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Why is it Important to Identify Residual Cells in Leukaemia Patients after Treatment? A Review Article

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Abstract

Introduction: Most children diagnosed with acute lymphoblastic leukemia are cured and are not at risk of relapse. However, 20% of children are at a high risk of experiencing relapse later on in their lives. In order to detect risk and obtain prognostic information, the quantification of minimal residual disease (MRD) can be utilized. Detection of MRD can lead to efficient identification of relapse risk. However, there is limited understanding of the association between MRD and long-term outcomes after treatment in children. Therefore, this systematic review will examine existing literature to determine the strength of association between MRD negativity and relapse risk in children and its importance in the prediction of relapse.

Methods: A systematic review of 5 articles centered around ALL in children was analyzed to examine the strength of association between MRD negativity and clinical outcomes of event-free survival (EFS) and overall survival (OS) following the PRISMA guideline. The literature search was done through databases such as NCBI, PubMed, and other childhood oncology databases. The inclusion criteria included peer-reviewed clinical studies that focus on ALL relapse risk and MRD detection. Additionally, reviews, abstracts, and studies with inadequate sample sizes or correlations were excluded. Data were extracted and organized based on criteria of MRD negativity, MRD detection type, and relapse risk level. The data collected from all studies were analyzed through a meta-analysis. The five publications discussed in this article were a total of 11,265 participants.

Results: The results portion of your abstract should concisely describe a summary of the main findings. A positive correlation was determined between EFS and OS hazard ratios and MRD detection.

Discussion: The analysis of the five publications demonstrated that MRD is an important marker and a strong predictor of relapse in children who are diagnosed with ALL.

Conclusion: MRD detection can be proposed as a method of predicting a high risk of relapse in children with ALL. In essence, this literature review has the potential to identify the clinical and therapeutic significance of MRD testing which can be utilized to predict and prevent relapse of ALL in children.

Keywords: minimal residual disease; acute lymphoblastic leukemia; pediatric cancer; relapse; remission; MRD negativity; event-free survival; overall survival; cancer

Introduction

Acute Lymphoblastic Leukemia (ALL) is a malignant form of cancer that can be characterized by the abnormal and exponential proliferation of lymphoblasts [1]. ALL prevalence is considered to be high in both adults and children. However, it is considered to be the most common form of pediatric cancer present in children [2]. Currently, due to advanced treatment methods and increased knowledge of ALL, most children with ALL are able to achieve high remission and event-free survival rates. It is estimated that in children diagnosed with ALL, the 5-year survival rate has increased from 57% to 92% over time [2,3]. However, even with high survival rates and remarkable recovery, some cases lead to a relapse of the illness despite treatment. It is estimated that in children diagnosed with ALL, around 20% are at risk of relapse [4]. This percentage is significant because relapse is considered one of the leading causes of treatment failure, which overall leads to poor prognosis and lower survival rates [5]. With such consequences, it is essential to utilize and formulate new treatment methods to prevent ALL relapse. In addition to advanced treatments, early detection of relapse risk can help inform therapeutic goals and improve prognosis. One highly utilized method consists of quantifying the risk of relapse through MRD detection [6]. Minimal residual disease (MRD), also known as measurable residual disease, is the presence of a small number of leukemia cells that remain inside the body during or after treatment [1]. The number of cells can be insignificant and may not cause any noticeable signs or symptoms [1,7]. MRD often also go undetected through traditional methods such as using a microscope or tracking abnormal serum proteins in the

blood. Therefore, advanced and precise techniques such as PCR are utilized for detection purposes. When detecting residual cells, a positive MRD test result following the treatment indicates the presence of residual cells, whereas a negative MRD test result signifies their absence [7]. MRD is considered to be one of the most powerful tools utilized to predict the overall response to treatment in children [8] and is recognized to be the strongest prognostic factor for disease relapse [8]. Research shows that MRD-positive pediatric patients who received augmented treatment had a 39% superior event-free survival rate and a 45% lower risk of relapse at 5 years compared with those who received standard therapy [8]. MRD can be detected using various techniques, some of which include flow cytometry, polymerase chain reaction (PCR), and next-generation sequencing (NGS) and these all assays are looking for any of the remaining cancer cells that cannot be seen in the patients when they are having their routine tests such as blood tests taken [8]. The paradigms for the management of MRD-positive pediatric patients are to treat the patients until they achieve complete remission which could be obtained through ALS treatments such as surgical resection, radiation, or chemotherapy [8].

Overall, following a specific therapeutic intervention, MRD demonstrates the effectiveness of therapeutic response and is a measure of disease burden. MRD status has a high potential to impact clinical management, trial designs, therapeutic design, and drug development. However, the exact outcome and advantage of the adoption of MRD as a meaningful endpoint to any treatment has not been fully understood. Therefore, this systematic review performed a literature-based meta-analysis of ALL studies distinguished by the criteria to understand the association of MRD with clinical outcomes of event-free survival (EFS) and overall survival (OS). EFS is the length of time a patient in a clinical trial remains free of certain complications or events that the treatment was intended to prevent and delay, in this case, ALL. Whereas, the overall survival (OS) is the length of time from either the date of diagnosis or the start of treatment for a disease, ALL in this case, that patients diagnosed with the disease are still alive. During clinical trials, OS is one of the many ways to identify if a new treatment is effective and works in treating patients. In addition, this review also takes into account the extent of MRD absence correlation with progressing long-term clinical outcomes in terms of therapies studied and considered in literature articles.

Methods

Data Resources and Literature Search Strategies

According to the PRISMA guidelines, a systematic review of ALL in children was performed to analyze the strength of association between MRD negativity in children and relapse risk. The systematic literature search was done through databases such as NCBI, PubMed, and childhood oncology databases such as POGO by searching keywords in the search engine of these databases. The terms that were used in the research strategy included MRD negativity, acute lymphoblastic leukemia relapse in children, detection of MRD, and relapse risk level. Through these key terms, the scholarly peer-reviewed articles published from 2008 and onwards, in English were collected and thoroughly studied. During the literature search, the specific geographical regions of the studies collected were not considered and all studies that met the inclusion and exclusion criteria were taken into account.

Eligibility and Study Selection

The inclusion criteria included peer-reviewed clinical studies that focused on ALL relapse risk and MRD detection. Studies with children ages 18 and younger were included. Additionally, reviews, abstracts, and studies that were found using research strategies but with inadequate sample size or correlations were excluded. Moreover, studies that had a follow-up period of fewer than 5 years, had a large participant pool (>100), as well as the studies that provided an insufficient description of the MRD assessment and that provided no information regarding patient survival endpoints (i.e. EFS or OS) by MRD status were also excluded. Data were extracted and organized based on criteria of MRD negativity, MRD detection type, and relapse risk level.

Data Extraction and Quality Assessment

For each study used in this review, data and study design, patient population size and age, follow-up time, MRD detection method and outcome, treatments and available outcomes of interests, as well as survival outcomes were carefully extracted and used for meta-analyses. Limitations and biases included in the studies that were used in this review were also taken into consideration.

Data Synthesis and Data Analysis

From all the articles that were found on PubMed, NCBI, and Childhood Oncology Database, 5 articles were selected depending on the selection criteria. The studies that were excluded from this systematic review were the ones with non-English language articles, studies with MRD method insufficiently described, and those with no survival end-points. Overall, the 5 studies included a total of 7589 participants. Moreover, the search as well and the screening process followed the PRISMA Guidelines which helped in improving the reporting of the systematic reviews and the meta-analyses of the studies used [9]. Characteristics of the individual studies are presented in Table 1. The data collected from all studies will be analyzed through a meta-analysis.

Table 1. Characteristics of the studies included in the meta-analysis

	Age Group	First Author	Year Published	MRD Detection	MRD Cut-Off (%)	Sample	Follow Up (years)	Survival Endpoint
Study 1	1-18	C-H Pui	2016	Induction	< 0.01 0.01-0.99 > 0.01	488	7	OS, EFS, and CIR
Study 2	1-18	Federica Lovisa	2018	Induction	0.001	119	9-11	EFS & OS
Study 3	0-18	Lei Cui	2018	Induction	0.01	2231	5	OS, EFS, and CIR
Study 4	1-18	Valentino Conter	2009	Induction	0.001	4741	6	EFS
Study 5	1-10	Michael J. Borowitz	2008	Induction	0.01	3686	5	EFS

Results

Studies Used for Analysis

To understand and review the importance of identifying residual cells in leukemia patients after treatment, this study utilized five journal articles to systematically review the importance of identifying residual cells in Leukemia patients after treatment. All the articles were identified through the given inclusion criteria described earlier in this article. In the identified articles, the MRD statuses were examined using various methods. Throughout the articles, the effectiveness of MRD was studied by following up with patients after at least 5 years. Additionally, some studies were compilations of several clinical trials merged into a single study of MRD.

The studies used various types of survival endpoints, including EFS and OS, to examine the effectiveness and importance of MRD detection and correlate it to survival.

MRD and Outcomes

Study 1:

Pui *et al* assessed the clinical impacts of minimal residual disease in children with different subtypes of acute lymphoblastic leukemia treated with response adapted therapy through a sample of 488 evaluable pediatric patients. Out of these 488 patients, 482 attained adverse events that occurred subsequently included 49 relapses, 3-second malignancies, and 11 deaths in common. According to the results of the study, the 10-year cumulative risk of relapse was 11.6%, the 10 year EFS was 85.8%, and the 10-year overall survival was 92.5% [10].

Study 2:

Pre- and post-transplant minimal residual disease predicts relapse occurrence in children with acute lymphoblastic leukemia [11]. According to Lovisa *et al* 119 patients, out of which 57 had a cumulative incidence of 50%. Overall, 67 out of the 119 patients are alive, 61 of which are disease-free after their transplantation, resulting in an estimated 10 year OS and EFS probability of 54% and 50% respectively. Ten patients could not survive during remission from transplantation-related diseases. The cumulative incidence of relapse and non-relapse mortality was found to be 41% and 9%, respectively [11].

Study 3:

The study done by Cui *et al*, Outcome of children with newly diagnosed acute lymphoblastic leukemia treated with CCLG-ALL 2008: The first nationwide prospective multicenter study in China assessed 2231 patients registered in a total of 10 hospitals. The overall OS and EFS at five years into the study were 85.3% and 79.9%, respectively. The cumulative incidence of relapse was 15.3% at five years. 183 patients could not survive during the study due to reasons related to induction, infections, transplantation, and non-relapse reasons. Cui *et al* made an MRD group and non-MRD group (different treatments for both groups) and it was found that the MRD group has higher EFS rate than the non-MRD group with the MRD group having an EFS of 82.4% and the non-MRD group having an EFS of 78.3% [12].

Study 4:

According to the study done by the overall 7-year EFS was 80.7%. For 1329 AIEOP (acute childhood idiopathic thrombocytopenic purpura) patients the 7-year EFS 77.4% and 83.0% EFS for 1855 BFM (benign familial megalencephaly) patients. The difference in EFS was consistent in all subgroups of patients stratified

by MRD. In total, 43 patients died and 22 patients had a secondary neoplasm. The cumulative incidence for MRD was 6.0% for MRD-SR (MRD-standard risk), 21.0% for MRD-IR (MRD-intermediate risk), and 34.9% for MRD-HR [13].

Study 5:

Borowitz *et al* conducted a study based on the clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors. The study was conducted on 3686 patients. The five-year EFS value was found out to be 59%. An early relapse rate of 6.8% was seen among MRD negative patients and 28% was seen among MRD positive and the late relapse was 4.6% and 24%, respectively concerning prognostic factors [14].

Overall, the EFS result for the pediatric patients studied throughout the studies was higher for patients who attained MRD negativity. The overall systematic review of the results section of all the articles identified that the EFS percentage increases when the MRD rate decreases. The OS results were also similar to the EFS as the OS result for the pediatric patients studied throughout the studies was better for patients who attained MRD negativity.

Discussion

The significance of MRD detection as a predictor of relapse has been the topic of study for several studies. Similarly, the practice of using MRD detection to inform and guide treatment decisions is another field that has gained interest over the years. In this review, we explored the relationship between MRD detection and its impact on relapse risk. A total of five studies on MRD and pediatric ALL were carefully examined and discussed. Each of the studies explored MRD measurements with the main goal of improving the treatment of ALL in pediatric patients while examining survival rates. A common finding in all the studies was that different MRD levels were significantly associated with varying amounts of risk of any form of relapse. The types included in this review are event-free survival (EFS) and overall survival (OS). Both of these measures were utilized to also understand relapse risk with survival rates.

Overall, an analysis of the articles suggested that there exists a strong association between MRD detection and clinical outcomes. For instance, throughout the studies, a common finding was the impact of MRD on EFS in patients. In cases where MRD detection frequency was higher, the chances of EFS were higher. This association highlights the significance of MRD detection in predicting survival rates and preventing relapse. Lovisa *et al* retrospectively evaluated the outcome of a large cohort of children and adolescents with ALL given allogeneic HSCT (Hematopoietic stem cell transplantation) and correlated the outcome with pre and post-transplant MRD detection [11]. They found that pre-transplant MRD allows early identification of patients at higher risk of relapse, after allogeneic HSCT [11]. Similarly, Conter *et al* found that MRD response in ALL detected by highly sensitive and well-standardized PCR technique is highly predictive of relapse [13]. Borowitz *et al* echoed that the presence of MRD is a very strong predictor of relapse in children with ALL [14]. MRD was a strong predictor of outcome in all analyses done in study five and higher levels of MRD were associated with increasingly poor outcomes.

Additionally, while sharing similarities, each study under review made use of distinct treatment methods, statistical analysis, and thus had different results according to treatments that were utilized. The specific treatments and methods from each study highlighted additional findings. For instance, Pui *et al* found that MRD varied according to time of measurement and leukemia subtype, even in the context of contemporary response-adapted therapy [10]. In that case, the study recommends that patients with favorable presenting and undetectable MRD after two weeks of remission induction therapy receive the de-intensified therapy [10]. Furthermore, it calls for novel approaches to be considered for patients with high levels of MRD at the end of induction therapy [10]. Lovisa *et al* identified that the impact of pre-transplant MRD positivity is different in patients transplanted with different treatments [11]. Furthermore, Cui *et al* came up with the conclusion that MRD detection is widely used for early response assessment but still requires standardization and quality control [12]. Additionally, it was found that MRD monitoring done during the study on patients upstaged 30% of patients from standard risk to Intermediate risk/high risk to receive a more intensive chemotherapy regimen [12]. Therefore, MRD detection was utilized in guiding treatment to improve the chances of EFS [12]. The authors concluded that future AIEOP-DFM treatment strategies should use MRD for early detection and response as it will benefit the patient [12]. Adding to that, Borowitz *et al* concluded their study with the finding that MRD after induction therapy is the most important prognostic factor for predicting outcomes in children with ALL [14].

Additionally, MRD cut-off levels were also found to have an impact on the survival endpoints. Compared to MRD negative and low-level MRD cut-offs (< 0.01%), MRD cut-offs greater than 0.01%, which refers to a positive high level of MRD and signifies the presence of ALL cells after treatment, were found to be correlated with higher EFS and OS outcomes [9, 10, 11, 12, 13].

Overall, in all the studies reviewed in this systematic review, it can be inferred that MRD is an important marker and a strong predictor of relapse in children with ALL. Although all five studies used different analytical methods and treatment strategies, they all summed up to the same conclusion. In all five of these studies, prognostic factors did affect at some point during the duration of the study, however, many other variables are associated with MRD detection or relapse outcomes in children with ALL.

In all of the studies, many patients died due to relapse, infections, and infections after receiving a transplant. However, a lot of the patients in each study survived and saw a decrease in the risk of relapse after receiving treatment.

While this review does a good job at explaining the significance of MRD detection in the prediction of survival and relapse risk in pediatric ALL patients, it does have limitations. Firstly, a limitation of this review is the number of studies under review. Due to the recent and diverse nature of MRD detection, finding studies that satisfied our inclusion criteria resulted in a decrease in the availability of studies for review. In the future, it might be helpful to increase the number of studies so more concrete conclusions can be reached. Secondly, another limitation of this systematic review article is that since there are no standards, every article is evaluated differently in terms of their respective cut-off values and the exact time the articles chosen in this study took samples from their patients. An additional limitation of this review is that the treatment methods utilized in each study were different. Since it was found through the analysis that treatment method and detection method have an impact on risk and survival, studying the same treatment frameworks can help reach more specific conclusions about the significance of MRD detection.

Conclusions

To conclude, throughout the review it was established that it is important to identify residual cell leukemia patients after treatment because there is always a chance that a patient might relapse. After reviewing all five studies, this review concludes that MRD detection is an effective and efficient way to predict relapse in children with ALL. Furthermore, it also highlights the importance of utilizing MRD detection within treatment frameworks and plans to guide therapeutic goals. In order to further understand MRD detection and to use it up to its full potential, additional and more specific research is required. Overall, MRD detection seems to be a promising detection tool to improve the prognosis and survival of pediatric ALL.

List of Abbreviations Used

MRD: minimal residual disease
ALL: acute lymphoblastic leukemia
EFS: event free survival
OS: overall survival
CCLG: children's cancer leukemia group
AIEOP: acute childhood idiopathic thrombocytopenic purpura
BFM: benign familial megalencephaly
MRD-SR: minimal residual disease standard risk
MRD-IR: minimal residual disease intermediate risk
MRD-HR: minimal residual disease high risk

Conflicts of Interest

All the author(s) of this study declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This study did not require ethics approval and/or participant consent as it is a literature review that analyzed and interpreted journal articles.

Authors' Contributions

HBY: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published.
JI: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published
MA: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published

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