Clinica Chimica Acta 483 (2018) 6–13

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Review

Prognostic role of microRNA-155 in patients with leukemia: A meta-analysis

Xiaoyu Zhang[a,1], Yong Wang[b,1], Qiang Guo[a], Yutao Diao[a], Hongyan Liu[a], Guanhua Song[a], Wei Wang[a], Zhiyong Zhang[a], Haipeng Yin[a], Lianlian Li[a,*]

[a] *Institute of Basic Medicine, Shandong Academy of Medical Sciences, Jinan 250062, China*
[b] *Shandong Xinchuang Biotechnology Co., LTD, Jinan 250102, China*

ARTICLE INFO

Keywords:
Leukemia
Meta-analysis
MicroRNA-155
Overall survival
Prognosis

ABSTRACT

Background: Recent studies have shown that microRNA-155 (miR-155) is correlated with clinical outcomes of leukemia. This meta-analysis explores to evaluate the prognostic value of miR-155 for survival in patients with leukemia.
Methods: Eligible studies were searched from PubMed and EMBASE databases. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for overall survival (OS), disease-free survival, event-free survival, progression-free survival and treatment-free survival were extracted, if available. Pooled HRs and 95% CIs were used to study any correlation between miR-155 and survival.
Results: 11 studies from 10 articles containing 1718 leukemia patients were included. Data showed that the pooled HR for OS was 1.67 (95% CI: 1.44–1.95, $P < 0.01$). Subgroup analyses for OS showed that the pooled HRs and their 95% CIs were 1.68, 1.41–2.00 ($P < 0.01$) and 1.73, 1.25–2.41 ($P < 0.01$) for acute myeloid leukemia and chronic lymphoblastic leukemia, respectively. Furthermore, there was no significant heterogeneity or publication bias among the enrolled datasets.
Conclusion: We conclude that high miR-155 expression was associated with shorter OS for leukemia patients, and that miR-155 might be a promising prognostic biomarker for this patient population.

1. Introduction

Leukemia is one major group of hematological malignancies, which are caused by the abnormal proliferation and differentiation of hematopoietic stem cells [1,2]. Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML) and chronic lymphoblastic leukemia (CLL) are more common types [3,4]. In USA, it was reported that the annual incidence rate and mortality for leukemia were 13.95 and 7.25 per 100,000 populations respectively (2009–2013), and leukemia accounted for 29% of all childhood cancers [5]. In China, the annual incidence rate and mortality for leukemia were 5.0 and 3.1 per 100,000 individuals respectively (2013) [6]. Despite the clinical outcomes of leukemia patients underwent significant improvement with the continuous development of chemotherapy and hematopoietic stem cell transplantation over the past few decades [7,8], deaths due to leukemia remain high. In recent years, with the understanding of the molecular pathogenesis of leukemia, some molecular targets as predictive biomarkers for leukemia have been used clinically to remarkably increase the survival rate and reduce the mortality [9–11]. Thus, we need to find better indicators for diagnosis, prognosis and precise treatment of leukemia.

MicroRNAs (miRNAs) may be potential biomarkers for leukemia diagnosis and therapy [12,13]. They are small non-coding single-stranded RNAs (19–24 nts) that regulate protein expression at the post-transcriptional level by binding to 3′-UTRs of target mRNAs [14]. MiRNAs are involved in various physiological and pathological processes, such as cell differentiation, proliferation and apoptosis, as well as in oncogenesis and immune responses [14]. MicroRNA-155 (miR-155) is encoded by the *MIR155 host gene* (*MIR155HG*), formerly called the *B-cell Integration Cluster* (*BIC*) located on human chromosome 21q21 [15,16], and plays a role in various physiological and pathological processes [17]. MiR-155 is being studied for its role in leukemia [18,19] and for its association with diagnosis and prognosis in leukemia patients [20]. Recently, studies showed that abnormal expression of miR-155 was tied to survival in leukemia patients [21–27]. Here, we performed a systematic meta-analysis to assess the relevance of miR-155 in leukemia patients. Our results indicate that miR-155 can be used as a promising prognostic biomarker for survival in leukemia patients.

---

[*] Corresponding author.
E-mail address: lotuslee1985@126.com (L. Li).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.cca.2018.04.015
Received 28 February 2018; Received in revised form 8 April 2018; Accepted 9 April 2018

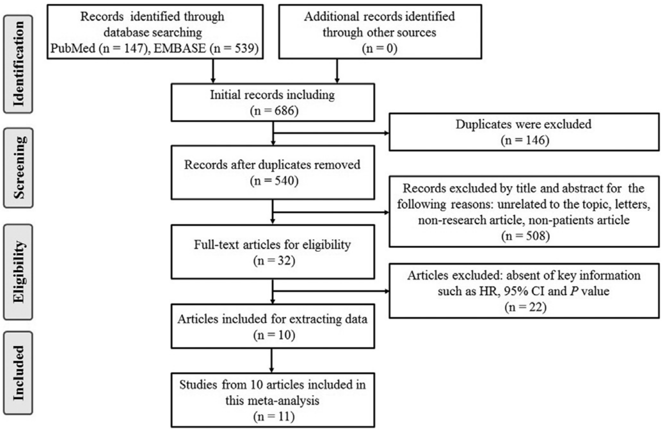

Fig. 1. Flow diagram of the screening and selection process of studies.

2. Materials and methods

2.1. Search strategy

A literature search was performed in PubMed and EMBASE databases, with the publication date from January 1, 2008 to January 5, 2018. The following terms were used to retrieve articles: ("mir-155" or "microRNA-155" or "mir155" or "microRNA155" or "miRNA-155" or "miRNA155") and ("leukemia" or "leukeamia").

2.2. Inclusion and exclusion criteria

Studies included in this meta-analysis should follow these criteria: (1) studies investigated the clinical outcomes of leukemia; (2) the expression levels of miR-155 were detected and divided into two groups; (3) the effect of miR-155 on survival outcomes was analyzed. Whereas studies were excluded following criteria as: (1) publications were identified as duplicates; (2) non-research articles, such as meta-analysis or review; (3) no full-text articles, such as abstracts or letters, (4) non-patients research, such as cells, mice; (5) important information, such as hazard ratio (HR), 95% confidence interval (CI) and *P* value, could not be obtained. When publications were identified duplicates, the newest was selected. Searching and selection of studies were accomplished by two independent researchers (Xiaoyu Zhang and Yong Wang) and supervised by a third author (Lianlian Li).

2.3. Quality assessment

According to Newcastle-Ottawa-Scale (NOS) for cohort studies, the quality assessment of all included studies was independently performed by two investigators (Hongyan Liu and Wei Wang), and any disagreement was settled by discussion. Scoring and the score introduction were referred to Guo et al. [28]. Studies with > 5 scores were considered to be high-quality studies.

2.4. Data extraction

The related data were independently extracted from included studies by two reviewers (Guanhua Song and Zhiyong Zhang), and a third reviewer (Haipeng Yin) addressed the disagreements by discussion. The extracted data included authors, journal, year and origin of publication, leukemia type, number of patients, specimen and detection method for determined the level of miR-155 expression, cut-off value, survival analysis, and HRs of miR-155 expression (high versus low expression group) for overall survival (OS), disease-free survival (DFS), event-free survival (EFS), progression-free survival (PFS) or treatment-free survival (TFS), as well as their 95% CIs and *P* value. HRs and their 95% CIs

Table 1
Main characteristics of 11 studies included in the meta-analysis.

Study	Publication year	Journal	Origin of publication	Leukemia type	Cases (high/low expression)	Specimen	Detection method	Cut-off value	Survival analysis	Outcome	Source of HR
Cui et al. [24]	2014	Blood	USA	CLL	86 (55/31)	Blood	qRT-PCR	Median	Multivariate	OS/TFS	Reported
Cui et al. [24]	2014	Blood	USA	CLL	181 (95/86)	Blood	Microarray	Median	Multivariate	OS/TFS	Reported
Ferrajoli et al. [23]	2013	Blood	USA	CLL	143 (63/80)	Plasma	qRT-PCR	Median	Multivariate	OS	Reported
Guinn et al. [36]	2015	Leukemia	USA	CLL	109 (53/56)	NA	nCounter	Median	Multivariate	OS/PFS	K-M curve/ Reported
Ishihara et al. [35]	2012	Cancer Epidemiology	Japan	ATL	35 (24/11)	Plasma	qRT-PCR	Median	K-M	OS	K-M curve
Marcucci et al. [22]	2013	Journal of Clinical Oncology	USA	CN-AML	363 (181/182)	BM and blood	nCounter	Median	Multivariate	OS/DFS	Reported
Metzeler et al. [25]	2013	Leukemia	USA	CN-AML	364 (174/190)	BM and blood	Microarray	Median	Multivariate	OS/DFS	Reported
Narayan et al. [37]	2017	Leukemia	Australia	AML	59 (10/49)	NA	qRT-PCR	10-fold	K-M	OS	K-M curve
Ramamurthy et al. [21]	2016	Pediatric Blood & Cancer	USA	NK-AML	198 (50/148)	BM	qRT-PCR	Median	Multivariate	OS/EFS	Reported
Rossi et al. [26]	2010	Blood	USA	CLL	104 (NA)	Blood	qRT-PCR	Median	Univariate	OS/TFS	Reported
Zhou et al. [27]	2017	Leukemia & Lymphoma	China	ALL	76 (38/38)	BM	qRT-PCR	Median	Multivariate	OS	Reported

(1), training dataset; (2), validation dataset; AML, acute myeloid leukemia; NK-AML, normal karyotype AML; CN-AML, cytogenetically normal AML; CLL, Chronic lymphocytic leukemia; ALL, acute lymphoblastic leukemia; ATL, adult T-cell leukemia; BM, bone marrow; NA, not available; qRT-PCR, quantitative real-time polymerase chain reaction; nCounter, NanoString nCounter assays; K-M, Kaplan–Meier; OS, overall survival; EFS, event-free survival; DFS, disease-free survival; PFS, progression free survival; TFS, treatment-free survival; HR, hazard ratio.