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Review Article

Association of Interleukin 10 (IL-10) Gene Polymorphism (819T > C) with Susceptibility to Acute Myeloid Leukemia: A Meta-Analysis

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Abstract

Background: Studies reported an association between interleukin (IL)-10 -819T>C polymorphism and the risk of developing Acute myeloid leukemia (AML), however due to inconsistency among these results, relationship between IL-10 -819T>C polymorphism and AML remained unclear. We herein performed this meta-analysis to investigate the association of IL-10 -819T >C polymorphism with the risk of AML.

Methods: A systematic search through PubMed, Embase, Scopus, Cochrane Library and OpenGrey was performed from inception to Jan 2021. Odds ratios (OR) with their corresponding 95% confidence intervals (CI) for five possible genetic models were calculated. Heterogeneity was assessed using the Cochran Q test and the I^2 statistic. A total of 404 AML cases and 635 healthy controls were included in our meta-analysis.

Results: Our results indicated no statically significant association between IL-10 -819T>C polymorphism and the risk of developing AML; dominant model (OR=0.87, 95% CI=0.42–1.81); recessive model (OR=1.17, 95% CI = 0.43–3.16); allelic model (OR=1.00, 95% CI=0.54–1.88); CC vs. TT (OR=1.00,95% CI=0.30–3.36); and TC vs. TT (OR=0.80, 95%CI =0.46–1.37).

Conclusion: IL-10 -819T > C polymorphism is not associated with the risk of AML. However further studies focusing on other parameters such as sex, gene-gene interactions and environmental factors are required to reveal the true association of IL-10 -819T > C polymorphism with AML.

Keywords: Interleukin 10; Acute myeloid leukemia; Polymorphism; Meta-analysis

Introduction

Acute myeloid leukemia (AML) is a complex and multifactorial human malignancy and the most common acute leukemia (AL) in adults (1). Although extensive research has been conducted to find the biological mechanisms and risk factors for developing this disorder, its mechanisms and associated risk factors are still rarely understood (2). Ionizing radiation, obesity, smoking and

chemical carcinogens are reported to be the possible risk factors (3). However, a small proportion of people exposed to these risk factors developed AML, which drew attention to the importance of genetic background as a possible etiology in AML; consequently, a growing body of studies have been carried out to find genetic differences among populations that made some groups of people more vulnerable to develop AML (4, 5). The most common heritable genetic differences are Single nucleotide polymorphisms (SNP) and there is mounting evidence about the association of SNPs with the risk of developing AML, however, the results of these studies are almost inconsistent (6). One of these controversial SNPs is -819T >C (rs1800871), a single nucleotide polymorphism within the interleukin 10 gene (IL-10) (7).

IL-10 is a multifunctional cytokine with a major role in immunoregulation and inflammation, its gene is located on chromosome 1 (q31-q32) and is primarily produced by monocytes and lymphocytes (8), intriguingly during cancer development it acts as a double-edged sword with promoting (immunosuppressive) and inhibiting (anti-angiogenic) effects (9). Although -819T > C (rs1800871) SNP, located in the IL-10 promoter region is associated with the risk of developing AML (7, 10, 11), there are conflicting reports as well (12). Consequently, due to inconsistency between the results of different studies, the association of this SNP with the risk of AML development is not still clear.

Therefore, we performed this meta-analysis to examine the association between the -819T > C polymorphism in the IL-10 gene and AML susceptibility.

Methods

Search Strategy

The present meta-analysis was performed based on observational studies in epidemiology (MOOSE) guidelines (13, 14). A comprehensive search was carried out in PubMed, Embase, Scopus, Cochrane Library and OpenGrey from inception to Jan 2021 to identify studies reporting the association between IL-10 -819T >C polymorphism and AML susceptibility, the following keywords were used; "interleukin 10", "IL-10", "polymorphism", "variation", "acute myeloid leukemia" "AML". Furthermore, references of all included papers were screened to find possibly eligible papers.

Eligibility criteria

Studies must meet all the following criteria to be included in this meta-analysis

- ✓ Case-control or cohort studies
- ✓ Measure the relationship between IL-10 -819T > C polymorphism and AML
- ✓ The results were reported as odds ratio (OR) and corresponding 95% confidence interval (95% CI) or with enough information to calculate it
- ✓ When same data was reported by same authors in two or more papers, the most recent or complete paper was included in our meta-analysis
- ✓ Full text published in English

Data Extraction and Quality Assessment

Two researchers (HRA and AJ) independently extracted the following data from included papers: The first author's name, year of publication, study country, number of cases and controls, genotyping method and frequency of genotype/allele in cases and controls. Any disagreement between two researchers was resolved by third expert. The Newcastle-Ottawa Scale (NOS) for non-randomized studies was employed to evaluate the methodological quality of included studies (15).

Statistical analysis

Deviation from Hardy-Weinberg equilibrium (HWE) was calculated using the Chi-Square test in control groups (16). To assess the association of IL-10 -819T > C polymorphism with AML, odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated for the following five genetic models (17), including allelic model (C vs.

T), recessive model (CC vs. TC/TT), dominant model (TC/CC vs. TT), heterozygote contrast (CT vs. TT), and homozygotes contrast (CC vs. TT). The heterogeneity across included studies was evaluated using Cochran's Q test and I^2 statistics (18, 19). A random-effects model (Der Simonian–Laird approach) was used, as the level of heterogeneity for all five genetic models was statistically Significant $P<0.1$ or I^2 >50%. Egger's linear regression test was employed to assess the publication bias (20). Analyses were carried out using STATA software (version 15.0; StataCorp LLC, College Station, TX, USA).

Results

Characteristics of the included studies

The initial search identified 91 studies on the association of IL-10 -819T >C with AML in the literature (PubMed: 8, Embase: 14 Scopus: 48, Cochrane Library: 0, OpenGrey: 21). Of those 20 articles were duplicates and 66 were excluded after title review and abstract reading, five articles were selected for full-text reading, another study was excluded because of reporting the data from same population, and in this case, we used the most informative article. Finally, four studies including 404 cases and 635 controls met the inclusion criteria and were included in our meta-analysis. The detailed study flow is given in Fig. 1. The main characteristics of included studies and distribution of genotypes and alleles in cases and controls have been summarized in Table 1 and Table 2. The NOS scores for all eligible studies ranged from 6 to 8.

Table 1: Characteristics of the included studies

First author	*Published year*	*Country*	*Genotyping method*	*Cases/Controls*
Chenjiao	2013	China	PCR-RLFP	115/137
Fei	2015	China	PCR-RLFP	167/328
Nursal	2016	Turkey	PCR	42/85
Rashed	2018	Egypt	PCR-RLFP	80/85

Table 2: Distribution of genotypes and alleles in cases and controls

Study	*AML cases*					*Healthy controls*						
	TT	TC	CC	T	C	TT	TC	CC	T	C	P-HWE	MAF
Chenjiao	68	38	9	169	61	56	63	18	175	99	0.96	0.36
Fei	57	72	38	186	148	137	137	54	411	245	0.051	0.37
Nursal	6	21	15	33	51	4	32	49	40	130	0.67	0.76
Rashed	26	23	31	75	85	40	36	9	116	54	0.83	0.32

Association between the IL-10 -819T > C polymorphism and AML

Analyses of four eligible studies revealed no significant association between IL-10 -819T>C polymorphism and the risk of developing AML in all five genetic models including: the dominant model (OR=0.87, 95% CI=0.42–1.81); recessive model (OR=1.17, 95% CI=0.43–3.16); allelic model(OR= 1.00, 95% CI = 0.54–1.88); CC vs. TT (OR = 1.00,95% CI = 0.30–3.36); and TC vs. TT (OR = 0.80, 95%CI = 0.46–1.37) (Table 3). The forest plots for all five genetic models are given in Figs. 2-3.

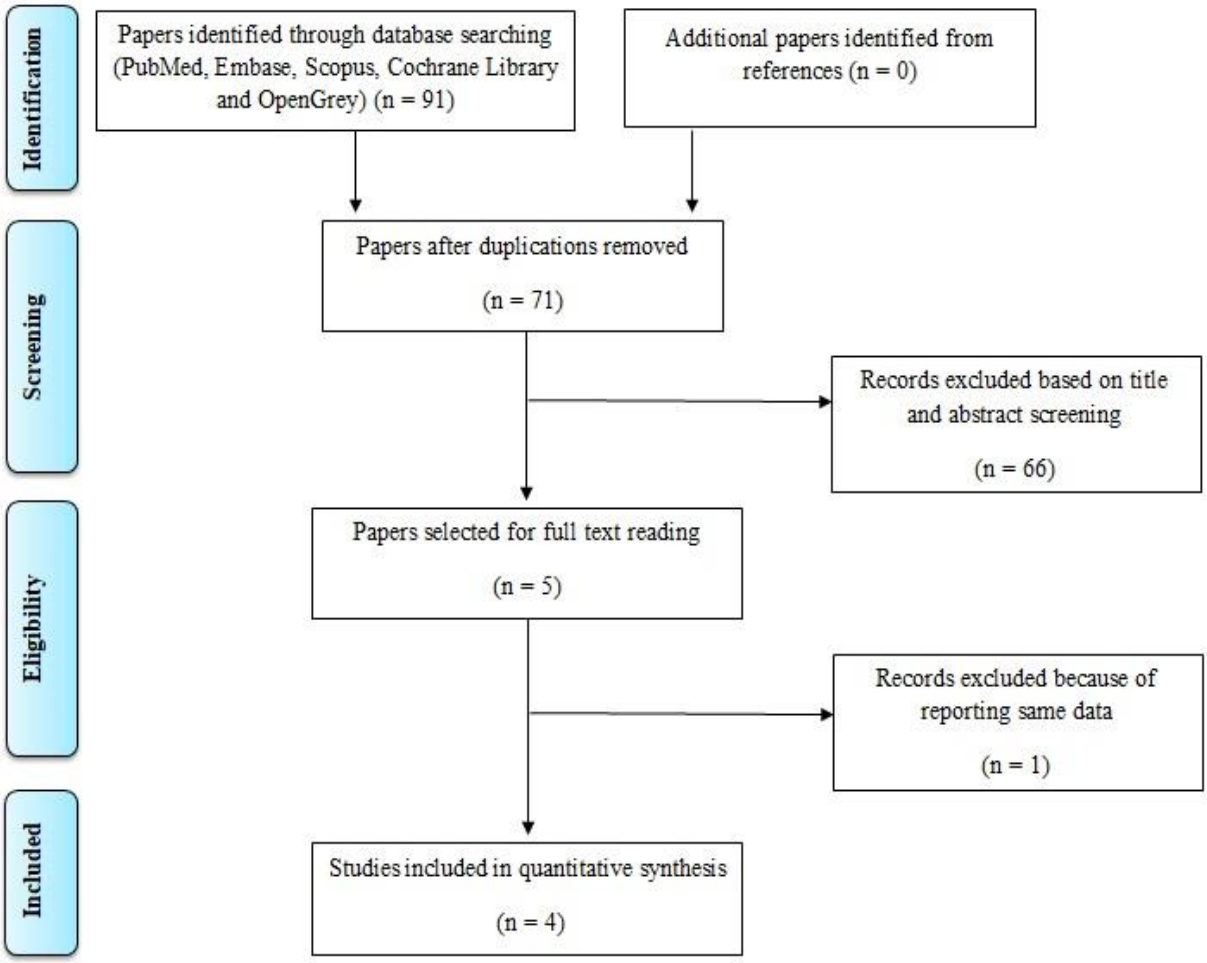

Fig. 1: Flow chart of study selection

Publication Bias

There was a significant heterogeneity within included studies for all five genetic models including: dominant model (I^2 = 83.1%), recessive model (I^2 = 87.5%), allelic model (I^2 = 90.0%), CC vs. TT model (I^2 = 87.5%), and TC vs. TT model (I^2 = 63.0%). The results of Egger's test showed no evidence of publication bias in this meta-analysis (Table 3).

Table 3: Main results of pooled ORs in meta-analysis of IL-10 819 T>C polymorphism and AML

Variable	*Test of association*		*Test of heterogeneity*		*Test of publication bias*	
Genetic model	OR	95% CI	I^2 (%)	P	T	P
Dominant model	0.87	0.42-1.81	83.1	0.000	-0.61	0.604
Recessive model	1.17	0.43-3.16	87.5	0.000	-0.24	0.834
Allelic model	1.00	0.54-1.88	90.0	0.000	-0.51	0.662
CC vs. TT	1.00	0.30-3.36	87.5	0.000	-0.74	0.537
TC vs. TT	0.80	0.46-1.37	63.0	0.044	-0.79	0.511

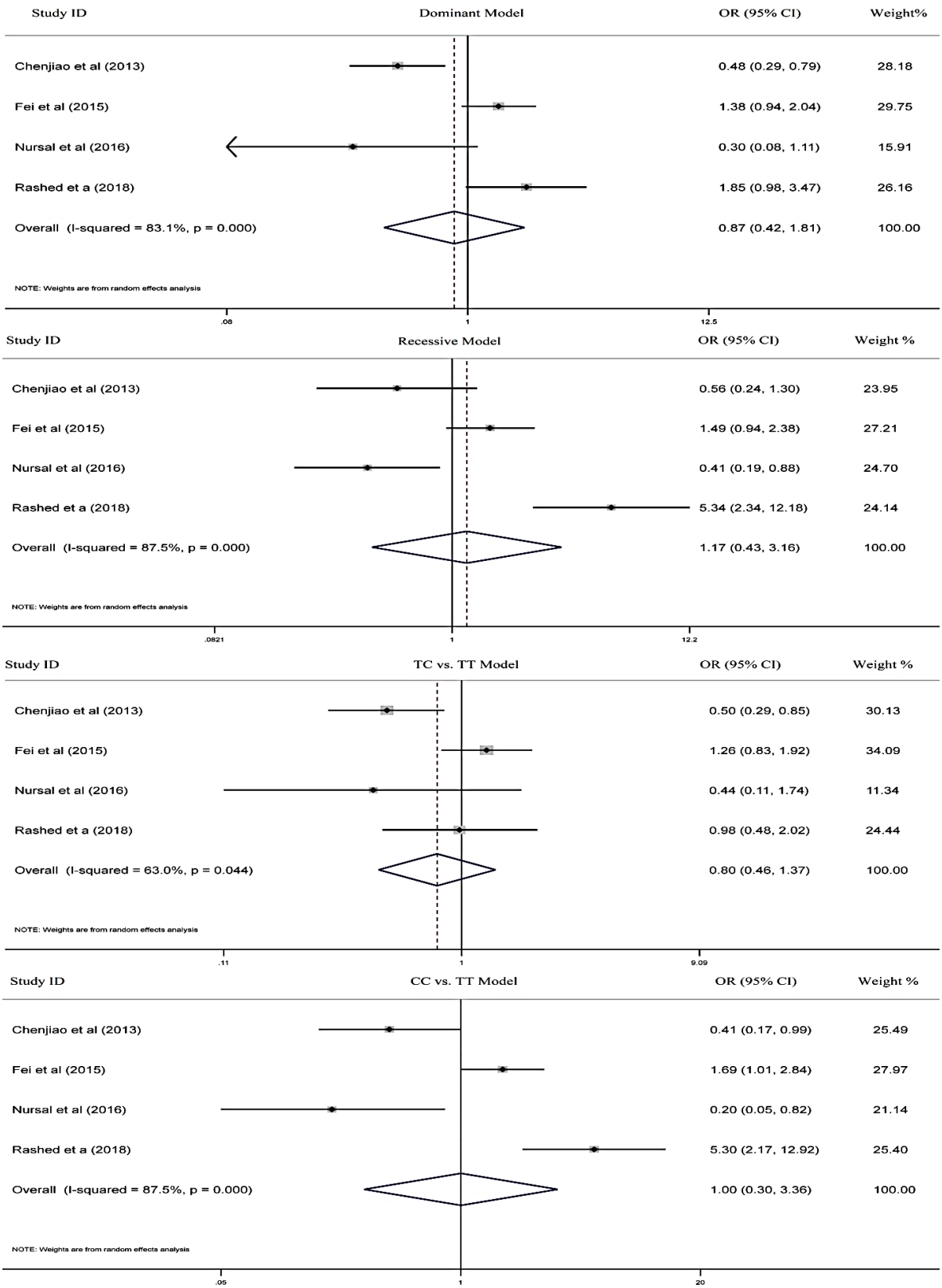

Fig. 2: Forest plot of association between IL-10 -819T > C polymorphism and AML under the Dominant Model, Recessive Model, TC vs. TT and CC vs. TT Models

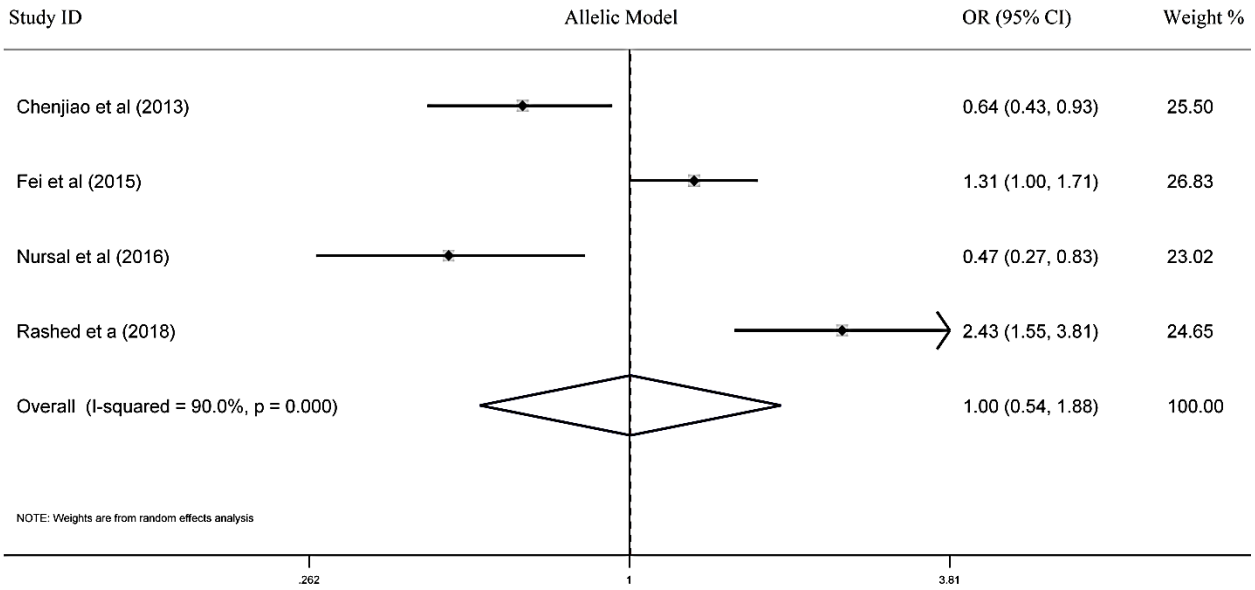

Fig. 3: Forest plot of association between IL-10 -819T > C polymorphism and AML under the Allelic Model

Discussion

Single nucleotide polymorphisms (SNPs) are the most common genetic variations among individuals, accounting for almost 90% of all variations (21). Although it is a variation of a single nucleotide between individuals, SNPs and SNP interactions can increase the risk of developing various diseases (22). Therefore plenty of research has been carried out to find SNPs that are associated with the risk of developing disease; however, results are almost inconsistent (6, 23). Meta-analysis appeared to be a powerful tool to reduce the heterogeneity among studies and reveal the true association of gene polymorphism with the risk of developing disease (24).

Herein, due to inconsistency among published results on the association of IL-10 polymorphism (819T > C) and the risk of AML, we performed this meta-analysis to find the true association. Results of the present study indicated that IL-10 polymorphism (819T > C) might not be associated with the risk of AML: dominant model (OR=0.87, 95% CI=0.42–1.81); recessive model (OR = 1.17, 95% CI = 0.43–3.16); allelic model(OR = 1.00, 95% CI = 0.54–1.88); CC vs. TT (OR = 1.00,95% CI = 0.30–3.36); and TC vs. TT (OR = 0.80, 95%CI = 0.46–1.37).

In contrast to our results, IL-10 -819 T > C may affect the IL-10 mRNA expression and the risk of developing AML in individuals with -819TT genotype is 2.492 times higher than the -819 CC genotype (OR=2.492; 95% CI: 1.013–5.825)(11). Furthermore, lower incidence of AML was reported in individuals with C allele (OR= 0.476, 95% CI: 0.271–0.835). However, the risk of developing AML was increased in individuals with -819CC genotype (OR = 1.72; 95% CI: 1.01–2.97) and C allele (OR = 1.38; 95% CI: 1.04–1.81), and higher frequency of -819 CC genotype and C allele was reported among AML patients (7). Plasma level of this cytokine is reported to be significantly elevated in AML patients and suggested a protective role for IL-10, by inhibiting the AML cell growth through down-regulation of pro-leukemic cytokines (TNF-α, GM-CSF, L-1α, IL-1β and IL-6) and consequently increased survival rates (25). IL-10 -819T >C polymorphism is lo-

cated in promoter region of IL-10 gene and significantly affect its transcription and expression (26).

Overall our results indicated lack of association between IL-10 -819T > C polymorphism and the risk of developing AML, however, the result of this meta-analysis do not allow us to rule out the potential role of IL-10 -819T > C polymorphism in development of AML, as other parameters such as sex, gene-gene interactions and environmental factors should be considered.

The present meta-analysis faced two main limitations: firstly, the number of eligible studies was limited; secondly, lack of enough information in included studies made in impossible to investigate the effects of other parameters such as sex, gene-gene interaction and environmental factors.

Conclusion

IL-10 -819T > C polymorphism might not be associated with the risk of developing AML, while studies are reporting the association of IL-10 -819T > C polymorphism with AML, therefore further studies with considering other parameters such as gene-gene interactions, sex and environmental condition are needed to reveal the true association of IL-10 -819T>C polymorphism with AML.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of interest

The authors declare that there is no conflict of interest.

References

1. Coombs CC, Tallman MS, Levine RL (2016). Molecular therapy for acute myeloid leukaemia. *Nat Rev Clin Oncol,* 13:305-18
2. De Kouchkovsky I, Abdul-Hay M (2016). Acute myeloid leukemia: a comprehensive review and 2016 update. *Blood Cancer J,* 6:e441.
3. Ilhan G, Karakus S, Andic N (2006). Risk factors and primary prevention of acute leukemia. *Asian Pac J Cancer Prev,* 7:515-7
4. Zhuo W, Zhang L, Wang Y, et al (2012). CYP1A1 MspI polymorphism and acute myeloid leukemia risk: meta-analyses based on 5018 subjects. *J Exp Clin Cancer Res,* 31:62.
5. Qin Y-T, Zhang Y, Wu F, et al (2014). Association between MTHFR polymorphisms and acute myeloid leukemia risk: a meta-analysis. *PLoS One,* 9:e88823.
6. Guo C, Wen L, Song J-K, et al (2018). Significant association between interleukin-10 gene polymorphisms and cervical cancer risk: a meta-analysis. *Oncotarget,* 9:12365-75.
7. Rashed R, Shafik RE, Shafik NF, Shafik HE (2018). Associations of interleukin-10 gene polymorphisms with acute myeloid leukemia in human (Egypt). *J CancerRes Ther,* 14:1083-86.
8. Liu P, Song J, Su H, et al (2013). IL-10 gene polymorphisms and susceptibility to systemic lupus erythematosus: a meta-analysis. *PLoS One,* 8:e69547.
9. Howell WM, Rose-Zerilli MJ (2007). Cytokine gene polymorphisms, cancer susceptibility, and prognosis. *J Nutr,* 137(1 Suppl):194S-199S.
10. Fei C, Yao X, Sun Y, et al (2015). Interleukin-10 polymorphisms associated with susceptibility to acute myeloid leukemia. *Genet Mol Res,* 14:925-30.
11. Chenjiao Y, Zili F, Haibin C, et al (2013). IL-10 promoter polymorphisms affect IL-10 production and associate with susceptibility to acute myeloid leukemia. *Pharmazie,* 68:201-206.
12. Nursal AF, Pehlivan M, Sahin HH, Pehlivan S (2016). The Associations of IL-6, IFN-c, TNF-a, IL-10, and TGF-b1 Functional Variants with Acute Myeloid Leukemia in

Turkish Patients. *Genet Test Mol Biomarkers,* 20(9):544-51.
13. Stroup DF, Berlin JA, Morton SC, et al (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA,* 283:2008-2012.
14. Abyadeh M, Heydarinejad F, Khakpash M, et al (2020). Association of Apolipoprotein E gene polymorphism with Preeclampsia: a meta-analysis. *Hypertens Pregnancy*, 39(2):196-202
15. Peterson J, Welch V, Losos M, Tugwell P (2011). The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Ottawa: Ottawa Hospital Research Institute*.1-2.
16. Wigginton JE, Cutler DJ, Abecasis GR (2005). A note on exact tests of Hardy-Weinberg equilibrium. *Am J Hum Genet,* 76:887-893.
17. Raoufi A, Kelarijani Br, Ahadi Hr, et al (2021). Association of MTHFR C677T and A1298C Polymorphisms with Susceptibility to Chronic Lymphocytic Leukemia: A Systematic Review and Meta-Analysis. *Iran J Public Health,* 50:83-92.
18. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J (2006). Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? *Psychol Methods,* 11:193-206.
19. Asefi Y, Gohari Mahmoudabad A, Habibian Sezavar A, Mirshahvaladi S, Abyadeh M, Abyareh M (2020). Association between maternal cadmium exposure and preterm birth: a meta-analysis. *Int J Environ Health Res,* 1-10.
20. Egger M, Smith GD, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ,* 315:629-634.
21. Collins FS, Brooks LD, Chakravarti A (1998). A DNA polymorphism discovery resource for research on human genetic variation. *Genome Res,* 8:1229-1231.
22. Schwender H, Ruczinski I, Ickstadt K (2011). Testing SNPs and sets of SNPs for importance in association studies. *Biostatistics,* 12:18-32.
23. Razi B, Anani Sarab G, Omidkhoda A, Alizadeh S (2018). Multidrug resistance 1 (MDR1/ABCB1) gene polymorphism (rs1045642 C> T) and susceptibility to multiple myeloma: a systematic review and meta-analysis. *Hematology,* 23:456-462.
24. Abyadeh M, Djafarian K, Heydarinejad F, Alizadeh S, Shab-Bidar S (2019). Association between Apolipoprotein E Gene Polymorphism and Alzheimer's Disease in an Iranian Population: A Meta-Analysis. *J Mol Neurosci*, 69(4):557-562.
25. Binder S, Luciano M, Horejs-Hoeck J (2018). The cytokine network in acute myeloid leukemia (AML): A focus on pro-and anti-inflammatory mediators. *Cytokine Growth Factor Rev,* 43:8-15.
26. Ouma C, Davenport GC, Were T, et al (2008). Haplotypes of IL-10 promoter variants are associated with susceptibility to severe malarial anemia and functional changes in IL-10 production. *Hum Genet,* 124:515-524.