ABSTRACT

Objectives Whether KMT2A-PTD has a prognostic impact on patients with acute myeloid leukaemia (AML) is controversial. Therefore, we conducted a meta-analysis to assess the prognostic value of KMT2A-PTD in patients with AML.

Methods Eligibility criteria: we included studies concerning the prognostic value of KMT2A-PTD in patients with AML.

Information sources: Eligible studies were identified from PubMed, Embase, Medline, Web of Science, Cochrane Library and Chinese Biomedical Database. The systematic search date was 19 December 2020.

Risk of bias: Sensitivity analysis was used to evaluate the stability and reliability of the combined results. Begg’s and Egger’s tests were used to assess the publication biases of studies.

Synthesis of results: We calculated the pooled HRs and their 95% CIs for overall survival (OS) and event-free survival (EFS) by Stata V.12 software.

Results Included studies: 18 studies covering 6499 patients were included.

Synthesis of results: KMT2A-PTD conferred shorter OS in total population (HR=1.30, 95% CI 1.09 to 1.51). In the subgroup analysis, KMT2A-PTD also resulted in shorter OS in karyotypically normal AML patients (HR=2.72, 95% CI 1.83 to 3.61) and old AML patients (HR=1.93, 95% CI 1.44 to 2.42). KMT2A-PTD indicated no prognostic impact on EFS in total population (HR=1.26, 95% CI 0.86 to 1.66). However, in the sensitivity analysis, KMT2A-PTD resulted in poor EFS (HR=1.34, 95% CI 1.04 to 1.64) when deleting the study with a relatively obvious effect on the combined HR. In the subgroup analysis, KMT2A-PTD was associated with poor EFS in old AML patients (HR=1.64, 95% CI 1.25 to 2.03).

Conclusion The findings indicated that KMT2A-PTD had an adverse impact on the prognosis of patients with AML in the total population, and the conclusion can also be applied to some subgroups including karyotypically normal AML and old AML patients. KMT2A-PTD may be a promising genetic biomarker in patients with AML in the future.

Trial registration number CRD42021227185.

INTRODUCTION

Acute myeloid leukaemia (AML) is a common haematological malignancy with a high recurrence rate and mortality. The growth of malignant cells is characterised by the interruption of normal intracellular signals caused by mutation or abnormal external signals. There are few effective treatments for AML, partly due to the molecular heterogeneity of AML. All patients with AML (excluding M3) are recommended to participate in the clinical trial first if conditions permit; otherwise, clinicians will select and dynamically adjust the treatment regimens (including chemotherapy, targeted therapy, demethylating agents, haematopoietic stem cell transplantation (HSCT), etc) according to the patient’s age, genetic risk stratification, response and tolerance to treatment, post-treatment measurable residual disease, etc. Molecular markers play an increasingly important role in the diagnosis and risk stratification of AML. Mutations, such as NPM1, CEBPA, FLT3, RUNX1, IDH1, IDH2, ASXL1 and KIT (among others) are important for diagnosis and prognosis in patients with AML (provided by WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues).

In recent years, many small molecule inhibitors have been applied for the treatment of AML patients with the rapid development of targeted therapy, such as FLT3 inhibitors (sorafenib, midostaurin, quizartinib and gilteritinib), IDH1/2 inhibitors (ivosidenib...
and enasidenib) and BCL2 inhibitors (venetoclax). Therefore, the detection of molecular markers can be used for disease diagnosis and risk stratification and can guide the targeted treatment of patients. Further understanding of the genomic and molecular landscape of AML has led to an important evolution of our understanding of AML biology and enabled accurate prognostication for patients who are induced by standard combination chemotherapy.4

Lysine (K) methyltransferase 2A (KMT2A), also known as mixed lineage leukaemia (MLL),5 is located on chromosome 11q23.3 and encodes a transcriptional coactivator that plays an important role in regulating gene expression in early development and haematopoiesis. The encoded protein includes multiple conserved functional domains. The SET domain, which is one of these conserved functional domains, controls histone H3 lysine 4 methyltransferase activity, mediating chromatin modifications linked with epigenetic transcriptional activation. The protein is processed into two fragments by the enzymes Taspase 1, MLL-C and MLL-N. These fragments are recombined and further assembled into different multiprotein complexes to regulate the transcription of specific target genes containing many HOX genes (provided by RefSeq, October 2010). Partial tandem duplication of KMT2A (KMT2A-PTD), also named MLL-PTD, is a common genomic aberration in AML.6 Although many studies have evaluated the prognostic effect of KMT2A-PTD in patients with AML, the results among these studies are still inconsistent. Some studies reported that KMT2A-PTD had a worse prognostic impact on patients with AML,7–10 whereas others showed no additional prognostic impact of KMT2A-PTD.11–14 Therefore, a meta-analysis was conducted to further discuss the relationship between KMT2A-PTD and prognosis in patients with AML.

METHODS

The meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements, and the protocol was registered in PROSPERO with number CRD42021227185.

Literature search and search strategy

Relevant studies were searched and collected by using PubMed, Embase, Medline, Web of Science, Cochrane Library and Chinese Biomedical Database. The MESH terms searched were as follows: “MLL”, “KMT2A”, “Mixed-lineage leukemia”, “Histone-lysine N-methyltransferase 2A”, “ALL-I”, “MLL-I”, “HRX”, “HTRX1”, “AML”, “mutation”, and “acute myeloid leukemia”.

Inclusion and exclusion criteria

The studies required the following conditions to be satisfied in our meta-analysis: (1) studies were published up to 19 December 2020, concerning the prognostic value of KMT2A-PTD in patients with AML; (2) studies provided overall survival (OS) or event-free survival (EFS) of KMT2A-PTD positive patients; (3) studies were original studies, while review articles, laboratory studies, conference abstracts, case reports and letters were all excluded; and (4) if there was overlapping data in multiple studies, only the highest quality study was included.

Two authors independently screened potentially eligible studies by reviewing the titles and abstracts, and then two investigators read the full text to screen qualified studies. Discrepancies between authors were resolved by consensus or consultation with a third participant.

Patient and public involvement

No patient was involved.

Data extraction

All required information from qualified studies was extracted by two investigators independently. Discrepancies were resolved by discussion. Extracting study information included the first author, the published year, population, the number of patients, gender, age, the number of KMT2A-PTD-positive and KMT2A-PTD-negative patients, detection methods and the classification of French–American–British.

In the meta-analysis, OS was the primary endpoint, and EFS was the secondary endpoint. OS refers to the time from randomisation to death due to any cause. For the patients who have lost the follow-up before death, the last follow-up time is usually calculated as the time of death. EFS refers to the time from the diagnosis of AML to the occurrence of any event, including death, disease progression, change of chemotherapy regimen, documentation of persistent leukaemia or last follow-up. We estimated the prognostic value of KMT2A-PTD in patients with AML by HRs and 95% CIs for OS and EFS. If the included studies did not offer the original data or related HR, we extracted the data from the Kaplan-Meier curve by using Engauge Digitizer V.4.1 software15 and calculated HRs and their corresponding 95% CIs by using the 1745-625-8-S1 Worksheet.16

Quality assessment

Two authors estimated the quality of the included studies by using the Newcastle-Ottawa quality assessment scale (NOS) independently.17 Discrepancies between the two authors were resolved by discussion. The NOS contains nine items divided into three major categories: selection (including four items), comparability (including two items) and exposure or outcome (including three items). The overall score of the study ranged from 1 to 9 points. The study with a score of 7–9 points was regarded as high quality.

Statistical analysis

We calculated the pooled HRs and their 95% CIs for OS and EFS by Stata V.12 software. KMT2A-PTD indicated poor prognosis when the pooled HRs for OS or EFS were >1 and their 95% CIs did not overlap 1. The heterogeneity was evaluated by the χ2 test; it was considered that
there was significant heterogeneity among studies when p was less than 0.1 and I² was greater than 50%. The random-effects model was selected to calculate the effect value when evident heterogeneity existed among studies (p was less than 0.1 and I² was greater than 50%); otherwise, the fixed-effects model was selected. Meta-regression was used to explore the source of heterogeneity among studies.

Sensitivity analysis and publication biases
We used sensitivity analysis to evaluate the impact of each individual study on the stability of the pooled effect by excluding one study each time sequentially. Begg’s and Egger’s tests were used to assess the potential publication biases of the included studies.

RESULTS
Study identification and selection
We initially collected 1232 studies, and 407 studies remained after preliminary screening and exclusion of review articles, fundamental studies, letters, etc. Subsequently, after reading the full text and excluding 255 studies with insufficient data, 135 studies of KMT2A rearrangement or other mutations excluding KMT2A-PTD, we obtained 19 articles in total. We finally kept 18 studies covering 6499 patients in our meta-analysis after being further screened and excluding one duplicate study. The screening process was performed in a flow chart (figure 1).

Characteristics of the selected studies
Among the 18 included studies, 17 studies were cohort studies, and one study was a randomised controlled trial. Six studies originated from Asia, nine from Germany, one from America and two were unclear (table 1). Among 6499 patients from the 18 studies, there were 705 KMT2A-PTD-positive AML patients and 5794 KMT2A-PTD-negative AML patients.

Quality assessment of the included studies
We used the NOS to evaluate the quality of the 17 cohort studies. The mean score of the 17 included cohort studies was 7.65 (5–8), indicating that the 17 included studies were of high quality. One study was a phase 3 randomised controlled trial, which was considered to be high quality (online supplemental table 1).

OS and EFS
We applied the pooled HR for OS from the 18 studies to assess the prognostic value of KMT2A-PTD in patients with AML. AML patients with KMT2A-PTD positivity had inferior OS (HR=1.30, 95% CI 1.09 to 1.51, p=0.015) compared with the KMT2A-PTD-negative AML patients. There was moderate heterogeneity (I²=46.9%) with the fixed-effects model (figure 2). The pooled HR for the EFS from eight studies had no prognostic impact on AML.

Figure 1 Flow diagram of study screening.
Table 1  Characteristics of the included studies in the meta-analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Population</th>
<th>Patients (n)</th>
<th>Median age, year (range)</th>
<th>Male/ female</th>
<th>KMT2A-PTD*/ KMT2A-PTD†</th>
<th>FAB classification</th>
<th>Karyotypically normal AML?</th>
<th>Detection methods</th>
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</thead>
<tbody>
<tr>
<td>Vetro et al²²</td>
<td>2019</td>
<td>Germany</td>
<td>190</td>
<td>58 (19-86)</td>
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<td>100/90</td>
<td>95/95</td>
<td>M0-M7*</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Wu et al²³</td>
<td>2018</td>
<td>NA</td>
<td>106</td>
<td>60 (21-88)</td>
<td>NA</td>
<td>57/49</td>
<td>9/97</td>
<td>M0-M7†</td>
<td>Yes/No</td>
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<tr>
<td>Kong et al²⁴</td>
<td>2017</td>
<td>Chinese</td>
<td>36</td>
<td>48 (22-72)</td>
<td>10.6 (2-28)</td>
<td>18/18</td>
<td>17/19</td>
<td>M2-M6†</td>
<td>Yes/No</td>
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<tr>
<td>Shiba et al¹⁰</td>
<td>2015</td>
<td>Japanese</td>
<td>369</td>
<td>10.8/7.0 (0-17.9)</td>
<td>NA</td>
<td>194/175</td>
<td>9/360</td>
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<td>Kao et al¹³</td>
<td>2014</td>
<td>Chinese</td>
<td>67</td>
<td>49.0 (0.3-97.9)</td>
<td>4.8 (NA-176.6)</td>
<td>45/22</td>
<td>5/62</td>
<td>M0</td>
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<td>Sano et al²⁵</td>
<td>2013</td>
<td>Japanese</td>
<td>153</td>
<td>6 (0-15)</td>
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<td>87/66</td>
<td>21/132</td>
<td>M0-M7*</td>
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<td>2012</td>
<td>Germany</td>
<td>952</td>
<td>66.8 (3.4-100.4)</td>
<td>23.7</td>
<td>537/463</td>
<td>57/895</td>
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<td>Haferlach et al²⁶</td>
<td>2011</td>
<td>Germany</td>
<td>252</td>
<td>65.7 (19.7-88.8)</td>
<td>NA</td>
<td>11/241</td>
<td>M0-M7*</td>
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<td>Gaidzik et al¹⁴</td>
<td>2011</td>
<td>Germany</td>
<td>884</td>
<td>48 (18-60)</td>
<td>54 (51.6-60)</td>
<td>473/411</td>
<td>72/724</td>
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<td>Fernandez et al²⁷</td>
<td>2009</td>
<td>American</td>
<td>657</td>
<td>47/48 (17-60)</td>
<td>25.2</td>
<td>335/322</td>
<td>31/586</td>
<td>M0-M7†</td>
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<td>Bacher et al²⁸</td>
<td>2008</td>
<td>Germany</td>
<td>1044</td>
<td>63.1 (17.5-91.8)</td>
<td>NA</td>
<td>84/960</td>
<td>M0-M7†</td>
<td>Yes</td>
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<td>Shih et al¹²</td>
<td>2006</td>
<td>Chinese</td>
<td>98</td>
<td>52 (15-85)</td>
<td>NA</td>
<td>44/54</td>
<td>62/36</td>
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<td>Yes/No</td>
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<td>Weisser et al²⁹</td>
<td>2005</td>
<td>Germany</td>
<td>145</td>
<td>63 (24-89)</td>
<td>6 (0.5-53)</td>
<td>82/63</td>
<td>137/49</td>
<td>M0-M6†</td>
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<td>Steudel et al¹¹</td>
<td>2003</td>
<td>Germany</td>
<td>956</td>
<td>NA</td>
<td>NA</td>
<td>48/908</td>
<td>M0-M7*</td>
<td>Yes/No</td>
<td>RT-PCR cDNA-Seq</td>
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<tr>
<td>Shahi et al²⁶</td>
<td>2002</td>
<td>Chinese</td>
<td>81</td>
<td>46 (0.3-80)</td>
<td>NA</td>
<td>42/39</td>
<td>9/72</td>
<td>M0-M7†</td>
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<td>Döhner et al³⁰</td>
<td>2002</td>
<td>Germany</td>
<td>221</td>
<td>46.8 (16-60)</td>
<td>19 (NA)</td>
<td>99/122</td>
<td>18/203</td>
<td>M0-M7†</td>
<td>Yes</td>
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<tr>
<td>Schnittger et al³¹</td>
<td>2000</td>
<td>Germany</td>
<td>217</td>
<td>62.3 (50.3)</td>
<td>NA</td>
<td>NA</td>
<td>16/211</td>
<td>M0-M7*</td>
<td>Yes</td>
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</tbody>
</table>

KMT2A-PTD: partial tandem duplication of lysine (K) methyltransferase 2A.
*FAB classification includes M3.
†FAB classification excludes M3.
cDNA-Seq, complementary DNA sequencing; FAB, French–American–British; NA, not available; qRT-PCR, quantitative real-time PCR; RQ-PCR, real-time quantitative PCR; RT-PCR, reverse-transcription PCR; Semi-PCR, semiquantitative PCR.
patients with KMT2A-PTD positivity (HR=1.26, 95% CI 0.86 to 1.66, \(p=0.023\)). There was moderate heterogeneity (\(I^2=56.9\%\)) with the random-effects model (figure 3).

Among the 18 included studies, five studies concerned AML patients with KMT2A-PTD positivity and cytogenetic normal (CN). The pooled HR for OS indicated that
KMT2A-PTD was an independently unfavourable prognostic factor in CN-AML patients (HR=2.72, 95% CI 1.83 to 3.61, p=0.571) with no heterogeneity (I²=0%) (figure 4A). Among five studies for patients with CN-AML, only three studies provided HR (95% CI) for EFS. The pooled HR for EFS suggested that KMT2A-PTD had no prognostic impact on CN-AML patients (HR=1.46, 95% CI 0.94 to 1.98, p=0.326) (figure 4B). However, due to the limited number of included studies and the wide range of 95% CI of the pooled HR for EFS in CN-AML, the result may not be reliable and needs further verification. Moreover, KMT2A-PTD conferred poor OS in AML, including M3 patients (HR=1.93, 95% CI 1.64 to 2.32, p=0.004), with no heterogeneity (I²=0%) (figure 5A). Although the results indicated that KMT2A-PTD had no prognostic impact on OS in patients with AML, excluding M3 (HR=1.61, 95% CI 0.90 to 2.32, p=0.563), it is difficult to draw a precise conclusion because of the wide CI and the large heterogeneity among studies (I²=64.5%) (figure 5B). Compared with the KMT2A-PTD-negative AML patients, KMT2A-PTD-positive AML patients had inferior OS (HR=1.93, 95% CI 1.44 to 2.42, p=0.053) and EFS (HR=1.64, 95% CI 1.25 to 2.03, p=0.039) in old patients (the median age of the patients included in the study was 60 years or older) with no heterogeneity of OS (I²=0%) and EFS (I²=1.2%)
Finally, we conducted a subgroup analysis according to the treatment regimens of patients. KMT2A-PTD conferred poor OS in patients with AML who received anthracycline in combination with cytarabine treatment (HR=1.75, 95% CI 1.22 to 2.28, p=0.446). Although the result indicated that KMT2A-PTD had no prognostic impact on OS in patients who underwent allogeneic HSCT (HR=3.34, 95% CI 0.36 to 6.31, p=0.984), it is difficult to draw a precise conclusion because of the limited number of included studies (online supplemental figure 2).

### Meta-regression analysis

Because of the limited number of the included studies focusing on EFS, meta-regression was only used to explore the potential source of heterogeneity for OS in the total population. Five factors, including population,
year of publication, median age, number of patients and detection methods, were included in the meta-regression analysis. The results showed that there was no significant relationship between the five factors and the source of the heterogeneity (table 2). Differing laboratory techniques have distinct sensitivities for detecting KMT2A-PTD mutation; thus, we included the detection methods in the regression analysis and found that detection methods had no significant effect on the pooled OS.

Sensitivity analysis

Sensitivity analysis, omitting one study at a time to evaluate the impact of each individual study on the pooled HR for OS and EFS, was conducted in our meta-analysis. The results indicated that two studies (Kao et al 2014 and Gaidzik et al 2011) for OS and one study (Gaidzik et al 2011) for EFS had no significant influence on their corresponding pooled HRs in the total population with the random-effects model but were relatively obvious with the fixed-effects model (online supplemental figure 3). Excluding the two studies with a relatively obvious effect on the pooled HR for OS, the pooled HR from 1.30 (95% CI 1.09 to 1.51) changed to 1.75 (95% CI 1.44 to 2.06), while the I^2 from 49.6% (p=0.015) decreased to 0% (p=0.481) (online supplemental figure 4). Moreover, the pooled HR for EFS from 1.26 (95% CI 0.86 to 1.66) changed to 1.34 (95% CI 1.04 to 1.64) when excluding the one study with a relatively significant effect on the combined HR for EFS (online supplemental figure 5). According to the previous results, we can conclude that the source of the heterogeneity was from the two studies. The Kao et al 2014 study only included patients with AML-M0, which may be the source of the heterogeneity of the study. The Gaidzik et al 2011 study accounted for 38.88% weight of the pooled HR for OS and 24.62% for EFS in the total population, which was the largest weight study in all included studies. The reasons described above may explain why this study had a significant influence on the combined HR.

Publication biases

No obvious publication bias was found by Begg’s test (p=0.820) and Egger’s test (p=0.220) for OS and Begg’s test (p=0.902) and Egger’s test (p=0.759) for EFS in the total population (online supplemental figure 6).

Discussion

The significance of the study

AML is a common haematological malignancy. Despite all our scientific advances, the prognosis of patients with AML still needs to be improved. The classification and diagnosis of patients with AML are based on genetics and morphology. With the rapid development of gene detection technologies, an increasing number of somatic gene mutations have emerged as important diagnostic and prognostic markers for AML. KMT2A is a common abnormal gene. The biological and clinical features of AML patients with KMT2A-rearrangement are well known, but the diagnostic and prognostic role of KMT2A-PTD is controversial. Although many studies have evaluated the prognostic effect of KMT2A-PTD in patients with AML, the results among these studies are still inconsistent. Therefore, we conducted a meta-analysis, hoping to solve this controversial problem.

Principal findings

In our meta-analysis, the primary outcome was OS, and KMT2A-PTD conferred shorter OS in the total population. In the subgroup analysis, KMT2A-PTD also conferred shorter OS in CN-AML patients, old AML patients and AML including M3 patients, compared with those with KMT2A-PTD negativity. The secondary outcome was EFS. KMT2A-PTD indicated no prognostic impact on EFS in the total population. However, in the sensitivity analysis, KMT2A-PTD resulted in poor EFS when deleting the study with a relatively obvious effect on the combined HR. Thus, the prognostic impact of KMT2A-PTD on EFS in the total population needs further verification. In the subgroup analysis of the pooled HR for EFS, KMT2A-PTD was associated with poor EFS in old AML patients but without prognostic impact on EFS in CN-AML patients. However, due to the small number of included studies and the wide range of 95% CI of the pooled HR for EFS in CN-AML patients, the result may not be reliable and needs further verification. In the meta-regression analysis, five factors, including the population, publication year, median age, number of patients and detection methods, showed no significant association with the source of heterogeneity. In the sensitivity analysis, two studies for OS and one study for EFS had no significant influence on their corresponding combined HR in the total population with the random-effects model but were relatively obvious with the fixed-effects model. After deleting the two studies, the pooled HR indicated that KMT2A-PTD played a poor prognostic impact on OS in patients with AML, which was consistent with the previous conclusion without removing the two studies. However, the pooled
HR for EFS from 1.26 (95% CI 0.86 to 1.66) changed to 1.34 (95% CI 1.04 to 1.64) when deleting the one study with a relatively significant effect on the combined HR. The Hsiao-Wen Kao et al. 2014 study only included patients with AML-M0, which may be the source of the heterogeneity of the study. The Gaidzik et al. 2011 study accounted for 38.88% weight of the pooled HR for OS and 24.62% weight of the pooled HR for EFS in the total population, which was the largest weight study in all included studies. The reasons described previously may explain the heterogeneity of this study. In addition, the number of studies for calculating the pooled HR for EFS was relatively small; thus, the result significantly changed when excluding the one study. The prognostic impact of KMT2A-PTD on EFS in the total population requires further research. In the publication bias tests, no significant publication bias was found in Begg’s test and Egger’s test for the OS and EFS in the total population.

Strengths and limitations

Our study is the first meta-analysis to discuss the controversial problem concerning the prognostic impact of KMT2A-PTD in patients with AML. The 95% CIs of HRs for OS in 9 studies contain 1 among the 18 studies included in the meta-analysis, which indicates the inconsistent conclusion of the role of KMT2A-PTD in the prognosis of patients with AML. Meta-analysis can improve the efficiency of statistical analysis, reveal the uncertainty in a single study and find common conclusions and differences between individual studies. Therefore, the conclusion obtained by meta-analysis is more reliable. However, there are several limitations in our meta-analysis. First, the results were from cohort studies rather than random controlled trials (only one randomised controlled trial was included), but the latter are more reliable. Second, raw data for each individual patient were not available, and the abstracted data were from published studies, but a meta-analysis based on individual patient data is more conducive to offering a more reliable estimate of the association. Third, we did not evaluate the potential effects of other factors, such as gender distribution of patients, chromosomal aberration, cytogenetic risk classification, gene lesions and time of follow-up.

CONCLUSION

In conclusion, KMT2A-PTD had a significantly unfavourable prognostic effect in patients with AML. This conclusion also applied to some subgroups, including karyotypically normal AML, old AML (>60 years old) and AML including M3 patients. These findings can provide help for justifying risk-adapted therapeutic strategies for patients with AML based on KMT2A-PTD. The molecular testing needed to detect the KMT2A-PTD mutation is not routine in practice and requires a specific PCR assay at the time of diagnosis, and standard, karyotype and fish do not routinely identify this lesion. Many genes associated with the diagnosis and prognosis of patients with AML have been revealed by gene sequencing, allele-specific PCR and other techniques, such as FLT3-ITD, NPM1, CEBPA, IDH1 and RUNX1. Combined with these significant genetic biomarkers, KMT2A-PTD will contribute to a more accurate risk stratification and treatment decision of patients with AML. The discovery of the conclusion can prompt us to further study the pathogenic mechanism of KMT2A-PTD in AML, which is helpful to deepen our understanding of the disease. Moreover, with a better understanding of the role of KMT2A-PTD, we can develop small inhibitors targeting KMT2A-PTD, which will provide significant help for the treatment of patients with AML.

Contributors

YW, MM and YG contributed to the study conception and design. Material preparation, data collection and analysis were performed by all authors. The first draft of the manuscript was written by YW and MM modified and supplemented the content of the manuscript, and all authors commented on previous versions of the manuscript. YW and MM contributed equally to this paper. All authors read and approved the final manuscript. YG is responsible for the overall content as guarantor and accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethics approval

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. No data are available.

Supplemental material

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