# E-26 Transformation-specific Related Gene Expression and Outcomes in Cytogenetically Normal Acute Myeloid Leukemia: A Meta-analysis

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## Abstract

**Background:** The E-26 transformation-specific related gene (*ERG*) is frequently expressed in cytogenetically normal acute myeloid leukemia (CN-AML). Herein, we performed a meta-analysis to investigate the relationship between the prognostic significance of *ERG* expression and CN-AML.

**Methods:** A systematic review of PubMed database and other search engines were used to identify the studies between January 2005 and November 2016. A total of 667 CN-AML patients were collected from seven published studies. Of the 667 patients underwent intensive chemotherapy, 429 had low expression of *ERG* and 238 had high expression of *ERG*. Summary odds ratio (*OR*) and the 95% confidence interval (*CI*) for the *ERG* expression and CN-AML were calculated using fixed- or random-effects models. Heterogeneity was assessed using Chi-squared-based *Q*-statistic test and $I^2$ statistics. All statistical analyses were performed using R.3.3.1 software packages (R Foundation for Statistical Computing, Vienna, Austria) and RevMan5.3 (Cochrane Collaboration, Copenhagen, Denmark).

**Results:** Overall, patients with high *ERG* expression had a worse relapse (*OR* = 2.5127, 95% *CI*: 1.5177–4.1601, *P* = 0.0003) and lower complete remission (*OR* = 0.3495, 95% *CI*: 0.2418–0.5051, *P* < 0.0001). With regard to the known molecular markers, both internal tandem duplications of the fms-related tyrosine kinase 3 gene (*OR* = 3.8634, 95% *CI*: 1.8285–8.1626, *P* = 0.004) and brain and acute leukemia, cytoplasmic (*OR* = 3.1538, 95% *CI*: 2.0537–4.8432, *P* < 0.0001) were associated with the *ERG* expression. In addition, the results showed a statistical significance between French-American-British (FAB) classification subtype (minimally differentiated AML and AML without maturation, *OR* = 4.7902, 95% *CI*: 2.7772–8.2624, *P* < 0.0001; acute monocytic leukemia, *OR* = 0.2324, 95% *CI*: 0.0899–0.6006, *P* = 0.0026) and *ERG* expression.

**Conclusion:** High *ERG* expression might be used as a strong adverse prognostic factor in CN-AML.

**Key words:** Leukemia, Myeloid, Acute; Meta-analysis; Prognosis; Recurrence

## Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease with diverse genomic aberrations in the subtypes.[1] While a great number of cytogenetic abnormalities has been identified in AML,[2] approximately 45% of *de novo* adult AML patients and 20% of pediatric AML patients are diagnosed with cytogenetically normal AML (CN-AML).[1,2] It is important to study the predictive molecular markers so that patients can get better treatment. The molecular aberrations that have been previously studied[3] in CN-AML patients include internal tandem duplications of the *fms*-related tyrosine kinase 3 gene (*FLT3-ITD*),[4-6] the nucleophosmin gene (*NPM1*) mutations,[7] MLL partial tandem duplication (*MLL-PTD*),[5,8] E-26 transformation-specific related gene (*ERG*)[9,10] and brain and acute leukemia, cytoplasmic (*BAALC*) expression levels.[11]

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The *ERG*, a member of the E-26 transformation-specific (*ETS*) family of transcription factors, plays a major role in multiple cancers, such as Ewing's sarcoma,[12,13] prostate cancer,[14] and leukemia.[10,15] The *ERG*, which is located on chromosome band 21q22, was involved in cell proliferation, apoptosis, and differentiation.[16] Moreover, *ERG* over-expression was demonstrated with complex karyotypes in AML patients and found in patients with CN-AML.[17] In addition, Marcucci *et al*.[18] also was the first time to study and report the prognostic significance of *ERG* in CN-AML. In accordance with the prior report, Marcucci *et al*.[19] sought to validate and demonstrated that the *ERG* overexpression was associated with worse outcome. Therefore, *ERG* overexpression might be used as important markers for CN-AML patients.

Until now, however, a comprehensive analysis of all reported *ERG*-related CN-AML is lacking. Therefore, in the current study, we assess the prognostic values of the expression of *ERG* in the patients with *de novo* CN-AML by a meta-analysis on all published studies. The well-established genetic markers were also investigated.

## Methods

### Search strategy

We searched the PubMed database and other search engines for all articles on the association between *ERG* and leukemia (last search update Nov 3, 2016). The following terms were used in the search: "*ERG* or *ETS*-related" and leukemia and "CN-AML or cytogenetically normal acute myeloid leukemia". All eligible studies on the topic were identified by a manual search for references of retrieved articles. Finally, 239 studies were identified.

### Selection criteria

The association studies between *ERG* overexpression and CN-AML were included if all the following conditions were met:[1,9,17-20] *ERG* gene expression was analyzed and grouped into "high" and "low" in studies; the cancer type is CN-AML; the study provides the total number of *ERG* high and low patients; the study is published in English or Chinese; the publication year range from January 2005 to November 2016.

The major exclusion criteria were as follows: Duplicate data; abstract, comment, review or editorial; poor study quality; the incomplete data.

We have no contact with authors. Ethical approval and informed patient consent are not required as this study is a literature review and have no direct patient contact or influence on patient care.

### Data extraction and quality assessment

Two investigators independently extracted data from each study by following the predefined selection criteria and discrepancies were resolved by consensus of all investigators. All study personnel was blinded throughout the meta-analysis.

The following information was recorded for each study: The surname of the first author; year of publish; cancer type; ethnicity; number of cases and controls; risk factors.

Two investigators conducted the risk of bias assessments independently using the Cochrane Collaboration tool.[21] To assess the quality of each eligible study, two investigators worked independently to determine the adequacy of the studies, and discrepancies were resolved by discussion with all investigators. All assessors were blinded throughout the meta-analysis.

### Statistical analysis

The Chi-squared-based $Q$-statistic test and $I^2$ statistics were used to assess the heterogeneity. When the result of the heterogeneity test was $P < 0.005$, the random-effects model was used.[22] Otherwise, the fixed-effects model was selected. Funnel plots were used to diagnose a potential publication bias.[23] For the possible publication bias, trim and fill method were used to evaluate the influence to the result.[24] Sensitivity analyses were performed to assess the stability of the results by excluding one study at a time. All analyses were performed using R.3.3.1 software package (R Foundation for Statistical Computing, Vienna, Austria). All the $P$ values were two-sided. The value of $P < 0.05$ was defined as statistical significance. The risk of bias assessment was performed in RevMan5.3 (Cochrane Collaboration, Copenhagen, Denmark).

## Results

### Characteristics of studies

Of the 239 studies identified initially, seven studies met criteria and were included in the analysis [Figure 1]. Overall, these studies contained a total of 667 patients with high/low expression of *ERG*. Characteristics of the included studies are summarized in Tables 1–4. The association analyses were performed between the *ERG* expression and the risk factor are indicated in Table 1.

### Association between the E-26 transformation-specific related gene expression level and gender risk

Gender information was included in the seven studies [Table 2]. The result showed a statistical significance of heterogeneity between studies ($\tau^2 = 0.2732$; $I^2 = 55.6\%$; $P = 0.0354$; Figure 2); thus, random effects model was used for this analysis. Compared with the low expression *ERG*, there was no statistically significant difference among gender (odds ratio [*OR*] = 0.9639, 95% confidence interval [*CI*]: 0.5640–1.6476, $P = 0.8932$).

### Association between the E-26 transformation-specific related gene expression level and race risk

It has been shown previously that the frequency of *ERG* overexpression varied significantly between white and nonwhite population.[17-19] Here, three studies were included to assess the effect of race [Table 2]. There was no evidence of heterogeneity between studies ($\tau^2 = 0$; $I^2 = 0$; $P = 0.9193$;

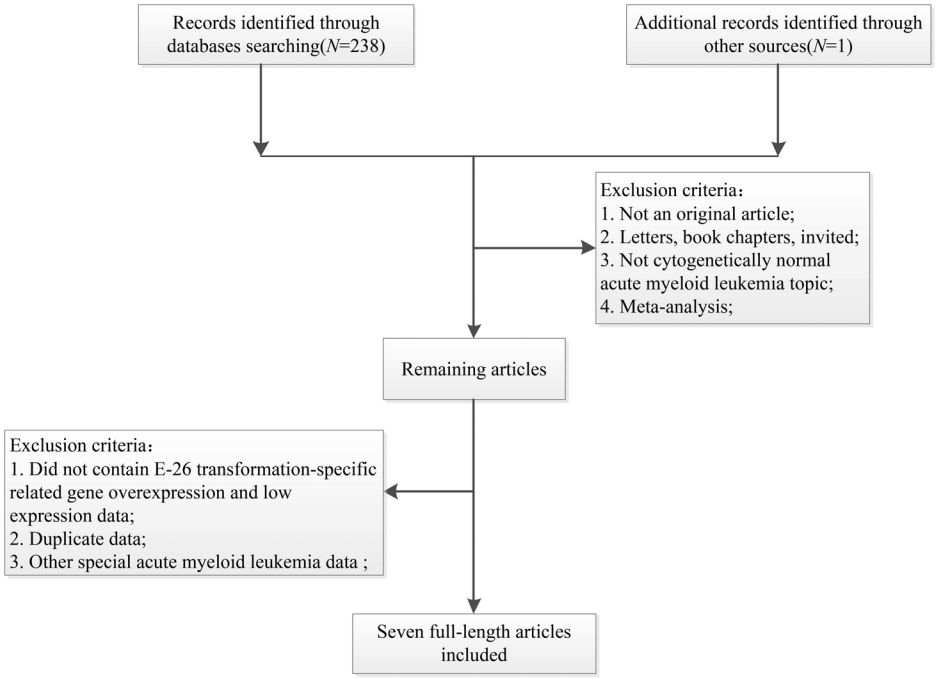


**Figure 1:** Flow chart of the study selection process.

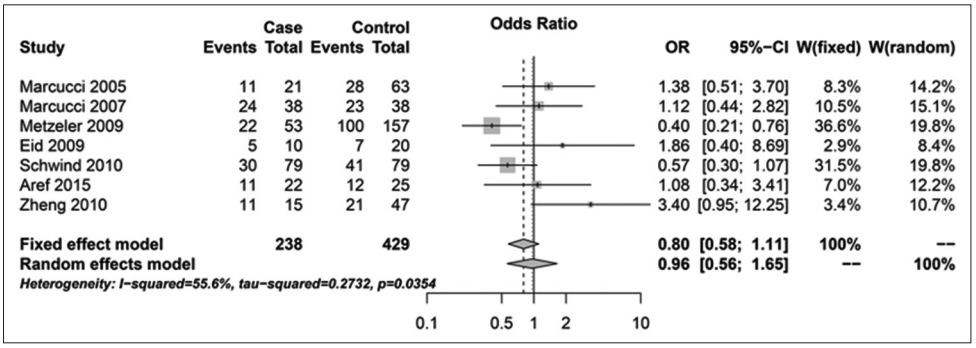


**Figure 2:** Forest plot of gender risk associated with *ERG* overexpression and *ERG* low expression level reported in the seven references. *ERG*: E-26 transformation-specific related gene.

**Table 1: General information of the patients reported in the seven references**

| References | Groups | Cases (*n*) | Age (years) | Risk factor |
|---|---|---|---|---|
| Marcucci *et al*.[18] | Low *ERG* | 63 | 18–59 | Sex; race; CR; relapse; FAB; M |
| | High *ERG* | 21 | 26–59 | Sex; race; CR; relapse; FAB; M |
| Marcucci *et al*.[19] | Low *ERG* | 38 | 19–59 | Sex; race; CR; relapse; M |
| | High *ERG* | 38 | 19–59 | Sex; race; CR; relapse; M |
| Metzeler *et al*.[9] | Low *ERG* | 157 | 17–83 | Sex; CR; relapse; M; FAB |
| | High *ERG* | 53 | 18–78 | Sex; CR; relapse; M; FAB |
| Eid *et al*.[20] | Low *ERG* | 20 | 18–42 | Sex; CR |
| | High *ERG* | 10 | 16–40 | Sex; CR |
| Schwind *et al*.[17] | Low *ERG* | 79 | 60–81 | Sex; CR; race; M |
| | High *ERG* | 79 | 60–83 | Sex; CR; race; M |
| Aref *et al*.[1] | Low *ERG* | 25 | 3–14 | Sex; CR; M |
| | High *ERG* | 22 | 2–15 | Sex; CR; M |
| Zheng YC[25] | Low *ERG* | 47 | 24–77 | Sex; CR; FAB |
| | High *ERG* | 15 | 20–76 | Sex; CR; FAB |

*ERG*: E-26 transformation-specific related gene; M: Relative gene mutations; CR: Complete remission; FAB: French-American-British.

Figure 3), thus fixed effects model was used for the analysis. Compared with the low expression *ERG*, there was no statistically significant difference among race (*OR* = 1.2012, 95% *CI*: 0.5645–2.5564, *P* = 0.6342).

**Table 2: *ERG* expression levels and clinic-pathologic report in the seven references**

| References | Groups | Sex (female), *n/N* | Race (white), *n/N* | CR, *n/N* | Relapse, *n/N* |
|---|---|---|---|---|---|
| Marcucci *et al*.[18] | Low *ERG* | 28/63 | 54/63 | 52/63 | 17/63 |
| | High *ERG* | 11/21 | 19/21 | 16/21 | 13/21 |
| Marcucci *et al*.[19] | Low *ERG* | 23/38 | 35/38 | 37/38 | 19/38 |
| | High *ERG* | 24/38 | 35/38 | 30/38 | 27/38 |
| Metzeler *et al*.[9] | Low *ERG* | 100/157 | – | 108/157 | 99/157 |
| | High *ERG* | 22/53 | – | 25/53 | 41/53 |
| Eid *et al*.[20] | Low *ERG* | 7/20 | – | 19/20 | – |
| | High *ERG* | 5/10 | – | 3/10 | – |
| Schwind *et al*.[17] | Low *ERG* | 41/79 | 70/79 | 60/79 | – |
| | High *ERG* | 30/79 | 71/79 | 51/79 | – |
| Aref *et al*.[1] | Low *ERG* | 12/25 | – | 21/25 | – |
| | High *ERG* | 11/22 | – | 9/22 | – |
| Zheng YC[25] | Low *ERG* | 21/47 | – | 31/42 | – |
| | High *ERG* | 11/15 | – | 6/15 | – |

*ERG*: E-26 transformation-specific related gene; CR: Complete remission; –: No data.

**Table 3: *ERG* expression levels and other molecular markers in the six references**

| References | Groups | *FLT3-ITD* (present), *n/N* | *MLL-PTD* (yes), *n/N* | *BAALC* (high), *n/N* | *NPM1* (mutation), *n/N* |
|---|---|---|---|---|---|
| Marcucci *et al*.[18] | Low *ERG* | 10/63 | 5/63 | 27/63 | – |
| | High *ERG* | 4/21 | 3/21 | 15/21 | – |
| Marcucci *et al*.[19] | Low *ERG* | 10/38 | 4/38 | 18/38 | 25/38 |
| | High *ERG* | 25/38 | 1/38 | 23/38 | 29/38 |
| Metzeler *et al*.[9] | Low *ERG* | 57/157 | 20/157 | – | 87/157 |
| | High *ERG* | 30/53 | 6/53 | – | 27/53 |
| Eid *et al*.[20] | Low *ERG* | – | – | 13/20 | – |
| | High *ERG* | – | – | 8/10 | – |
| Schwind *et al*.[17] | Low *ERG* | 12/79 | 4/79 | 28/79 | 45/79 |
| | High *ERG* | 46/79 | 2/79 | 51/79 | 52/79 |
| Aref *et al*.[1] | Low *ERG* | 0/25 | – | 6/25 | 1/25 |
| | High *ERG* | 6/22 | – | 17/22 | 4/22 |

*ERG*: E-26 transformation-specific related gene; *MLL-PTD*: Partial tandem duplication of the *MLL* gene; *FLT3-ITD*: Internal tandem duplication of the *FLT3* gene; *BAALC*: Brain and acute leukemia, cytoplasmic; *NPM1*: Nucleophosmin gene; –: No data.

**Table 4: *ERG* expression levels and FAB classification reports in the three references**

| References | Groups | M0/M1, *n/N* | M2, *n/N* | M4, *n/N* | M5, *n/N* | M6, *n/N* |
|---|---|---|---|---|---|---|
| Marcucci *et al*.[18] | Low *ERG* | 9/63 | 21/63 | 17/63 | 11/63 | 1/63 |
| | High *ERG* | 10/21 | 6/21 | 5/21 | 0/21 | 0/21 |
| Metzeler *et al*.[9] | Low *ERG* | 35/157 | 53/157 | 35/157 | 25/157 | 7/157 |
| | High *ERG* | 28/53 | 12/53 | 11/53 | 0/53 | 21/53 |
| Zheng YC[25] | Low *ERG* | 0/47 | 14/47 | 10/47 | 19/47 | 4/47 |
| | High *ERG* | 4/15 | 5/15 | 11/15 | 5/15 | 0/15 |

*ERG*: E-26 transformation-specific related gene; FAB: French-American-British; M0: Minimally differentiated acute myeloid leukemia; M1: Acute myeloid leukemia without maturation; M2: Acute myeloid leukemia with maturation; M4: Acute myelomonocytic leukemia; M5: Acute monocytic leukemia; M6: Erythroleukemia.

## Association between the E-26 transformation-specific related gene expression level and complete remission

Complete remission was reported in all seven studies,[1,9,17-20,25] and the results indicated that there was no heterogeneity between studies ($\tau^2 = 0.3021$; $I^2 = 49.7\%$; $P = 0.0634$; Figure 4), thus fixed effects model was employed in the merging analysis. Compared with the low expression *ERG*, there was statistically significant difference among complete remission (*OR* = 0.3495, 95% *CI*: 0.2418–0.5051, $P < 0.0001$).

## Association between the E-26 transformation-specific related gene expression level and relapse

The relapse information was reported in three studies.[9,18,19] Since there was no heterogeneity between studies ($\tau^2 = 0$; $I^2 = 0$; $P = 0.4739$; Figure 5), the fixed effects model was used for this analysis. Compared with the low expression *ERG*, there was statistically significant difference in relapse (*OR* = 2.5127, 95% *CI*: 1.5177–4.1601, $P = 0.0003$).

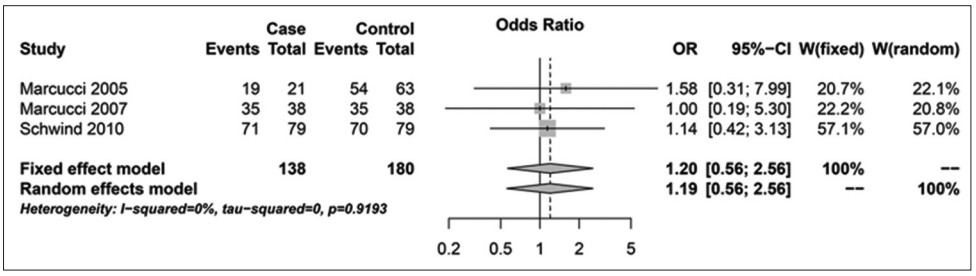


**Figure 3:** Forest plot of race risk of high *ERG* expression level and low *ERG* expression level reported in the three references. *ERG*: E-26 transformation-specific related gene.

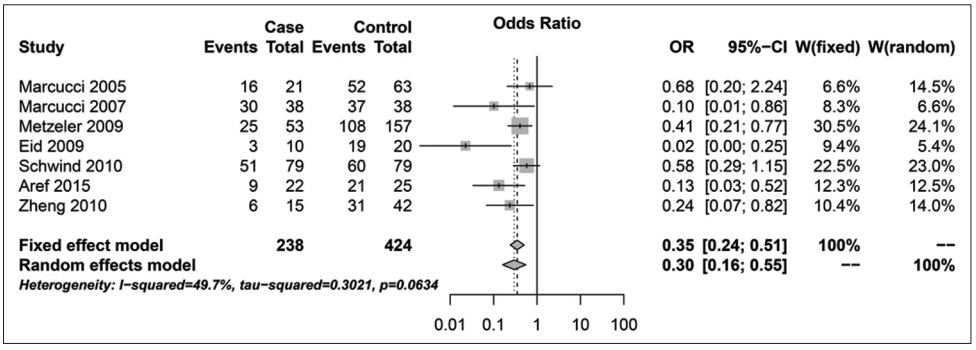


**Figure 4:** Forest plot of complete remission of high *ERG* expression level and low *ERG* expression level reported in the studies. *ERG*: E-26 transformation-specific related gene.

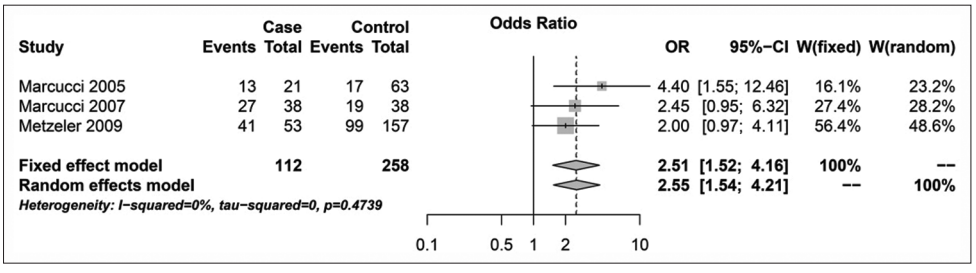


**Figure 5:** Forest plot of relapse of high *ERG* expression level and low *ERG* expression level reported in the studies. *ERG*: E-26 transformation-specific related gene.

## Association between the E-26 transformation-specific related gene expression level and internal tandem duplication of the fms-related tyrosine kinase 3 gene

A total of five studies reported data for *FLT3-ITD*.[1,9,17-19] There was evidence of statistically significant heterogeneity between studies ($\tau^2$ = 0.4047; $I^2$ = 62.0%; $P$ = 0.0325; Figure 6) and a random effects model was used for merging analysis. Compared with the low expression *ERG*, there was statistically significant difference in *FLT3-ITD* (*OR* = 3.8634, 95% *CI*: 1.8285–8.1626, $P$ = 0.004).

## Association between the E-26 transformation-specific related gene expression level and *MLL* partial tandem duplication

A total of four studies contained data for *MLL-PTD*.[9,17-19] There was no evidence of statistically significant heterogeneity between studies ($\tau^2$ = 0; $I^2$ = 0; $P$ = 0.4169; Figure 7). Compared with the low expression *ERG*, there was no statistically significant difference in *MLL-PTD* (*OR* = 0.7817, 95% *CI*: 0.3915–0.4078, $P$ = 0.4851).

## Association between the E-26 transformation-specific related gene expression level and brain and acute leukemia, cytoplasmic

A total of five studies reported data for *BAALC*.[1,17-20] There was no evidence of statistically significant heterogeneity between studies ($\tau^2$ = 0.0777; $I^2$ = 21.8%; $P$ = 0.2755; Figure 8). Compared with low expression *ERG*, there was statistically significant difference in *BAALC* (*OR* = 3.1538, 95% *CI*: 2.0537–4.8432, $P$ < 0.0001).

## Association between the E-26 transformation-specific related gene expression level and the nucleophosmin gene mutations

A total of four studies reported data for *NPM1* mutations.[1,9,17,19] There was no evidence of statistically significant heterogeneity between studies ($\tau^2$ = 0.046; $I^2$ = 19.0%; $P$ = 0.2953; Figure 9) and merging analysis is

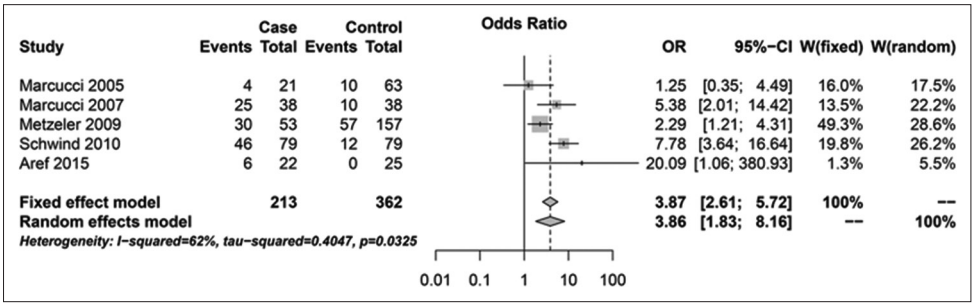


**Figure 6:** Forest plot of *FLT3-ITD* present of *ERG* overexpression and *ERG* low expression reported in the studies. *FLT3-ITD*: Internal tandem duplication of the *FLT3* gene; *ERG*: E-26 transformation-specific related gene.

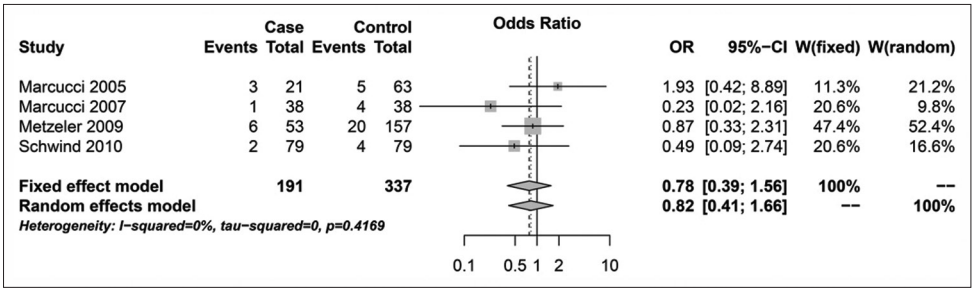


**Figure 7:** Forest plot of *MLL-PTD* present of *ERG* overexpression and *ERG* low expression reported in the studies. *MLL-PTD*: Partial tandem duplication of the *MLL* gene; *ERG*: E-26 transformation-specific related gene.

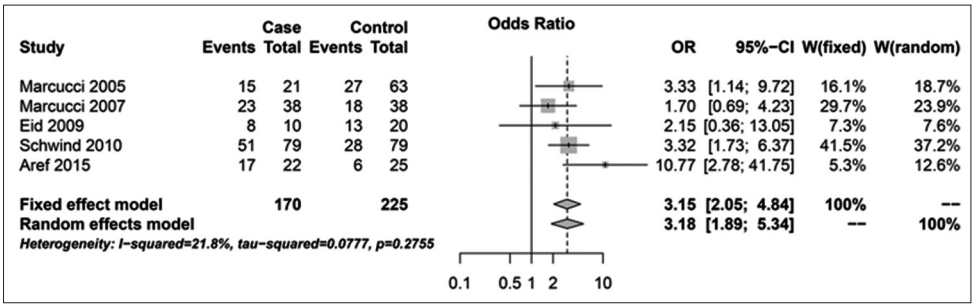


**Figure 8:** Forest plot of *BAALC* expression of *ERG* overexpression and *ERG* low expression reported in the studies. *BAALC*: Brain and acute leukemia, cytoplasmic; *ERG*: E-26 transformation-specific related gene.

using fixed effects model. Compared with low expression *ERG*, there was no statistically significant difference in *NPM1* (*OR* = 1.2471, 95% *CI*: 0.8378–1.8563, *P* = 0.2766).

## Association between the E-26 transformation-specific related gene expression level and French-American-British classification

A total of three studies reported data for French-American-British subtype.[9,18,25] Compared with low *ERG* expression, there was statistically significant difference in minimally differentiated AML (M0)/AML without maturation (M1) and acute monocytic leukemia (M5) [Table 5].

## Sensitivity analysis

Sensitivity analyses were performed by sequential removal of each eligible study to assess the influence of each study on the pooled *OR* in each comparison in complete remission. The results showed the reliability of the prognostic impact [Figure 10]. Due to the limited studies included in this analysis, we did not carry out the sensitivity analysis for the relapse risk factor.

## Subgroup analysis

Six studies[9,17-20,25] conducted in adult-only population for complete remission were selected for subgroup analysis. Compared with low expression *ERG*, there was statistically significant difference among complete remission (*OR* = 0.38, 95% *CI*: 0.2586–0.5584, *P* < 0.0001). There was no heterogeneity between studies ($\tau^2$ = 0.2663; $I^2$ = 47.8%; *P* = 0.0880; Figure 11); thus; fixed effects model was employed in the merging analysis.

Four studies[1,9,17,19] with median as criteria for *ERG* high and low expression were selected for subgroup analysis. Compared with low expression *ERG*, there was statistically significant difference among complete remission (*OR* = 0.3779, 95% *CI*: 0.2472–0.5778,

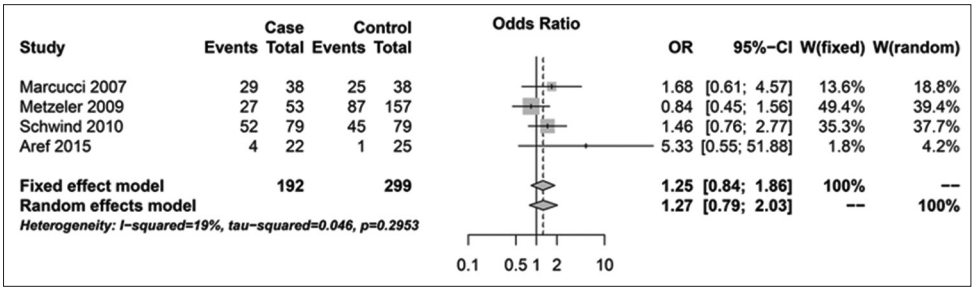


**Figure 9:** Forest plot of *NPM1* mutation of *ERG* overexpression and *ERG* low expression reported in the studies. *NPM1*: Nucleophosmin gene; *ERG*: E-26 transformation-specific related gene.

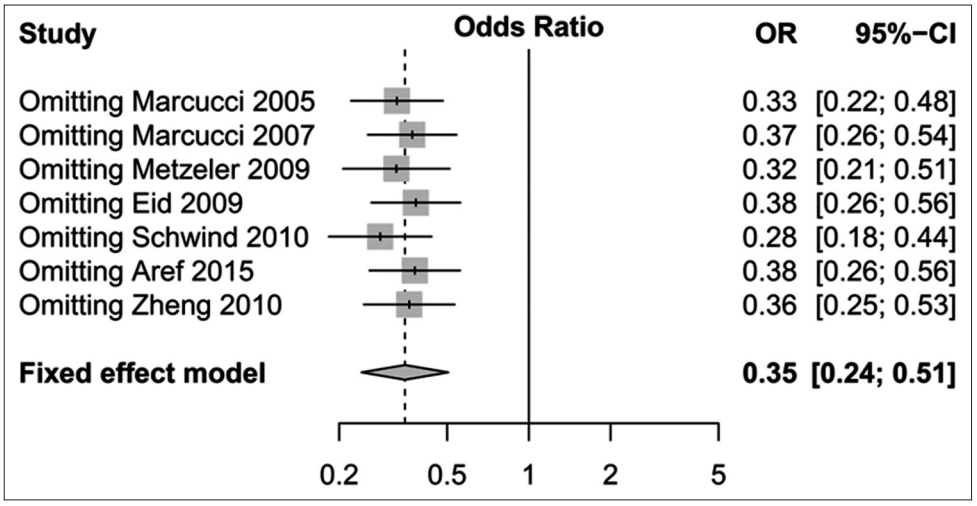


**Figure 10:** Sensitivity analysis of fixed effect model in the risk factor of complete remission.

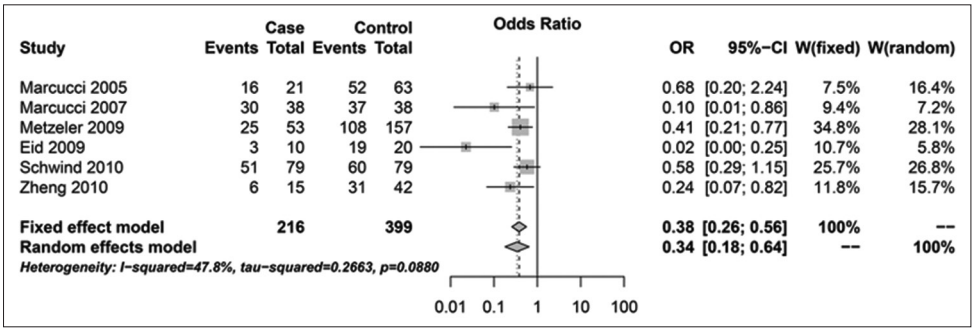


**Figure 11:** Forest plot graph: High *ERG* level versus low *ERG* level for complete remission in adult-only participants. *ERG*: E-26 transformation-specific related gene.

**Table 5: Analyses of FAB classification reports in the three references**

| FAB classification | *Q* | $I^2$ (%) | *P* | *OR* | 95% *CI* | *P* |
|---|---|---|---|---|---|---|
| M0/M1 | 2.23 | 10.2 | 0.3285 | 4.7902 | 2.7772–8.2624 | <0.0001 |
| M2 | 1.02 | 0.0 | 0.6016 | 0.7095 | 0.4143–1.2151 | 0.2112 |
| M4 | 10.37 | 80.7 | 0.0056 | 1.8455 | 0.4528–7.5214 | 0.3927 |
| M5 | 4.90 | 59.2 | 0.0863 | 0.2324 | 0.0899–0.6006 | 0.0026 |
| M6 | 8.07 | 75.2 | 0.0177 | 2.1898 | 0.1426–33.6154 | 0.5738 |

*CI*: Confidence interval; *OR*: Odds ratio; FAB: French-American-British; M0: Minimally differentiated acute myeloid leukemia; M1: Acute myeloid leukemia without maturation; M2: Acute myeloid leukemia with maturation; M4: Acute myelomonocytic leukemia; M5: Acute monocytic leukemia; M6: Erythroleukemia.

$P < 0.0001$). We selected four studies[1,9,17,19] and the results indicated that there was no heterogeneity ($\tau^2 = 0.1764$; $I^2 = 42.6\%$; $P = 0.1561$; Figure 12); thus, fixed effects model was employed in the merging analysis.

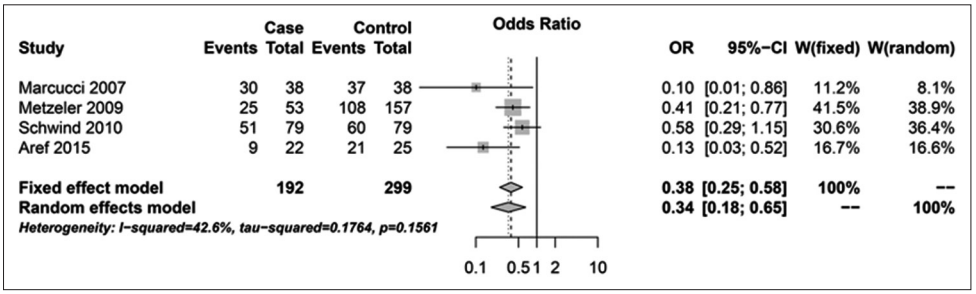


**Figure 12:** Forest plot graph: Median as cut-off *ERG* level for complete remission in participants. *ERG*: E-26 transformation-specific related gene.

## Risk of bias assessment

Assessments using the Cochrane Risk of Bias tool[21] are presented in Figure 13. Detailed are provided in Supplementary Information.

## Publication bias

The funnel plot found the evidence for publication bias in complete remission. The trim and fill method showed that the funnel plot needed three studies to be symmetrical [Figure 14]. Since there was heterogeneity between studies ($\tau^2 = 0.6399$; $I^2 = 62.9\%$; $P = 0.0039$), the merging analysis was performed using random effects model. Compared to the low expression *ERG*, there was statistically significant difference (*OR* = 0.4527, 95% *CI*: 0.2301–0.8905, $P = 0.0217$). We did not test the publication bias in relapse due to the limited number of relevant studies.

# Discussion

*ERG*, located on chromosome 21q22,[26] is widely overexpressed in AML patients with complex karyotypes. The product of *ERG* is involved in many important pathways, such as cell proliferation, differentiation, and apoptosis.[16,27,28] In this study, we performed a systematic study between *ERG* and cancer risk based on seven studies. Although the results suggested that there was no association with race (*OR* = 1.2012, 95% *CI*: 0.5645–2.5564, $P = 0.6342$) or gender (*OR* = 0.9639, 95% *CI*: 0.5640–1.6476, $P = 0.8932$), the analysis showed high *ERG* expression level was significantly associated with high relapse (*OR* = 2.5127, 95% *CI*: 1.5177–4.1601, $P = 0.0003$) and inferior complete remission (*OR* = 0.3495, 95% *CI*: 0.2418–0.5051, $P < 0.0001$). In accordance with previous studies, *ERG* overexpression predicted the increased relapse risk and fewer complete remission.[18,19]

*FMS*-like tyrosine kinase-3 gene (*FLT3*), a receptor tyrosine kinase, is important for the development of the hematopoietic and immune systems. Activating mutations of *FLT3* are now recognized as the most common molecular abnormality in AML. *FLT3/ITD* occurs in 20–30% of young adults with AML and is associated with poor prognosis.[29-31] In the meta-analysis, we detect an association between *FLT3-ITD* positive and *ERG* expression (*OR* = 3.8634, 95% *CI*: 1.8285–8.1626, $P = 0.004$), in line with the previous report by Marcucci *et al*.[9,19]

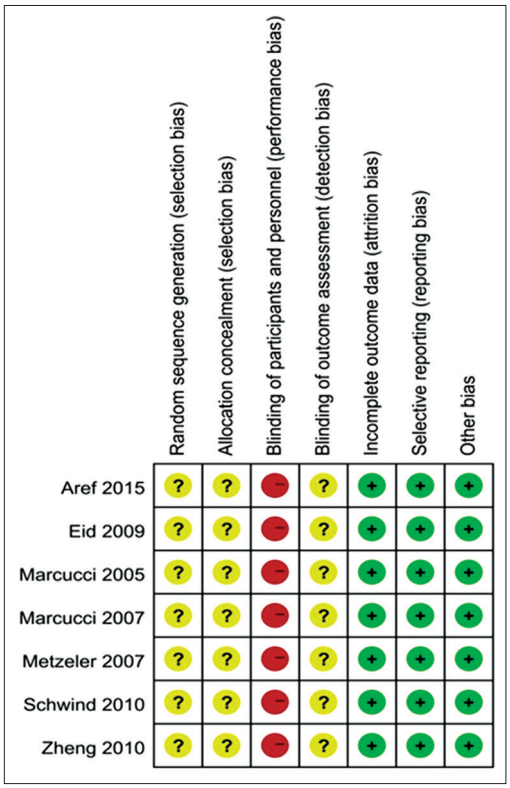


**Figure 13:** Risk of Bias assessment results. Green circle for low risk of bias, red circle for high risk of bias, yellow circle for unclear risk of bias.

*BAALC*, located on chromosome 8q22.3, is widely expressed in CN-AML.[32] While no significant association was observed between the mutations in *NPM1* and *ERG* expression, we found a correlation between *ERG* and *BAALC* expression (*OR* = 3.1538, 95% *CI*: 2.0537–4.8432, $P < 0.0001$). The association between high *ERG* expression and high *BAALC* was consistent with the previous studies.[1,9,19,33]

Although the number of the study was small in this meta-analysis, there was no heterogeneity among studies in complete remission ($\tau^2 = 0.3021$; $I^2 = 49.7\%$; $P = 0.0634$) and relapse ($\tau^2 = 0$; $I^2 = 0$; $P = 0.4739$), indicating the results were reliable. Publication bias was found in the complete remission, however, the trim and fill analysis proved that the combined effect was statistically significant (*OR* = 0.4527, 95% *CI*: 0.2301–0.8905, $P = 0.0217$) in random effect model. Moreover, sensitivity analysis results showed the results of

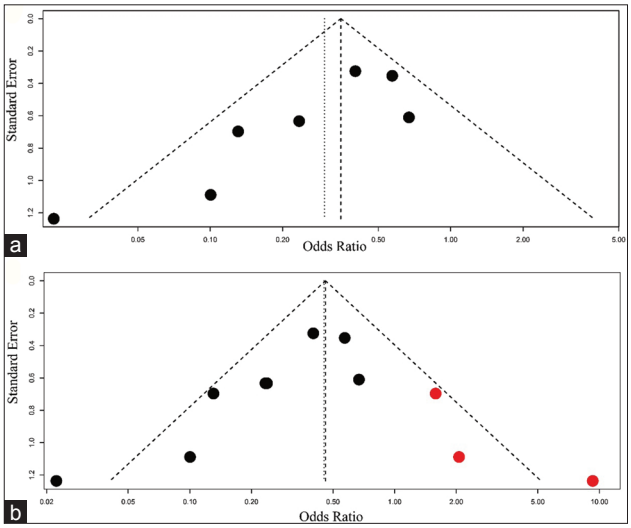


**Figure 14:** Funnel plots of meta-analysis before (a) and after (b) trim and fill adjustment for publication in complete remission. Each point represents a separate study for the indicated association. The red points represent the filled studies.

this meta-analysis were statistically reliable. Considering the age factor in CN-AML, we selected six adult-only studies to conduct the subgroup analysis. The results showed that high *ERG* expression was also associated with complete remission significantly in adult group (*OR* = 0.38, 95% *CI*: 0.2586–0.5584, *P* < 0.0001). Due to the criterion of *ERG* high/low group was not consistent in seven studies, we conducted the subgroup analysis with four studies using median as criteria, and there was also statistically significant difference (*OR* = 0.3779, 95% *CI*: 0.2472–0.5778, *P* < 0.0001) in the subgroup analysis. The results demonstrated the different criteria might not affect the analysis results, further studies will be needed in the future for validation.

There are some innovative points in this analysis. First, to the best of our knowledge, this is a rare meta-analysis study to explore the association between *ERG* expression and CN-AML. Second, the results found a correlation between *BAALC* expression and the *ERG* expression. Third, this meta-analysis was rarely to explore the relationship between the *ERG* expression and molecular markers.

However, there are some limitations for this meta-analysis. First, the selected studies are completely blind and lack of the detail clinical information. Second, the number of included studies is relatively small in this study which might be the major reason to create bias or heterogeneity. Due to the limited studies or the limited sample sizes, more studies with the large sample are required to confirm the results in the future.

In conclusion, the meta-analysis provides the prognostic value of the *ERG* expression in CN-AML. *ERG* expression appears to be associated with complete remission and relapse.

*Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.*

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## Conflicts of interest

There are no conflicts of interest.

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## Supplementary Information

**Table for Risk of Bias**

| Items | Authors' judgement/support for judgement | | | | | | |
|---|---|---|---|---|---|---|---|
| | Zheng YC[25] | Aref *et al.*[1] | Schwind *et al.*[17] | Eid *et al.*[20] | Metzeler *et al.*[9] | Marcucci *et al.*[19] | Marcucci *et al.*[18] |
| Random sequence generation (selection bias) | Unclear/no information on sequence generation was reported | Unclear/no information on sequence generation was reported | Unclear/no information on sequence generation was reported | Unclear/no information on sequence generation was reported | Unclear/no information on sequence generation was reported | Unclear/no information on sequence generation was reported | Unclear/no information on sequence generation was reported |
| Allocation concealment (selection bias) | Unclear/this information was not reported | Unclear/this information was not reported | Unclear/this information was not reported | Unclear/this information was not reported | Unclear/this information was not reported | Unclear/this information was not reported | Unclear/this information was not reported |
| Blinding of participants and personnel (performance bias) | High risk/the patients were treated | High risk/the patients were treated | High risk/the patients were treated | High risk/the patients were treated | High risk/the patients were treated | High risk/the patients were treated | High risk/the patients were treated |
| Blinding of outcome assessment (detection bias) | Unclear/this information was not provided | Unclear/this information was not provided | Unclear/this information was not provided | Unclear/this information was not provided | Unclear/this information was not provided | Unclear/this information was not provided | Unclear/this information was not provided |
| Incomplete outcome data (attrition bias) | Low risk/all participants completed the trial | Low risk/all participants completed the trial | Low risk/all participants completed the trial | Low risk/all participants completed the trial | Low risk/all participants completed the trial | Low risk/all participants completed the trial | Low risk/all participants completed the trial |
| Selective reporting (reporting bias) | Low risk/the outcome measures were reported | Low risk/the outcome measures were reported | Low risk/the outcome measures were reported | Low risk/the outcome measures were reported | Low risk/the outcome measures were reported | Low risk/the outcome measures were reported | Low risk/the outcome measures were reported |
| Other bias | Low risk/there was no exist inappropriate influence | Low risk/there was no exist inappropriate influence | Low risk/there was no exist inappropriate influence | Low risk/there was no exist inappropriate influence | Low risk/there was no exist inappropriate influence | Low risk/there was no exist inappropriate influence | Low risk/there was no exist inappropriate influence |