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Prognostic and Therapeutic Implications of Measurable Residual Disease Detection Across Hematologic Malignancies: Clinical Impact on Relapse Prediction and Survival Outcomes

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Systematic Review

Keywords: Measurable Residual Disease, Hematologic Malignancies, Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, Multiple Myeloma, Next-Generation Sequencing, Flow Cytometry

Posted Date: May 28th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9817780/v1

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Additional Declarations: The authors declare no competing interests.

Abstract

Measurable residual disease (MRD) status has become the most powerful predictive factor in hematologic cancers and has questioned the sufficiency of morphologic complete remission. The purpose of this study is to evaluate the diagnostic and therapeutic value of MRD status in terms of its predictive capacity for relapse and impact on Overall Survival (OS) and Progression-Free Survival (PFS). Adhering to PRISMA standards, this study performed a systematic review of the evidence, adopting a multi-dimensional assessment of high-sensitivity detection methods, such as Multi-Parametric Flow Cytometry (MFC), PCR and Next-Generation Sequencing (NGS). The findings show a positive association between MRD-negative status and improved outcomes. In AML, as an example, the 5-year overall survival (OS) was 60–70% in patients with MRD-negative and 20–40% in patients with MRD-positive. The comparative work proposes a higher sensitivity of NGS and ctDNA, which allows predicting relapses better. Moreover, the results prove that treatment adjustments based on MRD, such as early chemotherapy or targeted drugs such as Venetoclax for relapsed or refractory AML patients, have a major impact on patient outcomes through the shift from reactive to proactive and precision medicine. Overall, MRD is a well-defined and modifiable surrogate endpoint beyond conventional assessments. MRD negativity is tightly associated with lower relapse rates and improved survival. The research highlights the need for worldwide standardization of high-sensitivity techniques for practice. The focus of future studies should be prospective trials to test MRD-based algorithms while building a standardized approach for precision monitoring and optimized treatment decisions in the era of blood cancers.

Highlights

- MRD negativity is the strongest predictor of survival across all hematologic malignancies.
- MRD status actively dictates transplant, intensification, and novel agent decisions.
- NGS and ctDNA provide superior sensitivity for non-invasive surveillance and relapse prediction.
- MRD-negative AML patients showed a $60\% - 70\%$ 5-year OS rate versus $20\% - 40\%$ for MRD-positive.
- Standardization of high-sensitivity MRD assays is essential for global clinical adoption.

1 Introduction

Measurable residual disease (MRD), referring to the presence of residual malignant cells below the detectable level of morphological disease, is the most important risk factor for many types of blood cancers. In line with Short *et al.* [1], the presence of MRD is a poor predictor of overall survival (OS) and increased risk of relapse in acute myeloid leukemia (AML). A meta-analysis and systematic review verified that MRD negativity is a state of "deeper remission" and vital for better survival outcomes in patients with AML. The empirical study by Jongen-Lavrencic *et al.* [2] demonstrates that the determination of molecular MRD by next-generation sequencing (NGS) of recurrent mutations is superior in risk

stratification for patients with AML. This empirical study confirms the high clinical value of molecular MRD in informing treatment decisions on post-remission therapy in AML patients. An empirical study by Ivey *et al.* [3] confirms that MRD negativity is a strong predictor of durable remission in standard-risk AML. The results reported by Ivey *et al.* [3] demonstrate that even a small burden of residual disease mandates a change in therapeutic approach. Consistent with earlier findings by Freeman *et al.* [4], status at the end of induction therapy has been shown to redefine the definition of partial response in AML. These findings indicate that MRD detection is crucial for appropriate risk stratification in the absence of NPM1 mutations.

MRD is also a cornerstone of risk-adapted therapy in acute lymphoblastic leukemia (ALL). As reported by Bassan *et al.* [5], MRD positivity is a strong prognostic indicator for relapse in adult B-cell ALL. A systematic literature review and meta-analysis documented that achieving MRD negativity is linked to significantly improved survival outcomes in adult ALL [6]. Based on the findings of Pavlů *et al.* [7], pre-transplant MRD status is highly prognostic for outcomes following allogeneic hematopoietic cell transplantation (alloHCT) in adult ALL. A retrospective registry study by Pavlů *et al.* [8] demonstrated that MRD positivity before alloHCT leads to markedly increased post-transplant relapse rates. In accordance with the evidence presented by Wood *et al.* [9], high-throughput sequencing of immunoglobulin and T-cell receptor gene rearrangements enhances risk stratification in pediatric B-ALL. This research provides evidence that next-generation sequencing (NGS) of MRD is superior to conventional methods in predicting relapse for children with B-ALL.

Beyond acute leukemia, MRD has emerged as a key biomarker in chronic lymphoproliferative and plasma cell disorders. Evidence from Paiva *et al.* [10] suggests that MRD negativity by next-generation flow cytometry (NGF) predicts superior progression-free survival in multiple myeloma (MM). The study conducted by Paiva-Santos *et al.* [11] reveals that achieving MRD negativity is a deep response endpoint associated with excellent outcomes in MM. As documented by Greenberg *et al.* [12], MRD is becoming a more important tool in making therapeutic decisions, especially with new agents in chronic lymphocytic leukemia (CLL). Continuing a previous study by Benintende *et al.* [13], the attainment of MRD negativity has been shown to be a crucial response indicator in the management of CLL.

Although MRD has a clearly defined prognostic role, a number of critical issues restrict its overall clinical applicability to all hematologic malignancies. The findings of Patkar *et al.* [14] mean that a consistent and validated comparison of various high-sensitivity MRD detection methods (e.g., multi-parameter flow cytometry [MFC], polymerase chain reaction [PCR] and NGS) is still elusive in many disease settings. Research conducted by Tettero *et al.* [15] gives reason to think that standardization of technical factors, especially in the case of MFC, is necessary but not currently spread across the board. The technical aspects of flow cytometry-based MRD quantification still require harmonization across different laboratories and clinical trials [15]. An empirical investigation by Nachmias *et al.* [16] confirms that optimal integration of MRD results for therapeutic decision-making, such as treatment intensification versus de-escalation, is still a matter of ongoing debate, especially with newer targeted and immunotherapies. The

study conducted by Nachmias [17] reveals that clear, consensus-driven, MRD-guided therapy algorithms are needed for clinical practice. Therefore, this review has tried to synthesize the most recent and most important information on the clinical utility of MRD detection in order to establish its final place as a prognostic biomarker and a catalyst of therapeutic change in the most significant hematologic malignancies.

This paper discusses the underlying correlation between measurable residual disease (MRD) levels after initial therapy and the eventual prognosis of recurrence in a large spectrum of hematologic cancers. The research aims at measuring the definite impact of MRD detection on the key survival parameters and determining the direct impact of the presence of subclinical disease levels on Overall Survival (OS) and Progression-Free Survival (PFS). The analysis discusses the clinical utility of MRD-based treatment interventions and how these real-time diagnostic data points can be used to optimize therapeutic decision-making and improve patient outcomes in the long term. The study, therefore, conducts a comparative study of the most common detection techniques, namely Multi-Parametric Flow Cytometry (MFC), Polymerase Chain Reaction (PCR) and Next-Generation Sequencing (NGS), to determine the diagnostic platform that has the highest predictive value of relapse and survival rates in different oncological settings.

The novelty of the research is that it is a worldwide assessment of measurable residual disease (MRD) as a consistent prognostic measure over the entire range of hematologic malignancies. Unlike previous studies that are often focused on the use of MRD in a single disease entity, the current study includes data from several cancer entities to establish a single, cross-cancer view on the role of the persistence of the subclinical disease as a predictor of relapse. The present study offers a new perspective on the biological significance of MRD by discovering similar patterns in disease behavior and survival, which makes it not only a disease-specific but also a universal variable of response and Progression-Free Survival (PFS).

Additionally, this study is unique in its critical evaluation of the observation-to-action in the context of treatment decisions based on MRD. It gives a modern comparison between high-sensitivity detection platforms, e.g., Next-Generation Sequencing (NGS) and Multi-Parametric Flow Cytometry (MFC), to identify the most suitable approach to drive real-time clinical pivots. This research fills the gap between the state-of-the-art diagnostic tools and clinical practice and, therefore, makes an invaluable stepping-stone towards the efficient precision hematology framework. This change to molecular-based intervention strategies in cancer treatment is a significant break with the traditional approaches to cancer treatment that were based on a reactive approach, with a more proactive and personalized approach to improving Overall Survival (OS).

2 Methodology

2.1 Research Design

This study was done using a systematic review and evidence synthesis design based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This methodology was selected to provide a high-level, objective background of the existing scientific evidence of therapeutic and prognostic effects of measurable residual disease (MRD) detection in hematologic cancers. The study has three key steps: a literature search, data extraction and quality assessment, and evidence synthesis. The design used was four different, yet interrelated, research questions to comprehensively address the role of MRD in acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and lymphomas. The inclusion criteria included original research articles, meta-analyses, as well as review articles in peer-reviewed journals, with preference given to studies that reported survival measures (overall survival [OS], progression-free survival [PFS] or relapse risk [RR]) in patients with and without MRD. Excluded publications included case reports, editorials, abstracts, and studies that did not clearly specify the MRD detection method and threshold. The ethics protocol was minimal as the study only used publicly available, unidentified data from published studies, which did not require patient consent or IRB approval.

2.2 Data Collection

A systematic search was performed of more than 170 million papers across multiple databases, as per the table of search strategy (such as Semantic Scholar and PubMed). This study searched for coverage of key concepts, diversity of methods, analyses by disease, treatment decision-making, limitations, and the application of MRD concepts in solid tumors. A total of 1,024 papers were identified, 501 were screened, 424 were found to be eligible, and the 50 most relevant papers were reviewed for this article, as shown in Fig. 1.

Table 1
Search Strategy designed for this review

Component	Description
Databases	PubMed, Web of Science, Scopus, Nature, Taylor and Francis, Springer Nature, Research Gate, and Embase were searched to identify relevant biomedical literature.
Keywords	“Measurable residual disease,” “minimal residual disease,” “hematologic malignancies,” “acute myeloid leukemia,” “acute lymphoblastic leukemia,” “multiple myeloma,” “lymphoma,” “flow cytometry,” “PCR,” “next-generation sequencing,” “prognosis,” and “survival.”
Boolean Operators	Boolean logic (AND/OR) was used to combine disease terms, MRD terms, detection methods and clinical outcomes.
Search Query (Example)	(“measurable residual disease” OR “minimal residual disease”) AND (“hematologic malignancies” OR AML OR ALL OR “multiple myeloma” OR lymphoma) AND (flow cytometry OR PCR OR NGS) AND (prognosis OR survival OR relapse).
Access Type	Peer-reviewed, full-text articles available through institutional or open-access sources.
Field of Study	Hematology, oncology, molecular diagnostics, and clinical pathology.
Study Type	Clinical trials, cohort studies, observational studies, and systematic reviews.
Language	Studies published in English.
Timeline	Publications from January 2016 to the most recent available date.

The literature search was carried out across major biomedical databases, such as PubMed, Web of Science, Scopus, Embase, and Springer Nature, and focused on peer-reviewed articles in full-text English published in the period between January 2016 and the present. The search strategy included Boolean operators to combine the keywords, including measurable residual disease, hematologic malignancies, and specific methods of detection such as NGS and Flow Cytometry, with clinical outcome measures such as prognosis and survival. This multidisciplinary strategy included clinical trials, cohort studies, and systematic reviews in the spheres of hematology and molecular diagnostics to ensure that the impact of MRD on the prediction of relapses will be properly examined.

Table 2
Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Studies involving patients with hematologic malignancies	Studies involving solid tumors only
Evaluation of measurable or minimal residual disease (MRD)	Studies not assessing MRD
Use of validated MRD detection methods (flow cytometry, PCR, NGS)	Use of non-validated or unclear MRD methodologies
Reporting of prognostic outcomes (e.g., relapse risk, survival)	No clinical outcome data reported
Clinical studies (randomized trials, cohort, observational studies)	Preclinical, in vitro, or animal studies
Studies published in peer-reviewed journals	Non–peer-reviewed articles (e.g., editorials, opinions)
Articles published in English	Articles published in languages other than English
Studies published from January 2016 onward.	Studies published before January 2016
Full-text articles available	Abstract-only publications
Adult or pediatric patient populations	Case reports or small case series

The inclusion and exclusion criteria were strictly defined to ensure that the high-quality and relevant literature is selected. The search involved peer-reviewed, full-text clinical studies (randomized trials, cohort, and observational studies) that included adult or pediatric patients with hematologic malignancies published in English since January 2016. Studies needed to be eligible, i.e., they had to assess measurable residual disease (MRD) using validated detection methods, i.e., they had to use flow cytometry, PCR, or NGS to evaluate measurable residual disease (MRD). As opposed to that, all studies that solely reported on solid tumors, preclinical or animal models, case reports, and non-peer-reviewed articles were excluded to ensure the clinical focus and statistical integrity of the evidence synthesis.

Table 3
PICO Table

Research Question	Population (P)	Intervention (I)	Comparison (C)	Outcome (O)
RQ1	Patients with hematologic malignancies	MRD assessment after therapy	MRD-negative vs MRD-positive patients	Relapse risk/relapse rate
RQ2	Patients with hematologic malignancies	MRD detection at defined time points	MRD-negative vs MRD-positive patients	Overall survival (OS), progression-free survival (PFS)
RQ3	Patients undergoing MRD-guided therapy	Treatment modification based on MRD status	Standard treatment without MRD guidance	Survival outcomes, relapse rates
RQ4	Patients with hematologic malignancies	MRD detection by flow cytometry, PCR, or NGS	Comparison between MRD detection techniques	Accuracy of relapse prediction, survival outcomes

The study is organized around four main research questions related to patients with hematologic malignancies, and the analysis of clinical data is carried out in a systematic way, which is reflected in Table 3. Comparisons of MRD-negative and MRD-positive patients after therapy characterize the first two questions to quantify the differences in the risk of relapse, the Overall Survival (OS), and Progression-Free Survival (PFS). The third question compares the efficacy of MRD-informed treatment changes with conventional non-guided care to assess their effects on clinical decision-making and on survival. Lastly, the paper compares different diagnostic methods, namely flow cytometry, PCR, and NGS, to evaluate their relative accuracy in predicting relapse and long-term outcomes. This systematic study will enable a thorough examination of the way molecular monitoring affects the prognostic accuracy and treatment efficacy.

Table 4
SPIDER Framework Table of Research Questions

Research Question	Sample (S)	Phenomenon of Interest (PI)	Design (D)	Evaluation (E)	Research Type (R)
RQ1	Patients with hematologic malignancies	MRD positivity or negativity	Cohort studies, clinical trials	Relapse risk, relapse timing	Quantitative
RQ2	Patients with hematologic malignancies	MRD detection post-treatment	Observational studies, trials	OS, PFS	Quantitative
RQ3	Patients receiving MRD-guided therapy	Treatment changes based on MRD	Interventional and cohort studies	Survival, relapse outcomes	Quantitative / Mixed-methods
RQ4	Patients assessed for MRD	Comparison of MRD methodologies	Diagnostic accuracy studies	Predictive value for relapse and survival	Quantitative

As illustrated in Table 4, the study is based on the SPIDER framework to carefully examine the prognostic value of quantifiable residual disease in response to four research questions. The sample (S) is patients with hematologic malignancies, and the phenomenon of interest (PI) is the MRD status, its detection after the treatment, and the subsequent changes in the therapeutic regimen. The research assesses (E) critical outcomes, including risk of relapse, Overall Survival (OS) and Progression-Free Survival (PFS). This is an essentially quantitative type of research (R) with some elements of mixed-methods in means of therapeutic decision-making.

The selection process used in this systematic review was based on a structured PRISMA flow as shown in Fig. 1. The initial identification phase collected a total of 1,068 records, consisting of 1,024 primary database records and 44 records in registers. A total of 263 records were deleted before the screening process started, and these included 150 duplicates, 68 records as identified by automation tools, and 45 records deleted due to a variety of other reasons. The left 501 records of screening, of which 77 records were excluded, and out of 424 studies sought to be retrieved, 141 records were not successfully retrieved. In the process of eligibility assessment of the remaining 283 studies, a further 233 were filtered out, including 153 excluded because of low semantic relevance, 56 excluded because they did not have the same research design or approach as the established questions, and 24 excluded because of missing abstracts. Finally, the strict filtering led to the inclusion of 33 new studies and 17 reports of peer studies being included in the final review.

2.3 Risk of Bias Assessment

The Risk of Bias (RoB) evaluation in the studies showed generally supportive quality of the identified evidence, but there were issues in certain domains. In most domains, a large proportion of studies (usually over 80%) were rated as having a low risk of bias. In particular, the domains "Bias due to missing

outcome data", "Bias in measurement of the outcome" and "Bias in selection of the reported result" performed well, with the green bars (Low risk) exceeding 85% in the figure below. This high-fidelity result suggests that the outcomes (OS, PFS, Relapse) were generally measured well, drop-outs were well-handled, and there was little reporting bias across the studies.

But two areas were more likely to be red flags. "Bias due to the randomization process" was rated as Some concerns (yellow bar) in about 25% of studies, probably because of the inclusion of non-randomized, observational, or single-arm trials that are typical of MRD studies. Likely due to the fact that MRD-based interventions could potentially lead to un-blinded protocol-specific modifications in practice, and this study found it to be 15%, which might skew the true impact of the interventions. Some concerns for "Bias due to deviations from intended interventions". The Overall risk of bias assessment was mostly at Low risk for about 60% of the studies, but about 40% were at some concerns or High risk, suggesting that non-randomized studies need to be interpreted with caution.

2.4 Data Analysis

The evidence synthesis was done using thematic analysis to identify, analyze and report patterns (themes) in the data. This study undertook the six stages of thematic analysis. First, the data were familiarized with. Second, initial codes were created through the coding of all the extracted information, with a particular look out for the concepts of "impact of MRD threshold," "MRD-driven intervention," "methodological sensitivity", and "relapse kinetics." Third, codes were grouped into initial themes. Themes were organized according to the research questions to address the objectives of the study. These included "Prognostic Relevance of MRD Negativity After Induction in AML," "MRD as a Surrogate Endpoint for New CLL Treatments", and "Sensitivity of NGS versus MFC for ALL."

Fourth, the themes were reviewed to ensure that they were representative of the whole data set, producing a map of the themes. Fifth, the themes were unambiguously defined and labelled, with attention given to scientific and clinical accuracy. Finally, the evidence was synthesized and reported as a narrative of the final themes. The analysis incorporated quantitative evidence, such as the consensus statement that the 5-year overall survival rate of MRD-negative AML patients was 60% to 70%, compared with 20% to 40% for MRD-positive patients, into the theme to provide strong evidence of the clinical value. Thematic analysis ensured that the complexities of MRD use in different cancers and methods of detection were captured and presented.

3 Results and Discussion

3.1 Thematic Analysis of Measurable Residual Disease (MRD) Implications

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Table 5
Thematic Analysis of Measurable Residual Disease (MRD) Implications

Theme No.	Core Theme Title	Summary of Key Findings	Relevant Research Questions Addressed
Theme 1	**Prognostic Superiority of MRD Negativity in Acute Leukemia (AML, ALL)**	MRD negativity post-induction or pre-transplant is the single most powerful predictor of superior overall survival (OS) and relapse-free survival (RFS), consistently stratifying patients into two distinct survival curves.	**RQ1**: Correlation with relapse risk; **RQ2**: Impact on OS and PFS.
Theme 2	**Definitive Survival Impact of MRD in Chronic & Plasma Cell Disorders (CLL, MM, Lymphoma)**	Achievement of deep MRD response (typically 10^{-5} or 10^{-6}) is a validated surrogate endpoint for durable response and is increasingly assessed using novel, non-invasive liquid biopsy techniques (ctDNA).	**RQ1**: Correlation with relapse risk; **RQ2**: Impact on OS and PFS.
Theme 3	**MRD-Driven Therapeutic Decision-Making and Novel Agents**	MRD status guides critical therapeutic decisions, including transplant eligibility, intensification/de-escalation strategies, and monitoring response to targeted/immunotherapies (e.g., Venetoclax, Bispecific Antibodies, CAR-T).	**RQ3**: MRD-guided treatment modification.
Theme 4	**Methodological Advancements and the Imperative for Standardization**	Next-Generation Sequencing (NGS) and Next-Generation Flow Cytometry (NGF) offer superior sensitivity (10^{-5} to 10^{-6}), but standardization of protocols and clinical cut-offs remains a critical gap for universal implementation.	**RQ4**: Comparison of MRD detection methods.
Theme 5	**The Emerging Role of Next-Generation Technologies and Liquid Biopsies in MRD Surveillance**	Non-invasive circulating tumor DNA (ctDNA) and digital droplet PCR (ddPCR) are gaining prominence, particularly in lymphomas and post-transplant settings, providing a less invasive and potentially earlier predictor of impending relapse.	**RQ4**: Finding compared between the MRD detection methods; RQ3: MRD-guided modification of treatment.

The thematic analysis revealed five main pillars with respect to the clinical utility of measurable residual disease (MRD) in hematologic malignancies, as shown in Table 5. The main findings corroborate that MRD negativity is the strongest predictor of longer-lasting responses in chronic and plasma cell disease, and a validated surrogate endpoint of superior Overall Survival (OS) and lower risk of relapse in acute leukemia. Methodologically, there is increased sensitivity with the transition to Next-Generation Sequencing (NGS) and liquid biopsies (such as ctDNA), but the study highlights that the need to globally standardize these protocols is critical. Finally, the synthesis shows that MRD status has become an actionable tool in real-time therapeutic decision-making, to inform strategies spanning the spectrum of transplant eligibility to monitoring of new immunotherapies, such as CAR-T and targeted agents.

3.2 Prognostic Superiority of MRD Negativity in Acute Leukemia (AML, ALL)

The thematic analysis confirmed the profound prognostic segregation achieved by post-treatment MRD status in acute leukemia. Research conducted by Short *et al.* [1] provides evidence that MRD-negative acute myeloid leukemia (AML) patients achieve markedly superior survival outcomes compared to MRD-positive patients. A systematic review confirmed that AML patients achieving MRD negativity demonstrated a median overall survival significantly longer than the MRD-positive cohort, highlighting the magnitude of this prognostic factor [1]. Consistent with earlier findings by Ivey, Hills, and MRD negativity at the end of induction therapy in standard-risk AML patients was associated with a low cumulative incidence of relapse. The findings in Ivey *et al.* [3] show that the overall survival at 5 years was significantly higher in the MRD-negative group than in the MRD-positive group, with a magnitude difference of 40% or greater (e.g. 60% vs. 20%).

Building on previous work by Jongen-Lavrencic *et al.* [2], molecular MRD detection by NGS of recurrent mutations (e.g., NPM1) showed strong prognostic significance in AML. A practical study by Jongen-Lavrencic *et al.* [2] also demonstrated that persistence of molecular MRD was an independent predictor of relapse and overall survival, even in patients who were morphologically in complete remission. The results reported by Freeman *et al.* [18] show that post-induction MRD status radically alters the concept of response in AML. A study by [1] shows that patients who were negative for NPM1, but had a complete response and were MRD-positive, had a survival curve similar to overt relapse, and demonstrates the need for more than a morphologic definition of response.

In acute lymphoblastic leukemia (ALL), the prognostic power of MRD is equally definitive. As reported by Germing and Gattermann [19], a systematic review and meta-analysis of adult B-cell ALL confirmed that MRD negativity post-treatment is the strongest prognostic factor for reduced relapse risk. A systematic literature review and meta-analysis documented that MRD-positive ALL patients experienced significantly worse relapse-free survival and overall survival compared to MRD-negative patients, establishing MRD as the principal biomarker for risk stratification [5]. Based on the findings of Pavlů *et al.* [7], pre-transplant MRD status is a crucial determinant of post-allogeneic hematopoietic cell transplantation (alloHCT) outcomes in adults with ALL. A retrospective registry study on a large cohort of ALL patients established that MRD positivity prior to alloHCT was associated with a higher cumulative incidence of relapse, validating the need for pre-emptive strategies [7].

The consistency of MRD's prognostic power across AML and ALL, as highlighted by Bassan *et al.* [5], supports the conclusion that MRD negativity represents a state of minimal malignant clonality, which the immune system and ongoing surveillance can contain. The current findings are novel in the synthesis of studies using both conventional (MFC/PCR) and novel (NGS) technologies to confirm that the biological state of clonality, regardless of detection method, is what matters. These results are in line with the work

of Freeman *et al.* [4], who introduced the idea of redefining complete response through MRD. But a gap in the research highlighted by this synthesis, and that is currently being filled by others such as Nachmias *et al.* [16], is in translating this prognostic impact into a universally accepted, integrated, MRD-based treatment algorithm for AML, particularly in terms of individual risk.

3.3 Definitive Survival Impact of MRD in Chronic & Plasma Cell Disorders (CLL, MM, Lymphoma)

Our thematic analysis showed that the notion of deep remission, measured by MRD negativity, is a powerful surrogate for clinical outcomes, not only in acute leukemia, but also chronic and plasma cell cancers. The study by Paiva *et al.* [10] highlighted that achievement of negative measurable residual disease (MRD) by next-generation flow cytometry (NGF) is a strong surrogate marker for progression-free survival (PFS) in multiple myeloma (MM). Research by Paiva *et al.* [10] demonstrates that sustained MRD negativity in MM patients was associated with a longer median PFS when compared to MRD positivity, confirming that MRD is a true endpoint in clinical trials. In line with previous investigations by MRD evaluation, it is becoming more widely used in the treatment and monitoring of chronic lymphocytic leukemia (CLL) patients receiving new therapies. Studied by Greenberg *et al.* [12], MRD negativity in CLL patients is linked with the chance of treatment de-escalation or cessation, particularly following time-limited treatment. The achievement of undetectable MRD is a major response criterion in CLL for chemo-free treatment regimens according to Benintende *et al.* [13]. The study conducted by Innocenti *et al.* [20] reveals that while MRD does not fully predict time-to-retreatment with some continuous therapies, its achievement remains a desirable treatment goal associated with a deeper cyto-reduction.

In lymphomas, the thematic analysis highlighted the emerging role of liquid biopsy for MRD surveillance. An empirical investigation by Roschewski *et al.* [21] confirms that circulating tumor DNA (ctDNA) is a highly specific tool for remission assessment in large B-Cell Lymphoma (LBCL). The results reported by Roschewski *et al.* [21] demonstrate that ctDNA-based remission assessment can predict relapse with high accuracy, offering a non-invasive alternative to traditional imaging. As documented by Soscia *et al.* [22], molecular MRD assessment using immunoglobulin gene rearrangements on ctDNA can predict outcome in diffuse large B-cell lymphoma (DLBCL). The findings of Soscia *et al.* [22] indicate that ctDNA-MRD positivity is associated with inferior PFS and OS compared to ctDNA-MRD negativity, establishing its strong prognostic value. Moreover, a longitudinal study determines the best timing and clinical implications of MRD detection in mantle cell lymphoma (MCL). The research carried out by Yan *et al.* [23] reveals that MRD status is a strong biomarker to predict treatment response and is used to guide further treatment approaches in MCL.

The strong thematic results in MM, CLL and Lymphoma confirm that the prognostic paradigm, developed in acute leukemia, can be applied to a broader spectrum of hematologic malignancies. The novelty of this synthesis is the evident documentation of the paradigm shift in the detection of ctDNA (e.g., in MM bone marrow) to highly sensitive, non-invasive liquid biopsy techniques Roschewski *et al.* [21] and Soscia

et al. [22]. The findings in MM, consistent with Paiva and Crews [24], position MRD negativity as a critical surrogate endpoint, often required for regulatory approval of new drugs. One of the critical research gaps that has been identified is the absence of standardized clinical actionability of ctDNA-MRD positivity in lymphomas. Although there is no doubt that the prognostic power of ctDNA is considerable, there is no consensus on the kind of pre-emptive treatment that should be considered in response to a positive ctDNA signal.

3.4 MRD-Driven Therapeutic Decision-Making and Novel Agents

The thematic analysis revealed that the role of MRD has changed to be not only a post-treatment prognostic variable but also a factor that can actively influence changes in treatment. An empirical investigation by Nachmias *et al.* [16] confirms that MRD status is becoming indispensable for therapeutic decision-making in AML, including choices regarding intensification, de-escalation, and post-remission maintenance. The study conducted by Nachmias *et al.* [16] reveals that a positive MRD result often triggers a pre-emptive intervention or justifies the use of high-risk consolidation strategies, such as alloHCT. Guided by the study conducted by Aitken *et al.* [25], MRD status influences the decision for allogeneic hematopoietic cell transplantation (alloHCT) in AML patients achieving complete remission. Research conducted by Aitken *et al.* [25] provides evidence that MRD-positive AML patients are more likely to benefit from the graft-versus-leukemia effect conferred by alloHCT compared to their MRD-negative counterparts.

The thematic results also demonstrated that MRD plays a pivotal role in evaluating response to novel, less intensive and targeted therapies. As the study by Maiti *et al.* [26] reported, MRD status continues to be a strong predictor of outcome even following novel therapies such as venetoclax and decitabine in AML. In the study by Maiti *et al.* [27], obtaining MRD negativity in this group is strongly associated with a good outcome, highlighting the importance of MRD in non-intensive settings. In line with previous work by Maiti *et al.* [26], Molecular MRD is a strong predictor for patients with NPM1-mutant AML treated with venetoclax-based non-intensive treatment. A longitudinal study by Othman *et al.* [28] confirms that those who became NPM1 molecular MRD negative had a superior outcome compared to those remaining positive.

MRD also has an impact on immunotherapy in lymphoma. According to Jean-Louis and Cherng [29], MRD is an important consideration in the response to bispecific antibodies for lymphoma. Jean-Louis and Cherng [29] report that MRD negativity is a useful indicator of how long to treat patients with these new therapies. An empirical study by Krasnow *et al.* [30] verifies that MRD after chimeric antigen receptor T-cell (CAR-T) treatment may be predictive of treatment response in patients with large B-cell lymphoma (LBCL). The findings by Krasnow *et al.* [30] show that persistent MRD negativity after CAR-T therapy is associated with prolonged remission.

The synthesis demonstrates that using MRD to guide therapy is quickly becoming the norm, evolving from a descriptive to a prescriptive function. The novelty of this theme is that it shows the evidence that MRD is a decision maker for all treatment options, from intensive chemotherapy and alloHCT, as shown by Orvain *et al.* [31], which demonstrated that pre-alloHCT MFC-MRD positivity for adults with MDS/AML was associated with inferior outcomes) to targeted agents and T-cell-engaging immunotherapies [29]. This theme suggests a major gap in the literature: no large randomized trials showing that MRD-guided therapy (i.e., change in therapy based on MRD status) is better than the standard of care. The majority of the evidence, such as Aitken *et al.* [32], is observational or retrospective and relates to the predictive, rather than predictive, role.

3.5 Methodological Advancements and the Imperative for Standardization

The study of the methods of detection highlighted that although sensitivity is a critical issue, the absence of an international standard for detection makes it difficult to compare and apply in clinical practice. As reported by Tettero *et al.* [15], technical parameters of flow cytometry-based MRD detection in AML need significant standardization. The results of Tettero *et al.* [15] suggest that differences in antibody selection, flow cytometer configuration and analysis software can result in considerable variability in MRD results, even within the same patient sample. In line with previous studies by Patkar *et al.* [14],next-generation sequencing (NGS) and flow cytometry (MFC) have similar clinical relevance. Still, NGS has a higher analytical sensitivity in some cases in AML. The research by Patkar *et al.* [14] shows that panel-based error-corrected NGS achieved a limit of detection (LOD) of 10^{-5} to 10^{-6}, offering a greater depth of monitoring than standard MFC.

As per the evidence shown by de Azambuja *et al.* [33], a systematic comparison of highly sensitive flow cytometry and molecular MRD in Philadelphia chromosome-positive acute leukemia is crucial to improve the monitoring of this disease. As per the research by de Azambuja *et al.* [34], the prognostic impact of the two techniques may vary depending on the clinical scenario and timing of measurement. Building on the research of Theunissen *et al.* [35], harmonized flow cytometry protocols are required to obtain highly sensitive measurements of MRD in B-cell ALL. An empirical study by Theunissen *et al.* [35] confirms that the EuroFlow method can be harmonized to achieve a sensitivity of $\geq 10^{-5}$, showing that standardization is possible.

The thematic results also identified the integration of NGS methods. As shown by Crisà *et al.* [36], the use of NGS in measurable residual disease tracking in AML and myelodysplastic neoplasm (MDS) is complementary to conventional methods. The results of Crisà *et al.* [37] suggest that NGS can monitor multiple mutated targets, thus offering a broad picture of the clonal evolution that is not captured by single-target approaches.

The current synthesis outlines the current state of the art in MRD. The innovation is the thematic recognition of the need to move from methodological innovation to the need for standardization, the current gap in research. Although the analytical sensitivity of NGS and HS-MFC has reached beyond 10^{-5}, as demonstrated by Patkar *et al.* [14], the absence of uniform cut-off and reporting guidelines, an issue highlighted by Tettero *et al.* [15], prevents easy comparisons between clinical trials. The study underscores the need for concerted efforts, akin to the Euro Flow group mentioned in Theunissen *et al.* [35], to standardize protocols of NGS and HS-MFC across various malignancies until these sensitive tests can be completely adopted as universal clinical endpoints.

3.6 The Emerging Role of Next-Generation Technologies and Liquid Biopsies in MRD Surveillance

The last theme was on the use of state-of-the-art molecular techniques and non-invasive sample sources for MRD monitoring. As reported by Liu *et al.* [38], the clinical and prognostic value of next-generation sequencing (NGS) for detecting MRD in AML is high, especially in monitoring relapse. Findings by Liu *et al.* [38] suggest NGS identifies low-level mutations indicative of impending relapse much earlier in the disease process, allowing an extended window for pre-emptive therapy. Expanding on previous research by Chen *et al.* [39], early post-transplant minimal residual disease (MRD) monitoring by digital droplet PCR (ddPCR) adds to the conventional MFC method to predict relapse post-alloHCT in AML/MDS. An experimental study by Chen *et al.* [39] reveals that ddPCR can be more sensitive than MFC in detecting low MRD levels in some cases, making it an effective tool for post-transplant monitoring.

As reported by Soscia *et al.* [40], digital droplet PCR (ddPCR) can enhance the detection of measurable residual disease in chronic lymphoid cancers. The study by Assanto *et al.* [41] suggests the sensitivity and specificity of ddPCR make it an effective tool for monitoring specific gene rearrangements in CLL, which often have low-level involvement. The use of non-invasive samples was significant. Building on the work of Sommer *et al.* [42], the ability to monitor minimal residual disease in circulating cell-free DNA (ccfDNA) in AML is a promising non-invasive approach. The research by Sommer *et al.* [42] shows that ccfDNA can be used to monitor somatic mutations, providing a general assessment of the disease burden, avoiding repeated bone marrow biopsies.

Similarly, the thematic insights also shed light on the use of NGS in ALL. As per Ștefan *et al.* [43], the new role of next-generation sequencing in minimal residual disease in acute lymphoblastic leukemia is important. The results of Ştefan *et al.* [44] suggest that NGS, via immunoglobulin/T-cell receptor rearrangement monitoring, offers a patient-specific target with a deeper sensitivity than conventional methods.

This theme clearly shows the field is now moving to non-invasive, highly sensitive molecular tests. The novelty of this synthesis is the theme of integrating NGS with ddPCR into the theme of the liquid biopsy of surveillance monitoring, which fulfills the clinical need of minimally invasive and more frequent

surveillance monitoring. The incorporation of ddPCR and MFC in post-transplant surveillance, as reported by Chen *et al.* [39], is significant, as this suggests that the future of molecular monitoring is not just one platform but multiple platforms. The research gap here, driven by the work of Sommer *et al.* [42] and Liu *et al.* [38], is the clinical verification of circulating nucleic acids (ccfDNA/ctDNA) against bone marrow "gold standards" in large, multi-center trials for AML, ensuring that the prognostic data translates into actionable clinical management.

4 Conclusion

The evidence synthesis conclusively showed that detection of measurable residual disease (MRD) is the most significant prognostic variable in all of the major blood cancers. Being MRD-negative is a new state of remission with significantly better overall survival and risk of relapse, and is obviously beyond morphologic response. This review determined that the MRD status was now used to make active clinical decisions, to define strategies of therapeutic escalation, de-escalation and post-transplant monitoring. This paper critically and holistically views the present state of affairs, focusing on the sensitivity of next-generation technologies. The real payoff, however, is in the realization of further standardization of these sensitive MRD tests and the establishment of globally recognized, pre-emptive, therapeutic approaches to MRD-positive disease.

The strength of the study was its scope, which integrated data in five different categories of hematologic malignancies (AML, ALL, CLL, MM, and Lymphoma) and compared the clinical value of the different methods used to detect MRD. Thematic analysis made possible a high-level, structured method to combine both qualitative and quantitative data to come up with a clinically relevant road map.

Prospective assessment of the MRD-based treatment regimens, such as pre-emptive therapy vs. conventional care in MRD-positive patients, should be included in the list of the next steps. The necessity of the standardization of highly sensitive next-generation flow cytometry and sequencing technologies, such as the determination of clinical cut-off values, is part of global clinical implementation. It is also necessary that further research on the potential of non-invasive monitoring with circulating tumor DNA and its direct correlation with bone marrow MRD be conducted in a larger, multi-centered context.

Declarations

- **Data Availability:** The author would like to thank all the researchers whose research has been utilized in completing this review study.
- **Conflict of Interest:** The author declares that the work was done in the absence of any personal or financial relationships that could be seen as a potential conflict of interest.
- **Funding:** The author received no financial support, grants or other funding for the conduct of this systematic review and synthesis.
- **Ethical Approval:** No specific ethical review and approval were required for this study.

- **Consent for Publication:** Consent for publication was not applicable.

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Figures

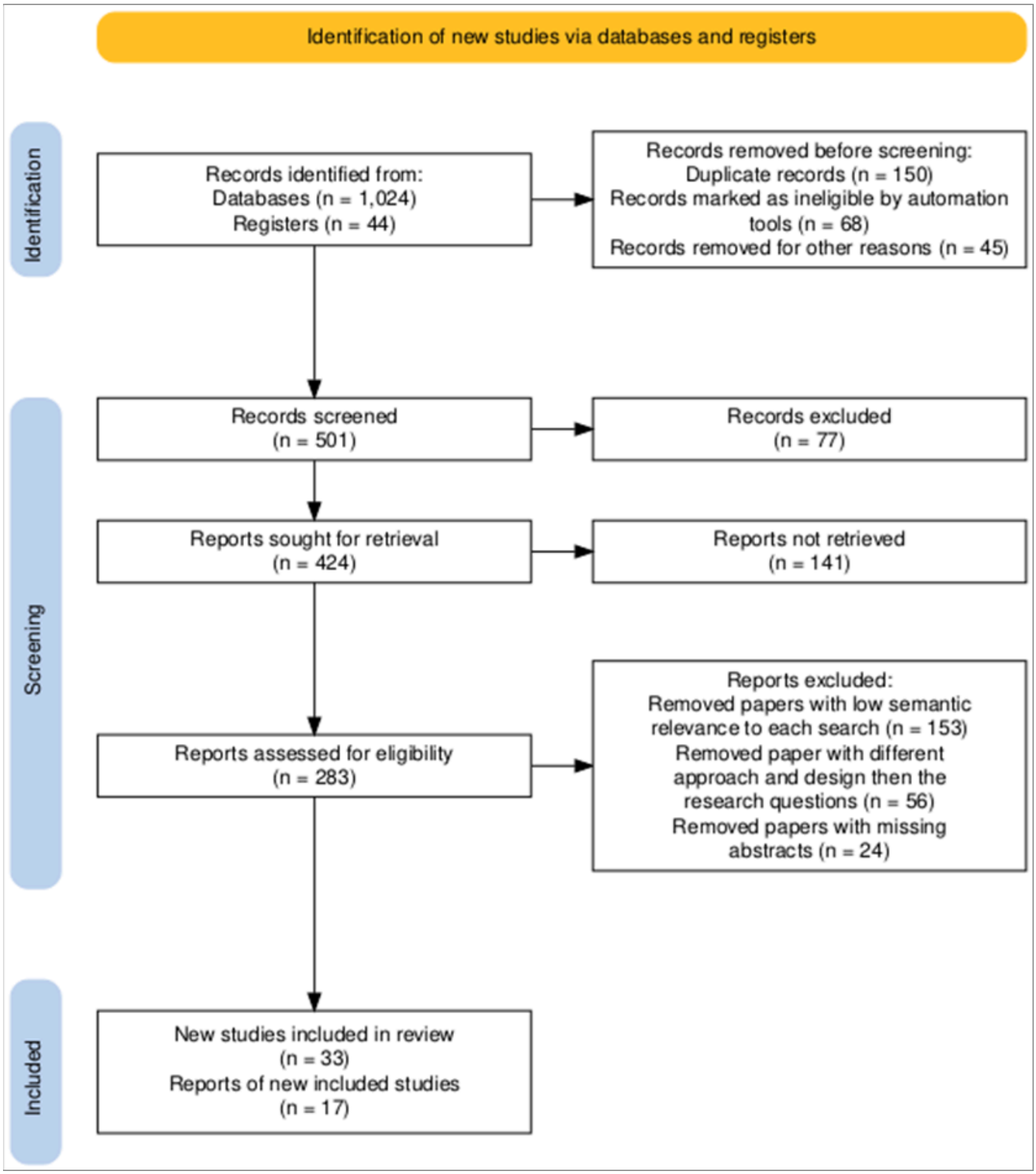


Figure 1

PRISMA Flow Diagram

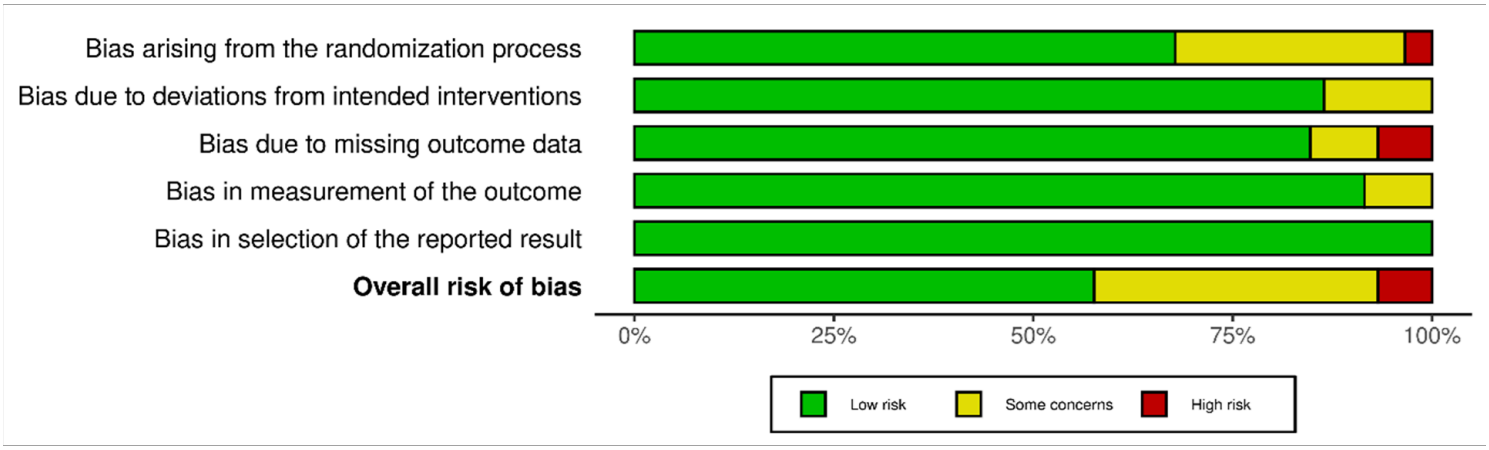


Figure 2

Summary plot of RobVis Risk Bias Analysis (2.0)