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ORIGINAL RESEARCH

The Significance of miRNAs as a Prognostic Biomarker for Survival Outcome in T Cell – Acute Lymphoblastic Leukemia Patients: A Systematic Review and Meta-Analysis

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Purpose: T-cell acute lymphoblastic leukemia (T-ALL) affects lymphoid cells. Previous studies have reported that miRNAs play a significant role in T-ALL prognosis and have the potential to function as biomarkers in T-ALL. Therefore, this systematic review and meta-analysis study was designed to evaluate the overall prognostic impact of miRNAs in T-ALL patients.

Methods: Eligible studies published between Jan 2010 and April 2018 were retrieved from online bibliographic databases based on multiple keywords to generate search strings. Meta-analysis was performed using the outcome measure, Hazard Ratio (HR). A survival analysis of all studies was conducted and a subsequent forest plot was generated to evaluate the pooled effect size, across all T-ALL patients. Subgroup analysis was conducted based on demographic characteristics and commonly represented miRNAs among the included studies.

Results: A total of 17 studies were included for systematic review, among which 16 studies were eligible for meta-analysis, which, in total discussed 32 different miRNAs. The mean effect size of HR value was 0.929 (CI 0.878–0984), which indicates a decrease in risk of death by 7.1%. The analysis was based on the random effects model with the heterogeneity measure index (I^2) being 84.92%. The pooled effect size (HR) of upregulated and down-regulated miRNA expressions on survival outcome in the T-ALL patient was 0.787 (CI 0.732–0.845) and 1.225 (CI 1.110–1.344) respectively. The subgroup analysis was performed based on demographic characteristics (age, gender, lactate dehydrogenase, WBC count) and expression of miR221 and miR46a.

Conclusion: Our systematic review and meta-analysis findings suggest that the overall miRNA expression is potentially associated with a decreased likelihood of death in T-ALL patients. Although our findings are inconclusive, the results point toward miRNA expression allowing for prognostic evaluation of T-ALL patients.

Keywords: microRNAs, prognosis, biomarkers, survival analysis, PRISMA

Introduction

T-cell acute lymphoblastic leukemia (T-ALL) is an aggravated lymphoid malignancy which is characterised by diffuse infiltration of bone marrow by malignant hematopoietic cells expressing immature T-cell markers.[1] T-ALL is a subtype of Acute Lymphoblastic Leukemia (ALL). In 1997, the World Health Organization (WHO) classified ALL into three types based on the

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morphology and cytogenic profiling which are B lymphoblastic, T Lymphoblastic and Burkitt lymphoma.[2] Clinically, patients with T-ALL present with elevated white cell counts in their blood as well as hematopoietic failure, neutropenia, anemia, and thrombocytopenia.

Age plays a significant role in T-ALL where the patients over age of 60 have poor outcomes where only 10–15% appeared to be longer survival.[3] It is twice as prevalent in males as in females.[4] Although T-ALL is a highly aggressive disease, it is potentially curable in adults, with a superior 5-year overall survival (OS) rate as compared to B-cell ALL (48% vs 41%).[5–7] African-American and Hispanic individuals have also been observed to have lower survival rates than Caucasian and Asian individuals.[8] However, poor access to treatment may underlie this ethnic/regional discrepancy seen with regards to survival rates in ALL.[8] MicroRNAs (miRNAs) are short non-coding RNAs that have been suggested to function as post-transcriptional repressors of specific target genes.[9] Several studies have elaborated on the role of microRNAs as oncogenes and tumour suppressors.[10,11] Oncogenic miRNAs (oncomiRs) such as miR19b, miR20a, miR26a, miR92, and miR223 have been identified downregulating the expression of known T-ALL associated tumour suppressor genes.[10] miR193-3p are involved in overexpression of T-ALL associated oncogenes where they regulate the expression of MYB and anti-apoptotic factor MCL1.[11] Inactivation of tumor suppressor miRNAs such as miR29, miR31, miR155, miR193-3p, miR128-3p and miR200 promotes leukemogenesis by activating the oncogenes HBPI, MCL1, PHF6 and MYB.[12,13] miR223 was found to be overexpressed in a subset of myeloid-like adult T-ALLs which appeared to have led to an unfavourable clinical outcome[14] and also it was regulated by T-ALL oncogenes such as NOTCH1 and TAL1.[15,16]

Rationale

The Importance of the Issue

The remarkable success of pediatric ALL therapy has not been achieved in adults. Furthermore, the outcomes in pediatric T-ALL are still been inferior to outcomes in pediatric B-cell ALL (B-ALL).[17,18] Prognostic factors are less evident in patients with T-ALL than in patients with B-ALL. Additionally, infiltration of the central nervous system (CNS) is a common risk factor, which remains an obstacle for long-term remission in T-ALL.[19] The risk stratification is also occasionally based on clinical factors such as age, genetic factors, white blood cell count and response to chemotherapy.[3] Recent studies have shown that miRNAs may play an essential role in T-ALL and could function oncogenes or tumour suppressors.[20] miRNA expression's effects towards T-ALL development, and by proxy, prognosis needs to be studied as there are very few relevant publications on T-ALL prognosis. There are no previously published systematic review and meta-analyses studies on evaluating the impact of miRNA in T-ALL patients' clinical outcomes, particularly regarding survival outcome.

How Will the Study Address This Issue?

A number of individual studies regarding miRNA expression in T-ALL, discussing either a single miRNA target or a set of miRNAs, report that there is potential prognostic value in using miRNAs as biomarkers. However, the results reported by these disparate studies need to be combined and the pooled effect size of survival outcome needs to be assessed to generate an accurate estimate of prognostic value of miRNA. Furthermore, no previous study has attempted to differentiate between the impacts of the upregulated and downregulated miRNAs in T-ALL. The results of this study will address this knowledge gap, and seek to inform clinicians and future researchers on the utility of miRNAs in T-ALL.

How Will It Help?

This systematic review and meta-analysis emphasises the significance of miRNAs, providing potential miRNA biomarkers for prognosis in T-ALL patients. The study intends to provide comprehensive knowledge on the survival outcome in T-ALL patients. This perspective will help us to identify specific miRNAs which may be capable of functioning as early prognostic biomarkers and aid in clinical outcomes of individualised treatment of T-ALL patients. It may also facilitate the clinical investigation of prognostic significance of miRNA expression in future longitudinal studies.

Methods

PROSPERO registration number: This study was registered in PROSPERO and was assigned the registration ID: CRD42017079090.

Search Strategy

This systematic review and meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic

Reviews and Meta-Analysis) guidelines and the PRISMA checklist[21] has provided as a Supplementary Information. Articles published between Jan 2010 to April 2018 were retrieved from online bibliographical databases such as Cochrane Library, EMBASE, Google Scholar, PubMed, Scopus and Web of Science. Apart from online databases, reference lists of the selected articles were also reviewed to identify further studies for inclusion, to increase the robustness of the search. The MeSH search terms used in a database as follows: 1) T-cell lymphoblastic leukemia [Topic], 2) Chronic leukemia [Topic] and Acute leukemia [Topic], 3) miRNA [Topic] 4) Prognosis[Topic], 5) lymphoblastic leukemia [Topic] or 2 [Topic], 6) T lineage leukemia [Topic], 7) Acute myeloid leukemia [Topic], 8) survival outcome [Topic], 9) microRNA [Topic], 10) AML [Topic] and ALL [Topic], 11) B cell leukemia [Topic] or Kaplan Meier curve [Topic]. Also, we searched for conference abstracts, summaries, and review references to find any potentially eligible articles that should not be missed in the current study.

Selection Criteria

The eligible studies have followed the demonstrated inclusion criteria and exclusion criteria:

Inclusion Criteria

(1) The study subjects were patients with T-lineage ALL. (2) Studies reported the prognosis of miRNA expression and survival outcomes of T-All patients. (3) The association between miRNA and survival endpoints was measured. (4) Studies published between 2010 and 2018. (5) Studies which reported the hazard ratio (HR) and 95% confidence interval (CI) in either the full-text or in supplementary data. (6) Studies which presented Kaplan–Meier (KM) curves detailing the survival of patient cohorts in case HR values were not available.

Exclusion Criteria

(1) Studies were not published in English or did not have official English translations. (2) Review articles, reports, conference abstracts, and unpublished thesis were excluded. (3) In-vitro or animal studies have excluded. (4) Studies were also excluded if the miRNA expression was reported from acute myeloid lineage (AML) samples. (5) Unrelated to miRNA in T-ALL patients. (6) Studies which overlaps patient selection with other studies.

Study Selection

After initial screening during search (based on relevance of the titles and abstracts) the articles were collated and input into EndNote™ bibliographical software.[22] The relevant publications based on the inclusion criteria were screened by two independent reviewers and these extracted articles were checked with the third reviewer along with the corresponding author.

Data Extraction and Management

The patient clinical history and miRNA expression results were observed, and the retrieved data were recorded in a custom "Data extraction form" generated using Microsoft Excel sheet for further evaluation of quality as well as data synthesis. The following details were extracted from the eligible studies. Relevant parameters including author details, the country from which patients were enrolled for study, publication year, sample size, follow-up period, a period of research, sampling procedure, the source of samples, methods used for miRNA detection were collected. Demographic characteristics were included which are age, gender, type of lineage, the sample size for B cell lineage patients if the study collaborated with T-cell lineage samples were also included in the excel sheet. Clinicopathological characteristics, biological characteristics of all included studies were recorded in the data extraction form. Treatment parameters, dysregulation of miRNA expression in T-ALL patients along with miRNA nomenclature were recorded. HR estimates with 95% confidence interval (CI) were also included.

Quality Assessment

Two reviewers evaluated the quality assessment from the included studies. The methodological quality was assessed by the quality assessment template based on the National Heart, Lung and Blood Institute (NHLBI) for Observational cohort and cross-sectional studies.[23] This methodology was adopted from previously published studies.[24,25] This assessment template used to evaluate the selected full-text studies considered the included studies with the overall rating of good, fair or poor. There were 14 elements, under which each study was assessed. These include sample size, population; follow-up period, survival outcome, evaluation of exposure and outcome variables, statistical adjustment and other factors. The checklist was used to ensure that all selected studies maintain a baseline standard quality, satisfying the core requirements of the study.

Meta-Analysis

Meta-analysis plays an important role in evidence-based medicine. It integrates the results of independent studies to provide an overall picture of results across all studies. All analyses in this study were conducted with the use of the Comprehensive Meta-Analysis (CMS) software.

Assessment of Heterogeneity

Heterogeneity assessment was based on Higgin's I^2 statistic and Cochran's Q-test, under the random-effects model.[26] Q test provides the difference between the fixed effect and observed effect which is done by summing up and squaring their differences.[27] As the I^2 statistic and the Q-statistic alone are not sufficient to assess heterogeneity (as they do not consider the threshold effect).[28,29] The Tau-squared statistic was used to complement the assessment of heterogeneity and study the variance between the studies as it incorporates the threshold effect.[30] A HR value > 1 indicates poor outcome for patient survival. Statistical significance will also be assessed, however, the effect size metric of HR will be given more credence as it indicates the direction of the outcome effect (similar to statistical significance), while simultaneously representing the magnitude of said outcome. The mean effect estimate of HR is more used in the meta-analysis evaluation than parameters of statistical significance and sampling studies.[31] Studies that presented insufficient data for meta-analysis were included in the systematic review (qualitative analysis)

Subgroup Analysis

Subgroup analysis will be considered based on the demographic characteristics which may results in the better resolution into the outcome effects observed in the primary meta-analysis. Three sets of Subgroup analyses were considered as follows:

- Age, gender, miRNA, tumour location, Immunohistochemical detection data (diagnostic criteria) and risk factors were considered for subgroup analysis. Survival data on diagnostic criteria may give additional support to know more about prognosis significance in T-ALL patients. Hence, it is chosen as an additional parameter in this study.
- Furthermore, miRNA subgroup analysis was also done the miRNA observed to follow a pattern of recurring in multiple included studies. The heterogeneity was also assessed using during the meta-analysis.
- Subgroup analysis on exclusive T-cell patients alone was conducted to know more about the T-cell patients, where those studies help to find out more clear results on the significance of miRNA prognosis. This specific subgroup analysis is more efficient and it really helps future researchers to consider miRNA as a biomarker.

Publication Bias

Publication bias needs to be assessed when conducting any meta-analysis study.[32] Publication bias was assessed visually by symmetry of funnel plots constructed based on Egger's bias indicator test. Orwin's and classic fail-safe N test,[33] Begg and Mazumdar Rank correlation test,[34] Harbord-Egger's Test of the intercept,[35] and "Duval and Tweedie's trim and fill" calculation[36] were used to assess and adjust for missing and small studies.

Results

Study Selection

A total of 17,800 articles was retrieved from the primary search of bibliographic databases. A total of 564 duplicates reports were removed leaving a total of 17,236 studies, out of which 5320 articles (after screening of titles) and 10,445 articles (after screening of abstracts) were excluded, respectively, in secondary screening. 904 articles were removed, as they did not meet inclusion/exclusion criteria. A final total of 567 articles were selected for full-text screening. After a careful review of all potential articles, 489 more studies were removed, as they were either unrelated to miRNA (n=157), had no survival outcome (n=71), were animal studies (n=73), did not report the survival results for T-ALL patients (n=56) or reported survival outcome from AML (acute myeloid leukemia) patients alone (n=132) and finally 78 articles were included for further evaluation.

Additionally, 61 articles were removed, as they;[1] did not report HR values, or lacked sufficient data to extract the required HR values;[2] missing prognosis results;[3] inaccurate sampling details;[4] low-quality studies;[5] lack of miRNA series/nomenclature. A final total of 17 articles were considered for systematic review and meta-analysis which met all the inclusion criteria and scored a good grade during quality assessment. A final total of 16

articles[37–52] were used for the meta-analysis as the HR and CI values of one study[53] were not available (Figure 1).

Study Characteristics

The main demographic characteristics of 17 enrolled studies are systematically summarised in Table 1. These studies investigated a total of 1753 patients from Brazil (17%), China (47%), Finland (6%), France (6%), Germany (6%), Iran (6%), Mexico (6%) and Spain (6%). Of the 1753 enrolled patients, 1048 patients were reported as T-cell lineage samples and remaining 705 samples were reported from B cell lineage samples. The study which has diagnosed and observed the miRNA prognosis from patients B cell lineage combined with T-cell lineage sampled study was also included. This is to avoid the missing of T-cell lineage reported studies in meta-analysis survey to produce a better idea on the T-ALL patients' survival outcome. The miRNA expression was detected from the samples such as fresh/preserved samples of plasma, tissue, bone marrow, peripheral blood, thymus cells, and FFPE (formaldehyde fixed-paraffin embedded) lymph node. The expression levels of miRNA were primarily analysed by Microarray analysis (n-4), qRT-PCR (quantitative Real Time-PCR) (n-11), Taqman microarray (n-1) and Agilent miRNA microarray system (n-1). Five studies[40,42,47,49,51] did not report the follow-up period details in regard to measuring the miRNA prognosis. The gender details were available from 13 studies, where four studies[43,47,49,51] did not provide the gender ratios in the included studies. From the total of 12 studies, 744 male and 437 female patients were reported. WBC (white blood cell) count and LDH (lactate dehydrogenase) analysis are the two most important diagnostic criteria in T-ALL and which was also included as one of the parameters, and eventually, it has been studied in the subgroup analysis. All the miRNA expressions (upregulated/downregulated) from the 17 studies were noted along with the endpoints measured for survival outcome.

Meta-Analysis and Survival Outcome

The prognostic significance of 32 miRNA across 16 studies was evaluated. 7 miRNA from one study could not be included due to non-availability of HR and CI values. The meta-analysis was studied by the forest plot constructed via both random- and fixed-effect models alongside using the heterogeneity observed from Higgins I^2 statistics from the pooled HR and the corresponding CI values.

Does miRNA Expression Affect T-ALL Survival Outcome?

The overall effect size of the miRNA from 16 studies was 0.929 indicating that the miRNAs decreased the likelihood of death in T-ALL patients' survival by 7.1%. The 95% confidence interval (CI) of the pooled HR value falls in between 0.878 and 0.984 when assessed by the random-effects model (Figure 2). The Z value for a test of the null hypothesis (whose mean risk ratio is 1.0) is −2.521, with the corresponding *P*-value of 0.012. Hence, we can accept the null hypothesis that the risk of death is not the same in both up-regulated and down-regulated miRNA groups, and also conclude that the risk of death is higher in down-regulated expression groups which is demonstrated in Figure 2.

Out of the 16 studies, about nine studies have reported upregulated miRNA expression in T-ALL patients' and 6 studies have reported miRNA expressions as downregulated. Among 32 miRNAs from studies above, 14 miRNAs were downregulated, and 18 miRNAs were upregulated. From the 14 downregulated miRNAs, 3 miRNAs were likely to increase patients' survival, and 11 miRNAs were associated with patients' poor survival. The pooled effect size of downregulated miRNA prognosis was demonstrated the HR 1.225 (1.110–1.344) and reported as patients who expressed downregulated miRNA are at risk and are associated with poor prognosis. Similarly, from the 18 upregulated miRNA, 13 miRNAs were associated with good prognosis, and five miRNAs were associated with poor survival. The pooled effect size of upregulated miRNA prognosis was demonstrated in the HR 0.787 (0.732–0.845) where the hazard risk ratio is below one. Hence, this analysis suggests that the mean value of HR of both upregulated and downregulated miRNA expression is not the same.

How Much Does the Effect Size Vary Across the Studies?

The Q-value was 232.16 with 35 degrees of freedom (df) and a *P*-value of 0.012. Since the observed variance falls within the range that can be attributed to sampling error, we cannot reject the null that the actual effect size was the same in all studies. Since the observed effect size does not prove the variance, we proceeded to extend the difference by estimation of I^2 statistics. The I^2 statistic tells us what proportion of the observed variance reflects variations in certain effect sizes rather

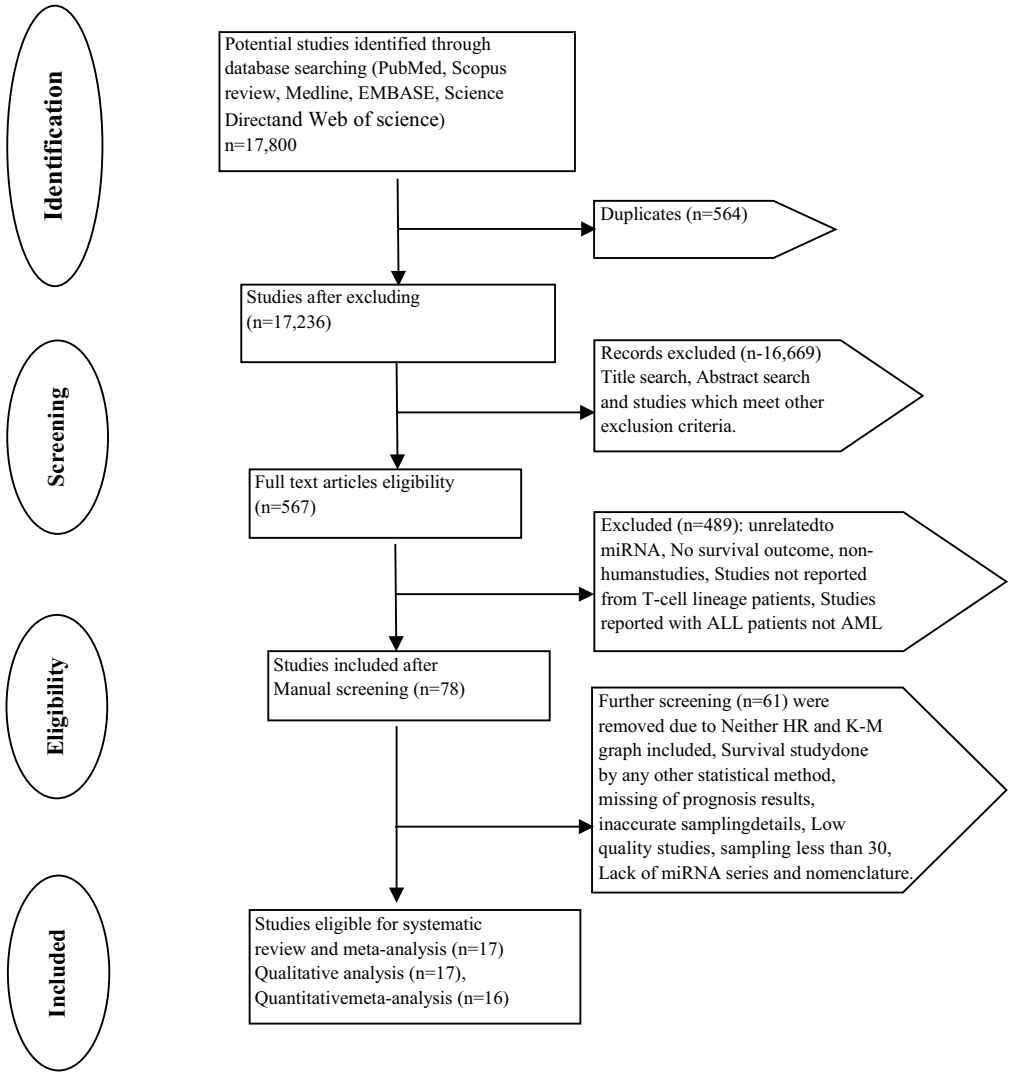

Figure 1 Flowchart for study selection and data acquisition.
Notes: The flow diagram explains the information on the different phases of the articles selection criteria in systematic review and side boxes explain the reason why the particular articles were removed. Each excluded articles were defined with appropriate excluded numbers.

than sampling error. Here, I^2 was 84.92%. T^2 demonstrates variance of actual effect sizes which is expressed in log units. Here, T^2 was 0.178. T demonstrates the standard deviation of actual effects. Here, T was 0.422.

Does the Effect Size Vary by Subgroup?

While the mean effect size across all studies is modest (a hazard ratio of 0.929 and Z value −2.521 corresponding *P*-value 0.012), it is possible that the mean hazard ratio varies by subgroups. We used the subgroup analysis to compare the effect size in studies that employed a high expression and low expression of miRNAs.

The mean risk ratios in the two groups were found to be 1.225 and 0.787 for downregulated and upregulated miRNAs, respectively. The mean effect size of HR value of upregulated miRNAs in T-ALL patient survival was 0.787 (CI 0.732–0.846; *P*-value 0.000) indicating the miRNAs decreased the likelihood of death in T-ALL patients' survival outcome by 21.3%. The HR and CI values of downregulated miRNAs in T-ALL patient's survival were 1.225 (CI 1.116–1.344; *P*-value 0.000) denoting the miRNAs increased the likelihood death of T-ALL patients' survival outcome by 22%. The Q value of the differences was 8.062 with one *df*, and *P*-value equals 0.005

Publication Bias and Sensitivity Analysis

The fundamental issue of publication bias relies upon and demonstrates that all completed studies were

Table 1 Descriptive Characteristics and Related Data from Included Studies

S.No	Study	Population	Study Period	Follow Up	Age	Sample Size	Nature of Sample	Gender M/F	Platform	WBC Count	LDH	miRNA Studied	Prognosis Results	End Point	HR Value	miRNA Expression
1	Gimenes-T et al 2013[37]	Brazil	May 1997 to April 2008	12 to 42 months	Studied	48	BM, thymic and PB	39/9	qRT-PCR	Studied	Not studied	miR221	Poor prognosis	OS, DFS	Provided	Upregulated
2	Guo HQ et al 2010[38]	China	2004–2008	3 mths-first 2 yrs: 6 mths for 3–5 yrs	Studied	79	Plasma	54/25	qRT-PCR	Studied	Studied	miR221	Poor prognosis	OS	Provided	Upregulated
3	Han et al 2011[39]	China	Not provided	36 months	Studied	122: T cell-20: B Cell-100	BM	75/47	qRT-PCR	Studied	Not studied	miR223, miR708, miR27a	Poor prognosis	RFS	Provided	Downregulated
4	Kaddar et al 2011[40]	France	1994 to 2002	Not provided	Studied	93: T-cell-31; B-cell-62	BM	58/35	qRT-PCR	Not reported	Not studied	miR16	Poor prognosis	OS, DFS	Provided	Downregulated
5	Li et al 2013[41]	China	Not provided	5 yr	Not studied	111: T cell-18; B cell-93	BM	75/36	qRT-PCR	Not reported	Not studied	miR100 and miR99a	Poor prognosis	OS, LFS	Not provided	Downregulated
6	Lv et al 2012[42]	China	Not provided	Not provided	Not studied	68	PB	43/25	qRT-PCR	Not reported	Not studied	miR-142-3p	Poor prognosis	OS	Not provided	Upregulated
7	Mei et al 2014[43]	China	Jan 2009 to Oct 2009	48 months	Not provided	76: T cell-10: B cell-66	BM	Not provided	qRT-PCR	Not reported	Not reported	miR-210	Poor prognosis	OS, LFS, EFS	Not provided	Downregulated
8	Mosakhani et al 2012[44]	Finland	2000–2009	Till death	Studied	79: T cell-11: B cell-68	BM	47/32	Agilent miRNA microarray system, qRT-PCR	Not reported	Not reported	miR-423-5p	Poor prognosis	OS, EFS	Not provided	Downregulated
9	Oliveira et al 2012[53]	Brazil	Jan 2002 to May 2005	34 to 74 months,	Not studied	128: T cell: 20: B Cell-108	BM	69/59	qRT-PCR	Not reported	Not reported	7 miRNA	Poor prognosis	EFS	Not provided	Upregulated

(*Continued*)

Table 1 (Continued).

S.No	Study	Population	Study Period	Follow Up	Age	Sample Size	Nature of Sample	Gender M/F	Platform	WBC Count	LDH	miRNA Studied	Prognosis Results	End Point	HR Value	miRNA Expression
10	Oliveira et al 2015[45]	Brazil	May 1997 and April 2008	27 months	Not provided	40	BM	29 M/8 F	Microarray analaysis, qRT-PCR	Not provided	Not provided	miR-29a	Poor prognosis	OS, DFS	Not provided	Upregulated
11	Organista N et al 2015[46]	Mexico	Sep 2005 and July 2013	Till death	Not studied	111	BM	70/41	qRT-PCR	Not studied	Not studied	miR-24	Poor prognosis	OS	Provided	Upregulated
12	Quian et al 2015[47]	China	Not provided	Not provided	Not studied	380	Tissue	Not provided	Microarray analysis	Not studied	Not studied	miR-374b	Poor Pprognosis	OS	Not provided	Downregulated
13	Rodroguez O et al 2011[48]	Spain	Jan 1990 and May 2007	50.9 months	Studied	200: T cell-39: B Cell-161	PB & BM	113/87	Taqman Microarray assay	Studied	Not studied	miR9	Poor prognosis	DFS, EFS, and OS	Provided	Downregulated
14	Schotte et al 2011[49]	Germany	Not provided	Not provided	Not studied	81	PB & BM	Not provided	MicroRNA array	Not studied	Not studied	14 miRNAs	Poor prognosis	DFS	Provided	Upregulated
15	Tavakoli et al 2011[50]	Iran	Not provided	14 months	Not provided	48: T cell-3: B Cell-45	PB	31/17	qRT-PCR	Not studied	Not studied	miR-146a	Good prognosis	OS	Provided	Upregulated
16	Wang et al 2010[51]	China	2002–2007	Not provided	Not provided	32	BM	Not provided	qRT-PCR	Not studied	Not studied	miR-146a, miR-181a/c, and miR-221	Good prognosis (miR221), poor prognosis (miR146a, miR181a/c	OS	Not provided	Upregulated
17	Xi et al 2015[52]	China	2001 and 2013	Month to 10 years.	Studied	57	FFPE lymph node	41/16	qRT-PCR	Not studied	Studied	miR17 & miR19	Bad prognosis	OS	Provided	Upregulated

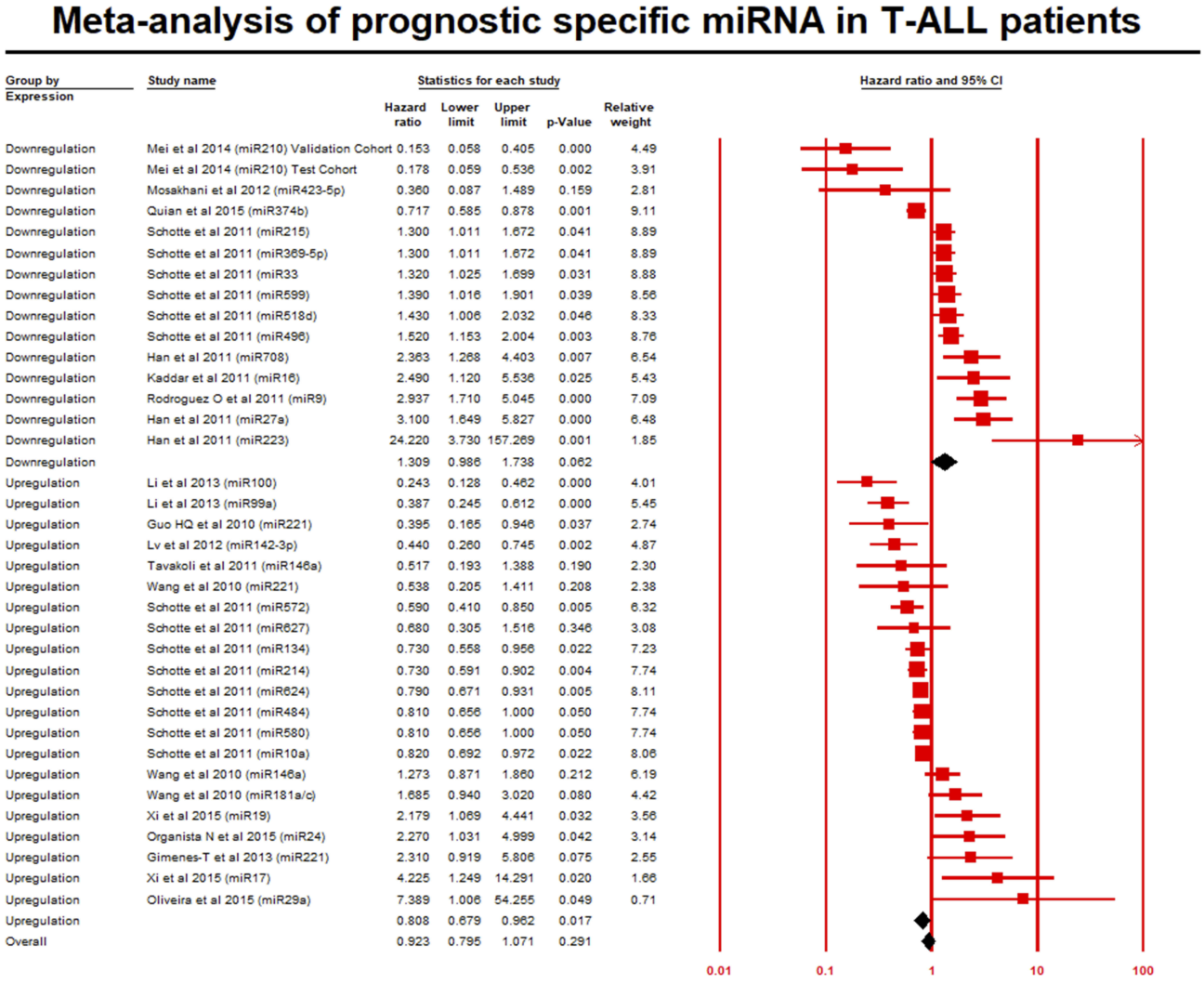

Figure 2 Forest plot for survival outcome of miRNAs in T-ALL patients.

Notes: The pooled hazard ratios of HR values of T-ALL prognostic data were calculated and analysed using CMA software (version 3.3.070, USA). The black diamond represents the combined effect estimate of survival for T-ALL patients randomly assigned to miRNA evaluation. The red square with line indicates the effect size of miRNA of the included studies with 95% confidence interval. The risk ratio of 1 suggests no difference in risk of T-ALL patients' survival. A risk ratio > 1 indicates an increased risk of patients' survival, whereas a risk ratio < 1 suggests a reduced risk of patients' survival. Favours Survival refers to better survival and Favours death indicates worse survival.

published and the selection process is not random and hence the bias occurs. The results of the tools are as follows.

Funnel Plot

Figure 3 shows that the funnel plot was slightly asymmetric across survival outcome studies. This asymmetry could be associated with small study effects (e.g., sampling errors) that might cause publication bias in the results of meta-analyses.

Classic and Orwin Fail-Safe N

This meta-analysis incorporates data from 36 studies (individual studies in forest plot), which yield a z-value of −0.55533 and a corresponding 2-tailed *P*-value of 0.57867. Since the combined result is not statistically significant, the Fail-Safe N (which addresses the concern that the observed significance may be spurious) is not relevant.

Begg and Mazumdar Rank Correlation Test

In this case, Kendall's tau b (corrected for ties, if any) is 0.02389, with a 1-tailed *P*-value (recommended) of 0.41905 or a 2-tailed *P*-value of 0.83811 (based on continuity-corrected normal approximation).

Egger's Test of the Intercept

In this case the intercept (B0) is 0.86811, 95% confidence interval (-0.72269, 2.45891), with t=1.10901, df=34. The 1-tailed *P*-value (recommended) is 0.13760, and the 2-tailed *P*-value is 0.27521.

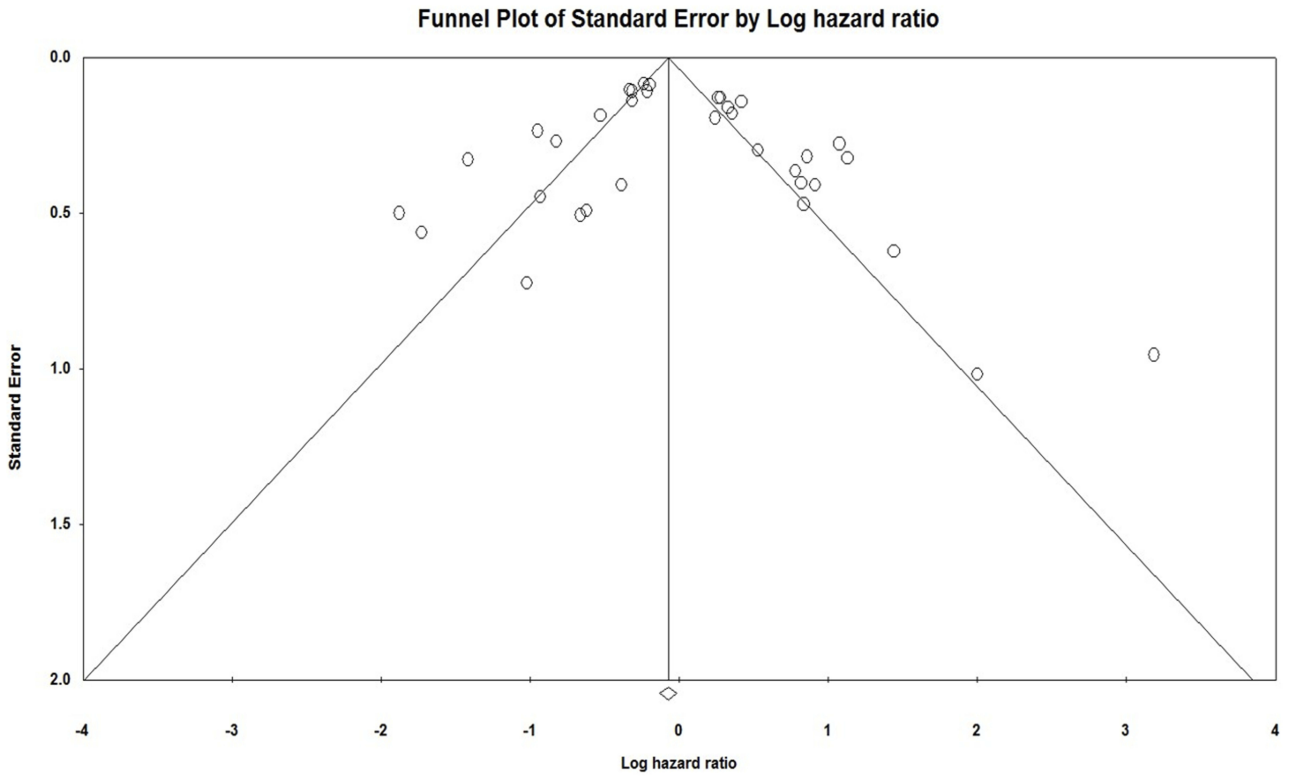

Figure 3 Funnel plot of studies correlating the overall patient survival and miRNA expression.
Notes: The funnel plot measures the study size standard error and precision on the vertical axis and function of effect size on the horizontal axis. The dots represent the individual study, and most of this area contains regions of high significance, which reveals that publication bias would be described in the form of asymmetry. This states the fact that smaller studies which appear toward the bottom are more likely to be published if they have larger than average effects and spreads on the right side of the plot, which makes them more likely to meet the criterion for statistical significance due to non-even distribution of studies.

Duval and Tweedie's Trim and Fill

The funnel plots for trimmed and imputed studies are displayed in Figure 4. This module demonstrated missing studies based on a fixed-effect model. This method suggests that the three studies are missing. Under the fixed-effect model, the point estimate and 95% confidence interval for the combined studies are 0.92928 (0.87779, 0.98381). Using Trim and Fill, the imputed point estimate is 0.92182 0.87083, 0.97579. Under the random-effect model, the point estimate and 95% confidence interval for the combined studies are 1.00355 (0.84722, 1.18872). Using Trim and Fill the imputed point estimate is 0.94735 (0.79709, 1.12593).

Subgroup Analysis

Subgroup analysis was conducted to explore the heterogeneity from covariates including diagnostic parameters (lactate dehydrogenase, WBC count), participant characteristics (age and gender), repeated miRNAs (miR221 and miR146a) and prognosis outcome from exclusively T-cell patients samples. Since the total meta-analysis has mixed with B-Cell lineage samples, to increase the strength of the study, we have done a phenomenal subgroup analysis in T-cell patient samples alone. The data included in each subgroup analysis and the study size of each parameter are tabulated in Table 2.

Subgroup Analysis of White Blood Cell Count

The subgroup analysis for WBC in T-ALL patients was performed by a random-effect model from three selected studies.[37,38,48] The subgroup analysis for WBC showed the Hazard ratio of 1.452 and 95% CI (0.971–2.173) with a P value of 0.069 with the I^2 value reporting no heterogeneity (I^2.= 0). The forest plot of subgroup analysis for WBC has displayed in Figure 5. Totally 327 patients were involved in this analysis, and the likelihood of death is 0.45%. The Q value for the differences was 0.242 with two *df*, and T^2 was 0.000.

Subgroup Analysis for Lactate Dehydrogenase

The subgroup analysis of T-ALL survival outcome on lactate dehydrogenase indicates a worse prognosis. The

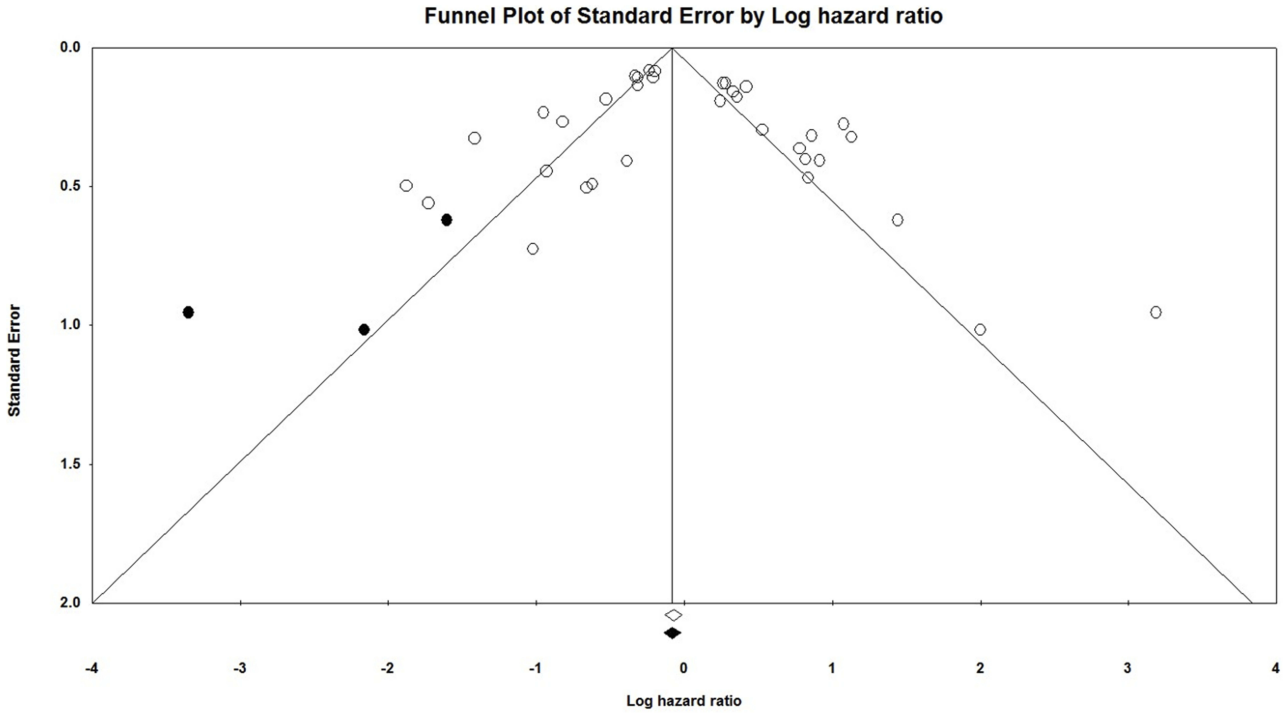

Figure 4 Funnel plot with observed and imputed studies.
Notes: Large studies appear outside the funnel and tend to cluster on one side of the funnel plot. Smaller studies appear toward the top of the graph, and (since there is more sampling variation in effect size estimates in the smaller studies) will be dispersed across a range of values.

two studies involved in the lactate dehydrogenase subgroup analysis were Guo et al 2010[38] and Xi et al 2015[52] with 136 patients included in this subgroup meta-analysis. The forest plot displayed the Hazard ratio of 2.682 and 95% CI (1.570–4.580) at P value 0.000 with the I^2 value reporting no heterogeneity (I^2. = 0) which is shown in Figure 6. Since the HR value is above 1, the survival outcome favours prognosis. The Q value for the differences was 0.031 with one *df*, and T^2 was 0.000.

Subgroup Analysis for Age at Diagnosis

Age plays a significant role in T-ALL. The subgroup analysis of the patient characteristics as age at diagnosis with 257 sample size was evaluated for the correlation between the survival outcome of T-ALL patients. About Six studies were included in this meta-analysis.[37–40,48,52] The forest plot displayed the HR 2.892 and 95% CI (1.953–40,283) at P value 0.000, Z value 5.302 with the I^2 value reporting no heterogeneity (I^2. = 13.322). The survival outcome of the meta-

Table 2 Subgroup Analysis of the Demographic Characters, miRNA221 and miRNA146a from the Studies Reporting the miRNA Prognosis in T-ALL Patients

Stratified Analysis	No. of Studies	No. of Patients	Pooled HR (95% CI)	Lower Limit	Upper Limit	*P* Value	I Squared Statistics	Q Value	*P* Value for Heterogeneity
White blood cell count	3	327	1.452	0.971	2.173	0.069	0	0.242	0.886
Lactate dehydrogenase	2	136	2.682	1.57	4.58	0	0	0.031	0.86
Age at diagnosis	6	257	2.892	1.953	4.282	0	13.322	5.768	0.329
Gender variables	3	247	0.965	0.604	1.54	0.88	0	0.93	0.628
miR221	3	159	0.778	0.458	1.321	0.352	75.694	8.228	0.016
miR146a	2	80	1.135	0.797	1.616	0.4484	63.881	2.769	0.096
Exclusively T-Cell patients Samples	9	1048	1.066	0.88	1.15	0.934	80.485	5.057	0.025

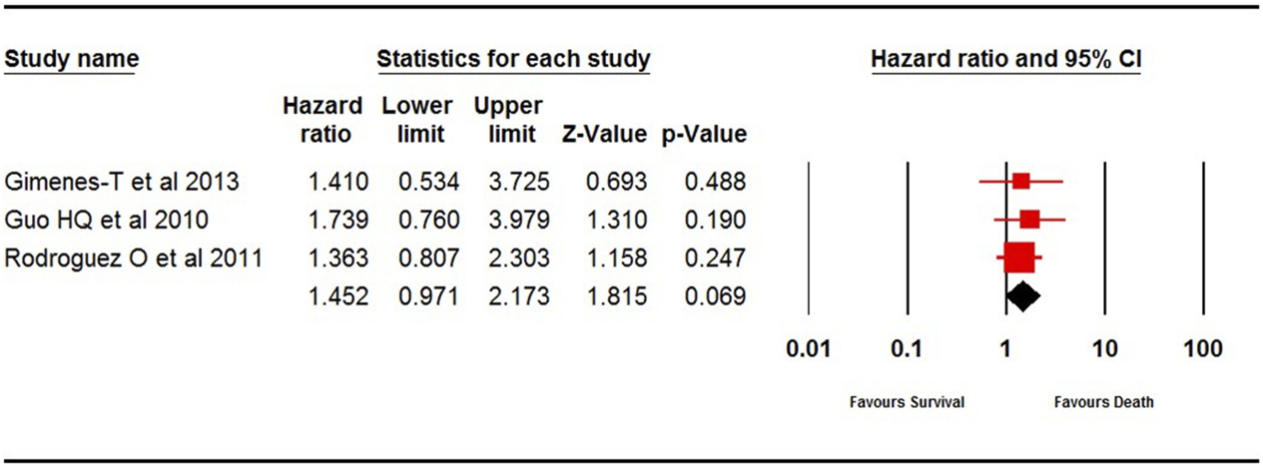

Figure 5 Subgroup analysis on WBC.

analysis displayed worse prognosis with a 1.8% likelihood of death. As we know, the adults were the high-risk group, and relapse occurs when compared to pediatrics. The complete details of age group distribution were not published in all the studies. Hence, the average age groups intensity could not be demonstrated. Figure 7 displays the subgroup analysis for age groups of six studies.

Subgroup Analysis of Gender

The Subgroup analysis of gender variables was conducted with three studies (Guo et al 2010,[38] Organista et al 2015[46] and Xi et al 2015[52] with 247 patients enrolled in this meta-analysis. The forest plot displayed HR 0.965 and 95% CI (0.604–1.540) at P value 0.880, Z value -0.151 the I^2 value reporting no heterogeneity (I^2. = 0.000). The survival outcome based on available gender data displays 0.1% likelihood of death, and better prognosis could be observed from the survival outcome in T-ALL. The total available ratio of male and female was 165 and 82, respectively. The Q value for the differences was 0.930 with two *df*, and T^2 was 0.000. The subgroup analysis of gender variables is displayed in Figure 8.

Subgroup Analysis of miRNA Expression in Exclusive T-Cell Patients Survival Outcome

The subgroup meta-analysis was performed on all T-ALL patients alone and studied the survival outcome concurrently to predict the conclusive results. Totally nine studies[37,38,42,45–47,49,51,52] has enrolled in this subgroup analysis with 24 miRNAs in which, seven miRNAs are down-regulated, and 17 miRNAs are upregulated. The overall effect size of 1.066 indicates the miRNA increase the likelihood death rate of 0.066% in exclusive T-ALL patients. The confidence interval of the overall effect of miRNA is 0.880–-1.150 at P value 0.018 which is demonstrated in Figure 9.

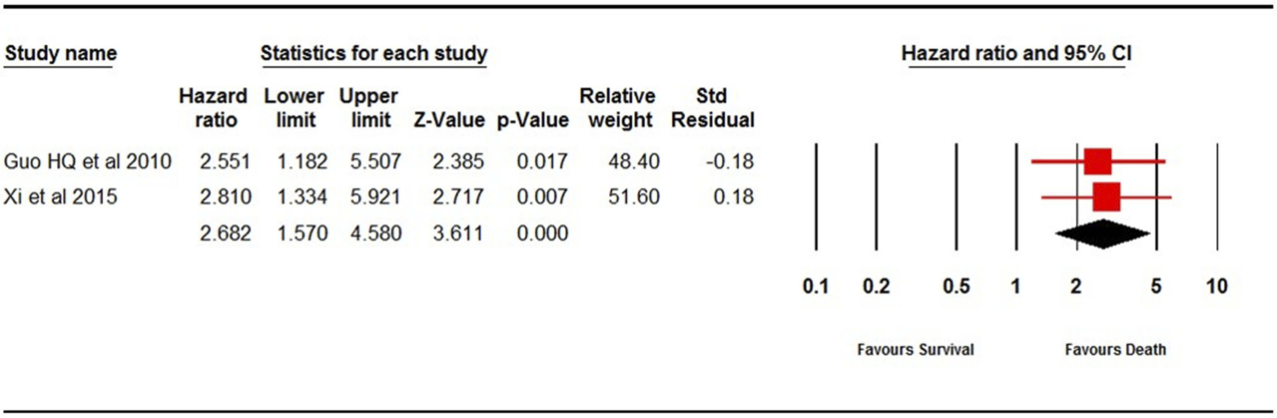

Figure 6 Subgroup analysis for lactate dehydrogenase.

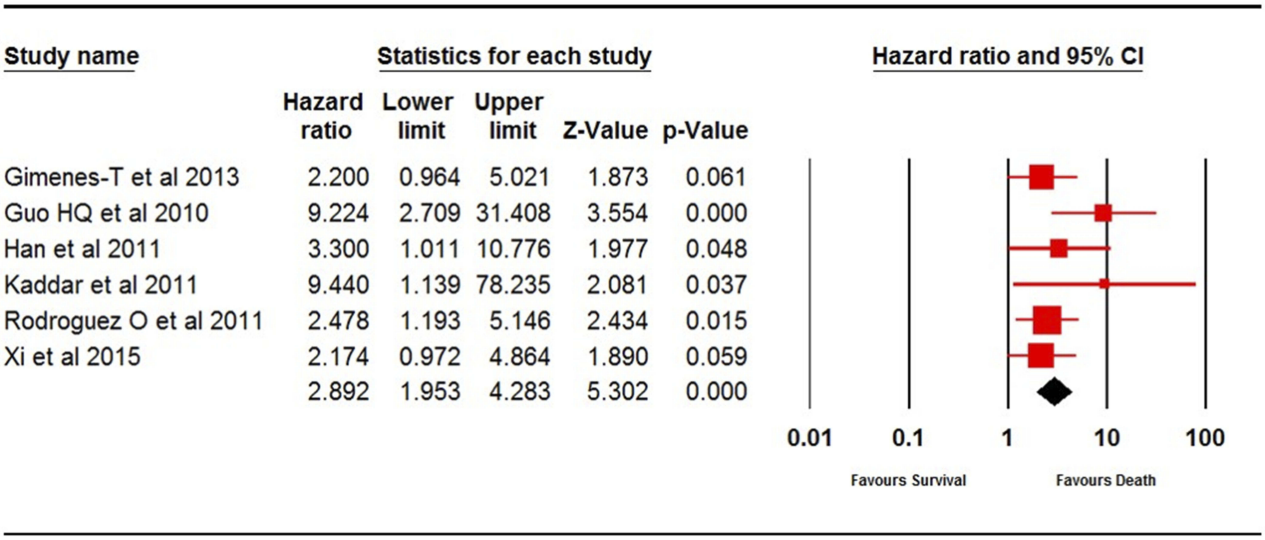

Figure 7 Subgroup analysis for age at diagnosis.

Subgroup Analysis of miR221

miR221 has shown the intensified role through subgroup analysis. The survival outcome of miR221 in T-ALL has reported by three studies from the collected articles.[37,38,51] The total number of patients enrolled in this meta-analysis is 159, and the survival outcome of the subgroup analysis is displayed the same as cumulative meta-analysis. In which the influence of miR221 from two studies (Guo et al 2010[38] and Wang et al 2010[51]) have been reported favourable to prognosis, and Gimenes-Teixeira et al 2013[37] have reported a worse prognosis.

Nevertheless, all the studies have published miR221 as downregulated. The forest plot displayed its heterogeneity as HR 0.778 and 95% CI (0.458–1.321) at P value 0.352, Z value −0.931 with I^2 was 75.694 which describes the presence of heterogeneity. Based on the Hazard risk evaluation, the survival outcome of miR221 expels 0.23% likelihood of death. The Q value for the differences was 8.228 with two *df*, and T^2 was 0.685. The subgroup analysis of miR221 is displayed in Figure 10.

Subgroup Analysis of miR146a

The subgroup analysis of miRNA146a was studied from two studies (Tavakoli et al 2011[50] and Wang et al 2010[51]) in 80 patients. The authors reported this miRNA expression to be downregulated. The subgroup analysis results displayed similar results for miR146a which is represented

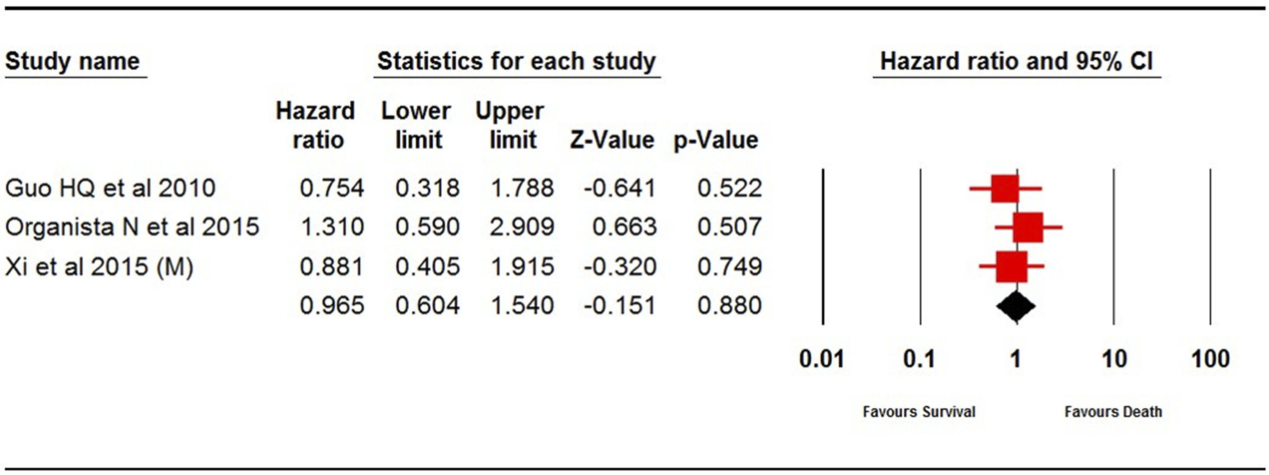

Figure 8 Subgroup analysis for gender variables.

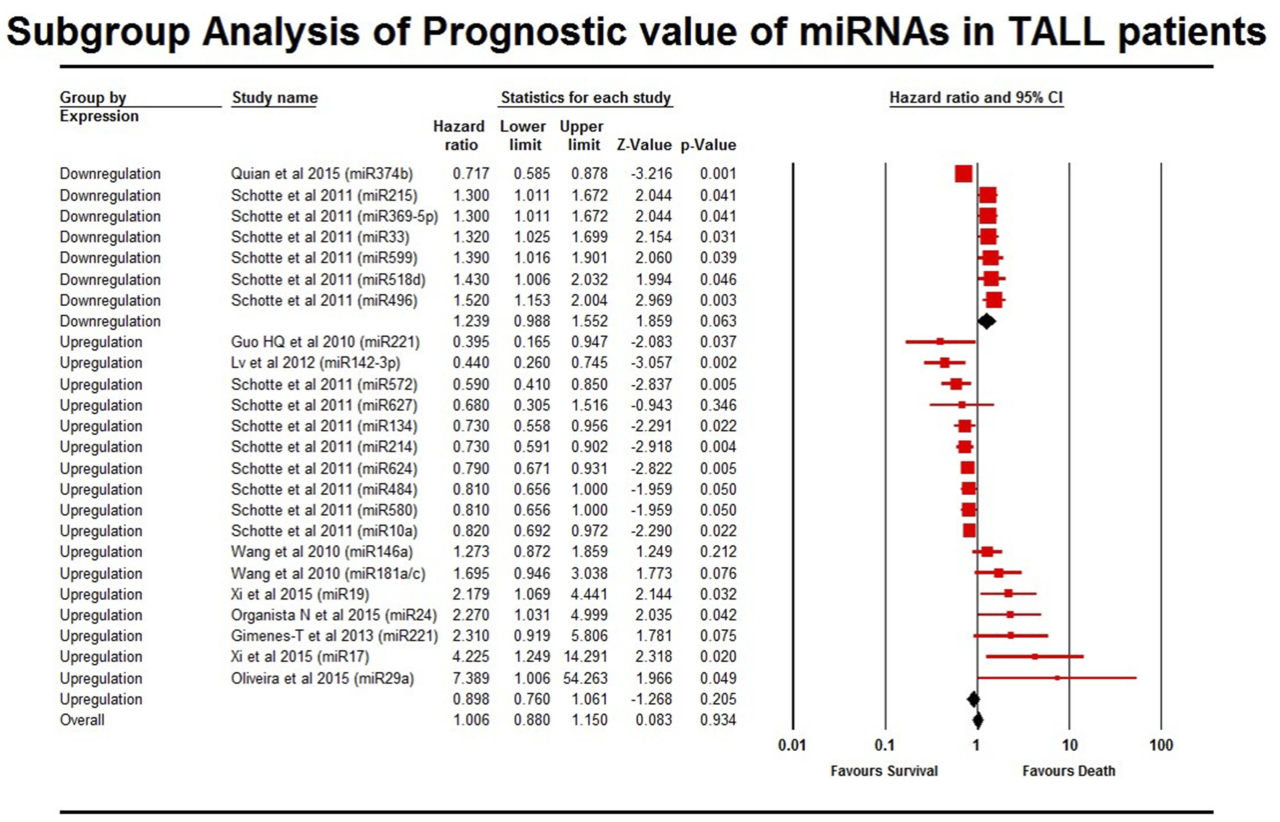

Figure 9 Subgroup analysis of miRNA expression in survival outcome of T-ALL patients exclusively.

in Figure 11. The forest plot exhibited HR 1.135 and 95% CI (0.797–1.616) at P value 0.484, Z value 0.700 with fixed-effect model. The Q value for the differences was 2.769 with one *df*, and T^2 was 0.259 with the I^2 value reporting heterogeneity (I^2. = 63.001).

Subgroup Analysis on Patient's Ethnicity

Among the included studies, the publication from Chinese populations were more in number. Hence, the current study has conducted a subgroup analysis from the studies, which are reported from china. About eight studies have evaluated the prognostic significance of miRNA in T-ALL patients.[38,39,42,43,47,51,52,54] The total HR and 95% CI values of the forest plot have displayed as 0.966 and 0.616–1.514, respectively, at the P values 0.880, which are insignificant. The results are displayed in Figure 12. The results supports the survival of patients by increasing the likelihood of death ration by 3.4%. About 925 Chinese patients were involved in this study, which is really interesting and helpful to be considered the impact of miRNAs on survival of particular ethnicity. The miRNA involved in this analysis are miR221, miR223, miR27a, miR708, miR99a, miR142-3p, miR210, miR374, miR146a, miR181a/c, miR221, miR17 and miR19. Among these, miR223, miR27a, miR708, miR210 and miR374b are downregulated. Rest all are highly expressed in Chinese patients.

Quality Assessment of Selected Studies

Table 3 describes the quality of the selected studies. The majority of the studies (16/17) had good quality scores indicating the good methodological quality of included studies and one study[53] had satisfactory scores. Though the scores varied between good and satisfactory, the final score (good – 16 studies, satisfactory – one study) was designated based on the results of HR and 95% CI values which were crucial for this study.

Discussion

Our study obtained through systematic review and meta-analysis of 17 articles, supports the hypothesis that the miRNA may have a prognostic role in T-ALL. The need for the independent prognostic molecular markers that are readily assayable before, during and after T-ALL treatment inspired this study. The recently published studies help us to understand more in detail about the current scenario and

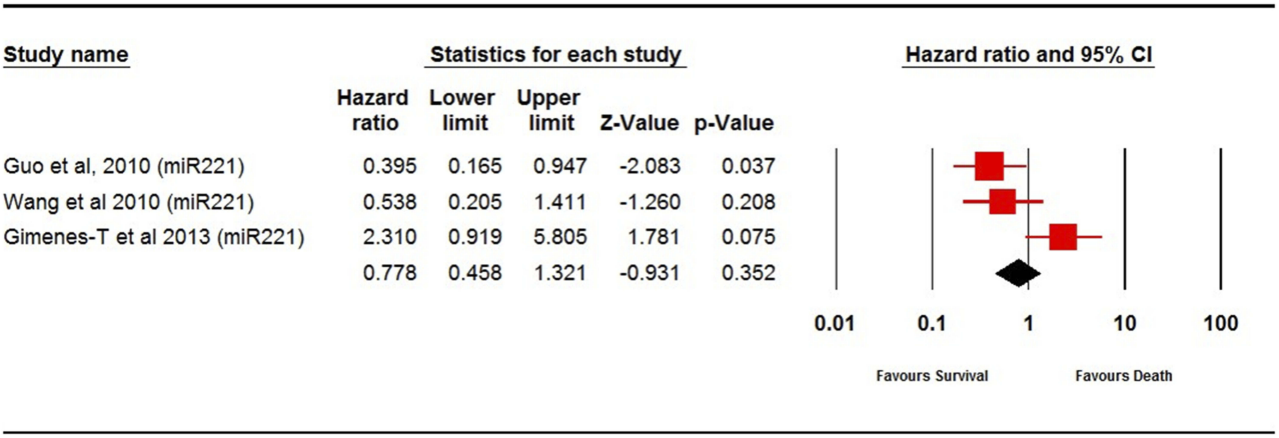

Figure 10 Subgroup analysis of miRNA221.

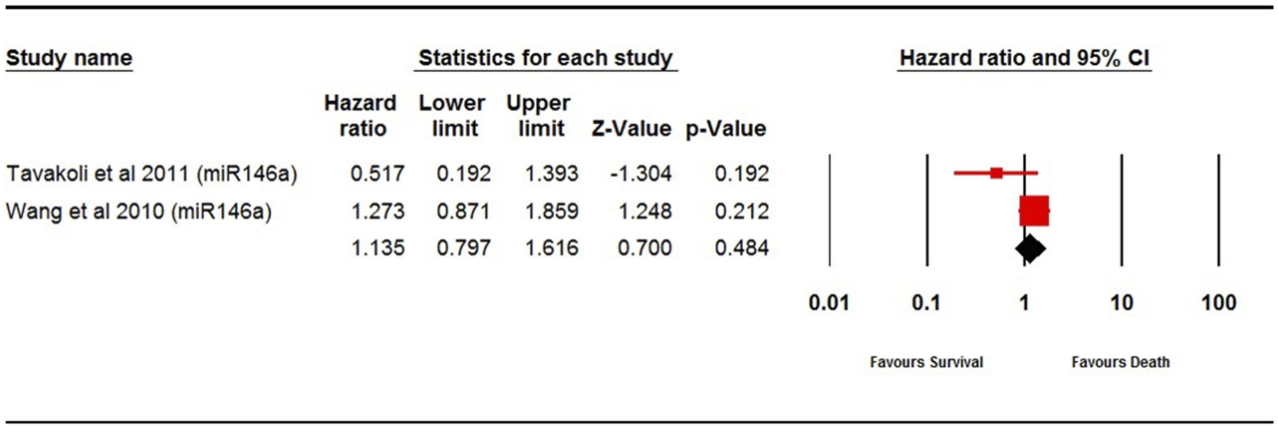

Figure 11 Subgroup analysis of miRNA146a.

the state of prognosis in T-ALL patients. Hence, we chose the year limit from 2010 to 2018. This is the first systematic review and meta-analysis study of our knowledge to conduct a thorough analysis effect on T-ALL with cause-specific events in patients suffering from T-cell Acute lymphoblastic leukemia. As mentioned earlier, previously published literature reviews[20,55–57] have hypothesised the possibility of use of miRNA in the prognosis of T-ALL patients.

We observed that 32 different miRNAs from both downregulated and up-regulated miRNA groups were involved in influencing the survival outcome of T-ALL. As mentioned in the results section, 18 miRNAs were upregulated and 14 miRNAs were downregulated in which the total meta-analysis displaying a decreased likelihood death rate by 7.1% in T-ALL patients.

The subgroup analysis was performed with miR221 and miR146a as subgroups. These meta-analysis subgroups highlighted potential miRNAs that may be considered as prognostic biomarkers in the future. Among these two miRNAs, miRNA146a (upregulated) displayed worse prognosis in T-ALL patients and miR221 (Upregulated) favour good prognosis in T-ALL patients. From this study, we observe that miRNA may play a significant role in oncogenesis and tumour suppression. The pooled meta-analysis results and the subgroup of downregulated miRNAs favours prognosis, whereas the upregulated miRNAs demonstrate an increased risk of death at 22%. From this study, miR210, miR423-5p, miR374b, miR100, miR99a, miR221, miR142-3p, miR146a (Tavakoli et al 2011),[50] miR572, miR627, miR134, miR214, miR624, miR484, miR580, miR10a, were correlated with good prognosis. In comparison, miR215, miR369-5p, miR33, miR599, miR518d, miR496, miR708, miR16, miR9, miR27a, miR223, miR146a (Wang et al 2010),[51] miR181a/c, miR19,

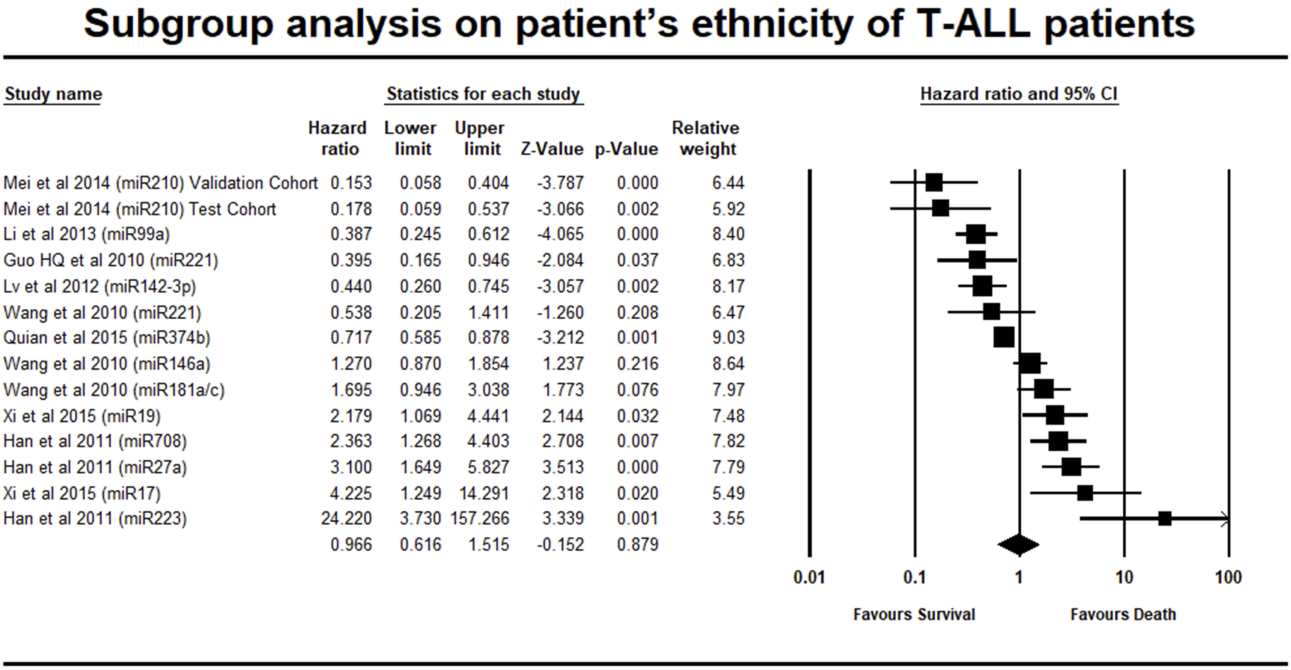

Figure 12 Subgroup analysis on patient's ethnicity.

miR24, miR221, miR17, and miR29a were associated with worse prognosis in T-ALL patients.

The subgroup analysis of miR146a has done from two studies[50,51] which are highly expressed and the forest plot displays poor prognosis with the HR 1.135 (0.797–1.616). It is to be noted that miR146a expression from Tavakoli et al[50] has exhibited better survival outcome in total meta-analysis. To predict the proper conclusion, more study reports are needed to confirm the prognostic significance of miR146a in T-ALL patients. Following the evaluation of HR, miR146a exhibited poor prognosis in T-ALL patients. Subgroup analysis of miR221 was been performed with three studies[37,38,51] which all reported miR-221 downregulation leading to good prognosis. Yang et al 2014 studied the prognostic role of miR221 in various human malignant neoplasms from 20 studies.[58] They conducted a review of different malignant diseases. One among them was T-ALL, and they used three studies

Table 3 Quality Assessment of the Selected Studies

S.No	Criteria	Bad (0–33%)	Satisfactory (33–66%)	Good (67–100%)
1	The objective of this paper stated	–	–	17 studies
2	Study population clearly specified	–	–	17 studies
3	Participation rate of eligible persons at least 50%	–	–	17 studies
4	Eligibility criteria	–	–	17 studies
5	Sample size justification	–	–	17 studies
6	miRNA Exposure assessed before outcome measurement	–	–	17 studies
7	Timeframe sufficient for the patients (OS, DFS or MFS)	–	–	17 Studies
8	Different levels of the exposure of interest (mode of treatment)	–	Six studies	11 studies
9	Exposure measures and assessment (staging of cancer, TNM)	–	Three studies	19 studies
10	Repeated exposure assessment	–	Seven studies	Ten studies
11	Outcome measures (HR, and CI)	–	One study	16 studies
12	Blinding of outcome assessors	NA	NA	NA
13	Follow-up rate	–	Five studies	12 studies
14	Statistical analysis	–	–	22 studies
	Total selected studies	0	1	16

which we have also included in this systematic review and meta-analysis. The authors conducted a meta-analysis and concluded that miR221 led to poor prognosis in T-ALL patients. We included the univariate analysis of miR221 values for our forest plot, whereas Yang et al included only multivariate analysis values from Guo et al 2010.[38] This might be the reason why the results regarding miR-221 differ. Based on our statistical evaluation (from both cumulative meta-analysis and subgroup analysis), we recommend miR221 to be focused on by future researches as a possible biomarker for diagnosis and prognosis in T-ALL patients.

As mentioned in the introduction, age is an important factor in T-ALL. We conducted a subgroup analysis from six studies from 257 patients. All the studies have done their survival analysis based on age category, but detail age details have not provided by the publisher except three studies (Xi et al 2015,[52] Guo et al 2010[38] and Rodriquez et al 2011[48]). The forest plot displayed 2.892 and 95% CI (1.953–4.028) which is associated with a worse prognosis. Liu et al 2017 have studied the subgroup analysis in T-ALL patients based on age-related to NOTCH 1 mutation.[59] They divided groups into adult and childhood from 826 T-ALL patients. The pooled OS results have displayed 0.76 (95% CI, 0.56–0.95; P = 0.02). The authors indicated that the survival outcomes are more favourable for NOTCH1 mutation-positive patients than for NOTCH1 mutation-negative patients and stated that child patients had a better prognosis than adult patients. Berry et al 2017 have done a meta-analysis study in association with clinical outcome in childhood and adult patients of T-ALL from 39 publications.[60] This research crew has done a subgroup analysis in T-ALL patients between Adult and childhood comparison in OS (Overall Survival) and EFS (Event-free Survival) and the results displayed worse prognosis from both the survival endpoints.

Also, Berry et al, 2017 have studied subgroup analysis for various parameters including cytogenetics, which is a critical detection method for T-ALL to detect its gene mutations. In addition, they conducted subgroup analysis on MRD detection method, subgroup on cut off values, subgroup on MRD detection period and on various endpoints. Similarly, the current study has focused on diagnostic parameters as WBC count and Lactate dehydrogenase. Based on both the detection methods, the survival outcome was poor in T-ALL patients. Subgroup analysis of WBC was performed in 327 T-ALL patients and lactate dehydrogenase analysis was performed in 136 patients. The HR and CI values of WBC count and lactate dehydrogenase subgroup analysis were demonstrated in Figures 3 and 4, respectively.

Lin and colleagues 2013 conducted the subgroup analysis of miR181 a/b in Hematological malignancies (cytogenetically normal AML, cytogenetically abnormal AML and CLL) on survival outcome in 566 patients.[61] The results showed only moderate heterogeneity between the studies of hematological malignancies (I^2= 36.1%, p=0.166) and the pooled HR was more significant than any single HR of each study (0.717, 95% CI: 0.631–0.816; P was 0.0001). Guo and colleagues 2017 studied the prognostic effect of miR181 in acute myeloid leukemia by systematic review and meta-analysis from 6 studies, 815 AML patients (American and Chinese patients).[62] The results showed increased survival in American patients, and worse prognosis in Chinese patients (Guo et al 2017).[62] The disease mentioned above was associated with the bone marrow and myeloid lineage cells with miR181 being regarded as having a high impact on survival outcome. Our study has also demonstrated the involvement of miR181 in T-ALL patients' survival in total meta-analysis which is displayed in Figure 2. Wang et al 2010[51] have studied the prognostic effect of miR181 a/c and reported Up-regulated expression. Form the meta-analysis forest plot graph, the miR181a/c has displayed worse prognosis in T-ALL patients with a relative weight 1.53.

The subgroup analysis of exclusive T-cell patients has demonstrated almost similar results from the cumulative meta-analysis. Both forest plot results demonstrated survival impact of miRNA in T-ALL survival. The likelihood death rate of 0.066% with HR and CI values are 1.066 (0.880–1.150) which slightly supports worse prognosis. These results are from nine studies, which are studied on T-ALL patients alone where none of the B-cell samples results has incorporated. Whereas the entire meta-analysis study has revealed better survival in which 0.071% likelihood death has been reduced on risks of miRNA impact of prognosis in selected studies with HR and CI values 0.929 (0.878–0.984). Since both the results are at the borderline which is harder to interpret how far the B-Cell samples from B-Cell ALL patients' samples are interrupting the results with T-ALL and also this helps to make us clear that the overall results of the miRNA impact on survival in T-ALL patients could be considered as good prognosis. This study may help future researchers on the topic of miRNA as a promising biomarker in T-ALL patients.[63]

The Strength of the Current Study

This meta-analysis study has some merits. First, the studies chosen for the systematic review are globally selected, and we strictly followed the inclusion criteria, which meets PRISMA guidelines. Secondly, we performed both up-regulated and down-regulated miRNAs separately to minimise heterogeneity and provides strength to the statistical analysis effectively. Third merit is the most important in which the current study focused to study the miRNA prognostic effect on T-cell patient's alone as well as the studies reported with the combination of T-cell and B-Cell lineages. This comparison will help future researchers to evaluate and publish the articles from separate patients to understand more closely on miRNA prognosis in T-ALL patients. From this point of view, this study brings out more value for future researchers and technicians in regard to predict the miRNA as a valuable prognostic biomarker. Fourth, subgroup analysis also took into consideration the demographic characters and repeated miRNAs to provide a better understanding of the survival outcome of T-ALL patients. In addition, the final strength of this study where this is the foremost systematic review and meta-analysis study on the prognostic utility of miRNAs in T-ALL patients.

Limitation of the Study

The shortcomings in this systematic review and meta-analysis are as follows: Firstly, there is paucity of high-quality clinical research regarding miRNA markers in T-ALL. Secondly, few studies have detected miRNA profiling by combining both the T-cell and B-cell lineages which may influence to report the exact miRNA expression on separate samples. Thirdly, the publication bias exists which could not be avoided in the observational studies. Publication bias may exist since the combination of B-cell and T-cell samples in few studies and also from different follow-up periods Fourth, because of the lack of unified survival endpoint (OS/DFS/EFS), more subgroup analysis on individual survival endpoint should be helpful to find out more accuracy on the prediction of miRNA as a biomarker for T-ALL. Fifth, HR and CI values have extracted from univariate and multivariate analysis from the selected studies due to non-availability data and hence focusing on either analysis will increase the strength of the analysis. Sixth, the subgroup analysis within the cumulative meta-analysis varies as down-regulated miRNAs was associated with poor prognosis, whereas the up-regulated miRNAs were associated with a good prognosis, but cumulative meta-analysis did not favour the death of T-ALL patients. This variation in the two groups may also affect the prognosis results. Hence, more clinical studies are needed to elaborate and verify the results obtained in this study.

Future Directions

There are few research publications concerning miRNAs' significance in T-ALL prognosis. Our recommendations to researchers are to produce more work on prognosis, diagnosis, and therapy. Though the T-ALL incidence is less when compared to B-ALL, the relapse rate is more than B-lineage leukemia. Hence, more work on T-ALL patients alone without merging the analysis on B cell patients, may bring better understanding on the mode of therapy. Through our meta-analysis results, we validate that miRNA play a significant role in T-ALL prognosis, and therefore it could be considered as a biomarker.

Conclusion

Our cumulative meta-analysis and subgroup analysis support that miRNAs may play a crucial role in T-ALL patients by influencing as well as indicating survival outcome. miR-221 and miR-146a appear to have a potential prognostic effect in T-ALL patients, and therefore could be considered as a biomarker for possible future diagnostic and therapeutic use for clinicians. Due to the lack of sufficient relevant data, further studies in larger sample sizes are needed to evaluate more about the correlation between miRNAs expression levels and survival outcome of T-ALL patients as before the stage of use of miRNAs for therapeutic use in clinical settings against T-ALL, is reached.

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We would like to acknowledge the Meta-analysis concepts and applications workshop manual by Michael Borenstein for his guidelines on reporting Meta-analysis, subgroup analysis and publication bias (www.meta-analysis-workshops.com).

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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