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The relationship of miR-181a expression level and AML: A systematic review protocol

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ABSTRACT

Introduction: The most common type of leukemia is acute myeloid leukemia (AML) with the lowest survival rate among all of the leukemias particularly in adults. The evidence has shown that dysregulation of miRNA expression is associated with AML. Therefore, the aim of this systematic review was to clarify the role of miR-181a expression in AML.

Methods and analysis: In the present study, observational studies of the roles of miR-181a expression in patients with AML will be included. Standards and indicators test should be performed for all patients. We will search PubMed, SCOPUS and ISI Web of Science with no restriction of language. The outcomes will be reviewed for association between miR-181a level and AML progression and the strength of this relationship with AML will be investigated. Selection of articles and data extraction will be performed by two independent reviewers. STROBE will be used for assessment of study quality. Publication bias and data synthesis will be an assessment by funnel plots and Beggs and Egger's tests using Stata software V.12.1.

Ethics and dissemination: There are no ethical issues.

Trial registration number: This systematic review protocol is registered in the PROSPERO (International Prospective Register of Systematic Reviews), and registration number CRD42016040080.

1. Introduction

Acute myeloid leukemia (AML) is the most common hematopoietic malignancy and it is a disorder of hematopoietic progenitor cells, identified by uncontrolled proliferation of white blood cells that gradually replace normal hematopoiesis in bone marrow [1]. The incidence of AML is 3.7 per 100,000 persons and range of mortality rate is from 2.7 to 18 persons per 100,000 which depend on the age [2]. Several factors are involved in the incidence of the diseases, including genetic disorders such as Down as well as Klinefelter's syndrome, chemical and physical agents (such as ionizing radiation) and viruses [3]. Moreover, studies have shown that associations between different microRNA signatures and specific molecular subtypes in this disease represent its potent role in AML pathogenesis [4]. However, microRNAs are involved in the processes such as hematopoietic cell differentiation, proliferation, and survival in AML. Indeed, they have effect on the treatment response and result of the intervention [5]. MicroRNAs (miRNAs) are the class of small non-coding RNAs that negatively regulate gene expression in the post-transcriptional levels, which have been identified as main regulators in normal and malignant biological processes [6]. Therefore, dysregulation of miRNAs, effects on their targeted genes and may provide potential biomarkers for diagnosis or prognosis of cancer and even though as therapeutic targets [7].

In AML, dysregulation of miRNAs is associated with different stages of differentiation of hematopoietic precursors, so, the role of miRNAs are in hematopoiesis and tumor genesis, as well as changes in the expression pattern of miRNAs [8,9]. Among the numerous RNAs, miR-181a could be as diagnostic candidate and prognostic biomarker, however, expression of this miRNA is up-regulated in some malignancies such as hepatic cancer, blood cancers (such as multiple myelomas, myelodysplastic syndrome and post-myelodysplastic syndrome (AML), and breast cancer known as an oncogenic miRNA which could promote carcinogenesis [10–13]. Debernardi et al. [14] reported that miR-181a plays a

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significant role in the development of tumor stages [14]. Increasing in expression of miR-181a in AML was found to be associated with cell proliferation [15]. This systematic review tries to answer what's the relationship of miR-181a expression level with AML?

2. Objectives

The primary objective was examination of the relationship between miR-181a expression and AML. The secondary objective was to determine the expression of miR-181a expression level in different types of AML. Indeed, it is trying to find the relationship between the miR-181a expression level with overall survival (OS) as well as to assess the heterogeneity and identification of potent sources of heterogeneity between studies.

3. Methods

The methods for this systematic review have been developed according to the guidelines of PRISMA checklist. STROBE Flow Diagram will be employed to describe information gathering through different phases of this systematic review [17]. The protocol of this systematic review has been registered in PROSPERO 2015 (registration No. CRD42015025001). This systematic review and meta-analysis protocol has being prepared in accordance with the PRISMA-P Guidelines [18].

4. Inclusion criteria

4.1. Types of the studies

Observational studies (all of the types of studies included cross-sectional, case-control (both nested and cohort case-control studies) as well as cohort studies and even case reports will be included. Studies assessing animal models, RCT, review articles, proceeding conferences and patients dead from AML will be excluded.

4.2. Participants

Patients with a diagnosis of AML will be included.

4.3. Index test miR-181a

The miRNAs with significant sequences can be used to control the expression of some genes involved in hematologic malignancies [16,19,20]. It has been shown increasing of miR-181a expression may be involved in AML [21,22]. It is a significant relationship between the expression of miR-181a and subtypes of AML. In the current review, expression of miR-181 in AML cells will be detected by real-Time PCR method.

4.4. Outcomes

4.4.1. Primary outcomes

Examination of the relationship between miR-181a expression and AML and the strength of this relationship.

4.4.2. Secondary outcomes

Determination of the expression levels of miR-181a in different types of AML.

The relationship between the expression of miR-181a and OS (overall survival).

Assessment of the heterogeneity and identification of potential sources of heterogeneity between studies.

5. Search methods for identification of studies

5.1. Electronic searches

Keywords well defined and selected from Mesh will be used for searching across several databases. There will be no language limitation in this study. We will search the following databases: PubMed, Web of Science and Scopus, from 2000 until the end of March 2018 with the following search strategies:

5.2. Medline

1. Acute Myelocytic Leukemia
2. (Myelocytic Leukemia AND Acute)
3. (Myelogenous Leukemia AND Acute)
4. (Myeloid Leukemia AND Acute) OR (Nonlymphoblastic Leukemia AND Acute) OR Acute Nonlymphoblastic Leukemia OR Acute Nonlymphoblastic Leukemias OR (Leukemia AND Acute Nonlymphoblastic)
5. Acute Myeloid Leukemia without Maturation OR (Leukemia AND Myeloid AND Acute AND M2) OR (Myeloid Leukemia AND Acute AND M2) OR Acute Myeloid Leukemia with Maturation)
6. 1 or 2 or 3 or 4 or 5
7. microRNA-181a microRNA AND human
8. microRNA-181a AND human) OR (miR-181a AND human) OR (hsa-mir-181a AND human))

9 7 OR 8

6 AND 9

5.3. Other resources

Reference lists of relevant primary studies, reviews and key journals will be searched for additional studies.

5.4. Data collection and analysis

The retrieved papers will be imported into an EndNote. Then duplicated papers will be excluded from the library. In data analysis, two reviewers (KMZ, MK) independently evaluated the title and abstract of papers to exclude non-relevant studies.

Two reviewers will screen the full texts of the remaining studies, and in case of any disagreement, we will consult a third author (HH). The following data will be extracted from all the included studies:

1. Study characteristics (author, year of publication, locations)
2. Participants' characteristics (age, gender, disease type, tumor stages).

5.5. Assessment of methodological quality

The methodological quality of primary studies will be assessed by a revised tool devised for STROBE quality assessment. The defined questions will be answered as a, b, c, d, e, and the score of each article will be calculated. Furthermore, two reviewers (MK and MN) will initially complete the pilot STROBE items in three studies. If they do not reach an agreement, we will refine the tool, and then the updated tool will be applied to complete the assessment for all included studies. In addition, disagreements will be resolved by consensus.

5.6. Assessment of heterogeneity

To investigate heterogeneity, we will include the study design (prospective or retrospective and year of publication) and

population characteristics (gender, ethnicity, age, types of diseases and stage distribution).

5.7. Assessment of reporting bias

Two reviewers (IT, MK) will independently assess the quality of the studies by using the STROBE tool.

6. Statistical analysis and data synthesis

6.1. Descriptive analysis

We will quantitatively combine the results of primary studies. We will not statistically combine studies if those studies have severe heterogeneity. However, for this purpose, we will use a meta-synthesis or narrative synthesis approach. If heterogeneity is severe or the primary studies are insufficient in number, meta-analysis will not be carried out. For gathering information, we will use different methods.

6.2. Inferential statistics

All procedures of meta-analysis are performed using STATA version 12.1 software. To combine the main index of effect size in early studies this systematic review will probably use Odds Ratio of Random Effect procedures and practices Der-Simonian Laird. OR combination of preliminary studies will be shown in the chart Forrest Plot. In preliminary studies heterogeneity is assessed using Cochran Q and I2 index is performed. In case of severe heterogeneity of the subgroup analysis to identify the cause of heterogeneity, and if the number of early studies is less than 10, the method of Meta-regression will be used for this purpose. Assessment of publication bias was using a Funnel Plot Subsequently, Begg and Egger methods will be used to assess this bias. Meanwhile, while all three methods funnel plot, Begg and Egger confirmed the existence of publication bias, used Fill & Trim method to correct this bias.

6.3. Subgroup analyses

Subgroup analyses will be conducted according to the age, gender, sample size, stage and grade and cancer subtypes.

7. Discussion

The role of miR-181a is still being debated in acute myeloid leukemia (AML). However, it is known that miR-181a can effect on differentiation, development, and also regulation of lymphocytes [23]. Moreover, it is found that miR-181a has a role in apoptosis, cell cycle, growth, development, differentiation and invasion of tumors. Our systematic review will hopefully clarify the relationship between changes of miRNA-181a expression in AML patients as a considered watch-out marker for diagnosis or/and prognosis tool for clinicians.

8. Data sharing statement

This study is a systematic review protocol, assessing relationship miR-181a expression with AML, from January 2000 to March 2018.

9. Strengths and limitations of this study

- The first systematic Review and meta-analysis study of Relationship of miR-181a expression and AML
- To obtain a deep understanding of miRNA181a on AML
- Further clinical studies in humans to prove this role
- Low human studies in the field

Ethical approval

There are no ethical issues.

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Author contribution

KMZ is the Corresponding author of the article. MK and KMZ prepared the final version of the manuscript. SM and MK developed a search strategy. KMZ and MK completed independent screening studies, data extracting, an assessment the risk of bias, inter-data into EndNote and eventually finished synthesis. SM will judge any disagreement during the study. All authors read and approved the manuscript version.

Conflict of interest statement

The authors have no conflicts of interest.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Research registration unique identifying number (UIN)

This systematic review protocol is registered in the PROSPERO (International Prospective Register of Systematic Reviews), and registration number CRD42016040080.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.isjp.2018.12.001.

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