Individual and combined effects of the GSTM1, GSTT1, and GSTP1 polymorphisms on leukemia risk: An updated meta-analysis

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Background: Several meta-analyses have analyzed the association of GSTM1 present/null, GSTT1 present/null, and GSTP1 Ile105Val polymorphisms with leukemia risk. However, the results of these meta-analyses have been conflicting. Moreover, they did not evaluate the combined effects of the three aforementioned gene polymorphisms. Furthermore, they did not appraise the credibility of the positive results. Finally, many new studies have been published. Therefore, an updated meta-analysis was conducted.

Objectives: To further explore the relationship of the three aforementioned gene polymorphisms with leukemia risk.

Methods: The crude odds ratios (ORs) and 95% confidence intervals (CIs) were applied to evaluate the association of the individual and combined effects of the three aforementioned genes. Moreover, the false-positive report probability (FPRP) and Bayesian false discovery probability (BFDP) were applied to verify the credibility of these statistically significant associations.

Results: Overall, the individual GSTM1, GSTT1, and GSTP1 Ile105Val polymorphisms added leukemia risk. On combining GSTM1 and GSTT1, GSTM1 and GSTP1, and GSTT1 and GSTP1 polymorphisms, positive results were also observed. However, no significant association was observed between the combined effects of these three polymorphisms with leukemia risk in the overall analysis. Moreover, when only selecting Hardy–Weinberg

Abbreviations: GSTs, glutathione S-transferases; GSTM1, glutathione S-transferase M1; GSTT1, glutathione S-transferase T1; GSTP1, glutathione S-transferase P1; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphoblastic leukemia; HC, healthy controls; NBDC, Nonblood disease controls; BFDP, Bayesian false discovery probability; FPRP, false-positive report probability; HWE, Hardy–Weinberg equilibrium; ORs, odds ratios; CIs, confidence intervals.
equilibrium (HWE) and medium- and high-quality studies, we came to similar results. However, when the FPRP and BFDP values were applied to evaluate the credibility of positive results, the significant association was only observed for the GSTT1 null genotype with leukemia risk in Asians (BFDP = 0.367, FPRP = 0.009).

Conclusion: This study strongly suggests a significant increase in the risk of leukemia in Asians for the GSTT1 null genotype.

KEYWORDS
glutathione S-transferases, GSTM1, GSTT1, GSTP1, leukemia

Introduction

Leukemia is a cancer of hematology, characterized by abnormal hematopoietic function and malignant cloning of white blood cells. Leukemia includes acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphoblastic leukemia (CLL) (Ouerhani et al., 2011). Over the past few decades, we have made giant progress in the early diagnosis of diseases and treatment, yet the number of new cases of leukemia are still increasing, and the death cases also continue to increase. Therefore, leukemia has become one huge threat to human health (Ferlay et al., 2015). As we all know, leukemia is deemed to be a complex disease, which is determined by hereditary and environmental factors (Arruda et al., 2001; Krajinovic et al., 2001). Although previous studies showed that chemicals, ionizing radiation, and viral infections were the potential pathogenic factors of leukemia (Maia Rda and Wünsch Filho, 2013; Schüz and Erdmann, 2016), there were great individual differences in disease susceptibility when these patients were exposed to the aforementioned carcinogenic agents. Therefore, research studies on hereditary factors that affect leukemia may improve our further understanding of the pathogenesis of leukemia; in addition, they might provide new evidence for the treatment of leukemia.

Glutathione S-transferase (GST) is a kind of phase II enzyme which includes M1, P1, and T1; the main functions of the three aforementioned genes were the metabolism of xenobiotics, reactive oxygen species, and carcinogens for detoxification and metabolism (Strange et al., 2001). A partial gene deletion of GSTM1 and GSTT1 (null genotypes) can result in the complete absence of GSTM1 and GSTT1 enzyme activities; the former is located on chromosome 1 (1p13.3) and the latter is situated at chromosome 22 (22q11.2) (Pearson et al., 1993; Webb et al., 1996; Strange and Fryer, 1999). GSTP1 gene polymorphism is a single-nucleotide polymorphism, whose polymorphism lies in exon 5 codon 105, when substitution of A with G leads to change in isoleucine (Ile) to valine (Val), thereby giving rise to decreased enzymatic activity (Harries et al., 1997; Ryberg et al., 1997). Previous research studies have indicated that the complete deletion of GSTM1, GSTT1, or GSTP1 polymorphisms can bring about diminished gene expression and enzymatic activity (Strange et al., 1998; Strange et al., 2001; Hollman et al., 2016). The GSTM1 and GSTT1 showed a high degree of polymorphism, one of the polymorphisms being the entire deletion of the gene that results in the lapse of enzymatic activity (Alves et al., 2002).

Several meta-analyses analyzed the association of GSTM1 present/null, GSTT1 present/null, and GSTP1 Ile105Val polymorphisms with leukemia risk. However, results of these meta-analyses were conflicting. Moreover, they did not evaluate the combined effects of the three aforementioned gene polymorphisms. Furthermore, they did not appraise the credibility of the positive results. Finally, many new studies have been published. Therefore, an updated meta-analysis was conducted.

Materials and methods

Search strategy

Five databases including PubMed, Embase, Web of Science, CNKI, and WanFang were applied to search the literature (deadline, 26 May 2022). The following retrieval strategy was employed: (glutathione S-transferase M1 OR GSTM1 OR glutathione S-transferase T1 OR GSTT1 OR glutathione S-transferase P1 OR GSTP1) AND (polymorphism OR genotype OR mutation OR variant OR allele) AND (leukemia OR leukaemia). Furthermore, if necessary, we contacted the corresponding authors by e-mail.

Inclusion and exclusion criteria

The studies that met the following criteria were included: 1) case-control or cohort study, 2) genotype data or odds ratio (OR) with 95% confidence interval (CI) provided, and 3) investigation of the association of the three aforementioned gene polymorphisms with the risk of leukemia. Studies such as overlapping data, case reports, editorials, reviews, letters, and meta-analyses were excluded.
Data extraction and quality assessment

Information was extracted and checked by two researchers from all selected studies. Any disagreement was solved through discussion. Extracted information is shown in Supplementary Tables S1–S3. Quality assessment was conducted by two authors independently (Supplementary Table S4). For GSTM1 and GSTT1 null genotypes, we considered studies that scored ≥10 as high quality; for GSTP1 Ile105Val, studies scoring ≥12 were deemed as high quality.

Statistical analysis

We used crude ORs and 95% CIs to estimate the associations between GST (M1, T1, and P1 Ile105Val) polymorphisms and leukemia risk. The Q statistic and I² value were carried out to evaluate heterogeneity (Higgins et al., 2003). Only a random-effect model was used because the pooled results were same when I² = 0% using random-effect and fixed-effect models (Der Simonian and Laird, 2015). We performed ORs with the corresponding 95% CIs following the genetic models. In GSTM1 and GSTT1 null genotypes, we used null vs. present model to calculate the pooled ORs with their 95% CIs. In GSTP1 Ile105Val, five genetic models were used (Val/Val vs. Ile/Ile, Ile/Val vs. Ile/Ile, Val/Val vs. Ile/Val + Ile/Ile, Val vs. Ile/Ile, and Val vs. Ile). In the combination of GSTM1 present/null and GSTT1 present/null, we applied the following six genetic models: model 1: M1 present/T1 null vs. M1 present/T1 present, model 2: M1 null/T1 present vs. M1 present/T1 present, model 3: M1 null/T1 null vs. M1 present/T1 present, model 4: All one risk genotypes vs. M1 present/T1 present, model 5: All risk genotypes vs. M1 present/T1 present, and model 6: M1 null/T1 null vs. M1 present/T1 present + M1 present/T1 null + M1 null/T1 present in the
TABLE 1 Meta-analysis of the association of GSTM1 polymorphism with risk of leukemia.

| Variable              | n     | Cases/Controls | Test of association | Test of heterogeneity | Model          |
|-----------------------|-------|----------------|---------------------|-----------------------|----------------|
|                       |       |                | OR (95%CI)           | \( P_h \)             | I^2 (%)        |
| Overall               | 98    | 13477/22523    | 1.28 (1.17–1.40)    | <0.001                | 68.3           |
| Ethnicity             |       |                |                     |                       |                |
| Indian                | 14    | 1600/2465      | 1.25 (0.89–1.77)    | <0.001                | 84.6           |
| Asian                 | 24    | 3265/6028      | 1.50 (1.29–1.73)    | 0.002                 | 51.2           |
| Caucasian             | 47    | 7466/11124     | 1.17 (1.07–1.28)    | <0.001                | 46.0           |
| African               | 6     | 662/886        | 1.99 (1.30–3.94)    | 0.006                 | 69.0           |
| Age group             |       |                |                     |                       |                |
| Adults                | 37    | 5811/9440      | 1.26 (1.11–1.43)    | <0.001                | 65.6           |
| Children              | 31    | 4377/7321      | 1.42 (1.23–1.64)    | <0.001                | 64.4           |
| Adults and Children   | 25    | 2668/5205      | 1.10 (0.89–1.37)    | <0.001                | 76.6           |
| Type of control       |       |                |                     |                       |                |
| HC                    | 65    | 7,442/11989    | 1.29 (1.15–1.44)    | <0.001                | 66.6           |
| NBDC                  | 32    | 5978/10282     | 1.29 (1.13–1.48)    | <0.001                | 71.9           |
| Matching              |       |                |                     |                       |                |
| Yes                   | 23    | 3819/5389      | 1.36 (1.12–1.65)    | <0.001                | 77.7           |
| No                    | 75    | 9658/17134     | 1.25 (1.14–1.38)    | <0.001                | 63.7           |
| Type of leukemia      |       |                |                     |                       |                |
| AML                   | 33    | 5530/10043     | 1.20 (1.04–1.38)    | <0.001                | 71.1           |
| ALL                   | 41    | 5082/7895      | 1.44 (1.25–1.65)    | <0.001                | 66.8           |
| CML                   | 20    | 2079/3426      | 1.17 (0.93–1.46)    | <0.001                | 71.0           |
| Sensitivity analysis  |       |                |                     |                       |                |
| Quality score≥10      | 54    | 9420/15146     | 1.18 (1.07–1.30)    | <0.001                | 65.6           |
| Ethnicity             |       |                |                     |                       |                |
| Indian                | 10    | 1133/1690      | 1.04 (0.71–1.52)    | <0.001                | 81.6           |
| Asian                 | 11    | 2323/4122      | 1.17 (1.05–1.31)    | 0.870                 | 0.0            |
| Caucasian             | 25    | 5293/7774      | 1.17 (1.06–1.30)    | 0.008                 | 45.5           |
| African               | 5     | 628/683        | 2.01 (1.23–3.30)    | 0.003                 | 75.1           |
| Age group             |       |                |                     |                       |                |
| Adults                | 28    | 5011/7863      | 1.31 (1.15–1.50)    | <0.001                | 63.2           |
| Children              | 10    | 2282/3632      | 1.21 (1.06–1.39)    | 0.196                 | 27.0           |
| Adults and Children   | 14    | 1892/3455      | 0.90 (0.71–1.14)    | <0.001                | 74.0           |
| Type of control       |       |                |                     |                       |                |
| HC                    | 36    | 5433/7693      | 1.21 (1.05–1.39)    | <0.001                | 69.4           |
| NBDC                  | 18    | 4114/7581      | 1.14 (0.99–1.30)    | 0.002                 | 56.8           |
| Matching              |       |                |                     |                       |                |
| Yes                   | 21    | 3525/4887      | 1.26 (1.05–1.52)    | <0.001                | 73.5           |
| No                    | 33    | 6023/10387     | 1.13 (1.02–1.27)    | <0.001                | 57.7           |
| Type of leukemia      |       |                |                     |                       |                |
| AML                   | 21    | 4598/8072      | 1.12 (0.97–1.28)    | <0.001                | 63.7           |
| ALL                   | 16    | 2626/3754      | 1.22 (1.01–1.46)    | <0.001                | 63.7           |
| CML                   | 14    | 1551/2417      | 1.23 (0.92–1.65)    | <0.001                | 76.3           |

HC, healthy control; NBDC, nonblood disease control; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; and CML, chronic myeloid leukemia.
### TABLE 2 Meta-analysis of the association of GSTT1 polymorphism with risk of leukemia.

| Variable                  | n   | Cases/Controls | Test of association | Test of heterogeneity | Model                  |
|---------------------------|-----|----------------|---------------------|-----------------------|------------------------|
|                           |     |                | OR (95%CI)          | \(P_h\)               | \(I^2\) (%)            |
| **Overall**               | 89  | 12357/20636    | 1.46 (1.32–1.60)   | <0.001                | 62.5                   | Random-effect          |
| **Ethnicity**            |     |                |                     |                       |                        |
| Indian                    | 14  | 1600/2465      | 1.74 (1.27–2.38)   | <0.001                | 71.9                   | Random-effect          |
| Asian                     | 24  | 3265/6028      | 1.30 (1.16–1.46)   | 0.140                 | 24.2                   | Random-effect          |
| Caucasian                 | 38  | 6346/9237      | 1.37 (1.17–1.59)   | <0.001                | 65.0                   | Random-effect          |
| African                   | 6   | 662/886        | 2.08 (1.32–3.26)   | 0.011                 | 66.5                   | Random-effect          |
| **Age group**            |     |                |                     |                       |                        |
| Adults                    | 37  | 581/9440       | 1.55 (1.32–1.82)   | <0.001                | 69.6                   | Random-effect          |
| Children                  | 27  | 3521/6123      | 1.24 (1.09–1.43)   | 0.028                 | 37.2                   | Random-effect          |
| Adults and Children       | 20  | 2424/4516      | 1.59 (1.27–1.99)   | <0.001                | 67.1                   | Random-effect          |
| **Type of control**      |     |                |                     |                       |                        |
| HC                        | 57  | 6522/10286     | 1.45 (1.28–1.66)   | <0.001                | 63.7                   | Random-effect          |
| NBDC                      | 31  | 5778/10105     | 1.46 (1.26–1.69)   | <0.001                | 62.7                   | Random-effect          |
| **Matching**             |     |                |                     |                       |                        |
| Yes                       | 23  | 8272/14543     | 1.80 (1.44–2.24)   | <0.001                | 74.8                   | Random-effect          |
| No                        | 66  | 4085/6093      | 1.35 (1.22–1.49)   | <0.001                | 51.7                   | Random-effect          |
| **Type of leukemia**     |     |                |                     |                       |                        |
| AML                       | 30  | 4851/9092      | 1.41 (1.19–1.66)   | <0.001                | 67.7                   | Random-effect          |
| ALL                       | 37  | 4665/7,215     | 1.33 (1.16–1.53)   | <0.001                | 53.0                   | Random-effect          |
| CML                       | 19  | 2068/3298      | 1.88 (1.47–2.41)   | <0.001                | 64.5                   | Random-effect          |
| **Sensitivity analysis** |     |                |                     |                       |                        |
| Quality score≥10         |     |                |                     |                       |                        |
| Overall                   | 52  | 8710/14300     | 1.52 (1.34–1.72)   | <0.001                | 66.9                   | Random-effect          |
| **Ethnicity**            |     |                |                     |                       |                        |
| Indian                    | 11  | 1225/1840      | 1.53 (1.08–2.17)   | <0.001                | 69.6                   | Random-effect          |
| Asian                     | 11  | 2323/4122      | 1.15 (1.01–1.31)   | 0.239                 | 21.5                   | Random-effect          |
| Caucasian                 | 22  | 4363/6650      | 1.64 (1.37–1.96)   | <0.001                | 64.5                   | Random-effect          |
| African                   | 5   | 628/683        | 2.12 (1.26–3.58)   | 0.007                 | 71.9                   | Random-effect          |
| **Age group**            |     |                |                     |                       |                        |
| Adults                    | 28  | 5011/7,863     | 1.58 (1.33–1.89)   | <0.001                | 71.3                   | Random-effect          |
| Children                  | 8   | 1552/2705      | 1.35 (1.00–1.82)   | 0.005                 | 65.1                   | Random-effect          |
| Adults and Children       | 14  | 1784/3428      | 1.45 (1.14–1.83)   | 0.001                 | 61.5                   | Random-effect          |
| **Type of control**      |     |                |                     |                       |                        |
| HC                        | 34  | 4704/6746      | 1.56 (1.31–1.86)   | <0.001                | 71.0                   | Random-effect          |
| NBDC                      | 18  | 4006/7,554     | 1.45 (1.23–1.72)   | 0.002                 | 56.7                   | Random-effect          |
| **Matching**             |     |                |                     |                       |                        |
| Yes                       | 21  | 3525/4887      | 1.73 (1.37–2.17)   | <0.001                | 73.6                   | Random-effect          |
| No                        | 31  | 5185/9413      | 1.41 (1.23–1.62)   | <0.001                | 59.2                   | Random-effect          |
| **Type of leukemia**     |     |                |                     |                       |                        |
| AML                       | 19  | 3937/7,249     | 1.35 (1.12–1.63)   | <0.001                | 68.3                   | Random-effect          |
| ALL                       | 16  | 2449/3603      | 1.49 (1.19–1.88)   | <0.001                | 64.2                   | Random-effect          |
| CML                       | 14  | 1551/2417      | 1.93 (1.44–2.59)   | <0.001                | 64.9                   | Random-effect          |

HC, healthy control; NBDC, nonblood disease control; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; and CML, chronic myeloid leukemia.
TABLE 3 Meta-analysis of the association of GSTP1 polymorphism with risk of leukemia.

| Variable                      | n (Cases/Controls) | Val/Val vs. Ile/Ile | Ile/Ile vs. Ile/Ile | Val/Val vs. Ile/Ile + Ile/Val | Val vs. Ile |
|-------------------------------|--------------------|---------------------|---------------------|-------------------------------|------------|
|                               |                    | OR (95%CI)          | P<sup>h</sup>/I<sup>2</sup>(%) | OR (95%CI)          | P<sup>h</sup>/I<sup>2</sup>(%) | OR (95%CI)          | P<sup>h</sup>/I<sup>2</sup>(%) |
| Overall                       | 34(5391/8729)      | 1.77 (1.40–2.24)    | 0.000/59.8          | 1.24 (1.08–1.43)    | 0.000/66.7          | 1.59 (1.29–1.95)    | 0.100/50.9          |
| Ethnicity                     |                    |                     |                     |                               |             |                               |                            |
| Indian                        | 10(1392/2094)      | 3.01 (1.60–5.66)    | 0.000/76.8          | 1.28 (1.08–1.53)    | 0.167/30.3          | 2.65 (1.47–4.79)    | 0.000/74.8          |
| Asian                         | 10(1895/3338)      | 1.27 (0.98–1.66)    | 0.381/65.6          | 1.25 (0.91–1.72)    | 0.000/78.8          | 1.22 (0.96–1.55)    | 0.799/0.0           |
| Caucasian                     | 12(1791/2976)      | 1.49 (1.10–2.01)    | 0.073/40.2          | 1.28 (0.98–1.68)    | 0.000/73.8          | 1.31 (1.04–1.65)    | 0.294/15.3          |
| Age group                     |                    |                     |                     |                               |             |                               |                            |
| Adults                        | 14(1392/2094)      | 1.39 (1.06–1.82)    | 0.102/34.1          | 1.17 (0.95–1.43)    | 0.000/67.3          | 1.27 (1.01–1.61)    | 0.233/20.2          |
| Children                      | 8(1392/2094)       | 1.68 (1.10–2.58)    | 0.115/39.6          | 1.14 (0.88–1.46)    | 0.038/52.8          | 1.60 (1.11–2.32)    | 0.223/25.8          |
| Adults and Children           | 9(1392/2094)       | 3.25 (1.61–6.53)    | 0.000/76.8          | 1.64 (1.16–2.31)    | 0.000/73.7          | 2.65 (1.41–5.02)    | 0.000/72.9          |
| Type of control               |                    |                     |                     |                               |             |                               |                            |
| HC                             | 21(2699/3569)     | 2.38 (1.66–3.41)    | 0.000/61.2          | 1.27 (1.05–1.54)    | 0.000/65.2          | 2.12 (1.53–2.94)    | 0.001/55.3          |
| NBDC                           | 13 (2692/5160)    | 1.19 (0.99–1.44)    | 0.395/51.1          | 1.19 (0.96–1.48)    | 0.000/71.0          | 1.14 (0.96–1.36)    | 0.836/0.0           |
| Matching                      |                    |                     |                     |                               |             |                               |                            |
| Yes                            | 14 (2510/3287)    | 1.37 (1.07–1.76)    | 0.203/23.1          | 1.07 (0.95–1.20)    | 0.665/0.0           | 1.30 (1.03–1.64)    | 0.244/19.2          |
| No                             | 20(2881/5442)     | 2.13 (1.49–3.06)    | 0.000/69.0          | 1.36 (1.08–1.71)    | 0.000/78.4          | 1.86 (1.36–2.54)    | 0.000/66.0          |
| Type of leukemia               |                    |                     |                     |                               |             |                               |                            |
| AML                            | 13 (2225/4667)    | 1.57 (1.10–2.24)    | 0.000/66.4          | 1.37 (1.02–1.84)    | 0.000/83.1          | 1.37 (1.01–1.84)    | 0.008/55.1          |
| ALL                            | 12 (1540/2445)    | 1.90 (1.28–2.81)    | 0.018/52.1          | 1.15 (0.96–1.38)    | 0.103/36.0          | 1.77 (1.25–2.53)    | 0.051/44.0          |
| CML                            | 6 (926/810)       | 1.29 (1.08–1.53)    | 0.009/67.3          | 1.13 (0.84–1.53)    | 0.068/51.3          | 2.13 (1.08–4.24)    | 0.028/60.1          |
| Sensitivity analysis           |                    |                     |                     |                               |             |                               |                            |
| HWE                            | Overall            | 1.58 (1.27–1.95)    | 0.118/26.3          | 1.18 (1.02–1.37)    | 0.000/59.0          | 1.45 (1.21–1.74)    | 0.361/7.3           |
| Ethnicity                      |                    |                     |                     |                               |             |                               |                            |
| Indian                        | 7 (842/1350)      | 1.83 (1.11–3.03)    | 0.033/56.3          | 1.24 (1.01–1.51)    | 0.333/12.7          | 1.67 (1.05–2.64)    | 0.055/51.3          |
| Asian                         | 6 (1376/2603)     | 1.14 (0.79–1.64)    | 0.728/0.0          | 1.04 (0.83–1.30)    | 0.129/41.4          | 1.15 (0.80–1.64)    | 0.799/0.0           |
| Caucasian                     | 9 (1250/1837)     | 1.70 (1.23–2.34)    | 0.257/21.0          | 1.30 (0.94–1.80)    | 0.000/75.8          | 1.50 (1.14–1.95)    | 0.524/0.0           |
| Age group                     |                    |                     |                     |                               |             |                               |                            |
| Adults                        | 10 (1835/3530)    | 1.39 (1.07–1.81)    | 0.493/0.0          | 1.20 (0.93–1.56)    | 0.000/72.1          | 1.31 (1.02–1.69)    | 0.717/0.0           |
| Children                      | 8 (1124/1633)     | 1.68 (1.10–2.58)    | 0.115/39.6          | 1.14 (0.88–1.46)    | 0.038/52.8          | 1.60 (1.11–2.32)    | 0.223/25.8          |
| Adults and Children           | 5 (622/848)       | 1.81 (0.95–3.44)    | 0.038/60.6          | 1.31 (0.99–1.72)    | 0.195/33.9          | 1.59 (0.91–2.79)    | 0.084/51.3          |

(Continued on following page)
| Variable | n (Cases/Controls) | Val/Val vs. lle/lle | Ile/Val vs. lle/lle | Val/Val vs. lle/lle + Ile/Val | Val vs. lle |
|----------|------------------|-----------------|-----------------|-----------------|-------------|
|          |                  | OR (95%CI)       | P_H/T² (%)       | OR (95%CI)       | P_H/T² (%)   |
|          |                  |                  |                  |                  |              |
| HC       | 17 (2099/2775)   | 1.86 (1.38–2.50) | 0.083/34.2       | 1.21 (0.98–1.50) | 0.000/63.8   |
|          |                  |                  |                  |                  |              |
| NBDC     | 7 (1682/3336)    | 1.21 (0.93–1.59) | 0.930/0.0        | 1.08 (0.93–1.26) | 0.289/18.4   |
|          |                  |                  |                  |                  |              |
| Matching |                   |                  |                  |                  |              |
| Yes      | 9 (1546/1696)    | 1.51 (1.11–2.05) | 0.787/0.0        | 1.12 (0.96–1.30) | 0.929/0.0    |
| No       | 15 (2235/4415)   | 1.66 (1.21–2.27) | 0.023/47.1       | 1.24 (0.98–1.56) | 0.000/73.6   |
| Type of leukemia |       |                  |                  |                  |              |
| AML      | 7 (1141/2762)    | 1.18 (0.86–1.62) | 0.424/0.0        | 1.17 (0.80–1.69) | 0.000/80.0   |
| ALL      | 10 (1345/2047)   | 1.60 (1.15–2.22) | 0.197/26.8       | 1.10 (0.91–1.31) | 0.180/28.8   |
| Quality score ≥12 | |                  |                  |                  |              |
| Overall  | 18 (3430/5975)   | 1.62 (1.25–2.11) | 0.018/45.7       | 1.16 (0.99–1.36) | 0.001/56.8   |
| Ethnicity|                   |                  |                  |                  |              |
| Caucasian| 6 (1064/2009)    | 1.54 (1.09–2.17) | 0.220/28.7       | 1.41 (0.98–2.04) | 0.001/76.9   |
| Indian   | 7 (1010/1448)    | 2.15 (1.22–3.76) | 0.013/62.6       | 1.17 (0.95–1.43) | 0.231/25.9   |
| Age group|                   |                  |                  |                  |              |
| Adults   | 11 (1392/2094)   | 1.42 (1.07–1.88) | 0.134/33.1       | 1.19 (0.97–1.46) | 0.001/67.4   |
| Type of control |       |                  |                  |                  |              |
| HC       | 13 (1856/2372)   | 1.94 (1.37–2.76) | 0.044/44.2       | 1.21 (0.97–1.50) | 0.002/62.1   |
| NBDC     | 5 (1574/3603)    | 1.14 (0.89–1.46) | 0.735/0.0        | 1.05 (0.88–1.27) | 0.152/40.4   |
| Matching |                   |                  |                  |                  |              |
| Yes      | 11 (2226/2966)   | 1.45 (1.11–1.90) | 0.283/16.9       | 1.06 (0.94–1.20) | 0.942/0.0    |
| No       | 7 (1204/3009)    | 1.81 (1.07–3.06) | 0.006/67.1       | 1.34 (0.90–2.00) | 0.000/83.3   |
| Type of leukemia |       |                  |                  |                  |              |
| AML      | 7 (1461/3684)    | 1.11 (0.88–1.41) | 0.470/0.0        | 1.21 (0.88–1.65) | 0.000/78.4   |
| CML      | 5 (855/743)      | 3.17 (1.89–5.32) | 0.308/16.7       | 1.18 (0.85–1.64) | 0.052/57.5   |
| HWE and Quality score ≥12 | |                  |                  |                  |              |
| Overall  | 16 (2750/4705)   | 1.63 (1.24–2.13) | 0.081/35.2       | 1.20 (1.00–1.44) | 0.001/61.8   |
| Ethnicity|                   |                  |                  |                  |              |
| Indian   | 6 (750/1200)     | 1.91 (1.07–3.40) | 0.020/62.6       | 1.23 (0.97–1.55) | 0.236/26.2   |
| Caucasian| 5 (644/987)      | 1.87 (1.28–2.74) | 0.649/0.0        | 1.55 (1.02–2.34) | 0.007/71.9   |
| Age group|                   |                  |                  |                  |              |
| Adults   | 9 (1735/3430)    | 1.38 (1.05–1.82) | 0.408/3.2        | 1.27 (0.97–1.66) | 0.000/72.2   |

(Continued on following page)
The combination of GSTM1 present/null and GSTP1 Ile105Val was also used for the six genetic models, model 1: M1 null/P1 Ile/Ile vs. M1 present/P1 Ile/Ile, model 2: M1 present/P1 Val* vs. M1 present/P1 Ile/Ile, model 3: (M1 null/P1 Ile/Ile + M1 present/P1 Val*) vs. M1 present/P1 Ile/Ile, model 4: M1 null/P1 Val* vs. M1 present/P1 Ile/Ile, model 5: All risk genotypes vs. M1 present/P1 Ile/Ile, and model 6: M1 null/P1 Val* vs. (M1 present/P1 Ile/Ile + M1 null/P1 Ile/Ile + M1 present/P1 Val*). There were six genetic models used in the combination of GSTT1 present/null and GSTP1 Ile105Val: model 1: T1 null/P1 Ile/Ile vs. T1 present/P1 Ile/Ile, model 2: T1 present/P1 Val* vs. T1 present/P1 Ile/Ile, model 3: (T1 null/P1 Ile/Ile + T1 present/P1 Val*) vs. T1 present/P1 Ile/Ile, model 4: T1 null/P1 Val* vs. T1 present/P1 Ile/Ile, model 5: All risk genotypes vs. T1 present/P1 Ile/Ile, and model 6: T1 null/P1 Val* vs. (T1 present/P1 Ile/Ile + T1 null/P1 Ile/Ile + T1 present/P1 Val*). In the combination of GSTM1 present/null, GSTT1 present/null, and GSTP1 Ile105Val, the following genetic models were employed: model 1: M1 null/T1 present/P1 Ile/Ile vs. M1 present/T1 present/P1 Ile/Ile, model 2: M1 present/T1 null/P1 Ile/Ile vs. M1 present/T1 present/P1 Ile/Ile, model 3: M1 present/T1 present/P1 Val vs. M1 present/T1 present/P1 Ile/Ile, model 4: all one high-risk genotype vs. M1 present/T1 present/P1 Ile/Ile, model 5: M1 null/T1 null/P1 Ile/Ile vs. M1 present/T1 present/P1 Ile/Ile, model 6: M1 null/T1 null/P1 Val vs. M1 present/T1 present/P1 Ile/Ile, model 7: M1 present/T1 null/P1 Val vs. M1 present/T1 present/P1 Ile/Ile, model 8: all two high-risk genotype vs. M1 present/T1 present/P1 Ile/Ile, model 9: M1 null/T1 null/P1 Val vs. M1 present/T1 present/P1 Ile/Ile, and model 10: M1 null/T1 null/P1 Val vs. M1 present/T1 present/P1 Ile/Ile + all one high-risk genotype + all two high-risk genotypes. Moreover, a metaregression analysis was used to explore sources of heterogeneity (Baker et al., 2009). Sensitivity analysis was conducted by excluding low-quality and Hardy–Weinberg disequilibrium (HWD) in control studies. The Hardy–Weinberg equilibrium (HWE) was checked using Chi-square goodness-of-fit test, which was deemed as HWE in controls if $p \geq 0.05$. Begg’s funnel plot (Begg and Mazumdar, 1994) and Egger’s test (Egger et al., 1997) were carried out to verify publication bias. Furthermore, we applied the FPRP (Wacholder et al., 2004), BFDP (Wakefield, 2007), and Venice criteria (Ioannidis et al., 2008) to appraise the credibility of statistically significant associations. All statistical analyses were performed using Stata 12.0 software in the current study.

**Results**

**Search results and study characteristics**

Overall, 91 articles (Supplemental References 1–91) were eligible (Figure 1), and Supplementary Tables S1–S3 show the characteristics and scores of each study. Multiple eligible studies were included in one article. Therefore, there were 98 eligible studies (13,477 leukemia cases and 22,523 controls, Table 1) on the GSTM1 present/null variance of the data. The combination of GSTM1 present/null and GSTP1 Ile105Val was also used for the six genetic models, model 1: M1 null/P1 Ile/Ile vs. M1 present/P1 Ile/Ile, model 2: M1 present/P1 Val* vs. M1 present/P1 Ile/Ile, model 3: (M1 null/P1 Ile/Ile + M1 present/P1 Val*) vs. M1 present/P1 Ile/Ile, model 4: M1 null/P1 Val* vs. M1 present/P1 Ile/Ile, model 5: All risk genotypes vs. M1 present/P1 Ile/Ile, and model 6: M1 null/P1 Val* vs. (M1 present/P1 Ile/Ile + M1 null/P1 Ile/Ile + M1 present/P1 Val*).

| Variable | n (Cases/Controls) | Val/Val vs. lle/lle | lle/Val vs. lle/lle | Val/Val vs. lle/Ile | Val vs. lle |
|----------|--------------------|---------------------|---------------------|---------------------|-----------|
|          | OR (95%CI)         | Ph/I2(%)            | OR (95%CI)          | Ph/I2(%)            | OR (95%CI) |
|          |                    |                     |                     |                     |           |
| Type of control |                  |                     |                     |                     |           |
| HC       |                    |                     |                     |                     |           |
| Matching |                    |                     |                     |                     |           |
| Yes      | 1.83 (1.29–2.55)   | 0.002/63.5          | 1.66 (1.23–2.25)    | 0.002/63.5          |           |
| No       | 1.51 (1.11–2.05)   | 0.004/69.3          | 1.34 (1.07–1.70)    | 0.004/69.3          |           |
| Type of leukemia |                |                     |                     |                     |           |
| AML      | 1.16 (0.82–1.64)   | 0.002/63.5          | 1.34 (1.07–1.70)    | 0.002/63.5          |           |
| ALL      | 1.16 (0.82–1.64)   | 0.002/63.5          | 1.16 (0.82–1.64)    | 0.002/63.5          |           |
| HC, healthy control; NBDC, non-blood disease control; AML, acute myeloblastic leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia. |
polymorphism, 89 eligible studies (12,357 leukemia cases and 20,636 controls, Table 2) on the GSTT1 present/null polymorphism, 34 studies (5,391 leukemia cases and 8,729 controls, Table 3) on the GSTP1 Ile105Val polymorphism, 25 studies (3,522 leukemia cases and 4,974 controls, Table 4) belonging to the combined effects of the GSTM1 and GSTT1 polymorphisms, six studies (737 leukemia cases and 995 controls, Table 5) describing the combined GSTM1 and GSTP1 effects, five studies (645 leukemia cases and 845 controls, Table 6) on the combined GSTT1 and GSTP1 effects, and seven studies (1,036 leukemia cases and 1,418 controls, Table 7) belonging to the combined effects of the three aforementioned polymorphisms with leukemia risk.

Quantitative synthesis

The GSTM1 null genotype significantly added leukemia risk in the overall analysis (OR = 1.28, 95% CI: 1.17–1.40, Table 1 and Figure 2) of Asians (OR = 1.50, 95% CI: 1.29–1.73), Caucasians (OR = 1.17, 95% CI: 1.07–1.28), and Africans (OR = 1.99, 95% CI: 1.30–3.94). However, it showed that the GSTM1 null genotype did not affect leukemia risk in Indians (OR = 1.25, 95% CI: 0.89–1.77). Moreover, similar association was also found in other subgroup analyses, such as in adult leukemia, child leukemia, AML, ALL, CML, and so on (Table 1).

The GSTT1 null genotype added leukemia risk in the overall population (OR = 1.46, 95% CI: 1.32–1.60, Table 2 and Figure 3). Moreover, an increased risk of leukemia was also found in Indians (OR = 1.74, 95% CI: 1.27–2.38), Asians (OR = 1.30, 95% CI: 1.16–1.46), Caucasians (OR = 1.37, 95% CI: 1.17–1.59), and Africans (OR = 2.08, 95% CI: 1.32–3.26) (Table 2; Figure 3). Similarly, the significantly increased risk of leukemia was also observed in adult leukemia, child leukemia, AML, ALL, and CML, and so on (Table 2).

The GSTP1 Ile105Val polymorphism yielded a significantly increased leukemia risk in overall population (Val/Val vs. Ile/Ile: OR = 1.77, 95% CI = 1.40–2.24; Ile/Val vs. Ile/Ile: OR = 1.24, 95% CI = 1.08–1.43; Val/Val vs. Ile/Ile + Ile/Val: OR = 1.59, 95% CI = 1.29–1.95; Val/Val + Ile/Val vs. Ile/Ile: OR = 1.32, 95% CI = 1.15–1.53; and Val vs. Ile: OR = 1.31, 95% CI = 1.16–1.47, Table 3 and Figure 4). Moreover, the GSTP1 Ile105Val polymorphism was associated with increased leukemia risk in Indians (Val/Val vs. Ile/Ile: OR = 3.01, 95% CI = 1.60–5.66; Ile/Val vs. Ile/Ile: OR = 1.28, 95% CI = 1.08–1.53; Val/Val vs. Ile/Ile + Ile/Val: OR = 2.65, 95% CI = 1.47–4.79; Val/Val + Ile/Val vs. Ile/Ile: OR = 1.45, 95% CI = 1.17–1.80; and Val vs. Ile: OR = 1.47, 95% CI = 1.19–1.80) and in Caucasians (Val vs. Ile/Ile: OR = 1.49, 95% CI = 1.10–2.01; Val/Val vs. Ile/Ile + Ile/Val: OR = 1.31, 95% CI = 1.04–1.65; Val/Val + Ile/Val vs. Ile/Ile: OR = 1.32, 95% CI = 1.02–1.72; and Val vs. Ile: OR = 1.28, 95% CI = 1.05–1.55). Similarly, the significantly increased risk of leukemia was also observed in adult leukemia, child leukemia, AML, ALL, CML, etc. (Table 3).

Combined GSTM1 and GSTT1 null genotypes were found to significantly increase leukemia risk in the overall analysis (M1 present/T1 null vs. M1 present/T1 present: OR = 1.66, 95% CI = 1.37–2.00; M1 null/T1 null vs. M1 present/T1 present: OR = 2.44, 95% CI = 1.86–3.21; all one risk genotypes vs. M1 present/T1 present: OR = 1.29, 95% CI = 1.11–1.50; all risk genotypes vs. M1 present/T1 present: OR = 1.44, 95% CI = 1.25–1.66; and M1 null/T1 null vs. M1 present/T1 present + M1 present/T1 null + M1 null/T1 present: OR = 2.16, 95% CI = 1.65–2.81; Table 4 and Figure 5). Moreover, there was a significantly increased leukemia risk in Indians (M1 present/T1 null vs. M1 present/T1 present: OR = 1.92, 95% CI = 1.18–3.12; M1 null/T1 null vs. M1 present/T1 present: OR = 3.16, 95% CI = 1.90–5.25; M1 null/T1 null vs. M1 present/T1 present + M1 present/T1 null + M1 null/T1 present: OR = 2.83, 95% CI = 1.73–4.64), Asians (M1 present/T1 null vs. M1 present/T1 present: OR = 1.43, 95% CI = 1.04–1.97; M1 null/T1 null vs. M1 present/T1 present: OR = 2.47, 95% CI = 1.55–3.95; all one risk genotypes vs. M1 present/T1 present: OR = 1.35, 95% CI = 1.02–1.80; all risk genotypes vs. M1 present/T1 present: OR = 1.57, 95% CI = 1.20–2.05; M1 null/T1 null vs. M1 present/T1 present + M1 present/T1 null + M1 null/T1 present: OR = 2.05, 95% CI = 1.40–3.00), and Caucasians (M1 present/T1 null vs. M1 present/T1 present: OR = 1.65, 95% CI = 1.14–2.39; M1 null/T1 null vs. M1 present/T1 present: OR = 1.98, 95% CI = 1.16–3.37; all one risk genotypes vs. M1 present/T1 present: OR = 1.30, 95% CI = 1.05–1.60; all risk genotypes vs. M1 present/T1 present: OR = 1.37, 95% CI = 1.17–1.61). Similar results were found in adult leukemia, AML, ALL, and so on (Table 4).

An increased risk of leukemia was yielded on the combined GSTM1 and GSTP1 polymorphisms (M1 null/P1 Val* vs. M1 present/P1 Ile/Ile: OR = 1.95, 95% CI = 1.35–2.80; M1 null/P1 Val* vs. M1 present/P1 Ile/Ile + M1 null/P1 Ile/Ile + M1 Present/P1 Val*: OR = 1.95, 95% CI = 1.37–2.77; Table 5 and Figure 6) in overall analysis. Moreover, increased leukemia risk was also demonstrated in Indians (M1 null/P1 Val* vs. M1 present/P1 Ile/Ile: OR = 1.72, 95% CI = 1.10–2.70; M1 null/P1 Val* vs. M1 present/P1 Ile/Ile + M1 null/P1 Ile/Ile + M1 Present/P1 Val*: OR = 1.65, 95% CI = 1.14–2.40). Furthermore, a similar connection was also found in ALL, CML, and so on (Table 5).

On combining GSTT1 and GSTP1 polymorphisms, there was a strong connection with leukemia risk in the overall analysis (T1 null/P1 Ile/Ile + T1 present/P1 Val*: vs. T1 present/P1 Ile/Ile: OR = 1.50, 95% CI = 1.04–2.15; T1 null/P1 Val* vs. T1 present/P1 Ile/Ile: OR = 4.24, 95% CI = 2.49–7.24; all risk genotypes vs. T1 present/P1 Ile/Ile: OR = 1.70, 95% CI = 1.30–2.22; and T1 null/P1 Val* vs. (T1 present/P1 Ile/Ile + T1 null/P1 Ile/Ile + T1 Present/P1 Val*) OR = 3.31, 95% CI = 1.85–5.91) and increased risk of leukemia among Indians.
| Variable          | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|-------------------|---------|---------|---------|---------|---------|---------|
|                   | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) |
| Overall           | 1.66 (1.37–2.00) | 1.11 (0.93–1.33) | 0.000/60.4 | 2.44 (1.86–3.21) | 0.002/51.2 | 1.29 (1.11–1.50) | 0.001/52.2 | 1.44 (1.25–1.66) | 0.002/51.5 | 2.16 (1.65–2.81) | 0.000/55.4 |
| Ethnicity         |         |         |         |         |         |         |
| Indian            | 1.92 (1.18–3.12) | 0.87 (0.54–1.40) | 0.017/66.6 | 3.16 (1.90–5.25) | 0.519/0.0 | 1.18 (0.76–1.85) | 0.067/72.4 | 1.32 (0.83–2.10) | 0.002/76.1 | 2.83 (1.73–4.64) | 0.759/0.0 |
| Asian             | 1.43 (1.04–1.97) | 1.34 (0.99–1.81) | 0.146/41.4 | 2.47 (1.55–3.95) | 0.051/57.5 | 1.35 (1.02–1.80) | 0.120/45.3 | 1.57 (1.20–2.05) | 0.129/44.0 | 2.05 (1.40–3.00) | 0.090/50.3 |
| Caucasian         | 1.65 (1.14–2.39) | 1.15 (0.92–1.43) | 0.101/38.6 | 1.98 (1.16–3.37) | 0.005/61.5 | 1.30 (1.05–1.60) | 0.082/41.3 | 1.37 (1.17–1.61) | 0.317/13.7 | 1.71 (0.94–3.09) | 0.000/71.8 |
| Age group         |         |         |         |         |         |         |
| Adults            | 1.44 (1.18–1.76) | 1.27 (1.04–1.54) | 0.013/50.7 | 2.51 (1.71–3.68) | 0.001/60.0 | 1.34 (1.15–1.57) | 0.087/35.3 | 1.50 (1.29–1.74) | 0.104/33.0 | 2.26 (1.53–3.33) | 0.000/65.8 |
| Adults and children | 1.63 (0.87–3.07) | 0.75 (0.50–1.12) | 0.122/45.0 | 2.05 (0.96–4.37) | 0.063/55.1 | 0.99 (0.66–1.49) | 0.044/59.2 | 1.10 (0.73–1.71) | 0.016/67.2 | 1.94 (1.04–3.46) | 0.131/43.6 |
| Type of control   |         |         |         |         |         |         |
| HC                | 1.73 (1.31–2.30) | 1.02 (0.76–1.38) | 0.000/69.8 | 2.59 (1.71–3.93) | 0.012/51.1 | 1.27 (1.00–1.60) | 0.060/69.9 | 1.45 (1.16–1.80) | 0.001/60.3 | 2.33 (1.52–3.58) | 0.002/59.7 |
| NBDC              | 1.60 (1.22–2.10) | 1.29 (1.11–1.50) | 0.466/0.0 | 2.31 (1.56–3.43) | 0.021/55.7 | 1.36 (1.18–1.57) | 0.421/1.6 | 1.49 (1.25–1.78) | 0.147/33.9 | 1.86 (1.33–2.61) | 0.059/46.7 |
| Matching          |         |         |         |         |         |         |
| Yes               | 1.60 (1.29–1.99) | 1.13 (0.85–1.50) | 0.000/70.1 | 2.57 (1.61–4.12) | 0.002/64.2 | 1.31 (1.09–1.58) | 0.075/41.0 | 1.46 (1.24–1.73) | 0.129/33.8 | 2.33 (1.44–3.76) | 0.000/69.6 |
| No                | 1.67 (1.24–2.27) | 1.09 (0.86–1.40) | 0.013/51.6 | 2.38 (1.70–3.33) | 0.076/37.6 | 1.28 (1.00–1.63) | 0.002/60.7 | 1.43 (1.13–1.80) | 0.001/62.1 | 2.07 (1.52–2.81) | 0.084/56.5 |
| Type of leukemia  |         |         |         |         |         |         |
| AML               | 1.47 (0.96–2.62) | 1.24 (0.97–1.58) | 0.202/31.2 | 2.15 (1.35–3.43) | 0.049/55.1 | 1.29 (0.99–1.69) | 0.088/47.8 | 1.41 (1.09–1.82) | 0.095/46.7 | 1.85 (1.22–2.80) | 0.069/51.1 |
| ALL               | 2.15 (1.43–3.23) | 1.19 (0.77–1.85) | 0.008/65.2 | 2.79 (1.47–5.30) | 0.052/52.0 | 1.52 (1.13–2.05) | 0.094/44.5 | 1.66 (1.25–2.20) | 0.106/42.7 | 2.23 (1.20–4.14) | 0.036/55.4 |
| CML               | 1.54 (1.18–2.01) | 1.01 (0.72–1.42) | 0.000/69.7 | 2.58 (1.57–4.24) | 0.024/51.4 | 1.19 (0.92–1.56) | 0.004/61.4 | 1.37 (1.06–1.77) | 0.003/62.5 | 2.41 (1.45–4.00) | 0.012/55.8 |

**Sensitivity analysis**

**Quality score ≥10**

| Overall | 21 (3105/4266) | 0.132/26.3 | 1.12 (0.92–1.37) | 0.000/61.6 | 0.001/55.3 | 0.007/48.3 | 0.001/57.8 |

(Continued on following page)
| Variable                  | N (Case/Control) | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|---------------------------|------------------|---------|---------|---------|---------|---------|---------|
|                           |                  | OR (95%CI) | Ph/ I(%) | OR (95%CI) | Ph/ I(%) | OR (95%CI) | Ph/ I(%) | OR (95%CI) | Ph/ I(%) | OR (95%CI) | Ph/ I(%) | OR (95%CI) | Ph/ I(%) |
| Ethnicity                 |                  |          |         |          |         |          |         |          |         |          |         |          |         |
| Indian                    | 5 (555/829)      | 1.56 (1.28–1.91) | 0.075/52.9 | 0.87 (0.54–1.40) | 0.017/66.6 | 3.16 (1.90–5.25) | 0.519/0.0 | 1.18 (0.76–1.85) | 0.006/72.4 | 1.32 (0.83–2.10) | 0.002/76.1 | 2.83 (1.73–4.64) | 0.759/0.0 |
| Caucasian                 | 8 (1121/1352)    | 1.38 (0.96–1.98) | 0.260/21.4 | 1.21 (0.95–1.53) | 0.100/41.7 | 1.80 (0.96–3.37) | 0.008/63.6 | 1.28 (1.04–1.57) | 0.160/33.6 | 1.34 (1.13–1.58) | 0.341/11.5 | 1.63 (0.83–3.21) | 0.001/71.5 |
| Age group                 |                  |          |         |          |         |          |         |          |         |          |         |          |         |
| Adults                    | 14 (2317/2754)   | 1.43 (1.16–1.76) | 0.527/0.0 | 1.31 (1.08–1.60) | 0.020/48.8 | 2.40 (1.61–3.58) | 0.002/59.9 | 1.37 (1.16–1.61) | 0.089/35.8 | 1.51 (1.29–1.77) | 0.078/37.4 | 2.13 (1.43–3.18) | 0.000/64.7 |
| Adults and children       | 5 (488/1112)     | 1.63 (0.87–3.07) | 0.014/68.0 | 0.75 (0.50–1.12) | 0.122/45.0 | 2.05 (0.96–4.37) | 0.063/55.1 | 0.99 (0.66–1.49) | 0.044/59.2 | 1.10 (0.71–1.71) | 0.016/67.2 | 1.94 (1.04–4.36) | 0.131/43.6 |
| Type of Control           |                  |          |         |          |         |          |         |          |         |          |         |          |         |
| HC                        | 13 (1539/1826)   | 1.63 (1.21–2.18) | 0.103/34.9 | 1.06 (0.76–1.47) | 0.000/73.5 | 2.56 (1.60–4.10) | 0.009/55.0 | 1.25 (0.97–1.61) | 0.001/64.6 | 1.41 (1.11–1.80) | 0.001/63.6 | 2.39 (1.50–3.80) | 0.004/58.7 |
| NBDC                      | 8 (1566/2440)    | 1.47 (1.12–1.94) | 0.306/15.7 | 1.24 (1.06–1.45) | 0.693/0.0 | 2.17 (1.43–3.29) | 0.030/54.9 | 1.30 (1.12–1.50) | 0.724/0.0 | 1.41 (1.19–1.66) | 0.294/17.2 | 1.85 (1.27–2.69) | 0.045/51.3 |
| Matching                  |                  |          |         |          |         |          |         |          |         |          |         |          |         |
| Yes                       | 11 (1958/2382)   | 1.60 (1.29–1.99) | 0.493/0.0 | 1.13 (0.85–1.50) | 0.000/70.1 | 2.57 (1.61–4.12) | 0.002/64.2 | 1.31 (1.09–1.58) | 0.078/41.0 | 1.46 (1.24–1.73) | 0.129/33.8 | 2.33 (1.44–3.76) | 0.000/69.6 |
| No                        | 10 (1147/1884)   | 1.51 (1.04–2.19) | 0.044/48.0 | 1.11 (0.84–1.47) | 0.032/50.8 | 2.26 (1.45–3.53) | 0.051/46.7 | 1.22 (0.93–1.61) | 0.012/57.2 | 1.37 (1.03–1.82) | 0.002/65.1 | 2.04 (1.40–2.98) | 0.107/37.7 |
| Type of leukemia          |                  |          |         |          |         |          |         |          |         |          |         |          |         |
| ALL                       | 6 (623/958)      | 1.92 (1.28–2.86) | 0.213/29.6 | 1.22 (0.76–1.96) | 0.004/70.7 | 3.10 (1.48–6.49) | 0.036/58.1 | 1.43 (1.07–1.91) | 0.144/39.3 | 1.59 (1.18–2.14) | 0.100/45.8 | 2.66 (1.38–5.15) | 0.053/54.1 |
| CML                       | 10 (1127/1483)   | 1.55 (1.15–2.09) | 0.292/16.4 | 1.04 (0.73–1.51) | 0.000/71.8 | 2.39 (1.37–4.16) | 0.020/54.3 | 1.22 (0.91–1.64) | 0.003/64.6 | 1.38 (1.03–1.83) | 0.002/66.2 | 2.21 (1.26–3.87) | 0.012/57.7 |

Model 1, M1 present/T1 null vs. M1 present/T1 present; Model 2, M1 null/T1 present vs. M1 present/T1 present; Model 3, M1 null/T1 null vs. M1 present/T1 present; Model 4, all one risk genotypes vs. M1 present/T1 present; Model 5, all risk genotypes vs. M1 present/T1 present; Model 6, M1 null/T1 null vs. M1 present/T1 present + M1 present/T1 null + M1 null/T1 present; HC, healthy control; NBDC, nonblood disease control; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; and CML, chronic myeloid leukemia.
| Variable            | Sample size | Model 1 |         | Model 2 |         | Model 3 |         | Model 4 |         | Model 5 |         | Model 6 |         |
|---------------------|-------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|                     |             | OR      | (95%CI) | OR      | (95%CI) | OR      | (95%CI) | OR      | (95%CI) | OR      | (95%CI) | OR      | (95%CI) |
| Ph/I2(%)            |             | 0.83    | (0.55–1.26) | 0.038/57.5 | 1.16 | (0.74–1.84) | 0.017/63.9 | 1.02 | (0.74–1.39) | 0.063/52.2 | 1.95 | (1.35–2.80) | 0.272/21.5 | 1.19 | (0.90–1.58) | 0.100/45.9 | 1.95 | (1.37–2.77) | 0.208/30.4 |
| Overall 6 (737/995) |             |         |         |         |         |         |         |         |         |         |         |         |         |
| Ethnicity           |             | 0.75    | (0.39–1.45) | 0.015/71.4 | 1.26 | (0.74–2.13) | 0.021/69.2 | 1.05 | (0.65–1.68) | 0.018/70.2 | 1.72 | (1.10–2.70) | 0.211/33.5 | 1.18 | (0.77–1.79) | 0.030/66.4 | 1.65 | (1.14–2.40) | 0.292/19.6 |
| Type of control     |             | 0.74    | (0.49–1.12) | 0.081/51.9 | 1.14 | (0.65–2.02) | 0.008/71.1 | 0.97 | (0.68–1.38) | 0.052/57.5 | 1.82 | (1.21–2.74) | 0.249/25.9 | 1.13 | (0.83–1.54) | 0.097/49.1 | 1.88 | (1.23–2.89) | 0.143/41.8 |
| HC 5 (645/845)      |             |         |         |         |         |         |         |         |         |         |         |         |         |
| Matching            |             | 0.72    | (0.37–1.41) | 0.033/70.6 | 0.82 | (0.43–1.57) | 0.147/47.8 | 0.78 | (0.51–1.21) | 0.142/48.7 | 1.89 | (0.90–3.96) | 0.113/54.1 | 0.99 | (0.63–1.56) | 0.087/59.0 | 2.20 | (1.25–3.89) | 0.204/37.1 |
| Yes 3 (395/395)     |             |         |         |         |         |         |         |         |         |         |         |         |         |
| No 3 (342/600)      |             | 0.97    | (0.53–1.76) | 0.123/52.3 | 1.53 | (0.91–2.56) | 0.097/57.2 | 1.31 | (0.97–1.77) | 0.581/0.0 | 2.07 | (1.34–3.20) | 0.413/0.0 | 1.44 | (1.08–1.92) | 0.771/0.0 | 1.76 | (1.05–2.96) | 0.178/42.1 |
| Type of leukemia    |             | 0.83    | (0.34–2.03) | 0.008/79.5 | 0.98 | (0.70–1.38) | 0.403/0.0 | 0.91 | (0.53–1.57) | 0.083/69.3 | 1.86 | (1.01–3.43) | 0.125/51.9 | 1.08 | (0.63–1.84) | 0.028/72.0 | 1.92 | (1.30–2.83) | 0.498/0.0 |
| ALL 3 (342/600)     |             | 0.86    | (0.60–1.24) | 0.377/0.0 | 1.34 | (0.51–3.48) | 0.015/76.1 | 1.17 | (0.83–1.63) | 0.306/15.6 | 2.08 | (1.27–3.40) | 0.363/1.4 | 1.34 | (1.00–1.92) | 0.705/0.0 | 2.00 | (0.90–4.46) | 0.055/65.4 |
| CML 3 (395/395)     |             |         |         |         |         |         |         |         |         |         |         |         |         |
| Sensitivity analysis|             |         |         |         |         |         |         |         |         |         |         |         |         |
| HWE and Quality score ≥10 |       | 0.83    | (0.55–1.26) | 0.038/57.5 | 1.16 | (0.74–1.84) | 0.017/63.9 | 1.02 | (0.74–1.39) | 0.063/52.2 | 1.95 | (1.35–2.80) | 0.272/21.5 | 1.19 | (0.90–1.58) | 0.100/45.9 | 1.95 | (1.37–2.77) | 0.208/30.4 |

Model 1, M1 null/P1 Ile/Ile vs. M1 present/P1 Ile/Ile; Model 2, M1 present/P1 Ile/Ile vs. M1 present/P1 Val* vs. M1 present/P1 Ile/Ile; Model 3, (M1 null/P1 Ile/Ile + M1 present/P1 Val*) vs. M1 present/P1 Ile/Ile; Model 4 = M1 null/P1 Val* vs. M1 present/P1 Ile/Ile; Model 5, All risk genotypes vs. M1 present/P1 Ile/Ile; Model 6, M1 null/P1 Val* vs. (M1 present/P1 Ile/Ile + M1 null/P1 Ile/Ile + M1 Present/P1 Val*); HC, healthy control; NBDC, nonblood disease controls; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; and CML, chronic myeloid leukemia.
| Variable                        | Sample size | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|-------------------------------|-------------|---------|---------|---------|---------|---------|---------|
|                               |             | OR (95%CI) | P^2 | OR (95%CI) | P^2 | OR (95%CI) | P^2 | OR (95%CI) | P^2 | OR (95%CI) | P^2 | OR (95%CI) | P^2 |
| Overall                       | 5 (645/845) | 1.56 (0.76–3.19) | 0.009/70.6 | 1.49 (0.97–2.28) | 0.032/62.2 | 1.50 (1.04–2.15) | 0.041/59.8 | 4.24 (2.49–7.24) | 0.596/0.0 | 1.70 (1.30–2.22) | 0.207/32.2 | 3.31 (1.85–5.91) | 0.320/14.8 |
| Ethnicity                     |             |         |         |         |         |         |         |         |         |         |         |         |         |
| Indian                        | 3 (400/600) | 1.90 (0.99–3.66) | 0.086/59.3 | 1.45 (0.72–2.92) | 0.006/80.4 | 1.65 (1.05–2.59) | 0.072/61.9 | 4.39 (2.51–7.68) | 0.741/0.0 | 1.91 (1.45–2.50) | 0.365/0.8 | 3.39 (1.94–5.94) | 0.338/7.8 |
| Type of control               |             |         |         |         |         |         |         |         |         |         |         |         |         |
| HC                            | 5 (645/845) | 1.56 (0.76–3.19) | 0.009/70.6 | 1.49 (0.97–2.28) | 0.032/62.2 | 1.50 (1.04–2.15) | 0.041/59.8 | 4.24 (2.49–7.24) | 0.596/0.0 | 1.70 (1.30–2.22) | 0.207/32.2 | 3.31 (1.85–5.91) | 0.320/14.8 |
| Matching                      |             |         |         |         |         |         |         |         |         |         |         |         |         |
| Yes                           | 3 (395/395) | 1.44 (0.48–4.35) | 0.032/70.8 | 1.16 (0.65–2.08) | 0.082/60.0 | 1.18 (0.76–1.83) | 0.135/50.1 | 4.61 (1.64–12.97) | 0.301/16.8 | 1.40 (1.04–1.89) | 0.368/0.0 | 4.15 (0.78–7.37) | 0.278/21.9 |
| Type of leukemia              |             |         |         |         |         |         |         |         |         |         |         |         |         |
| CML                           | 3 (395/395) | 0.88 (0.41–1.88) | 0.218/34.3 | 1.91 (1.35–2.68) | 0.441/0.0 | 1.49 (0.89–2.51) | 0.059/64.6 | 3.29 (1.37–7.89) | 0.361/1.9 | 1.61 (1.05–2.47) | 0.133/50.4 | 2.40 (1.21–14.26) | 0.231/31.8 |
| Sensitivity analysis          |             |         |         |         |         |         |         |         |         |         |         |         |         |
| HWE and Quality score≥10     |             |         |         |         |         |         |         |         |         |         |         |         |         |
| Overall                       | 5 (645/845) | 1.56 (0.76–3.19) | 0.009/70.6 | 1.49 (0.97–2.28) | 0.032/62.2 | 1.50 (1.04–2.15) | 0.041/59.8 | 4.24 (2.49–7.24) | 0.596/0.0 | 1.70 (1.30–2.22) | 0.207/32.2 | 3.31 (1.85–5.91) | 0.320/14.8 |

Model 1, T1 null/P1 Ile/Ile vs. T1 present/P1 Ile/Ile; Model 2, T1 present/P1 Val* vs. T1 present/P1 Ile/Ile; Model 3, (T1 null/P1 Ile/Ile + T1 present/P1 Val*) vs. T1 present/P1 Ile/Ile; Model 4, T1 null/P1 Val* vs. T1 present/P1 Ile/Ile; Model 5, all risk genotypes vs. T1 present/P1 Ile/Ile; Model 6, T1 null/P1 Val* vs. (T1 present/P1 Ile/Ile + T1 null/P1 Ile/Ile + T1 Val*); HB, hospital-based studies; PR, population-based studies; HC, healthy control; NBDC, nonblood disease controls; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; and CML, chronic myeloid leukemia.
TABLE 7 Meta-analysis of the combined effects of GSTM1 present/null, GSTT1 present/null, and GSTP1 Ile105Val on leukemia risk.

| Variable Sample | OR (95% CI) | Ph | OR (95% CI) | Ph | OR (95% CI) | Ph | OR (95% CI) | Ph |
|-----------------|-------------|----|-------------|----|-------------|----|-------------|----|
| Overall 7 (1036/1418) | 0.93 (0.72–2.07) | 0.945/0.0 | 1.38 (0.87–2.07) | 0.723/0.0 | 1.07 (0.87–1.33) | 0.486/0.0 | 0.81 (0.57–1.21) | 0.000/90.1 |
| Sensitivity analysis | | | | | | | | |
| Quality score >8 | 7 (1036/1418) | 0.945/0.0 | 1.38 (0.86–2.07) | 0.261/22.0 | 1.12 (0.83–1.47) | 0.402/2.2 | 0.69 (0.40–1.14) | 0.076/49.9 |
| Yes | 6 (603/705) | 0.987/0.0 | 1.38 (0.83–2.31) | 0.179/34.4 | 1.11 (0.83–1.46) | 0.604/0.0 | 1.05 (0.70–1.56) | 0.238/55.3 |

Heterogeneity and sensitivity analyses

The metaregression analysis showed that race (p = 0.000) and quality score (p = 0.038) were sources of heterogeneity for the GSTM1 null genotype. For GSTP1 Ile105Val polymorphism, in Val/Val vs. Ile/Ile + Ile/Val, type of controls (p = 0.002), matching studies (p = 0.023), and HWE (p = 0.005) were the heterogeneity sources. Similar results were observed in Val/Val vs. Ile/Ile + Ile/Val where type of controls (p = 0.001), matching studies (p = 0.037), and HWE (p = 0.007) were the sources of heterogeneity. For the combined GSTM1 and GSTT1 polymorphisms, the sample size (model 1; p = 0.015) was the source of heterogeneity (Table 8). Three methods were performed to appraise the sensitivity analysis, and all results did not change (Tables 1–7), indicating that the present study was stable.

Publication bias

Publication bias was found for the GSTM1 null genotype (p = 0.003, Figure 9), GSTT1 null genotype (p = 0.041, Figure 10), and GSTP1 Ile105Val (Val/Val vs. Ile/Ile vs. Ile/Ile + Ile/Val, type of controls (p = 0.001, Ile/Ile vs. Ile/Ile = 0.030, Val/Val vs. Ile/Ile + Ile/Val = 0.020, Val/Val + Ile/Val vs. Ile/Ile = 0.022, Val vs. Ile = 0.033, Figure 11). Then, we used nonparametric "trim and fill" to adjust publication bias, and the results did not change (data not shown).

Credibility of the positive results

The "reliable results" was defined as the positive results that met the following criteria (Theodoratu et al., 2012). First, these positive results were observed in at least two of the genetic models (exclude individual GSTM1 and GSTT1 polymorphisms with the risk of leukemia), second, FPRP <0.2 and BFDP <0.8, third, I² < 50%, and fourth, statistical power >80%. Table 9 lists the credibility of the present meta-analysis on the individual and the composite effects of GSTM1, GSTT1, and GSTP1 Ile105Val polymorphisms with the risk of leukemia. Only the GSTT1 null genotype with leukemia risk in Asians was considered as "positive" results (OR = 1.30, 95% CI = 1.16–1.46, I² = 24.2%, statistical power = 0.992, FPRP = 0.009, and
FIGURE 2
Forest plot for the association between GSTM1 polymorphism and leukemia risk in ethnicity subgroup analysis.
FIGURE 3
Forest plot for the association between GSTT1 polymorphism and leukemia risk in ethnicity subgroup analysis.
BFDP = 0.367). All other important connections were regarded as less-credible results, also shown in Table 9.

**Discussion**

Leukemia is characterized by abnormal hematopoietic function and malignant cloning of white blood cells (Ouerhani et al., 2011). Gene polymorphisms play a significant role in the development of leukemia, and GST null has been studied by many scholars. Studies demonstrated that complete deletion of GSTM1, GSTT1, or GSTP1 polymorphisms brought about diminished gene expression and enzymatic activity (Strange et al., 1998; Strange et al., 2001; Hollman et al., 2016). Thus, it is significant to study the connection between GST polymorphisms and leukemia risk. Many studies have analyzed the roles of M1, T1, and P1 polymorphisms in leukemia risk. Regrettably, no reliable testimony has been obtained to show whether there is an association between them. This may be due to heterogeneities such as ethnicity, small sample size, matching, type of leukemia, etc. Therefore, an updated meta-analysis was generated to explore these issues. At this point, totally 91 articles were finally selected to provide proof...
FIGURE 5
Forest plot of the association between combined effects of GSTM1 present/null and GSTT1 present/null polymorphisms and leukemia risk in ethnicity subgroup analysis [(A) Model 1; (B) Model 2; (C) Model 3; (D) Model 4; (E) Model 5; and (F) Model 6].
FIGURE 6
Forest plot of the association between combined effects of GSTM1 present/null and GSTP1 11e105Val polymorphisms and leukemia risk in ethnicity subgroup analysis (A) Model 1, (B) Model 2, (C) Model 3, (D) Model 4, (E) Model 5, and (F) Model 6.
FIGURE 7
Forest plot of the association between the combined effects of GSTTI present/null and GSTP1 11e105Val polymorphisms and leukemia risk in ethnicity subgroup analysis. (A) Model 1; (B) Model 2; (C) Model 3; (D) Model 4; (E) Model 5; and (F) Model 6.
FIGURE 8
Forest plot of the association between the combined effects of GSTM1 present/null, GSTT1 present/null, and GSTP111e105Val polymorphisms and leukemia risk in the ethnicity subgroup analysis. (A): Model 1; (B) Model 2; (C) Model 3; (D) Model 4; (E) Model 5; (F) Model 6; (G) Model 7; (H) Model 8; (I) Model 9; and (J) Model 10.
for the association between GST polymorphisms and leukemia risk.

Overall, the present study showed that the GSTM1, GSTT1, and GSTP1 polymorphisms significantly added the risk of leukemia in the overall and several subgroups. Moreover, with the combined GSTM1 and GSTT1, GSTM1 and GSTP1, and GSTTI and GSTP1 polymorphisms, there were six gene models to explore the association with leukemia risk, and positive results were observed in partial gene models. However, there was no significant contact between the composite effects of these three polymorphisms with

| Variables | Type of leukemia | Age group | Ethnicity | Sample size | Type of control | Matching | HWE | Quality score |
|-----------|------------------|-----------|-----------|-------------|----------------|----------|-----|--------------|
| Genotype  |                  |           |           |             |                |          |     |              |
| GSTM1     | 0.342            | 0.957     | 0.000     | 0.137       | 0.777          | 0.137    | —   | 0.038        |
| GSTT1     | 0.075            | 0.781     | 0.974     | 0.111       | 0.913          | 0.052    | —   | 0.930        |
| GSTP1     |                  |           |           |             |                |          |     |              |
| Ile105Val | Val/Val vs. lle/ll 0.144 | 0.546 | 0.074 | 0.134 | 0.002 | 0.023 | 0.005 | 0.617 |
|          | lle/Val vs. lle/ll 0.385 | 0.450 | 0.767 | 0.892 | 0.445 | 0.190 | 0.280 | 0.714 |
|          | Val/Val vs. lle/ll + lle/Val 0.185 | 0.648 | 0.081 | 0.100 | 0.001 | 0.037 | 0.007 | 0.642 |
|          | Val vs. lle 0.328 | 0.616 | 0.463 | 0.528 | 0.106 | 0.064 | 0.073 | 0.878 |
| The combined effects of GSTM1 and GSTT1 polymorphisms | Model 1 | 0.648 | 0.067 | 0.432 | 0.015 | 0.622 | 0.212 | — | 0.478 |
|          | Model 2 | 0.349 | 0.281 | 0.071 | 0.537 | 0.234 | 0.532 | — | 0.886 |
|          | Model 3 | 0.702 | 0.917 | 0.792 | 0.686 | 0.739 | 0.714 | — | 0.699 |
|          | Model 4 | 0.341 | 0.979 | 0.215 | 0.161 | 0.721 | 0.987 | — | 0.753 |
|          | Model 5 | 0.402 | 0.939 | 0.124 | 0.268 | 0.850 | 0.974 | — | 0.644 |
|          | Model 6 | 0.882 | 0.801 | 0.956 | 0.361 | 0.627 | 0.667 | — | 0.796 |

FIGURE 9
Begg’s funnel plot to assess publication bias.

FIGURE 10
Begg’s funnel plot to assess publication bias.
leukemia in overall analysis. Furthermore, in sensitivity analysis, when selecting Hardy–Weinberg equilibrium (HWE) and medium and high-quality studies, we had come to a similar conclusion.

Finally, in view of the quantities of genomic data being produced currently, we used a more exact Bayesian measure of false-positive found in genetic epidemiological studies in the present study. Using FPRP and BFDP to correct the positive results, in all of these positive results we found previously, only the association between GSTT1 null and leukemia risk was watched in ethnicity (BFDP = 0.367, FPRP = 0.009). Our results indicated that the false-positive associations were common between SNP and disease risk. Moreover, these results further confirmed that the occurrence of leukemia was the result of multiple genes.

Thirteen previous meta-analyses analyzed the links between GSTM1, GSTT1, and GSTP1 polymorphisms and the risk of leukemia. Tang et al. (2014), Ye and Song (2005), Wang et al. (2019), Zhang et al. (2017), Das et al. (2009), and He et al. (2014) discussed the association between GSTM1 and GSTT1 null genotypes and the risk of leukemia, and their results suggested that there was a significant association between GSTM1 and GSTT1 polymorphisms and leukemia risk. The studies of Ma et al. (2014) and Tang et al. (2013) showed that GSTM1 null genotypes increased the risk of acute leukemia. The results of Moulik et al. (2014) demonstrated that there was a significant connection between GSTP1 polymorphism with the risk of leukemia; however, Huang et al. (2013) discussed the association between GSTP1 polymorphism and the risk of leukemia, and the results showed that there was no significant connection. The number of studies and sample sizes in the current study were larger than the published meta-analyses. When comparing to the present meta-analysis, previous studies had several defects. First, none of the previous studies performed quality assessments. Second, HWE was not reported in any published meta-analysis. Third, all previous meta-analyses did not adjust the positive results for multiple comparisons, and only five previous meta-analyses (Ye and Song, 2005; Huang et al., 2013; Tang et al., 2013; Tang et al., 2014; Zhang et al., 2017) conducted subgroup analysis. Fourth, there were no published meta-analyses that performed sensitivity analysis. Moreover, previous meta-analyses had a small sample size; most eligible studies were not assessed for quality assessment; and the reliability of positive results was not evaluated using FPRP, BFDP, and Venice criteria. In addition, they failed to establish a more complete genetic model. Thus, their meta-analyses might have lower credibility.

The current meta-analysis had some advantages over previously published meta-analyses. 1) We explored the credibility by applying the Venice criteria, FPRP, and BFDP. 2) The qualified studies were evaluated for quality. 3) The sample size was larger and the data collected were more detailed over the previous meta-analyses. 4) We conducted more subunit analyses, such as ethnicity, age group, type of control, matching or not, type of leukemia, quality score, and HWE. 5) We established a more complete genetic model. 6) Our study is the first one to explore the combined effects of GSTM1, GSTT1, and GSTP1 polymorphisms with leukemia risk. Nonetheless, there are still some potential limitations for this current study. First, in this study, we only studied published research studies, and as we all know, the positive results are more likely to be published than the
## TABLE 9 Credibility of the current meta-analysis.

| Variables          | Model                | OR (95%CI)          | I2 (%) | Statistical power | Credibility |
|--------------------|----------------------|---------------------|--------|-------------------|-------------|
|                    |                      |                     |        |                   | Prior probability of 0.001 |
|                    |                      |                     |        |                   | FPRP | BFDP   |
|                   |                      |                     |        |                   |     |        |
| GSTM1              |                      |                     |        |                   |     |        |
| Overall Null vs present | 1.28 (1.17–1.40)  | 68.3                | 1.000  |                   | <0.001 | 0.006 |
| Asian Null vs present | 1.50 (1.29–1.73)  | 51.2                | 0.500  |                   | <0.001 | 0.002 |
| Caucasian Null vs present | 1.17 (1.07–1.28) | 46.0                | 1.000  |                   | 0.381  | 0.973 |
| African Null vs present | 1.99 (1.30–3.94)  | 69.0                | 0.209  |                   | 0.996  | 0.998 |
| Adults Null vs present | 1.26 (1.11–1.43) | 65.6                | 0.997  |                   | 0.257  | 0.940 |
| Children Null vs present | 1.42 (1.23–1.64)  | 64.4                | 0.772  |                   | 0.002  | 0.096 |
| HC Null vs present | 1.29 (1.15–1.44)  | 66.6                | 0.996  |                   | 0.008  | 0.273 |
| NBDC Null vs present | 1.29 (1.13–1.48) | 71.9                | 0.984  |                   | 0.222  | 0.924 |
| Matching Null vs present | 1.36 (1.12–1.65) | 77.7                | 0.840  |                   | 0.684  | 0.981 |
| Nonmatching Null vs present | 1.25 (1.14–1.38) | 63.7                | 1.000  |                   | 0.010  | 0.408 |
| AML Null vs present | 1.20 (1.04–1.38)  | 71.1                | 0.999  |                   | 0.914  | 0.997 |
| ALL Null vs present | 1.44 (1.25–1.65)  | 66.8                | 0.722  |                   | <0.001 | 0.010 |
| Sensitivity analysis |                      |                     |        |                   |     |        |
| Quality score ≥10 |                      |                     |        |                   |     |        |
| Overall Null vs present | 1.16 (1.05–1.27)  | 62.2                | 1.000  |                   | 0.569  | 0.986 |
| Asian Null vs present | 1.17 (1.05–1.31)  | 0.0                 | 1.000  |                   | 0.866  | 0.996 |
| Caucasian Null vs present | 1.17 (1.06–1.30) | 45.5                | 1.000  |                   | 0.777  | 0.993 |
| African Null vs present | 2.01 (1.23–3.30)  | 75.1                | 0.124  |                   | 0.979  | 0.990 |
| Adults Null vs present | 1.31 (1.15–1.50)  | 63.2                | 0.975  |                   | 0.087  | 0.816 |
| Children Null vs present | 1.21 (1.06–1.39) | 27.0                | 0.999  |                   | 0.876  | 0.996 |
| HC Null vs present | 1.21 (1.05–1.39)  | 69.4                | 0.999  |                   | 0.876  | 0.996 |
| Matching Null vs present | 1.26 (1.05–1.52) | 73.5                | 0.966  |                   | 0.942  | 0.997 |
| Nonmatching Null vs present | 1.13 (1.02–1.27) | 57.7                | 1.000  |                   | 0.976  | 0.999 |
| ALL Null vs present | 1.22 (1.01–1.46)  | 63.7                | 0.988  |                   | 0.968  | 0.998 |
| GSTT1              |                      |                     |        |                   |     |        |
| Overall Null vs present | 1.46 (1.32–1.60)  | 62.5                | 0.710  |                   | <0.001 | <0.001 |
| Indian Null vs present | 1.74 (1.27–2.38)  | 71.9                | 0.177  |                   | 0.749  | 0.934 |
| Asian Null vs present | 1.30 (1.16–1.46)  | 24.2                | 0.992  |                   | 0.009  | 0.367 |
| Caucasian Null vs present | 1.37 (1.17–1.59) | 65.0                | 0.884  |                   | 0.037  | 0.619 |
| African Null vs present | 2.08 (1.32–3.26) | 66.5                | 0.720  |                   | 0.999  | 0.971 |
| Adults Null vs present | 1.55 (1.32–1.82)  | 69.6                | 0.344  |                   | <0.001 | 0.006 |
| Children Null vs present | 1.24 (1.09–1.43) | 37.2                | 0.996  |                   | 0.754  | 0.991 |
| Adults and Children Null vs present | 1.59 (1.27–1.99) | 67.1                | 0.305  |                   | 0.143  | 0.655 |
| HC Null vs present | 1.45 (1.28–1.66)  | 63.7                | 0.688  |                   | <0.001 | 0.005 |
| NBDC Null vs present | 1.46 (1.26–1.69)  | 62.7                | 0.641  |                   | 0.001  | 0.024 |
| Matching Null vs present | 1.80 (1.44–2.24) | 63.7                | 0.051  |                   | 0.003  | 0.008 |
| Nonmatching Null vs present | 1.35 (1.22–1.49) | 51.7                | 0.982  |                   | <0.001 | <0.001 |
| AML Null vs present | 1.41 (1.19–1.66)  | 67.7                | 0.771  |                   | 0.046  | 0.622 |
| ALL Null vs present | 1.33 (1.16–1.53)  | 53.0                | 0.954  |                   | 0.065  | 0.758 |
| CML Null vs present | 1.88 (1.47–2.41)  | 64.5                | 0.037  |                   | 0.017  | 0.033 |

(Continued on following page)
TABLE 9 (Continued) Credibility of the current meta-analysis.

| Variables         | Model                  | OR (95%CI) | I2 (%) | Statistical power | Credibility |
|-------------------|------------------------|------------|--------|-------------------|-------------|
|                   |                        |            |        |                   | Prior probability of 0.001 |
|                   |                        |            |        |                   | FPRP | BFDP |
| Sensitivity analysis | Quality score ≥10 | | | | |
| Overall           | Null vs present        | 1.52 (1.34–1.72) | 66.9   | 0.417             | <0.001 | <0.001 |
| Indian            | Null vs present        | 1.53 (1.08–2.17) | 69.6   | 0.456             | 0.974 | 0.996 |
| Asian             | Null vs present        | 1.15 (1.01–1.31) | 21.5   | 1.000             | 0.973 | 0.999 |
| Caucasian         | Null vs present        | 1.64 (1.37–1.96) | 64.5   | 0.163             | <0.001 | 0.003 |
| African           | Null vs present        | 2.12 (1.26–3.58) | 71.9   | 0.098             | 0.981 | 0.989 |
| Adults            | Null vs present        | 1.58 (1.33–1.89) | 71.3   | 0.285             | 0.002 | 0.030 |
| Adults and Children | Null vs present       | 1.45 (1.14–1.83) | 61.5   | 0.612             | 0.741 | 0.978 |
| HC                | Null vs present        | 1.56 (1.31–1.86) | 71.0   | 0.331             | 0.002 | 0.038 |
| NRDC              | Null vs present        | 1.45 (1.23–1.72) | 56.7   | 0.651             | 0.030 | 0.475 |
| Matching          | Null vs present        | 1.73 (1.37–2.17) | 73.6   | 0.109             | 0.019 | 0.093 |
| Nonmatching       | Null vs present        | 1.41 (1.23–1.62) | 59.2   | 0.809             | 0.002 | 0.069 |
| AML               | Null vs present        | 1.35 (1.12–1.63) | 68.3   | 0.863             | 0.676 | 0.981 |
| ALL               | Null vs present        | 1.49 (1.19–1.88) | 64.2   | 0.522             | 0.597 | 0.956 |
| GSTP1             |                        |            |        |                   |     |     |
| Overall           | Val/Val vs lle/lle     | 1.77 (1.40–2.24) | 59.8   | 0.084             | 0.023 | 0.089 |
|                  | lle/Val vs lle/lle     | 1.24 (1.08–1.43) | 67.7   | 0.996             | 0.757 | 0.991 |
|                  | Val/Val vs lle/lle + lle/Val | 1.59 (1.29–1.95) | 50.9 | 0.288 | 0.028 | 0.273 |
|                  | Val/Val/lle/Val vs lle/lle | 1.32 (1.15–1.53) | 72.6   | 0.955             | 0.193 | 0.905 |
|                  | Val vs lle             | 1.31 (1.16–1.47) | 75.0   | 0.989             | 0.004 | 0.220 |
| Indian            | Val/Val vs lle/lle     | 3.01 (1.60–5.66) | 76.8   | 0.015             | 0.976 | 0.961 |
|                  | lle/Val vs lle/lle     | 1.28 (1.08–1.53) | 30.3   | 0.959             | 0.874 | 0.994 |
|                  | Val/Val vs lle/lle + lle/Val | 2.65 (1.47–4.79) | 74.8   | 0.030             | 0.977 | 0.974 |
|                  | Val/Val/Val/Val vs lle/lle | 1.45 (1.17–1.80) | 57.2   | 0.621             | 0.549 | 0.957 |
|                  | Val vs lle             | 1.47 (1.19–1.80) | 72.1   | 0.578             | 0.250 | 0.869 |
| Caucasian         | Val/Val vs lle/lle     | 1.49 (1.10–2.01) | 40.2   | 0.517             | 0.946 | 0.994 |
|                  | Val/Val vs lle/lle + lle/Val | 1.31 (1.04–1.65) | 15.3   | 0.875             | 0.961 | 0.997 |
|                  | Val/Val/Val/Val vs lle/lle | 1.32 (1.02–1.72) | 75.6   | 0.828             | 0.980 | 0.998 |
|                  | Val vs lle             | 1.28 (1.05–1.55) | 74.0   | 0.948             | 0.924 | 0.996 |
| Adults            | Val/Val vs lle/lle     | 1.39 (1.06–1.82) | 34.1   | 0.710             | 0.959 | 0.996 |
|                  | Val/Val vs lle/lle + lle/Val | 1.27 (1.01–1.61) | 20.2   | 0.915             | 0.981 | 0.999 |
|                  | Val vs lle             | 1.18 (1.02–1.37) | 64.6   | 0.999             | 0.968 | 0.999 |
| Children          | Val/Val vs lle/lle     | 1.68 (1.10–2.58) | 39.6   | 0.302             | 0.983 | 0.996 |
|                  | Val/Val vs lle/lle + lle/Val | 1.60 (1.11–2.32) | 25.8   | 0.367             | 0.973 | 0.995 |
| Adults and Children | Val/Val vs lle/lle   | 3.25 (1.61–6.53) | 76.8   | 0.015             | 0.984 | 0.974 |
|                  | lle/Val vs lle/lle     | 1.64 (1.16–2.31) | 73.7   | 0.305             | 0.938 | 0.989 |
|                  | Val/Val vs lle/lle + lle/Val | 2.65 (1.41–5.02) | 72.9   | 0.040             | 0.986 | 0.986 |
|                  | Val/Val/Val/Val vs lle/lle | 1.82 (1.29–2.57) | 77.3   | 0.136             | 0.831 | 0.945 |
|                  | Val vs lle             | 1.72 (1.29–2.30) | 80.4   | 0.176             | 0.588 | 0.883 |
| HC                | Val/Val vs lle/lle     | 2.38 (1.66–3.41) | 61.2   | 0.006             | 0.278 | 0.118 |
|                  | lle/Val vs lle/lle     | 1.27 (1.05–1.54) | 65.2   | 0.955             | 0.940 | 0.997 |

(Continued on following page)
TABLE 9 (Continued) Credibility of the current meta-analysis.

| Variables | Model | OR (95%CI) | I2 (%) | Statistical power | Credibility |
|-----------|-------|------------|--------|--------------------|-------------|
|           |       |            |        |                    | Prior probability of 0.001 |
|           |       |            |        |                    | FPRP | BFDP |
|           |       |            |        |                    |     |     |
| Prior probability of 0.001 |     |     |
| Nonmatching |       |            |        |                    |     |     |
| Val/Val vs. lle/lle + lle/Val | 2.12 (1.53–2.94) | 55.3 | 0.019 | 0.259 | 0.239 |
| Val/Val+lle/Val vs. lle/lle | 1.39 (1.15–1.69) | 69.6 | 0.778 | 0.552 | 0.967 |
| Val vs lle | 1.40 (1.19–1.63) | 71.5 | 0.813 | 0.018 | 0.419 |
| Nonmatching |       |            |        |                    |     |     |
| Val/Val vs. lle/lle | 1.37 (1.07–1.76) | 23.1 | 0.761 | 0.948 | 0.996 |
| Val/Val+lle/Val vs. lle/lle | 1.30 (1.03–1.64) | 19.2 | 0.886 | 0.968 | 0.998 |
| Val vs lle | 1.13 (1.03–1.24) | 6.1 | 1.000 | 0.908 | 0.998 |
| Nonmatching |       |            |        |                    |     |     |
| Val/Val vs. lle/lle | 2.13 (1.49–3.06) | 69.0 | 0.029 | 0.598 | 0.628 |
| lle/Val vs. lle/lle | 1.36 (1.08–1.71) | 78.4 | 0.799 | 0.914 | 0.994 |
| Val/Val vs. lle/lle + lle/Val | 1.86 (1.36–2.54) | 60.6 | 0.088 | 0.518 | 0.760 |
| Val/Val+lle/Val vs. lle/lle | 1.47 (1.17–1.86) | 81.7 | 0.567 | 0.701 | 0.972 |
| Val vs lle | 1.44 (1.19–1.74) | 82.8 | 0.664 | 0.193 | 0.852 |
| AML |       |            |        |                    |     |     |
| Val/Val vs. lle/lle | 1.57 (1.10–2.24) | 66.4 | 0.401 | 0.970 | 0.995 |
| lle/Val vs. lle/lle | 1.37 (1.02–1.84) | 83.1 | 0.727 | 0.980 | 0.998 |
| Val/Val vs. lle/lle + lle/Val | 1.37 (1.01–1.84) | 55.1 | 0.727 | 0.980 | 0.998 |
| Val/Val+lle/Val vs. lle/lle | 1.42 (1.06–1.89) | 84.8 | 0.646 | 0.962 | 0.996 |
| Val vs lle | 1.34 (1.07–1.68) | 85.1 | 0.836 | 0.930 | 0.996 |
| ALL |       |            |        |                    |     |     |
| Val/Val vs. lle/lle | 1.90 (1.28–2.81) | 52.1 | 0.118 | 0.917 | 0.968 |
| Val/Val vs. lle/lle +lle/Val | 1.77 (1.25–2.53) | 44.0 | 0.182 | 0.905 | 0.974 |
| Val/Val+lle/Val vs. lle/lle | 1.26 (1.03–1.53) | 51.4 | 0.961 | 0.953 | 0.998 |
| Val vs lle | 1.29 (1.08–1.53) | 61.0 | 0.958 | 0.782 | 0.990 |
| CML |       |            |        |                    |     |     |
| Val/Val vs. lle/lle | 1.29 (1.08–1.53) | 67.3 | 0.958 | 0.782 | 0.990 |
| Val/Val vs.lle/lle + lle/Val | 2.13 (1.08–4.24) | 60.1 | 0.159 | 0.995 | 0.997 |
| Sensitivity analysis |       |            |        |                    |     |     |
| HWE |       |            |        |                    |     |     |
| Overall | Val/Val vs. lle/lle | 1.58 (1.27–1.95) | 26.3 | 0.314 | 0.061 | 0.455 |
| lle/Val vs. lle/lle | 1.18 (1.02–1.37) | 59.0 | 0.999 | 0.968 | 0.999 |
| Val/Val vs. lle/lle + lle/Val | 1.45 (1.21–1.74) | 7.3 | 0.642 | 0.092 | 0.722 |
| Val/Val+lle/Val vs. lle/lle | 1.25 (1.07–1.45) | 64.1 | 0.992 | 0.764 | 0.991 |
| Val vs lle | 1.24 (1.10–1.40) | 64.4 | 0.999 | 0.339 | 0.959 |
| Indian | Val/Val vs. lle/lle | 1.83 (1.11–3.03) | 56.3 | 0.220 | 0.988 | 0.996 |
| lle/Val vs. lle/lle | 1.24 (1.01–1.51) | 12.7 | 0.971 | 0.971 | 0.998 |
| Val/Val vs. lle/lle + lle/Val | 1.67 (1.05–2.64) | 51.3 | 0.323 | 0.989 | 0.997 |
| Val/Val+lle/Val vs. lle/lle | 1.34 (1.06–1.69) | 42.1 | 0.830 | 0.942 | 0.996 |
| Val vs lle | 1.33 (1.06–1.66) | 61.2 | 0.856 | 0.932 | 0.996 |
| Caucasian | Val/Val vs. lle/lle | 1.70 (1.23–2.34) | 21.0 | 0.221 | 0.837 | 0.964 |
| Val/Val vs. lle/lle +lle/Val | 1.50 (1.14–1.95) | 0.0 | 0.500 | 0.831 | 0.982 |
| Val/Val+lle/Val vs. lle/lle | 1.39 (1.01–1.90) | 76.4 | 0.684 | 0.983 | 0.998 |
| Val vs lle | 1.36 (1.08–1.70) | 72.8 | 0.805 | 0.896 | 0.993 |
| Adults | Val/Val vs. lle/lle | 1.39 (1.07–1.81) | 0.0 | 0.714 | 0.953 | 0.996 |
| Val/Val vs.lle/lle + lle/Val | 1.31 (1.02–1.69) | 0.0 | 0.851 | 0.978 | 0.998 |
| Val vs lle | 1.22 (1.01–1.46) | 67.7 | 0.988 | 0.968 | 0.998 |
| Children | Val/Val vs. lle/lle | 1.68 (1.10–2.58) | 39.6 | 0.302 | 0.983 | 0.996 |
| Val/Val vs.lle/lle + lle/Val | 1.60 (1.11–2.32) | 25.8 | 0.367 | 0.973 | 0.995 |

(Continued on following page)
| Variables          | Model | OR (95%CI)          | I2 (%) | Statistical power | Credibility | Credibility |
|--------------------|-------|---------------------|--------|-------------------|-------------|-------------|
|                    |       |                     |        |                   | Prior probability of 0.001 | FPRP | BFDP |
| Adults and Children|       |                     |        |                   |             |             |
| HC                 |       |                     |        |                   |             |             |
|                    | Val/Val vs. lle/lle | 1.39 (1.01–1.92) | 57.0   | 0.678             | 0.985 | 0.998 |
|                    | Val/Val vs. lle/lle + lle/Val vs. lle/lle | 1.71 (1.33–2.21) | 16.0   | 0.158             | 0.207 | 0.603 |
|                    | Val vs lle | 1.31 (1.05–1.62) | 69.8   | 0.894             | 0.934 | 0.996 |
| Matching           |       |                     |        |                   |             |             |
|                    | Val/Val vs. lle/lle | 1.51 (1.11–2.05) | 0.0    | 0.483             | 0.945 | 0.993 |
|                    | Val/Val vs. lle/lle + lle/Val vs. lle/lle | 1.43 (1.07–1.93) | 0.0    | 0.623             | 0.969 | 0.997 |
|                    | Val vs lle | 1.17 (1.01–1.35) | 0.0    | 1.000             | 0.969 | 0.999 |
| Non matching       |       |                     |        |                   |             |             |
|                    | Val/Val vs. lle/lle | 1.66 (1.21–2.27) | 47.1   | 0.263             | 0.851 | 0.972 |
|                    | Val/Val vs. lle/lle + lle/Val vs. lle/lle | 1.50 (1.15–1.94) | 28.8   | 0.500             | 0.800 | 0.979 |
|                    | Val vs lle | 1.31 (1.03–1.66) | 76.9   | 0.869             | 0.967 | 0.998 |
| ALL                |       |                     |        |                   |             |             |
|                    | Val/Val vs. lle/lle | 1.60 (1.15–2.22) | 26.8   | 0.350             | 0.933 | 0.989 |
|                    | Val/Val vs. lle/lle + lle/Val vs. lle/lle | 1.53 (1.14–2.06) | 17.8   | 0.448             | 0.919 | 0.990 |
|                    | Val vs lle | 1.21 (1.03–1.43) | 52.6   | 0.994             | 0.962 | 0.998 |
| Quality score≥12  |       |                     |        |                   |             |             |
| Overall            |       |                     |        |                   |             |             |
|                    | Val/Val vs. lle/lle | 1.62 (1.25–2.11) | 45.7   | 0.284             | 0.549 | 0.910 |
|                    | Val/Val vs. lle/lle + lle/Val vs. lle/lle | 1.49 (1.18–1.89) | 35.6   | 0.522             | 0.660 | 0.964 |
|                    | Val vs lle | 1.23 (1.05–1.44) | 64.0   | 0.993             | 0.910 | 0.996 |
| Caucasian          |       |                     |        |                   |             |             |
|                    | Val/Val vs. lle/lle | 1.54 (1.09–2.17) | 28.7   | 0.440             | 0.969 | 0.995 |
|                    | Val/Val vs. lle/lle + lle/Val vs. lle/lle | 1.28 (1.01–1.64) | 0.0    | 0.895             | 0.983 | 0.999 |
|                    | Val vs lle | 1.48 (1.04–2.10) | 77.2   | 0.530             | 0.981 | 0.997 |
| Indian             |       |                     |        |                   |             |             |
|                    | Val/Val vs. lle/lle | 2.15 (1.22–3.76) | 62.6   | 0.103             | 0.986 | 0.992 |
|                    | Val/Val vs. lle/lle + lle/Val vs. lle/lle | 1.97 (1.16–3.35) | 60.3   | 0.157             | 0.987 | 0.995 |
|                    | Val vs lle | 1.29 (1.03–1.63) | 47.1   | 0.897             | 0.973 | 0.998 |
| Adults             |       |                     |        |                   |             |             |
|                    | Val/Val vs. lle/lle | 1.42 (1.07–1.88) | 33.1   | 0.649             | 0.957 | 0.996 |
|                    | Val/Val vs. lle/lle + lle/Val vs. lle/lle | 1.29 (1.02–1.64) | 17.3   | 0.891             | 0.977 | 0.998 |
|                    | Val vs lle | 1.24 (1.01–1.51) | 68.9   | 0.971             | 0.971 | 0.998 |
| HC                 |       |                     |        |                   |             |             |
|                    | Val/Val vs. lle/lle | 1.94 (1.37–2.76) | 44.2   | 0.076             | 0.750 | 0.874 |
|                    | Val/Val vs. lle/lle + lle/Val vs. lle/lle | 1.77 (1.29–2.44) | 36.9   | 0.156             | 0.758 | 0.930 |
|                    | Val vs lle | 1.30 (1.05–1.62) | 64.8   | 0.899             | 0.956 | 0.997 |
| Matching           |       |                     |        |                   |             |             |
|                    | Val/Val vs. lle/lle | 1.45 (1.11–1.90) | 16.9   | 0.597             | 0.922 | 0.993 |
|                    | Val/Val vs. lle/lle + lle/Val vs. lle/lle | 1.41 (1.08–1.83) | 18.9   | 0.679             | 0.935 | 0.995 |
|                    | Val vs lle | 1.14 (1.04–1.25) | 0.0    | 1.000             | 0.841 | 0.996 |
| Non matching       |       |                     |        |                   |             |             |
|                    | Val/Val vs. lle/lle | 1.81 (1.07–3.06) | 67.1   | 0.242             | 0.991 | 0.997 |
|                    | Val/Val vs. lle/lle + lle/Val vs. lle/lle | 1.58 (1.02–2.46) | 55.9   | 0.409             | 0.991 | 0.998 |
| CML                |       |                     |        |                   |             |             |
|                    | Val/Val vs. lle/lle | 3.17 (1.89–5.32) | 16.7   | 0.002             | 0.845 | 0.489 |

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TABLE 9 (Continued) Credibility of the current meta-analysis.

| Variables                                      | Model | OR (95%CI) | I2 (%) | Statistical power | Credibility |
|------------------------------------------------|-------|------------|--------|-------------------|-------------|
|                                                |       |            |        |                   |             |
|                                                |       |            |        | Prior probability |             |
|                                                |       |            |        | of 0.001          |             |
|                                                |       |            |        | FPRP              | BFP         |
| Val/Val vs lle/lle + lle/Val                   | 2.80  | (1.79–4.39) | 0.0    | 0.003             | 0.688       |
| Val vs lle                                    | 1.41  | (1.05–1.89) | 68.3   | 0.661             | 0.970       |
| HWE and Quality score ≥ 12                    |       |            |        |                   |             |
| Overall Val/Val vs lle/lle                    | 1.63  | (1.24–2.13) | 35.2   | 0.271             | 0.559       |
| Val/Val vs lle/lle + lle/Val                  | 1.49  | (1.18–1.88) | 20.2   | 0.522             | 0.597       |
| Val/Val lle/Val vs lle/lle                    | 1.27  | (1.06–1.53) | 66.8   | 0.960             | 0.925       |
| Val vs lle                                    | 1.26  | (1.08–1.46) | 67.7   | 0.990             | 0.680       |
| Indian Val/Val vs lle/lle                     | 1.91  | (1.07–3.40) | 62.6   | 0.206             | 0.993       |
| Val/Val vs lle/lle + lle/Val                  | 1.74  | (1.03–2.96) | 57.8   | 0.292             | 0.993       |
| Val/Val lle/Val Val vs lle/lle                | 1.34  | (1.02–1.76) | 51.7   | 0.791             | 0.978       |
| Val vs lle                                    | 1.34  | (1.04–1.74) | 67.4   | 0.801             | 0.972       |
| Caucasian Val/Val vs lle/lle                  | 1.87  | (1.28–2.74) | 0.0    | 0.129             | 0.911       |
| Val/Val vs lle/lle + lle/Val                  | 1.55  | (1.02–2.34) | 71.9   | 0.438             | 0.988       |
| Val/Val lle/Val Val vs lle/lle                | 1.59  | (1.11–2.30) | 0.0    | 0.379             | 0.973       |
| Val vs lle                                    | 1.63  | (1.22–2.37) | 68.7   | 0.332             | 0.969       |
| Adults Val/Val vs lle/lle                     | 1.50  | (1.17–1.91) | 56.4   | 0.500             | 0.668       |
| Val vs lle                                    | 1.38  | (1.05–1.82) | 3.2    | 0.723             | 0.969       |
| HC Val/Val vs lle/lle                         | 1.24  | (1.02–1.52) | 70.4   | 0.967             | 0.973       |
| Val/Val vs lle/lle + lle/Val                  | 1.83  | (1.29–2.58) | 40.3   | 0.128             | 0.815       |
| Val/Val lle/Val Val vs lle/lle                | 1.66  | (1.23–2.25) | 28.2   | 0.257             | 0.809       |
| Val vs lle                                    | 1.33  | (1.05–1.68) | 66.7   | 0.844             | 0.952       |
| Val/Val vs lle/lle + lle/Val                  | 1.32  | (1.09–1.59) | 66.8   | 0.911             | 0.791       |
| Matching Val/Val vs lle/lle                   | 1.51  | (1.11–2.05) | 0.0    | 0.483             | 0.945       |
| Val/Val vs lle/lle + lle/Val                  | 1.43  | (1.07–1.93) | 0.0    | 0.623             | 0.969       |
| Val/Val lle/Val Val vs lle/lle                | 1.17  | (1.01–1.35) | 0.0    | 1.000             | 0.969       |
| Val vs lle                                    | 1.18  | (1.05–1.32) | 0.0    | 1.000             | 0.792       |
| Nonmatching Val/Val vs lle/lle                | 1.81  | (1.07–3.06) | 67.1   | 0.242             | 0.991       |
| Val/Val vs lle/lle + lle/Val                  | 1.58  | (1.02–2.46) | 55.9   | 0.409             | 0.991       |
| The combined effects of GSTM1 and GSTT1 polymorphisms |      |            |        |                   |             |
| Overall Model 1                               | 1.66  | (1.37–2.00) | 30.3   | 0.143             | 0.001       |
| Model 3                                       | 2.44  | (1.86–3.21) | 51.2   | <0.001            | 0.001       |
| Model 4                                       | 1.29  | (1.11–1.50) | 52.2   | 0.975             | 0.489       |
| Model 5                                       | 1.44  | (1.25–1.66) | 51.5   | 0.713             | 0.001       |
| Model 6                                       | 2.16  | (1.65–2.81) | 55.4   | 0.003             | 0.003       |
| Indian Model 1                                | 1.92  | (1.18–3.12) | 52.9   | 0.159             | 0.981       |
| Model 3                                       | 3.16  | (1.90–5.25) | 0.0    | 0.002             | 0.816       |
| Model 6                                       | 2.83  | (1.73–4.64) | 0.0    | 0.006             | 0.863       |
| Asian Model 1                                 | 1.43  | (1.04–1.97) | 22.1   | 0.615             | 0.979       |
| Model 3                                       | 2.47  | (1.55–3.95) | 57.5   | 0.019             | 0.896       |
| Model 4                                       | 1.35  | (1.02–1.80) | 45.3   | 0.764             | 0.982       |
| Model 5                                       | 1.57  | (1.20–2.05) | 44.0   | 0.369             | 0.713       |
| Model 6                                       | 2.05  | (1.40–3.00) | 50.3   | 0.054             | 0.803       |
| Caucasian Model 1                             | 1.65  | (1.14–2.39) | 40.6   | 0.307             | 0.963       |

(Continued on following page)
TABLE 9 (Continued) Credibility of the current meta-analysis.

| Variables         | Model | OR (95%CI) | I2 (%) | Statistical power | Credibility |
|-------------------|-------|------------|--------|-------------------|-------------|
|                   |       |            |        |                   | FPRP | BFDP |
| Prior probability |       |            |        |                   | of 0.001 |
| of 0.001          |       |            |        |                   |     |
| Adults            | Model 1 | 1.44 (1.18–1.76) | 0.0 | 0.655 | 0.360 | 0.923 |
|                   | Model 2 | 1.27 (1.04–1.54) | 50.7 | 0.955 | 0.940 | 0.997 |
|                   | Model 3 | 2.51 (1.71–3.68) | 60.0 | 0.004 | 0.367 | 0.131 |
|                   | Model 4 | 1.34 (1.15–1.57) | 35.3 | 0.919 | 0.242 | 0.919 |
|                   | Model 5 | 1.50 (1.29–1.74) | 33.0 | 0.500 | < 0.001 | 0.006 |
| Adults and children | Model 6 | 2.26 (1.53–3.33) | 65.8 | 0.019 | 0.662 | 0.610 |
| HC                | Model 1 | 1.73 (1.31–2.30) | 39.2 | 0.163 | 0.498 | 0.835 |
|                   | Model 3 | 2.59 (1.71–3.93) | 51.1 | 0.005 | 0.600 | 0.310 |
|                   | Model 5 | 1.45 (1.16–1.80) | 60.3 | 0.621 | 0.549 | 0.957 |
|                   | Model 6 | 2.33 (1.54–3.58) | 59.7 | 0.022 | 0.8361 | 0.811 |
| NBDC              | Model 1 | 1.60 (1.22–2.10) | 25.7 | 0.321 | 0.687 | 0.949 |
|                   | Model 2 | 1.29 (1.11–1.50) | 0.0 | 0.975 | 0.489 | 0.971 |
|                   | Model 3 | 2.31 (1.56–3.43) | 55.7 | 0.016 | 0.672 | 0.589 |
|                   | Model 4 | 1.36 (1.18–1.57) | 1.6 | 0.909 | 0.029 | 0.572 |
|                   | Model 5 | 1.49 (1.25–1.78) | 33.9 | 0.529 | 0.020 | 0.338 |
|                   | Model 6 | 1.86 (1.33–3.33) | 46.7 | 0.107 | 0.756 | 0.904 |
| Matching          | Model 1 | 1.60 (1.29–1.99) | 0.0 | 0.281 | 0.079 | 0.491 |
|                   | Model 3 | 2.57 (1.61–4.12) | 64.2 | 0.463 | 0.999 | 0.999 |
|                   | Model 4 | 1.31 (1.09–1.58) | 41.0 | 0.922 | 0.837 | 0.992 |
|                   | Model 5 | 1.46 (1.24–1.73) | 33.8 | 0.623 | 0.019 | 0.367 |
|                   | Model 6 | 2.33 (1.44–3.76) | 69.6 | 0.036 | 0.937 | 0.942 |
| Nonmatching       | Model 1 | 1.67 (1.24–2.27) | 48.0 | 0.247 | 0.811 | 0.963 |
|                   | Model 3 | 2.38 (1.70–3.33) | 37.6 | 0.004 | 0.106 | 0.027 |
|                   | Model 5 | 1.43 (1.13–1.80) | 62.1 | 0.658 | 0.779 | 0.983 |
|                   | Model 6 | 2.07 (1.52–2.81) | 36.5 | 0.019 | 0.137 | 0.133 |
| AML               | Model 3 | 2.15 (1.35–3.43) | 55.1 | 0.065 | 0.953 | 0.970 |
|                   | Model 5 | 1.41 (1.09–1.82) | 46.7 | 0.683 | 0.924 | 0.994 |
|                   | Model 6 | 1.85 (1.22–2.80) | 51.1 | 0.161 | 0.957 | 0.986 |
| ALL               | Model 1 | 2.15 (1.43–3.23) | 39.9 | 0.041 | 0.846 | 0.880 |
|                   | Model 3 | 2.79 (1.47–5.30) | 52.0 | 0.029 | 0.983 | 0.981 |
|                   | Model 4 | 1.52 (1.13–2.05) | 44.5 | 0.465 | 0.929 | 0.991 |
|                   | Model 5 | 1.66 (1.25–2.20) | 42.7 | 0.240 | 0.636 | 0.922 |
|                   | Model 6 | 2.23 (1.20–4.14) | 55.4 | 0.105 | 0.991 | 0.994 |
| CML               | Model 1 | 1.54 (1.18–2.01) | 7.2 | 0.423 | 0.778 | 0.973 |
|                   | Model 3 | 2.58 (1.57–4.24) | 51.4 | 0.016 | 0.919 | 0.880 |
|                   | Model 5 | 1.37 (1.06–1.77) | 62.5 | 0.756 | 0.955 | 0.996 |
|                   | Model 6 | 2.41 (1.45–4.00) | 55.8 | 0.033 | 0.952 | 0.953 |

(Continued on following page)
### TABLE 9 (Continued) Credibility of the current meta-analysis.

| Variables                  | Model     | OR (95%CI) | I2 (%) | Statistical power | Credibility |
|---------------------------|-----------|------------|--------|-------------------|-------------|
|                           |           |            |        |                   | Prior probability of 0.001 |
|                           |           |            |        |                   | FPRP | BFDP |
| Sensitivity analysis      |           |            |        |                   |     |
| Quality score ≥10 Models  |           |            |        |                   |     |
| Overall                   | Model 1   | 1.56 (1.28–1.91) | 26.3   | 0.352             | 0.045 | 0.413 |
|                           | Model 3   | 2.41 (1.76–3.29) | 55.3   | 0.001             | 0.021 | 0.002 |
|                           | Model 4   | 1.27 (1.09–1.48) | 48.3   | 0.983             | 0.691 | 0.986 |
|                           | Model 5   | 1.42 (1.22–1.65) | 51.7   | 0.763             | 0.006 | 0.201 |
|                           | Model 6   | 2.17 (1.61–2.94) | 57.8   | 0.009             | 0.063 | 0.033 |
| Indian                    | Model 1   | 1.92 (1.18–3.12) | 52.9   | 0.159             | 0.981 | 0.993 |
|                           | Model 3   | 3.16 (1.90–5.25) | 0.0    | 0.002             | 0.816 | 0.412 |
|                           | Model 6   | 2.83 (1.73–4.64) | 0.0    | 0.006             | 0.863 | 0.674 |
| Caucasian                 | Model 1   | 1.43 (1.16–1.76) | 33.6   | 0.674             | 0.950 | 0.997 |
|                           | Model 3   | 1.34 (1.13–1.58) | 11.5   | 0.910             | 0.354 | 0.947 |
| Adults                    | Model 1   | 1.31 (1.08–1.60) | 48.8   | 0.908             | 0.899 | 0.995 |
|                           | Model 2   | 2.40 (1.61–3.58) | 59.9   | 0.011             | 0.626 | 0.463 |
|                           | Model 4   | 1.37 (1.16–1.61) | 35.8   | 0.862             | 0.132 | 0.843 |
|                           | Model 5   | 1.51 (1.29–1.77) | 37.4   | 0.467             | 0.001 | 0.022 |
|                           | Model 6   | 2.13 (1.43–3.18) | 64.7   | 0.043             | 0.834 | 0.875 |
| Adults and children       | Model 1   | 1.94 (1.04–4.36) | 43.6   | 0.267             | 0.998 | 0.999 |
| HC                        | Model 1   | 1.63 (1.21–2.18) | 34.9   | 0.288             | 0.774 | 0.961 |
|                           | Model 3   | 2.56 (1.60–4.10) | 55.0   | 0.013             | 0.875 | 0.798 |
|                           | Model 5   | 1.41 (1.11–1.80) | 63.6   | 0.690             | 0.894 | 0.992 |
|                           | Model 6   | 2.39 (1.50–3.80) | 58.7   | 0.024             | 0.904 | 0.890 |
| NBDC                      | Model 1   | 1.47 (1.12–1.94) | 15.7   | 0.557             | 0.921 | 0.992 |
|                           | Model 2   | 1.24 (1.06–1.45) | 34.9   | 0.991             | 0.876 | 0.995 |
|                           | Model 3   | 2.17 (1.43–3.29) | 54.9   | 0.041             | 0.865 | 0.893 |
|                           | Model 4   | 1.30 (1.12–1.50) | 54.9   | 0.975             | 0.251 | 0.931 |
|                           | Model 5   | 1.41 (1.19–1.66) | 17.2   | 0.771             | 0.046 | 0.622 |
|                           | Model 6   | 1.85 (1.27–2.69) | 51.3   | 0.136             | 0.904 | 0.967 |
| Matching                  | Model 1   | 1.60 (1.29–1.99) | 0.0    | 0.281             | 0.379 | 0.491 |
|                           | Model 4   | 2.57 (1.61–4.12) | 64.2   | 0.463             | 0.999 | 0.999 |
|                           | Model 5   | 1.31 (1.09–1.58) | 41.0   | 0.922             | 0.837 | 0.992 |
|                           | Model 6   | 1.46 (1.24–1.73) | 33.8   | 0.623             | 0.019 | 0.367 |
| Nonmatching               | Model 1   | 2.33 (1.44–3.76) | 69.6   | 0.036             | 0.937 | 0.942 |
|                           | Model 3   | 1.51 (1.04–2.19) | 48.0   | 0.486             | 0.984 | 0.997 |
|                           | Model 5   | 2.26 (1.45–3.53) | 46.7   | 0.036             | 0.904 | 0.915 |
|                           | Model 6   | 1.37 (1.03–1.82) | 65.1   | 0.734             | 0.976 | 0.998 |
|                           | Model 6   | 2.04 (1.40–2.98) | 37.7   | 0.056             | 0.802 | 0.876 |
| ALL                       | Model 1   | 1.92 (1.28–2.86) | 29.6   | 0.112             | 0.922 | 0.969 |
|                           | Model 3   | 3.10 (1.48–6.49) | 58.1   | 0.027             | 0.990 | 0.988 |
|                           | Model 4   | 1.43 (1.07–1.91) | 39.3   | 0.627             | 0.961 | 0.996 |
|                           | Model 5   | 1.59 (1.18–2.14) | 45.8   | 0.350             | 0.863 | 0.980 |
|                           | Model 6   | 2.66 (1.38–5.15) | 54.1   | 0.045             | 0.988 | 0.989 |

(Continued on following page)
| Variables | Model | OR (95%CI) | I2 (%) | Statistical power | Credibility |
|-----------|-------|------------|--------|-------------------|-------------|
|           |       |            |        |                   | Prior probability of 0.001 |
|           |       |            |        |                   | FPRP | BFDP |
| CML       | Model 1 | 1.55 (1.15–2.09) | 16.4 | 0.415 | 0.907 | 0.988 |
|           | Model 3 | 2.39 (1.37–4.16) | 54.3 | 0.050 | 0.976 | 0.981 |
|           | Model 5 | 1.38 (1.03–1.83) | 66.2 | 0.719 | 0.972 | 0.997 |
|           | Model 6 | 2.21 (1.26–3.87) | 27.7 | 0.088 | 0.984 | 0.990 |
| Overall   | Model 4 | 1.95 (1.35–2.80) | 21.5 | 0.078 | 0.793 | 0.897 |
|           | Model 6 | 1.95 (1.37–2.77) | 30.4 | 0.071 | 0.729 | 0.857 |
| Indian    | Model 4 | 1.72 (1.10–2.70) | 33.5 | 0.276 | 0.985 | 0.996 |
|           | Model 6 | 1.65 (1.14–2.40) | 19.6 | 0.309 | 0.966 | 0.993 |
| HC        | Model 4 | 1.82 (1.21–2.74) | 25.9 | 0.177 | 0.959 | 0.987 |
|           | Model 6 | 1.88 (1.23–2.89) | 41.8 | 0.152 | 0.964 | 0.987 |
| Matching  | Model 6 | 2.20 (1.25–3.89) | 37.1 | 0.094 | 0.986 | 0.992 |
| Non-matching | Model 4 | 2.07 (1.34–3.20) | 0.0 | 0.074 | 0.935 | 0.964 |
|           | Model 5 | 1.44 (1.08–1.92) | 0.0 | 0.610 | 0.955 | 0.995 |
|           | Model 6 | 1.76 (1.05–2.96) | 42.1 | 0.273 | 0.992 | 0.997 |
| ALL       | Model 4 | 1.86 (1.01–3.43) | 51.9 | 0.245 | 0.995 | 0.998 |
|           | Model 5 | 1.76 (1.05–2.96) | 42.1 | 0.273 | 0.992 | 0.997 |
|           | Model 6 | 1.82 (1.14–2.40) | 19.6 | 0.309 | 0.966 | 0.993 |
| CML       | Model 4 | 2.08 (1.27–3.40) | 1.4 | 0.096 | 0.973 | 0.986 |

**Sensitivity analysis**

**HWE and Quality score≥10**

| Overall  | Model 4 | 1.95 (1.35–2.80) | 21.5 | 0.078 | 0.793 | 0.897 |
|          | Model 6 | 1.95 (1.37–2.77) | 30.4 | 0.071 | 0.729 | 0.857 |

**The combined effects of GSTM1 and GSTP1 polymorphisms**

| Overall  | Model 3 | 1.50 (1.04–2.15) | 59.8 | 0.500 | 0.982 | 0.997 |
|          | Model 4 | 4.24 (2.49–7.24) | 0.0 | 0.000 | 0.632 | 0.027 |
|          | Model 5 | 1.70 (1.30–2.22) | 32.2 | 0.179 | 0.352 | 0.765 |
|          | Model 6 | 3.31 (1.85–5.91) | 14.8 | 0.004 | 0.933 | 0.780 |
| Indian   | Model 3 | 1.65 (1.05–2.59) | 61.9 | 0.339 | 0.989 | 0.997 |
|          | Model 4 | 4.39 (2.51–7.68) | 0.0 | 0.000 | 0.721 | 0.049 |
|          | Model 5 | 1.91 (1.45–2.50) | 0.8 | 0.039 | 0.059 | 0.106 |
|          | Model 6 | 3.39 (1.94–5.94) | 7.8 | 0.002 | 0.901 | 0.617 |
| HC       | Model 3 | 1.50 (1.04–2.15) | 59.8 | 0.500 | 0.982 | 0.997 |
|          | Model 4 | 4.24 (2.49–7.24) | 0.0 | 0.000 | 0.632 | 0.027 |
|          | Model 5 | 1.70 (1.30–2.22) | 32.2 | 0.179 | 0.352 | 0.765 |
|          | Model 6 | 3.31 (1.85–5.91) | 14.8 | 0.004 | 0.933 | 0.780 |
| Matching | Model 4 | 4.61 (1.64–12.97) | 16.8 | 0.017 | 0.996 | 0.994 |
|          | Model 5 | 1.40 (1.04–1.89) | 0.0 | 0.674 | 0.976 | 0.998 |
| CML      | Model 2 | 1.91 (1.35–2.68) | 0.0 | 0.881 | 0.690 | 0.849 |
|          | Model 4 | 3.29 (1.37–7.89) | 1.9 | 0.039 | 0.995 | 0.995 |
|          | Model 5 | 1.61 (1.05–2.47) | 50.4 | 0.373 | 0.987 | 0.997 |
|          | Model 6 | 2.40 (1.21–4.26) | 31.8 | 0.303 | 0.999 | 0.999 |

**Sensitivity analysis**

**HWE and Quality score≥10**

| Overall  | Model 3 | 1.50 (1.04–2.15) | 59.8 | 0.500 | 0.982 | 0.997 |
|          | Model 4 | 4.24 (2.49–7.24) | 0.0 | 0.000 | 0.632 | 0.027 |
|          | Model 5 | 1.70 (1.30–2.22) | 32.2 | 0.179 | 0.352 | 0.765 |
|          | Model 6 | 3.31 (1.85–5.91) | 14.8 | 0.004 | 0.933 | 0.780 |
negative ones. Second, the mechanism of leading to leukemia is greatly sophisticated, and thus a single-gene mutation is not likely to generate remarkably to its development. Third, no consideration was given to if the genotype distribution of GSTM1 and GSTT1 polymorphisms in control group was in HWE because we could not calculate the HWE on these two genes. Fourth, the heterogeneity of GSTM1, GSTT1, and GSTP1 was large; therefore, the random-effect model was selected, and after subgroup and sensitivity analysis, no source of heterogeneity was found. Hence, the current meta-analysis with a large sample size and enough subgroups will be conducive to confirm our discoveries.

This meta-analysis strongly suggests that only a minority of meaningful associations are credible results. Hence, larger-scale investigations of this topic should be performed in the future to verify or rebut our findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding authors.

Author contributions

YZ: research design and performance, data collection, data analysis, and manuscript-writing; DW and C-YZ: data collection; Y-JL, X-HW, M-YS, and WW: data recheck; and X-LS and X-FH: research design and manuscript review.

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Conflict of interest

Author WW was employed by the company Beijing Zhendong Guangming Pharmaceutical Research Institute.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.976673/full#supplementary-material
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