this problem.

In summary, we performed a systematic literature search and conducted meta-analyses to investigate the association of the *WT1* SNP rs16754 with AML risk and outcomes. We did not find

any significant association between SNP rs16754 and AML risk, but we observed favorable outcomes associated with SNP rs16754 GA/GG genotype. Further case-control studies are warranted to obtain data among different ethnic groups, including Caucasians and Africans. More research is need to take into account linkage disequilibrium between SNP rs16754 and other *WT1* polymorphisms.

Author contributions

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