

Prognostic Value of *EVII* Expression in Pediatric Acute Myeloid Leukemia: A Systematic Review

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ABSTRACT

Acute myeloid leukemia (AML) as a distortion of blood cells involves the differentiation of hematopoietic stem cells. Several studies established the irregular overexpression of specific genes is a common finding in patients with AML. The ectopic viral integration site-1 (*EVII*) gene is a proto-oncogene subject to alternative splicing, and encodes a zinc-finger protein that acts as a transcriptional regulator in early development. Forced overexpression of *EVII* in hematopoietic progenitors later induced a myeloid differentiation block. The current review aimed at determining the prognostic value of *EVII* expression in patients with AML in the age range of one month to fifteen years.

The scientific databases including PubMed, Google Scholar, EMBASE, Scopus, and ISI published up to January 2016 were searched using the conformity keywords and a total of four articles were studied.

Three articles declared higher overexpression of *EVII* in patients with mixed-lineage leukemia (MLL) rearrangements. The percentage of overall survival (OS), reported in two articles, decreased in AML patients with high *EVII* expression. A study reported that the relationship between *EVII* expression and OS was negligible in cases with and without *EVII* expression. Another study showed significant differences in event free survival (EFS) and OS in the group of patients with positive MLL-AF9 between *EVII*⁺ and *EVII*⁻ patients.

The current study revealed that high *EVII* expression was not a poor prognostic factor in pediatric patients with AML. And this gene expression was mainly prognostic concomitantly by other factors such as MLL rearrangement, *MEL1* expression, and white blood cell (WBC) count.

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Introduction

Acute myeloid leukemia (AML) is characterized by blocked or distorted differentiation of hematopoietic stem cells. This malignancy emerges as the results of abnormal rearrangement and inhibition of maturation in blood cells (1, 2).

Several studies demonstrated that the aberrant overexpression of specific genes is a common finding in patients with AML; whereas some clinically relevant biological subsets are defined, which lack other cytogenetic or molecular prognostic markers (3).

The ectopic viral integration site-1 (*EVII*) is a proto-oncogene that encodes a zinc-finger protein and controls transcription in early development (4). The gene was first identified as a common site of viral integration in retrovirus inducing murine leukemia; it suggests a role for *EVII* in hematopoietic cells transformation (5). Further researches demonstrated that forced overexpression of *EVII* (*EVII*⁺) in hematopoietic progenitors induces myeloid differentiation block; it increases self-renewal and survival of transformed progenitors (6).

Increased *EVII* expression is mainly caused by chromosomal rearrangements involving chromosome band 3q26, where *EVII* is located; it is applied as a prognostic factor (7). Overexpression of the *EVII* gene is associated with adverse prognosis (8).

Aberrant *EVII* expression is reported in 8%-10% of human AML adults and obviously up to 27% of pediatric mixed-lineage leukemia (MLL). AML accounts for 25% of all cases of children with acute leukemia; it is accountable for >50% mortality in the mentioned populations (10, 11).

To the best of authors' knowledge, the prognostic

value of *EVII* expression in pediatric patients with AML is not systematically reviewed. Hence, the current study aimed at determining the prognostic value of *EVII* expression in patients with AML in the age range of one month to fifteen years.

Materials and methods

Search strategy and literature selection

The current systematic review was presented with the preferred reporting items for systematic reviews and meta-analyses plans (PRISMA); PRISMA diagram was adapted too (Figure 1).

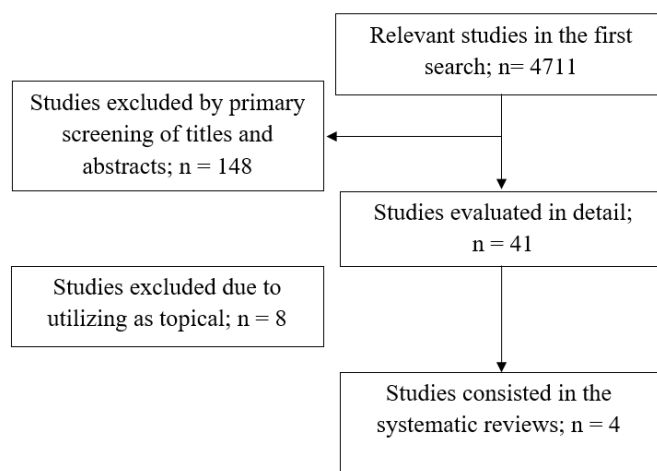


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses. Flow Diagram: Screening Procedure of Selected Articles

Conformity keywords were used in various combinations: “*EVII*” and “AML” or “acute myeloid leukemia” and “pediatric” or “children” or “infants” and “prognosis”, “*EVII* expression” and pediatric AML” or “*EVII* expression” and “molecular disorders” and “prediction” or “*EVII*” and “AML” and “prognosis” or “*EVII*” and “acute myeloid leukemia” and “forecast” or “prospects”. The keywords were planned to proper MeSH terms.

The following inclusion criteria were used: 1- Articles published in English, which focused on patients with childhood AML; 2-Articles evaluating any prognostic outcomes including overall survival (OS), event-free survival (EFS) or both, according to *EVII* expression status (high and low expression rates).

The exclusion criteria were as follows: 1- Review

articles; 2- Expert opinions; 3- Case reports; 4- Articles with no available prognostic data; 5- Papers that were a subset of article by the same authors (for multiple reports of single study, only the most recent or most complete article was considered and examined); 6- Samples obtained from cell and tissue cultures; 7- Studies including patients over 15 years old.

A reviewer evaluated the titles and abstracts of the identified publications; potentially relevant articles were retrieved in full.

After removal of duplicate studies, the data were extracted based on PRISMA guidelines Including author's name, year of publication, region of the study, patient information (including numbers and median white blood cell (WBC) count) (Table 1), OS, and EFS rate and prognosis.

Table 1. Data Extracted From Studied Articles on the Effect of *EVII* Expression on Pediatric AML Patients

First Author	Publication (region/yr)	Sample Size	Follow-up	Median WBC Count ($10^9/L$)
BV Balgobind	Netherlands, 2010	228	4 year	39.7_42.2
Phoenix A.HO	USA,2013	206	5 year	15.4_35
Hidemasa Matsuo	Japan, 2014	443	NR	48.4_88.7
A Jo	Japan, 2015	130	4 year	NR

NR : data not reported
WBC, white blood cell

Results

Totally, four articles were studied in detail shown in Table 1. All studies were retrospective articles that evaluated prognostic value of *EVII* gene expression in pediatric AML. The studied patients were from various countries and all of them were diagnosed with AML and were in the age range of one month to fifteen years.

Total population included 1007 patients, ranging 130 to 443 in the enrolled studies. *EVII* expression was reported 12.29% to 36% with the mean of 26.57%. In all selected articles, real-time quantitative polymerase chain reaction (RQ-PCR) method was used for *EVII* expression evaluation.

Three out of 4 papers did not report any relationships between *EVII* expression and gender (12, 13, 14); and even one article declared no relationships between age and WBC count (13). While one study declared that *EVII* expression mostly occurred in older patients ($P=0.03$) and it was associated with higher WBC count ($P=0.01$) (12).

Another article stated that high expression of *EVII* was more common in infants less than one year old (up to 40%); lower counts of WBC were reported in cited patients ($P= 0.061$) (14). Only one paper reported bone marrow blast mean; it was similar in patients with and without *EVII* expression (14).

Conflict was concluded from the reviewed articles by investigating the correlation between *EVII* expression and French-American-British (FAB) classifica-

tion of AM.

A study reported high expression of *EVII* in M4 and M5 FAB subtypes of AML; it was expressed that 33% and 22% in M4 and M5 patients, respectively (12).

Another study declared high rate of *EVII* expression in AML-M5 (36%) (13). Two studies observed highest expression of *EVII* (up to 24%) in AML-M7 (14,15); one of the cited studies showed high *EVII* expression in M4/M5 subtypes of leukemia with MLL rearrangements in addition to AML-M7 (15).

Molecular disorders and *EVII* expression

Gene mutations and chromosome abnormalities such as FLT3-ITD and NPM1 mutations are assessed with cytogenetic investigations.

Selected articles disagreed on FLT3-ITD mutation and *EVII* expression. As Hidemasa et al., stated that FLT3-ITD mutation frequency was significantly higher in patients with *EVII* expression ($P=0.04$) (12). Balgobind et al., declared that only one patient with *EVII* expression had FLT3-ITD mutation; 19.70% of patients with *EVII*- had FLT3-ITD mutation too (4.0% vs. 19.7%; $P =0.05$) (13).

Other published papers claimed that FLT3-ITD mutations were observed in both groups, with and without *EVII* expression, equally (14).

Three of the selected papers examined the NPM1 mutation too. These three studies showed that NPM1 mutation is not correlated with *EVII* expression (12, 13, 14).

Two articles assessed monosomy7 disorder and reported higher expression of *EVII* in all cases with monosomy7 (rate: 8%; $P=0.006$) (13, 14).

One article compared the changes of *EVII* expression in CEBPA mutant individuals; the authors reported just one CEBPA mutant patient with *EVII* overexpression (14). While other studies did not report *EVII* expression in individuals with mutant CEBPA (12).

Cytogenetic disorders and *EVII* expression

MDS1/EVII transcript is a marker to detect cryptic 3q26 aberrations. Balgobind et al., evaluated 3q26 aberration and *MDS1/EVII* transcript; they found three of 25 patients with *EVII+* that lacked the *MDS1/EVII* transcript (13).

However, by combined data of the gene expression profiling and RQ-PCR in all cases with *EVII+*, cryptic 3q26 rearrangements were not detected (13).

Also, two other studies did not detect 3q26 rearrangement in EBV (Epstein-Barr virus) positive cases.

In all articles, the association between *EVII* expression and MLL type rearrangement was investigated. An article reported that *EVII* expression was not correlated with MLL translocation partners (12). Another article declared that higher frequency of *EVII* overexpression (27.65%) was observed in patients with MLL rearrangements (13).

Also, another study detected this gene rearrangement in 40% of high expressed *EVII* patients (14).

EVII expression and clinical outcome

All of the articles on OS, EFS, and patients follow-ups were evaluated in terms of high or low *EVII* expression.

In three papers, the association between the expression status of *EVII* gene and OS was reported ($P=0.45$ to $P<0.001$). The calculated OS, provided in two article, decreased in patients with AML and high *EVII* expression ($51\% \pm 14\%$; $P=0.05$) (14).

A study assessed the relationship between *EVII* expression and OS; it was negligible in cases with and without *EVII* expression ($P=0.45$ and $P=0.34$, respectively) (12, 13).

Also in another study, clinical outcomes were compared between *EVII+* and *EVII-* cases in the group of patients with MLL-AF9. The results showed significant difference in EFS ($P<0.0001$) and OS ($P=0.0008$) (12).

An article declared that there was a link between *EVII* overexpression and EFS. Over expressed patients had lower rates of five-year OS ($51\% \pm 14\%$; $P=0.015$) and EFS ($40\% \pm 13\%$; $P=0.042$) (14).

Another study showed that patients with *EVII* overexpression had significantly a higher four-year EFS ($28\% \pm 11\%$; $P=0.04$) in comparison with patients without *EVII* overexpression (13).

A study reported poor survival in patients with high *EVII* and MEL1 expression (four-year EFS: 39%; OS: 44%); while survival of patients just with *EVII* overexpression was slightly inferior in the analysis of total patient (15).

Discussion

AML survival is influenced by factors such as age, genetic abnormalities such as gene mutations, aberrant expression of genes, etc. (16). Age is the most vital predictive factor for patients with AML; adults older than 60 years have a lower OS in comparison with younger cases (17, 18). Also, cytogenetic disorders dramatically influenced clinical outcomes of AML (19).

EVII plays an important role in upregulation of cell proliferation; it impairs cell differentiation, and induces cell transformation (21). Increased *EVII* expression in AML mainly occurs after chromosomal rearrangements involving chromosome band 3q26, inv (3) (q21q26)/t (3; 3) (q21; q26)/t (3, 21) (q26; q22) (7). Increased *EVII* expression is observed in *EVII*-rearranged AML, and in patients with other cytogenetic abnormalities (22) such as monosomy7 and 11q23 rearrangements involving MLL as well as cytogenetically normal AML (CN-AML). In contrast, Groschel et al., established that overexpression of *EVII* was mostly absent in cytogenetically favorable-risk group and in NPM1 mutated AMLs (23).

Interestingly, Aria et al., reported that the specific MLL-ENL fusion triggers *EVII* transcription in un-

differentiated hematopoietic cells (24). The prognostic value of high *EVII* expression and the correlation between these markers and AML are not thoroughly evaluated in pediatric patients with AML. Furthermore, in the current systematic review four related articles to the prognostic role of *EVII* in pediatric AML were analyzed.

Matsuo et al., proposed that *EVII* overexpression was not correlated with adverse prognostic factor; since it was associated with reduced remission duration in pediatric patients with AML and MLL-rearrangement, especially in patients with MLL-AF9 rearrangement (12).

Moreover, Lugthart et al., declared that adult patients with AML and *EVII* overexpression, irrespective of harboring 3q26 aberrations, had poor prognosis (20). In contrast to adult AML, Balgobind et al., demonstrated no correlations between chromosome 3q26 abnormality, and *EVII* expression in pediatric AML. Also, they reported that cases with *EVII*⁺ had no independent prognostic value for pediatrics; Patients with high *EVII* expression had a significantly inferior four-year EFS compared with that of the patients with no *EVII* overexpression. Conversely, the OS was not significantly different between *EVII*⁺ and *EVII*⁻ groups. Also, in the MLL-rearranged AML patients no significant differences were reported in terms of EFS and OS between the cited groups. They proposed an association between the types of pediatric AML and intermediate to unfavorable prognosis; for example, MLL-AF6 and monosomy7 cause poor prognosis for patients with *EVII* expression (13).

Phoenix A. Ho et al., did not detect any chromosomal rearrangements of 3q26 in pediatric patients with AML. *EVII* overexpression mechanisms seem to be distinct in pediatric AML from *EVII* overexpression in the setting of chromosome 3 aberrations in adult AML.

They investigated that patients with high *EVII* expression had significantly lower rates of five-year OS (51%±14%) and EFS (40%±13%). Also, favorable-risk was a strong predictor of improved OS compared with intermediate-risk. Multivariate analysis showed

that high *EVII* expression did not retain an independent prognostic significant factor for OS among other established prognostic markers (14).

Jo et al., declared that patients with high *EVII* or MEL1 expression had very poor rates of EFS and OS for a four-year period (EFS: 39%, OS: 44%); EFS and OS rates were even lower in patients without overexpression. Also, they reported no inferior survival (EFS and OS) rates in patients with M7 subtype and *EVII* overexpression.

Concomitantly, overexpression of *EVII* and MEL1 (PRDM16), an *EVII* family member, might act as an even better prognostic marker in pediatric AML compared with *EVII* overexpression alone (15).

Conclusion

According to the results of review studies, it was observed that high *EVII* expression was not a poor prognostic factor in pediatric patients with AML. Generally, this gene expression was a prognostic factor compatible with other factors such as MLL rearrangement, MEL1 expression, and WBC count.

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Conflict of Interest

The authors declare that there was no conflict of interest.

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