Meta-Analysis of Observational Studies in Epidemiology

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The single nucleotide polymorphisms of interleukin-10 are associated with the risk of leukaemia

Evidence from 18 case-control studies

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Abstract

Interleukin-10(IL-10) is an immunosuppressive cytokine and plays an important role in inflammation and cancers. Numerous studies have explored the association between single nucleotide polymorphisms of IL-10 and leukemia, but their results were conflicting, so we performed this meta-analysis to elucidate the association between 3 common single nucleotide polymorphisms of IL-10 (rs1800896, rs1800871 and rs1800872) and risk of leukemia.

We conducted a comprehensive research in Pubmed, Chinese Biomedical Literature Database disc and Embase using related terms. After strict selection, 18 studies with 2264 cases and 3846 controls were included into this meta-analysis. Odds ratio and 95% confidence interval were used to evaluate the strength of the association.

We found that polymorphism of IL-10-1082A/G was associated with decreased risk of leukemia both in overall analysis and in stratified analysis according to ethnicity and cancer type. A strong relationship was also uncovered between polymorphism of IL-10-592C/A and increased risk of leukemia in non-Chinese.

GG genotype of IL-10-1082A/G is associated with decreased risk of leukemia, especially chronic lymphocytic leukemia. CC genotype of -592C/A is associated with decreased risk of leukemia in non-Chinese.

Abbreviations: CI = confidence interval, CLL = chronic lymphocytic leukemia, IL-10 = interleukin-10, OR = odds ratio, SNPs = single nucleotide polymorphisms.

Keywords: interleukin-10, leukemia, meta-analysis, polymorphism

1. Introduction

Leukemia is 1 of the commonest cancers across the world, with a top ten incidence and mortality in both sex and all ages.[1] The incidence and mortality increased to the fifth place among children, adolescents and young adults.[2] However, the mechanisms underlying leukemia are complex and not fully known.

More and more researches revealed the indispensable participation of immunity during the process of cancers. Immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor-β play important roles in the immunity of tumor.[3,4] IL-10 belongs to Th2 pathway. It can counterbalance the immune system by regulating both adaptive and innate immune system to protect host from exacerbated inflammation.[3,5] Altered expression of IL-10 may lose the control of immune homeostasis, thereby increasing the risk of cancers.[6]

Recent genetic studies disclosed the important role of single nucleotide polymorphisms (SNPs) in many kinds of cancers.[7] SNPs in gene regulating and coding areas can alter the expression level or function of these gene or the products they encode. So SNPs are increasingly found to be critical in the mechanisms of cancers.[8,9]

SNPs in the transcriptional start area of IL-10 gene influence the production of IL-10 thus may increase or decrease the risk of cancers,[10–12] including leukemia, but the conclusions are inconsistent. For example, Ovsepyan, V. A. et al[13] found SNP in the IL-10-1082A/G was associated with the risk of chronic lymphoid leukemia, while Lo, W. J. et al[14] found no association between IL-10-1082A/G and leukemia. Conflicting results may be due to small sample size. So we performed this pooled analysis to elucidate the relations between leukemia and 3 common SNPs of IL-10(-1082A/G, -819C/T, -592C/A).

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Ethics approval and consent to participate was not applicable.

Consent for publication was not applicable.

All data and material are provided in this article.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Material and method

2.1. Patient involvement and ethical approval

There was no patient involvement in this study. Ethical approval is not necessary for a meta-analysis.

2.2. Literature search and identification

We conducted a comprehensive search in Pubmed, Chinese Biomedical Literature Database disc, EMBASE with following related terms: ("IL-10" OR "IL10" OR "interleukin10" OR "rs1800896" OR "rs1800871 " OR "rs1800872 ") AND ("polymorphism*" OR "variant*" OR "gene*" OR "variation*" OR "SNP*") AND ("leukemia" OR "leukaemia"). All publications were updated to April 22, 2019. We included studies with inclusion criteria as follows:

(1) written in English or Chinese;
(2) human case-control studies about the association between leukemia and any 1 of the 3 SNPs mentioned above;
(3) available genotype data for estimation of an odds ratio (OR) and 95% confidence interval (CI).

The exclusion criteria were:

(1) reviews, letters, editorial articles or case reports;
(2) without controls or genotype data. The latest study was adopted when overlapping with previous studies.

2.3. Data extract

Title and abstract of all articles were screened by 2 reviewers independently and eligible studies were identified according to the inclusion and exclusion criteria. Two investigators extracted data independently from selected studies. From each study, the following information was obtained: the first author's name, publication year, country where study was conducted, source of control, genotyping method, cancer type, and genotypes of cases and controls.

2.4. Statistics analysis

For each study, Pearson $\chi 2$ and P value were calculated to test whether the genotype frequencies in controls were consistent with Hardy-Weinberg equilibrium. We estimated odds ratio and 95% CI to assess the linkage between risk of leukemia and 3 SNPs under 4 comparisons (homozygote comparison, heterozygote comparison, dominant and recessive genetic model comparison). For IL-10 -1082A/G (rs1800896), they were GG vs AA, GA vs AA, GG+GA vs AA, GG vs GA+AA respectively. For IL-10 -819C/T (rs1800871), they were TT vs CC, TC vs CC, TT+TC vs CC, TT vs TC+CC. For IL-10 -592C/A (rs1800872), they were AA vs CC, AC vs CC, AA+AC vs CC, AA vs AC+CC. Subgroup analysis was conducted by ethnicity (Chinese or non-Chinese), phase (acute or chronic) and cancer type (acute myelocytic leukemia, acute lymphoblastic leukemia, chronic myelocytic leukemia and chronic lymphocytic leukemia [CLL]). Heterogeneity among studies was calculated using Q-statistics and I^2 statistics. We thought there was no significant heterogeneity when $P > 0.1$ or $I^2 < 50\%$, then fixed-effects models were adopted, otherwise random-effects models were adopted.[15] We also performed stratified analysis to figure out the cause of heterogeneity and to reduce it. Z-test was conducted to exam the significance of ORs and 2-sided $P < .05$ was considered significant. Sensitivity analysis was conducted by recalculating overall ORs after omitting each individual study in turn. We also used Begg funnel plot and Egger linear regression test to detect publication bias.[16] All analysis was performed using Review Manager 5.0.23 (Cochrane Library Software, Oxford) and STATA14.0 software (STATA Corporation, College Station, Texas).

3. Results

3.1. Characteristics of studies

After searching on Pubmed, Chinese Biomedical Literature Database disc, and Embase using retrieval strategy mentioned above, 425 articles were recruited. 387 studies were excluded (107 duplicates, 280 studies unrelated), with 38 articles being left for full-text review. Next, 20 articles were removed for the following reasons: 5 articles were not case-control studies; 6 articles lack available data; 6 articles were not about the association between leukemia and SNPs of IL-10; 1 study studied other SNPs of IL-10; 1 article overlapped with another study; 1 article was written in Turkish. Finally, there were 18 studies with 2264 cases and 3846 controls included into this meta-analysis. The process of selecting included studies is shown in Figure 1.

The details of eligible studies are presented in Table 1. Most studies were performed in non-Chinese ethnicity,[13,17–29] with 4 studies in Chinese population.[14,30–32] We found that controls in 6 studies were not consistent with Hardy-Weinberg equilibrium[14,17,18,24,29,30] maybe because of genotyping error or selection bias during controls' recruitment.

3.2. Quantitative synthesis

The association between 3 SNPs of IL-10 and leukemia by overall analysis and subgroup analysis is shown in Table 2 and Table 3. The overall analysis indicated that rs1800896 polymorphism was associated with risk of leukemia under recessive genetic model comparison (GG vs GA+AA: OR, 0.83; 95% CI, 0.83 [0.71,0.98], $P = .03$, Fig. 2).

Stratified analysis by ethnicity indicated that polymorphism of IL10 -1082 A/G(rs1800896) was associated with leukemia in non-Chinese under homozygote comparison and recessive genetic model comparison (GG vs AA: OR, 0.80; 95% CI, 0.80[0.66,0.97], $P = .03$; GG vs GA+AA: OR, 0.80; 95% CI, 0.80 [0.67,0.95], $P = .01$). Besides, subgroup analysis of IL10 -1082 A/G by phase of leukemia indicated that GG genotype was associated with decreased risk of chronic leukemia (GG vs AA: OR, 0.74; 95% CI, 0.74[0.57,0.95], $P = .02$; GG vs GA+AA: OR, 0.78; 95% CI, 0.78[0.62,0.98], $P = .03$.), especially CLL, for stratified analysis by cancer type showed a strong link between this polymorphism and risk of CLL under homozygote comparison and recessive genetic model comparison (GG vs AA: OR, 0.74; 95% CI, 0.74[0.55,0.98], $P = .04$; GG vs GA+AA: OR, 0.77; 95% CI, 0.77[0.60,0.99], $P = .04$ Fig. 3).

We found no association between IL-10 -819 C/T (rs1800871) and leukemia in overall analysis and subgroup analysis.

We found no association between IL-10 -592C/A (rs1800872) and leukemia in overall analysis. But we found a strong association between rs1800872 and leukemia in non-Chinese under heterozygote comparison and dominant genetic model comparison. (AC vs CC: OR, 1.24; 95% CI, 1.24[1.02,1.50], $P = .03$, Fig. 4. AA+AC vs CC: OR,1.22; 95%CI,1.22[1.01,1.46], $P = .04$).

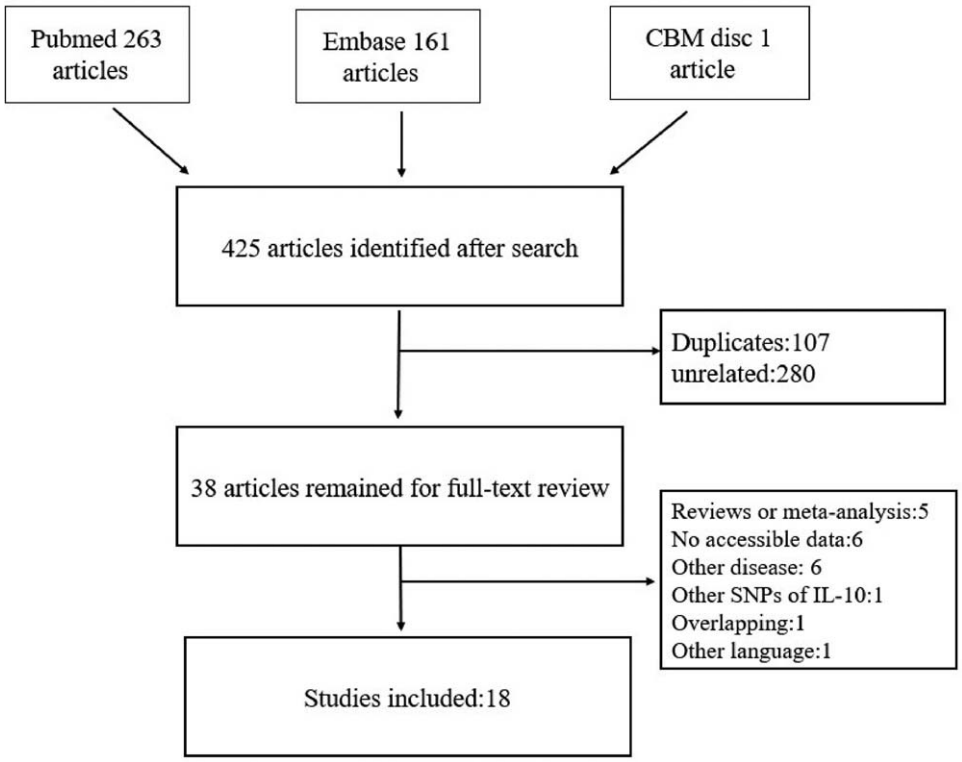

Figure 1. Process of selecting included studies in this meta-analysis.

3.3. Test of heterogeneity

For the overall test of heterogeneity, most comparisons had low or moderate heterogeneity. The heterogeneity of rs1800896 was low or moderate(GG vs AA: $P=.21$, $I^2=22\%$; GA vs AA:$P=.02$, $I^2=48\%$; GG+GA vs AA:$P=.006$, $I^2=54\%$; GG vs GA+AA: $P=.48$, $I^2=0\%$.), while the heterogeneity of rs1800871(TT vs CC: $P<.0001$, $I^2=73\%$; TC vs CC: $P=.0004$, $I^2=66\%$; TT+TC vs CC:$P<.0001$, $I^2=69\%$; TT vs TC+CC: $P<.00001$, $I^2=79\%$.) and rs1800872(AA vs CC: $P<.00001$, $I^2=81\%$; AC vs CC:$P=.003$, $I^2=61\%$; AA+AC vs CC:$P=.0001$, $I^2=70\%$; AA vs AC+CC: $P<.00001$, $I^2=88\%$.) was moderate or high. In the subgroup analysis according to ethnicity, the heterogeneity of rs1800872 was moderate or high in Chinese (AA vs CC: $P<.00001$, $I^2=93\%$; AC vs CC:$P=.04$, $I^2=64\%$; AA+AC vs CC:$P=.0002$, $I^2=84\%$; AA vs AC+CC: $P<.00001$, $I^2=96\%$.) while low or moderate in non-Chinese(AA vs CC: $P=.15$, $I^2=35\%$; AC vs CC:$P=.58$, $I^2=0\%$; AA+AC vs CC:$P=.45$, $I^2=0\%$; AA vs AC+CC: $P=.17$, $I^2=33\%$.).

Table 1

Characteristics of published studies included in this meta-analysis.

					-1082							-819							-592						
			Geno-typing	Cancer	Case			Control				Case			Control				Case			Control			
Author +year	Country	SOC	method	type	GG	GA	AA	GG	GA	AA	HWE	TT	TC	CC	TT	TC	CC	HWE	AA	AC	CC	AA	AC	CC	HWE
Amirzargar, A. A.2005	Iran	PB	PCR	CML	0	13	17	0	34	6	NO	5	14	11	0	19	21	NO	5	14	11	0	19	21	NO
Basturk, B.2005	Turkey	PB	PCR	CML	3	13	14	6	16	38	NO	1	16	13	9	22	29	YES	1	16	13	9	22	29	YES
Bonaventure, A.2018	France	PB	PCR	ALL	88	215	131	98	211	133	YES	20	153	229	28	153	261	YES	24	170	229	28	153	261	YES
Ennas, M. G.2008	Italy	PB	Taqman	CLL	4	20	15	7	43	61	YES														
Fei, C.2015	China	HB	PCR	AML	22	70	75	35	134	159	YES	57	72	38	137	137	54	YES	54	74	39	126	142	59	YES
Guzowski, D.2005	USA	PB	PCR	CLL	4	9	4	4	12	9	YES	2	6	9	1	10	14	YES	3	5	9	2	11	12	YES
Hiroki, C. H.2015	Brazil	PB	PCR	ALL	13	31	23	10	32	33	YES														
Lech-Maranda, E.2013	Poland	PB	Taqman	CLL	58	152	82	50	94	48	YES														
Lo, W. J.2016	China	HB	PCR	ALL	11	50	205	12	52	202	NO	170	85	11	142	96	28	YES	117	101	48	170	85	11	YES
Nieters, A.2006	Germany	PB	PCR	CLL	23	44	33	150	302	208	NO														
Nursal, A. F.2016	Turkey	PB	PCR	AML	3	17	22	17	36	32	YES	6	21	15	4	32	49	YES	6	21	15	4	32	49	YES
Ovsepyan, V. A.2015	Russia	PB	PCR	CLL	40	106	85	81	142	91	YES														
Ozdilli, K.2014	Turkey	PB	PCR	CML	11	33	41	47	131	122	YES	5	40	40	21	126	153	YES	5	40	40	21	126	153	YES
Pehlivan, M.2014	Turkey	PB	PCR	CML	7	22	31	10	36	28	YES	3	32	25	4	33	37	YES	3	32	25	4	33	37	YES
Rashed,R.2018	Egypt	PB	PCR	AML								26	23	31	40	36	9	YES							
Wang,Ci2011	China	HB	PCR	ALL								52	46	17	53	238	32	NO	50	46	19	38	235	50	NO
Winkler, B.2015	Germany	PB	PCR	ALL	21	51	22	99	138	92	NO	7	28	59	26	109	194	YES	7	28	59	26	109	194	YES
Yao,C.J.2013	China	HB	PCR	AML								68	38	9	56	63	18	YES	68	38	9	56	63	18	YES

ALL = acute lymphoblastic leukemia, AML = acute myelocytic leukemia, CLL = chronic lymphocytic leukemia, CML = chronic myelocytic leukemia, HB = hospital-based controls, HWE = hardy-weinberg equilibrium, PB = population-based controls, PCR = polymerase chain reaction, SOC = source of controls.

Table 2

Overall analysis of association between 3 SNPs of IL-10 and risk of leukaemia.

				Statistics		Heterogeneity		Publication bias	
Loci	No.a	Case/control	Genetic model	OR (95%CI)	*P*	*P*heterogeneity	I^2(%)	*P*begg	*P*Egger
-1082	15	1954/3301	GG VS AA	0.84[0.70,1.01]	.06	.21	22%	.274	.757
(rs1800896)			GA VS AA	0.97[0.85,1.11]	.63	.02	48%	.921	.813
			GG+GA VS AA	0.93[0.76,1.14]	.48	.006	54%	.921	.868
			GG VS GA+AA	0.83[0.71,0.98]	.03	.48	0%	.381	.796
-819									
(rs1800871)	13	1535/2494	TT VS CC	1.19[0.70,2.02]	.52	<.0001	73%	.502	.259
			TC VS CC	1.00[0.73,1.37]	.99	.0004	66%	.951	.466
			TT+TC VS CC	1.08[0.79,1.48]	.62	<.0001	69%	.502	.863
			TT VS TC+CC	1.28[0.81,2.01]	.29	<.00001	79%	.669	.906
-592									
(rs1800872)	12	1455/2409	AA VS CC	1.16[0.61,2.20]	.64	<.00001	81%	.537	.511
			AC VS CC	0.97[0.72,1.31]	.85	.003	61%	.945	.127
			AA+AC VS CC	1.03[0.75,1.41]	.87	.0001	70%	.537	.295
			AA VS AC+CC	1.29[0.71,2.37]	.41	<.00001	88%	.373	.106

No.a = number of articles.

Table 3

Stratified analysis of association between 3 SNPs of IL-10 and risk of leukemia.

Loci	Comparison	Category	Category	studies	OR(95%CI)	*P*-value	*P* for heterogeneity
-1082	GG VS AA	ethnicity	Chinese	2	1.17[0.72,1.90]	.54	.46
(rs1800896)			non-Chinese	13	0.80[0.66,0.97]	.03	.22
		acute/chronic	acute	6	0.96[0.75,1.24]	.76	.24
			chronic	9	0.74[0.57,0.95]	.02	.36
		cancer type	AML	2	0.95[0.56,1.61]	.84	.03
			ALL	4	0.97[0.72,1.29]	.81	.59
			CML	4	0.74[0.42,1.31]	.31	.7
			CLL	5	0.74[0.55,0.98]	.04	.14
	GA VS AA	ethnicity	Chinese	2	1.03[0.77,1.38]	.84	.6
			non-Chinese	13	0.95[0.74,1.22]	.7	.009
		acute/chronic	acute	6	1.08[0.89,1.30]	.44	.59
			chronic	9	0.87[0.61,1.23]	.44	.007
		cancer type	AML	2	099[0.67,1.47]	.96	.29
			ALL	4	1.10[0.89,1.37]	.38	.49
			CML	4	0.62[0.26,1.47]	.28	.003
			CLL	5	0.97[0.75,1.24]	.79	.35
	GG+GA VS AA	ethnicity	Chinese	2	1.05[0.80,1.38]	.73	.46
			non-Chinese	13	0.90[0.71,1.16]	.43	.004
		acute/chronic	acute	6	1.04[0.87,1.24]	.68	.4
			chronic	9	0.85[0.60,1.19]	.34	.004
		cancer type	AML	2	0.86[0.42,1.75]	.67	.08
			ALL	4	1.05[0.86,1.29]	.61	.58
			CML	4	0.62[0.28,1.38]	.24	.003
			CLL	5	0.95[0.69,1.31]	.76	.13
	GG VS GA+AA	ethnicity	Chinese	2	1.14[0.71,1.83]	.58	.52
			non-Chinese	13	0.80[0.67,0.95]	.01	.51
		acute/chronic	acute	6	0.89[0.71,1.11]	.3	.24
			chronic	9	0.78[0.62,0.98]	.03	.48
		cancer type	AML	2	0.95[0.57,1.57]	.83	.05
			ALL	4	0.87[0.68,1.12]	.3	.46
			CML	4	0.84[0.49,1.44]	.52	.96
			CLL	5	0.77[0.60,0.99]	.04	.29
-819	TT VS CC	ethnicity	Chinese	4	1.63[0.71,3.72]	.25	.0007
(rs1800871)			non-Chinese	9	0.97[0.48,1.99]	.94	.003
		acute/chronic	acute	8	1.17[0.62,2.21]	.62	<.0001
			chronic	5	1.24[0.44,3.53]	.69	.17
		cancer type	AML	4	0.99[0.30,3.31]	.99	<.0001
			ALL	4	1.42[0.76,2.66]	.27	.03
			CML	4	1.10[0.33,3.71]	.87	.13

(*continued*)

Table 3

(continued).

Loci	Comparison	Category	Category	studies	OR(95%CI)	*P*-value	*P* for heterogeneity
			CLL	1	3.11[0.24,39.54]	.38	
	TC VS CC	ethnicity	Chinese	4	0.90[0.43,1.87]	.78	.004
			non-Chinese	9	1.07[0.75,1.52]	.72	.009
		acute/chronic	acute	8	0.87[0.55,1.36]	.54	<.001
			chronic	5	1.31[0.94,1.84]	.12	.96
		cancer type	AML	4	0.78[0.32,1.91]	.59	.0008
			ALL	4	0.94[0.53,1.66]	.83	.002
			CML	4	1.34[0.95,1.90]	.1	.95
			CLL	1	0.93[0.25,3.47]	.92	
	TT+TC VS CC	ethnicity	Chinese	4	1.15[0.57,2.32]	.7	.003
			non-Chinese	9	1.06[0.73,1.54]	.74	.002
		acute/chronic	acute	8	0.98[0.62,1.53]	.92	<.00001
			chronic	5	1.29[0.93,1.79]	.12	.93
		cancer type	AML	4	0.86[0.32,2.33]	.76	<.0001
			ALL	4	1.08[0.69,1.70]	.73	.02
			CML	4	1.31[0.93,1.83]	.12	.84
			CLL	1	1.13[0.33,3.90]	.85	
	TT VS TC+CC	ethnicity	Chinese	4	1.75[0.87,3.54]	.12	<.00001
			non-Chinese	9	0.93[0.57,1.51]	.77	.1
		acute/chronic	acute	8	1.34[0.80,2.23]	.27	<.00001
			chronic	5	1.10[0.38,3.23]	.86	.14
		cancer type	AML	4	1.15[0.55,2.42]	.7	.0005
			ALL	4	1.53[0.73,3.17]	.26	<.0001
			CML	4	0.95[0.28,3.20]	.93	.11
			CLL	1	3.20[0.27,38.43]	.36	
-592 (rs1800872)	AA VS CC	ethnicity	Chinese	4	0.95[0.26,3.55]	.94	<.00001
			non-Chinese	8	1.23[0.71,2.14]	.47	.15
		acute/chronic	acute	7	1.13[0.50,2.55]	.76	<.00001
			chronic	5	1.19[0.45,3.14]	.73	.19
		cancer type	AML	3	1.76[0.52,5.94]	.36	.003
			ALL	4	0.83[0.24,2.93]	.77	<.00001
			CML	4	1.10[0.33,3.71]	.87	.13
			CLL	1	2.00[0.27,14.59]	.49	
	AC VS CC	ethnicity	Chinese	4	0.59[0.34,1.03]	.07	.04
			non-Chinese	8	1.24[1.02,1.50]	.03	.58
		acute/chronic	acute	7	0.84[0.55,1.29]	.43	.0004
			chronic	5	1.28[0.91,1.79]	.15	.81
		cancer type	AML	3	1.19[0.64,2.20]	.58	.11
			ALL	4	0.66[0.35,1.25]	.2	.0002
			CML	4	1.34[0.95,1.90]	.1	.95
			CLL	1	0.61[0.15,2.37]	.47	
	AA+AC VS CC	ethnicity	Chinese	4	0.68[0.31,1.50]	.34	.0002
			non-Chinese	8	1.22[1.01,1.46]	.04	.45
		acute/chronic	acute	7	0.91[0.57,1.46]	.7	<.00001
			chronic	5	1.26[0.91,1.75]	.16	.85
		cancer type	AML	3	1.39[0.61,3.16]	.43	.01
			ALL	4	0.69[0.35,1.35]	.28	<.0001
			CML	4	1.31[0.93,1.83]	.12	.84
			CLL	1	0.82[0.24,2.82]	.75	
	AA VS AC+CC	ethnicity	Chinese	4	1.41[0.47,4.18]	.54	<.00001
			non-Chinese	8	1.12[0.66,1.88]	.68	.17
		acute/chronic	acute	7	1.36[0.65,2.86]	.41	<.00001
			chronic	5	1.11[0.40,3.08]	.84	.14
		cancer type	AML	3	1.55[0.64,3.73]	.33	.002
			ALL	4	1.21[0.35,4.23]	.77	<.00001
			CML	4	0.95[0.28,3.20]	.93	.11
			CLL	1	2.46[0.37,16.62]	.35	

CML = chronic myelocytic leukemia

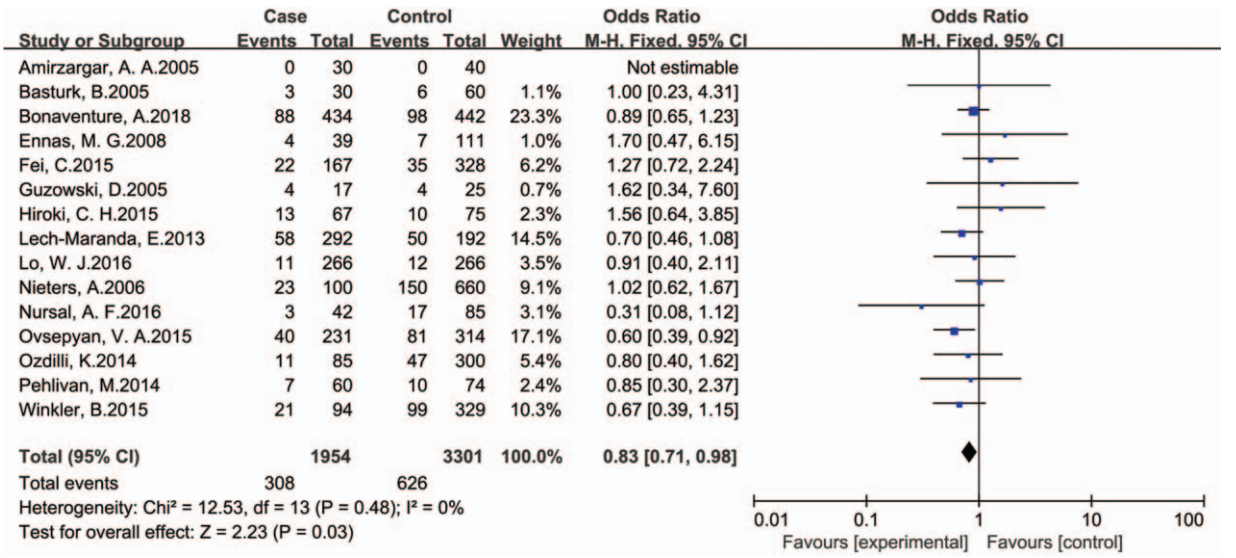

Figure 2. Overall analysis for the association between IL-10 rs1800896 polymorphism and leukemia risk (GG vs GA+AA).

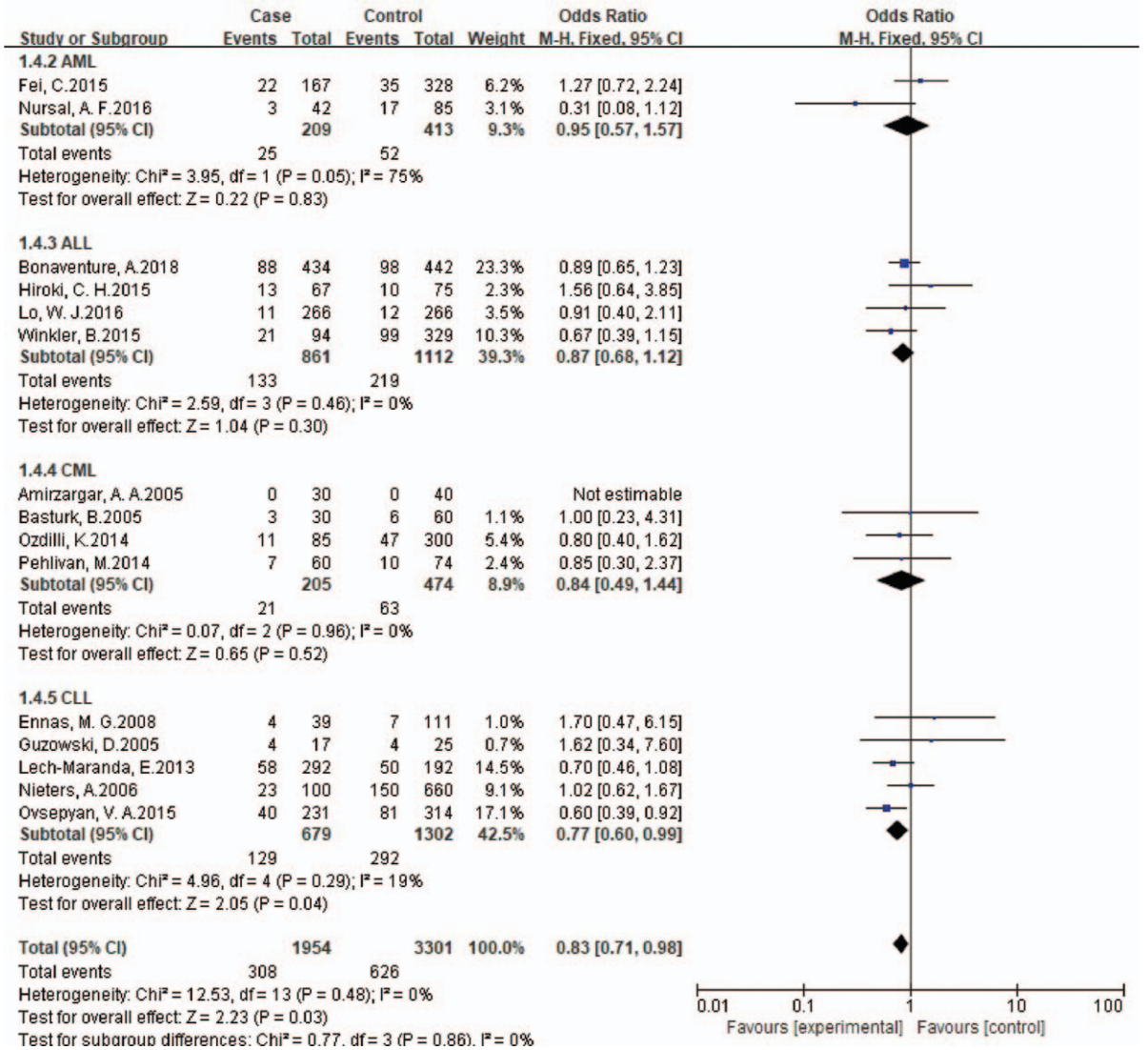

Figure 3. Subgroup analyses for the association between IL-10 rs1800896 polymorphism and leukemia risk according to cancer type (GG vs GA+AA).

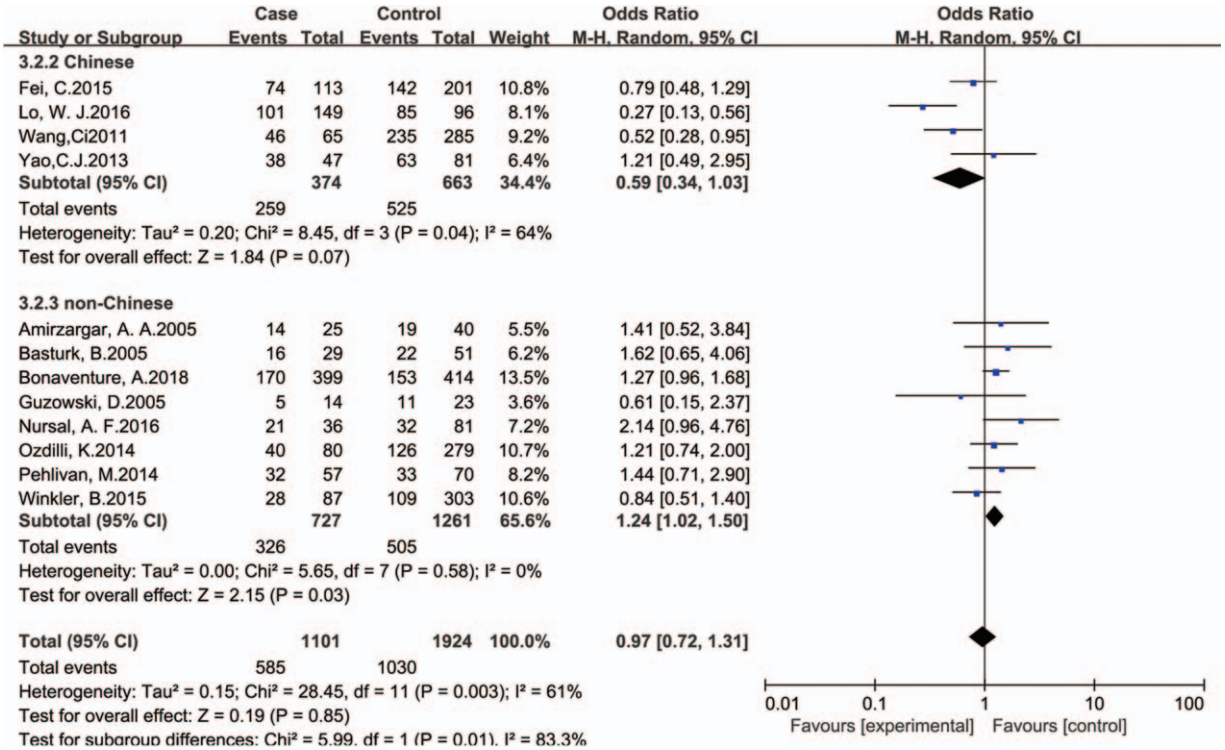

Figure 4. Subgroup analyses for the association between IL-10 rs1800872 polymorphism and leukemia risk according to ethnicity (AC vs CC).

3.4. Sensitivity analysis

Sensitivity analysis was conducted by omitting each study in turn. There was no big change when omitting each article, indicating the result was stable and trustworthy. Figure 5 shows the sensitivity analysis for the association between polymorphism of rs1800896 and risk of leukemia under recessive genetic model comparison (GG vs GA+AA).

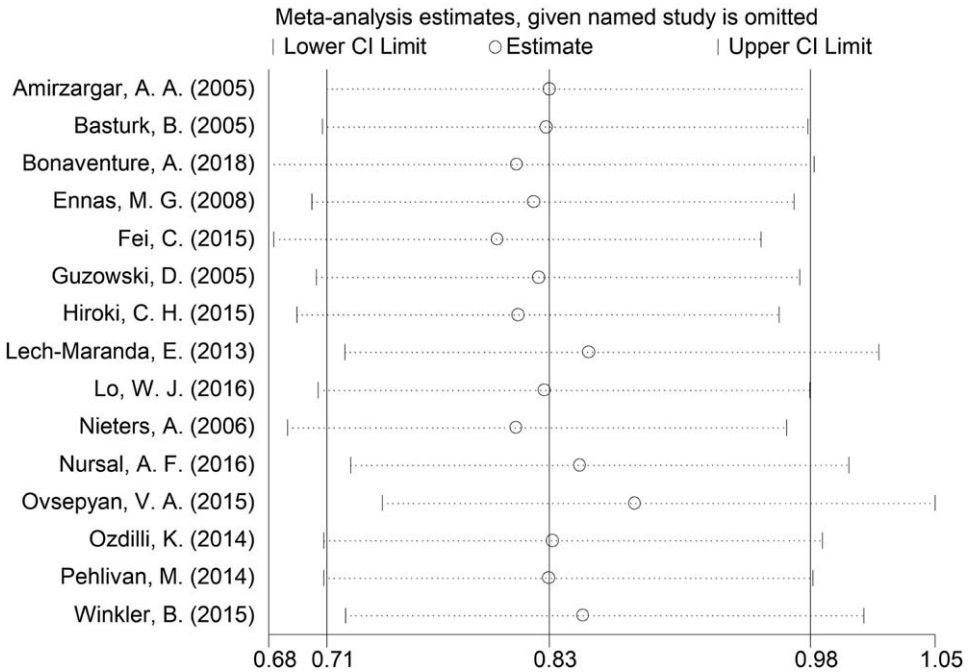

Figure 5. Sensitivity analysis for the association between polymorphism of rs1800896 and risk of leukemia under recessive genetic model comparison (GG vs GA +AA).

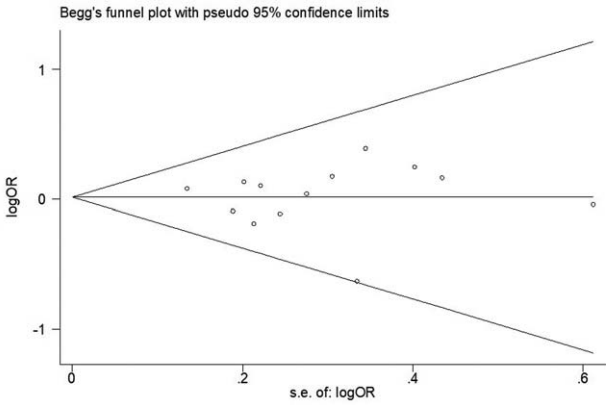

Figure 6. Begg funnel plot for publication bias of overall analysis for the association between polymorphism of rs1800871 and leukemia (TC vs CC; *P* for bias = .951).

3.5. Publication bias

Figure 6 shows the Begg funnel plot for the association between polymorphism of rs1800871 and leukemia under heterozygote comparison (TC vs CC). There was no evidence of publication bias both in Begg funnel plots and Egger test. The symmetry of the Begg funnel plot was good and *P* values for Begg tests and Egger tests were >0.05. Begg funnel plots for the association between polymorphism of rs1800871 and leukemia under homozygote comparison (TT vs CC) in non-Chinese are shown in Figure 7. These data indicated that there was no significant publication bias in this meta-analysis.

4. Discussion

More and more researches concentrate on immunity when exploring the etiology of cancers. IL-10 plays a suppressive role on many types of cells in general,[33] but it has pleiotropic functions on tumor. IL-10 can impose both stimulatory and inhibitory impact on T cells.[34] There are studies revealing that IL-10 can fight against tumor by activating $CD8^+$ T cells and cause the accumulation of tumor infiltrating lymphocytes (TILs),[33,35] while others indicate that IL-10 can promote the development and progression of tumors.[36–38] It has been reported that polymorphisms in the promoter region of IL-10 may influence the production of IL-10.[39] There are many studies and systematic analyses reporting the association between SNPs of IL-10 and other cancers, including gastric cancer40,[40] cervical cancer,[41] breast cancer,[42] and prostate cancer.[43]

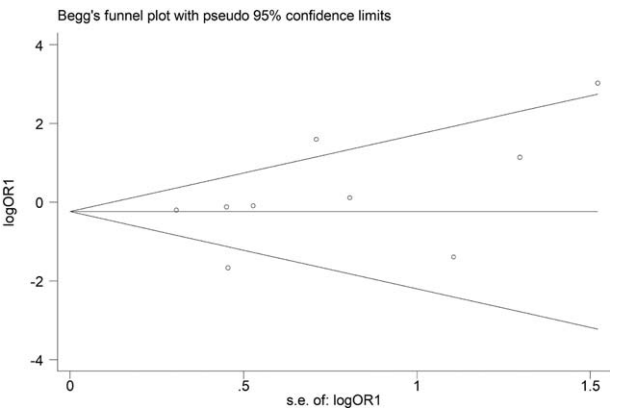

Figure 7. Begg funnel plot for publication bias of stratified analysis for the association between polymorphism of rs1800871 and leukemia in non-Chinese (TT vs CC; *P* for bias = .076).

Recently, numerous studies focus on the association of SNPs in the promoter of IL-10 (such as rs1800896, rs1800871 and rs1800872) and risk of leukemia, but their results are conflicting. There is 1 pooled analysis involving 4 studies found that there was no association between SNP of IL-10 and CLL,[44] but it only surveyed 1 SNP of IL-10, rs1800896. Besides, it only focused on CLL, ignoring the other 3 kinds of leukemia. In addition, it only took 4 studies into analysis. So we conducted this meta-analysis involving 18 articles with 2264 cases and 3846 controls to illuminate the link between 3 common SNPs of IL-10 and leukemia.

In the overall analysis, we found a strong association between polymorphism of rs1800896 and leukemia under recessive genetic model comparison (GG vs GA+AA) which means GG genotype of rs1800896 was associated with decreased risk of leukemia in overall population. However, rs1800871 and rs1800872 exerted no impact on the susceptibility to leukemia in overall analysis.

In the subgroup analysis according to ethnicity, a strong association was found between rs1800896 and leukemia in non-Chinese under homozygote comparison (GG vs AA) and recessive genetic model comparison (GG vs GA+AA) while the result was negative in Chinese under the same comparison. So in non-Chinese, individuals with GG genotype of rs1800896 may have lower risk of leukemia when compared with those carrying GA or AA genotype. When stratified by cancer types, we found GG genotype of rs1800896 was associated with decreased risk of chronic leukemia, especially CLL under homozygote comparison (GG vs AA) and recessive genetic model comparison (GG vs GA +AA). However, no association was found between rs1800871 and leukemia when stratified by ethnicity and cancer type. Stratified analysis by ethnicity has effectively minimized the heterogeneity. Heterogeneity was low or moderate in non-Chinese while moderate or high in Chinese, maybe because types of leukemia were different in these 4 Chinese studies (2 of them were acute myelocytic leukemia and the other 2 were acute lymphoblastic leukemia) or patients with different comorbidities were recruited or caused by other statistic or methodological reasons, so we adopted random-effects model. Under random-effects model, rs1800872 was associated with leukemia risk in non-Chinese under heterozygote comparison (AC vs CC) and dominant genetic model comparison (AA+AC vs CC), which means in non-Chinese, individuals with AA or AC genotype may have increased risk of leukemia. As for Chinese group, perhaps there was no significant association between rs1800872 and leukemia. No association was found when stratified by cancer type.

The fact that heterogeneities of some comparisons were high cannot be ignored. Although we have carried out a careful research when searching articles, selected eligible studies strictly following inclusion and exclusion criterion, paid attention to every process of this analysis, some comparisons still had high heterogeneity. Heterogeneity was effectively minimized after stratified analysis, but significant heterogeneity still existed in some comparisons, maybe because of different source of control (controls of some studies are hospital-based), different genotyp-

ing methods, sample error or other unidentified reasons. There was no evidence of publication bias both in Begg funnel plot and Egger test.

There are several limitations of this meta-analysis. Firstly, we did not perform a stratified analysis according to sex or age because of lacking relevant original data. Secondly, the number of studies about the association between rs1800871 or rs1800872 and CLL is too small, including only 1 original article. Thirdly, Chinese studies about the association between rs1800896 and leukemia are limited, including only 2 studies. More studies are needed. Lastly, we only took articles written in English or Chinese into analysis, which may produce unavoidable bias.

5. Conclusions

In conclusion, this meta-analysis indicated that GG genotype of rs1800896 was associated with decreased risk of leukemia when compared with GA + AA. Strong association was found between GG genotype of rs1800896 and decreased risk of leukemia in non-Chinese compared with AA or GA + AA. In addition, GG genotype of rs1800896 was associated with decreased risk of chronic leukemia, especially CLL compared with AA or GA + AA. Lastly, we found CC genotype of rs1800872 was associated with decreased risk of leukemia in non-Chinese compared with AA or AA + AC.

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Author contributions

SG searched literature, selected eligible studies, extracted and analysed data and drafted manuscript. KT and JC participated in article selection and data extraction. JW supervised literature search, data extraction, data analysis and drafted manuscript.

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