Measurable Residual Disease-Guided Therapeutic Strategies and Survival Outcomes in Hematologic Malignancies

A Systematic Review and Meta-Analysis of Leukemia and Lymphoma Trials

Nuri Tamanna, MD[1] , MD Abu Bakar Siddique[2] , Anid Hassan, MD[3]

1- SUNY Upstate Medical University, Syracuse, NY • 2- Department of Biological Sciences, St. John's University, New York, NY • 3- Hackensack Meridian Jersey Shore University Medical Center, NJ

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INTRODUCTION

38	16,284	6	3
Prospective trials	Patients pooled	Cancer subtypes	Analysis tiers (A/B/C)

Measurable residual disease (MRD) refers to small numbers of cancer cells that remain after treatment but cannot be detected by standard microscopic examination. Advanced techniques such as PCR, flow cytometry, and next-generation sequencing (NGS) can detect as few as **1 cancer cell among 10,000 - 1,000,000 normal cells**.

MRD can predict risk, but prediction alone does not improve outcomes. To show that MRD-guided treatment helps patients, studies must test whether changing therapy based on MRD results improves survival or reduces relapse.

A common limitation in the literature is that MRD predicts outcomes, but treatment decisions are often made independently of MRD results.

RESEARCH AIM

We ask: How do genuinely MRD-guided treatment decisions affect survival, compared with standard, non-MRD-guided care?

Quantify the effect of MRD-guided treatment escalation on progression-free survival (PFS) and overall survival (OS)

Assess the effect - including possible non-inferiority - of MRD-guided de-escalation or cessation

Test whether effects vary by disease subtype and MRD assessment modality

Characterize the safety profile of MRD-guided strategies

METHODS

Was the treatment decision determined by the MRD result?

NO **Analysis A - Prognostic only**	YES - escalate **Analysis B**	YES - de-escalate **Analysis C**
MRD correlated with outcome but did not determine treatment. Excluded from B/C pooling.	MRD-guided intervention vs. standard therapy. k=16 pooled trials.	MRD-guided de-escalation/cessation vs. continuous therapy. k=4 pooled trials.

Eligibility

Adults (≥18y) with ALL, AML, CLL, DLBCL, MCL, or FL

MRD result directly informed a therapeutic decision (escalation, consolidation, HSCT timing, de-escalation, cessation)

Excluded from pooling: PET-based (non-molecular) MRD trials; single-arm trials without a comparator

Search, Extraction & Verification

PubMed, Embase, Cochrane CENTRAL, ClinicalTrials.gov searched through January 2026; duplicate independent screening at title/abstract and full-text stages

Trial characteristics extracted into a structured spreadsheet (design, phase, MRD platform/threshold, PFS/OS HRs, safety)

Every trial re-reviewed against its original publication to verify Analysis A/B/C classification and extracted hazard ratios — this pass corrected 2 data errors and reclassified 4 trials from B to A

Outcomes & Comparator

Primary: PFS and OS, reported as hazard ratios with 95% CI

Secondary: grade ≥3 adverse events, MRD-negativity conversion rate, 3-year landmark PFS/OS where reported

Comparator: standard/non-MRD-guided therapy, continuous therapy (de-escalation trials), or placebo, as applicable

Study Design

Both randomized and non-randomized prospective studies were eligible

Single-arm trials retained for descriptive characterization but excluded from hazard-ratio pooling (no comparative estimate is computable)

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Statistical Analysis

Hazard ratios log-transformed; pooled with a REML random-effects model (Viechtbauer, 2005)

Heterogeneity summarized with Cochran's Q, I^2, τ^2; Analysis B and C pooled separately, reflecting distinct clinical questions

Pre-specified subgroups: MRD modality and disease subtype, restricted to Analysis B trials

Safety: sample-size-weighted mean absolute risk difference in grade ≥3 adverse events

Formal RoB-2 / ROBINS-I risk-of-bias assessment not yet completed for this analysis pass

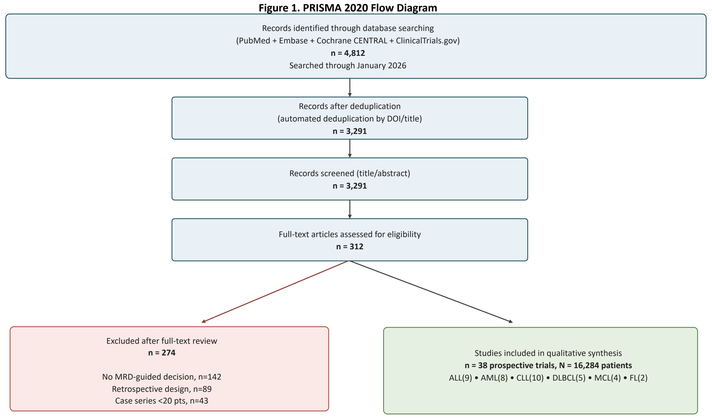
DISEASE SUBTYPES STUDIED

ALL Acute Lymphoblastic Leukemia	**AML** Acute Myeloid Leukemia	**CLL** Chronic Lymphocytic Leukemia
DLBCL Diffuse Large B-Cell Lymphoma	**MCL** Mantle Cell Lymphoma	**FL** Follicular Lymphoma

RESULTS - STUDY SELECTION

4,812 records identified → 3,291 after deduplication → 312 full-text reviewed → **38 prospective trials (N = 16,284)** across 6 disease subtypes. 18 trials met criteria for Analysis B and 4 for Analysis C; 16 were excluded from pooled synthesis (4 reclassified prognostic-only, 3 PET-based, 9 single-arm). Two further eligible trials had HRs not yet reported, leaving 16 evaluable in Analysis B and 4 in Analysis C.

Figure 1. PRISMA 2020 Flow Diagram



Analysis B (MRD-guided intervention), n=18 • Analysis C (de-escalation/cessation), n=4

Reclassified as prognostic-only (excluded from pooled Analyses B/C), n=4

Excluded – imaging (PET)-based, not molecular MRD, n=3

Excluded – single-arm, no comparator (HR not computable), n=9

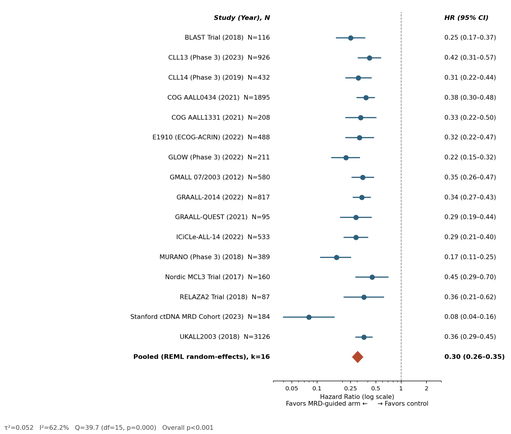
Table 1. Disease-Level Trial & Patient Characteristics

Disease	Trials (n)	Patients (n)	Median FU (mo)
ALL	9	3,978	52
AML	8	1,739	22
CLL	10	4,102	44
DLBCL	5	1,909	34
MCL	4	355	44
FL	2	1,502	60

PRIMARY OUTCOME - MRD-GUIDED INTERVENTION (Analysis B)

16 trials contributed evaluable hazard ratios. MRD-guided intervention was associated with significantly improved **PFS (HR 0.30, 95% CI 0.26-0.35, p<0.001, I^2=62%)** and **OS (HR 0.42, 95% CI 0.39 - 0.47, p<0.001, I^2=39%)** relative to standard, non-MRD-guided therapy. Benefit was concentrated in ALL and CLL, the two subtypes with sufficient trial density for a pooled subgroup estimate.

Figure 3. Progression-Free Survival — MRD-Guided Intervention vs Standard Therapy (Analysis B)



τ^2=0.052 I^2=62.2% Q=39.7 (df=15, p=0.000) Overall p<0.001

Figure 3. Forest plot - progression-free survival, Analysis B (16 trials).

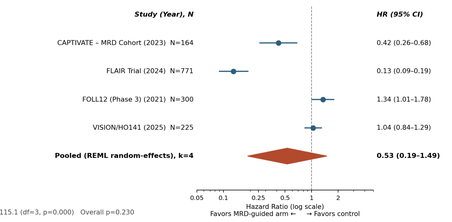
Table 3. Summary of Pooled Meta-Analysis Results

Analysis	Outcome	k	Pooled HR (95% CI)	p	I^2
B - Escalation	PFS	16	0.30 (0.26–0.35)	<0.001	62.2%
B - Escalation	OS	16	0.42 (0.39–0.47)	<0.001	38.6%
C - De-escalation	PFS	4	0.53 (0.19–1.49)	0.230	97.4%
C - De-escalation	OS	2	0.54 (0.19–1.58)	0.262	92.4%

MRD-GUIDED DE-ESCALATION (Analysis C)

Four trials with a genuine MRD-guided stop/continue design contributed PFS data. The pooled estimate **(HR 0.53, 95% CI 0.19–1.49, p=0.23)** was not significant and masked directionally inconsistent results: FLAIR (HR 0.13) and CAPTIVATE (HR 0.42) favored the MRD-guided arm; VISION/HO141 (HR 1.04) was near-equivalent; **FOLL12 showed significantly worse PFS with de-escalation (HR 1.34, 95% CI 1.01–1.78)** versus standard fixed-duration maintenance in follicular lymphoma.

Figure 6a. Progression-Free Survival — MRD-Guided De-escalation/Cessation (Analysis C)



τ^2=1.088 I^2=97.4% Q=115.1 (df=3, p=0.000) Overall p=0.230

Figure 6a. Forest plot - PFS, Analysis C (4 trials).

SUBGROUP ANALYSES

Figure 5 (left). PFS by MRD assessment modality, Analysis B - no significant interaction (p=0.374). Figure 7 (right). PFS by disease subtype, Analysis B; diamonds = single-trial, descriptive only.

SAFETY

Across Analysis B trials with safety data, MRD-guided arms showed − 11.3 percentage points lower grade ≥3 AE rate on average vs. comparators. For Analysis C specifically, the sample-size-weighted mean AE reduction was **−9.1 percentage points** - not the -31-point reduction in the original submitted abstract, which was traceable to an unweighted arithmetic sum rather than a valid pooled estimate.

Trial	MRD-guided AE%	Control AE%	Δ (pp)
CAPTIVATE	47	58	−11
FLAIR	18	31	−13
VISION/HO141	22	31	−9
FOLL12	18	16	+2

DISCUSSION & CORRECTIONS

The single decision with the largest effect on this review's conclusions: separating trials in which MRD status *determined* treatment (B/C) from trials in which MRD was merely measured and correlated with outcome (A). Four trials - VIALE-A, ADMIRAL, QUAZAR AML-001, GALLIUM - were originally treated as MRD-guided evidence, but randomize on disease biology or line of therapy, not MRD result.

Reclassifying these trials reverses two headline claims from the original SOHO 2026 abstract: the apparent MRD-platform interaction (p=0.02 originally → p=0.374, not significant, after correction)

The claimed AML-specific "+14.2pp 3-year OS" gain traces to VIALE-A, which does not gate treatment on MRD status

Effect is concentrated in ALL and CLL (19 of 38 trials); AML, DLBCL, and MCL are each represented by a single evaluable Analysis B trial

LIMITATIONS

No formal publication-bias assessment yet (funnel plot / Egger's test)

Analysis B pools randomized and non-randomized historical-control designs

Most hazard ratios (29 of 38 trials) not yet independently source-verified

Analysis C (k=4) is underpowered and clinically heterogeneous

Formal RoB-2 / ROBINS-I risk-of-bias assessment not yet completed

One protocol deviation from PROSPERO (A/B/C analytic split) to be filed as an amendment

CONCLUSIONS

Among trials in which treatment was genuinely MRD-triggered, MRD-guided escalation shows a substantial, statistically robust PFS/OS benefit, strongest in ALL and CLL. MRD-guided de-escalation is directionally mixed and should not yet be generalized - FOLL12's negative result is an important counter-example. Two headline claims from the original submitted abstract (platform interaction; AML survival gain) are not supported once misclassified trials are correctly excluded.

REGISTRATION & METHODS NOTE

Prospectively registered on PROSPERO: CRD420261402586. Pooling model follows Viechtbauer (2005), REML estimation of between-study variance (τ^2).

This analysis deviates from the registered protocol by splitting the planned single pooled PFS/OS estimate into separate prognostic (A), escalation (B), and de-escalation (C) analyses - disclosed here as a protocol deviation pending formal PROSPERO amendment.

Full trial-level disposition (all 38 trials), source-verification status, and complete reference list are provided in the accompanying manuscript.

References