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Association of Measurable Residual Disease With Survival Outcomes in Patients With Acute Myeloid Leukemia
A Systematic Review and Meta-analysis

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IMPORTANCE Measurable residual disease (MRD) refers to neoplastic cells that cannot be detected by standard cytomorphologic analysis. In patients with acute myeloid leukemia (AML), determining the association of MRD with survival may improve prognostication and inform selection of efficient clinical trial end points.

OBJECTIVE To examine the association between MRD status and disease-free survival (DFS) and overall survival (OS) in patients with AML using scientific literature.

DATA SOURCES Clinical studies on AML published between January 1, 2000, and October 1, 2018, were identified via searches of PubMed, Embase, and MEDLINE.

STUDY SELECTION Literature search and study screening were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Studies that assessed DFS or OS by MRD status in patients with AML were included. Reviews, non–English-language articles, and studies reporting only outcomes after hematopoietic cell transplantation or those with insufficient description of MRD information were excluded.

DATA EXTRACTION AND SYNTHESIS Study sample size, median patient age, median follow-up time, MRD detection method, MRD assessment time points, AML subtype, specimen source, and survival outcomes were extracted. Meta-analyses were performed separately for DFS and OS using bayesian hierarchical modeling.

MAIN OUTCOMES AND MEASURES Meta-analyses of survival probabilities and hazard ratios (HRs) were conducted for OS and DFS according to MRD status.

RESULTS Eighty-one publications reporting on 11 151 patients were included. The average HR for achieving MRD negativity was 0.36 (95% bayesian credible interval [CrI], 0.33-0.39) for OS and 0.37 (95% CrI, 0.34-0.40) for DFS. The estimated 5-year DFS was 64% for patients without MRD and 25% for those with MRD, and the estimated OS was 68% for patients without MRD and 34% for those with MRD. The association of MRD negativity with DFS and OS was significant for all subgroups, with the exception of MRD assessed by cytogenetics or fluorescent in situ hybridization.

CONCLUSIONS AND RELEVANCE The findings of this meta-analysis suggest that achievement of MRD negativity is associated with superior DFS and OS in patients with AML. The value of MRD negativity appears to be consistent across age groups, AML subtypes, time of MRD assessment, specimen source, and MRD detection methods. These results support MRD status as an end point that may allow for accelerated evaluation of novel therapies in AML.

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Acute myeloid leukemia (AML) is a heterogeneous disease with a widely variable prognosis and likelihood of cure that is dependent on both patient- and disease-related characteristics.[1,2] Pretreatment characteristics, such as age, karyotype, and genomic alterations, are well established factors associated with clinical outcomes of patients with newly diagnosed AML receiving first-line therapy.[3,4] Assessment of early response to therapy by conventional morphologic analysis also provides important information about the chemosensitivity of leukemia in an individual that cannot necessarily be estimated by pretreatment factors.[5] Further refinement of prognosis may be accomplished through evaluation of measurable residual disease (MRD), also called minimal residual disease, which refers to low levels of residual leukemia that cannot be detected by morphologic assessment alone.[6,7]

The persistence of MRD has been shown to be associated with higher rates of relapse and worse disease-free survival (DFS) and overall survival (OS) in several leukemias, including chronic myeloid leukemia, chronic lymphocytic leukemia, and acute lymphoblastic leukemia (ALL).[8-11] For example, a meta-analysis of 39 publications on children and adults with ALL reported that the presence of MRD confers worse event-free survival and OS regardless of the subgroups evaluated.[12] In pediatric ALL, MRD information is also routinely used to risk stratify patients and determine appropriate consolidation strategies.[13,14] A meta-analysis of 19 studies suggested that the presence of MRD before hematopoietic cell transplantation for AML was associated with higher rates of relapse and inferior survival.[15] Individual studies have similarly suggested that the detection of MRD is associated with inferior outcomes in patients with AML undergoing frontline therapy. Based on the consistent association of MRD with clinical outcomes across multiple studies, consensus guidelines support the use of *complete remission without MRD* as an official AML response criterion.[5]

Although many publications have suggested substantial clinical value of MRD assessment in AML, the optimal use of MRD information to risk stratify patients and inform clinical decision-making has been limited in part by the heterogeneity of these reports.[16-22] Frequently used MRD detection methods include multiparameter flow cytometry (MFC), polymerase chain reaction (PCR) for recurrent gene fusions or other genomic alterations, and next-generation sequencing (NGS), among others. However, these methods vary in their sensitivities and applicability to different patient populations. Studies reporting the association of MRD with outcomes in AML also vary in the patient populations tested (eg, age or AML subtypes), timing of MRD assessment, and the specimen source (eg, bone marrow or peripheral blood). These variances all contribute to uncertainty about the broad use of MRD testing in clinical practice and its potential adoption as a clinical trial end point.[23]

To use MRD information to guide clinical decision-making in AML and support its use as a meaningful clinical end point, it is necessary to understand the strength of the association of MRD with survival outcomes and the consistency of this association across patient-related, disease-related, and methodologic variables. To address these issues, we performed a literature-based meta-analysis of published AML studies reporting the association of MRD with DFS or OS. We also assessed the association between achieving MRD negativity and long-term clinical outcomes in relevant subgroups.

Key Points

Question What is the association between measurable residual disease (MRD) and survival outcomes in patients with acute myeloid leukemia?

Findings In a systematic review and meta-analysis of 81 publications reporting on 11 151 patients with acute myeloid leukemia, the estimated 5-year disease-free survival was 64% for patients without MRD and 25% for those with MRD. The estimated overall survival was 68% for patients without MRD and 34% for those with MRD.

Meaning The findings of this study suggest that, in patients with acute myeloid leukemia, achievement of MRD negativity is associated with superior long-term survival and warrants consideration as a clinical trial end point that may allow for more rapid evaluation of the efficacy of novel therapies.

Methods

Data Sources and Selection

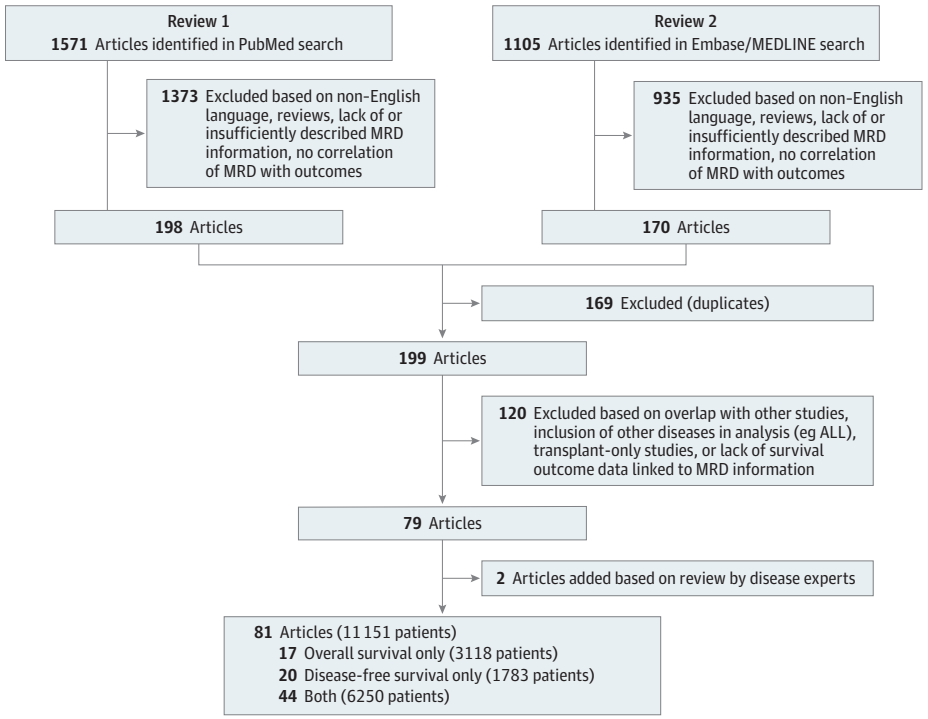
For this systematic review and meta-analysis, 2 investigators (N.J.S. and F.R.) conducted independent searches of PubMed, MEDLINE, and Embase for articles published between January 1, 2000, and October 1, 2018, that included the key words *AML*, *acute myeloid leukemia*, or *acute myelogenous leukemia* in combination with the key words *MRD*, *minimal residual disease*, or *measurable residual disease*. Disease experts (R.B.W., S.D.F., and C.S.H.) reviewed the resultant list and provided recommendations for additional article inclusions. This project was approved by the University of Texas MD Anderson Cancer Center Institutional Review Board. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[24]

We excluded review articles, non-English-language articles, studies that included non-AML diseases in their analysis, studies that used overlapping data sets, and studies that had insufficient description of MRD information or lacked an association with DFS or OS. We also excluded studies that only reported outcomes after hematopoietic cell transplantation (**Figure 1**).

Data Extraction and Synthesis

We extracted the following information from publications when it was available: study sample size, median age and age range, median follow-up time, MRD detection method (eg, PCR, MFC, NGS, cytogenetics and/or fluorescence in situ hybridization [FISH], or others), MRD assessment time points, AML subtype (eg, core-binding factor [CBF] or others), specimen sources (eg, bone marrow or peripheral blood), and survival

Figure 1. Flow Diagram of the Study Selection Process



ALL indicates acute lymphoblastic leukemia; MRD, measurable residual disease.

outcomes. Polymerase chain reaction–based studies were further subdivided into those evaluating expression of Wilms tumor 1 (*WT1*) and those evaluating specific gene targets or translocations. All studies used real-time quantitative PCR, with the exception of one study that used digital droplet PCR.[25] Other methods of MRD detection included brain and acute leukemia cytoplasmic expression, and multigene expression.[26-28]

We used a sequential approach to collect 3 different types of survival information comparing patients who achieved MRD negativity with those who did not: (1) if Kaplan-Meier curves were provided with the number of patients at risk and number of events for both MRD-negative and MRD-positive groups, we used commercial graph digitizer software (DigitizeIt, version 2.1; Bormisoft) to extract coordinates of points on the curves and applied a numeric algorithm to reconstruct survival data for each MRD group[29]; (2) when Kaplan-Meier curves were not available, we used reported hazard ratios (HRs) and their 95% CIs; and (3) for articles that only provided survival proportions at fixed time points (eg, 3 or 5 years), we used the reported survival rates and their SDs.

Searches of PubMed and Embase/MEDLINE found 1571 and 1105 articles, respectively, for the date range of January 1, 2000, to October 1, 2018. After removing duplicate studies between the 2 searches, 199 articles remained. Additional criteria were applied to exclude studies with non-AML diseases in their analysis, those reporting only on patients with acute promyelocytic leukemia, those with overlapping data sets, those that only reported posttransplantation survival outcomes, and those that did not report on the association of MRD with survival end points, which reduced the total number to 79 publications. Two articles were subsequently added based on review by disease experts.

To eliminate duplicate data, only one type of data was used from each study. With the highest priority, Kaplan-Meier curves for both MRD-negative and MRD-positive groups were extracted from 24 studies to reconstruct survival results for OS and from 16 studies for DFS. When Kaplan-Meier curves were unavailable for reconstruction, we used observed HRs and their CIs from 28 studies for OS and 38 studies for DFS. In 9 studies for OS and 12 studies for DFS, neither Kaplan-Meier curves nor HRs were reported, and thus survival rates at specific time points were used.

Statistical Analysis

The primary end points were DFS and OS, which were modeled separately. Overall survival was defined from the time of treatment start until death or last follow-up. Disease-free survival was defined as the time of remission until relapse, death, or last follow-up. We included disease-free, event-free, leukemia-free, recurrence-free, and relapse-free survival in the definition of DFS.

We used 2 different approaches for statistical analysis, both of which allowed for the possibility that MRD status could have different HR effects in different studies. The primary analysis used a bayesian hierarchical model with a time-varying HR effect.[30,31] The other approach was a traditional frequentist random-effects model assuming a constant proportional HR over time.[32,33]

In the bayesian analysis, we modeled the time-varying effects by assuming that hazards were constant within each

6-month period of follow-up and truncated results of all studies at 11 years. Each 6-month segment has its own study-specific hazard rate and therefore also its own HR for MRD-negative vs MRD-positive groups.[12] Studies that reported the observed HRs depending on MRD status and the associated CIs (type 2 data) contribute directly to the probability distributions of the log HRs of the studies considered and, in particular, to inferences about the mean of the studies. The baseline hazard rates within each time segment were estimated by the studies that reported Kaplan-Meier curves (type 1) and survival rates (type 3) for MRD-positive and MRD-negative groups.[34] Log-normal distributions were proposed for segments in time-varying baseline hazard rates, the time-varying HRs, and the study-specific HR effects with noninformative previous distributions for the mean and SD parameters.

We plotted the posterior means of DFS and OS distributions for patients who achieved MRD negativity vs those who did not. We used shading to show the 95% bayesian credible intervals (CrIs) of these Kaplan-Meier curves. The difference in restricted mean survival time (ie, the area under survival curves up to given time points)[35-37] was added as a robust estimate of treatment effect. For forest plots, we present the HR average over time for MRD-negative vs MRD-positive groups and the corresponding 95% CrI. Unless indicated otherwise, all results reported, including subgroup analyses, were based on bayesian hierarchical analysis. The comparisons between different groups were conducted using posterior probabilities.

Because closed forms of the full-conditional distributions are not available for bayesian analyses, we identified the joint posterior distributions of model parameters using Markov chain Monte Carlo methods.[31] We used statistical software R, version 3.5.3 (R Project for Statistical Computing, with packages survival_v2.43-3, rjags_v4-8, coda_v0.19-3, lattice_v0.20-38, and ggplot2_v3.2.0) and JAGS, version 4.3.0 statistical software for data analysis.

Results

Eighty-one distinct publications including 11 151 patients were included in this analysis (17 studies for OS, 20 studies for DFS, and 44 for both outcomes). These studies formed the basis of our statistical analyses.[16-22,25-28,38-107] The characteristics of the individual studies are presented in eTable 1 in the Supplement. The number of studies included in each subgroup analysis are reported in the **Table**.

The survival curves for MRD-negative and MRD-positive groups are shown in **Figure 2**. Both OS and DFS were better for patients who achieved MRD negativity. At 5 years, the estimated OS was 68% (95% CrI, 63%-73%) for the MRD-negative group vs 34% (95% CrI, 28%-40%) for the MRD-positive group. Similarly, at 5 years, the estimated DFS was 64% (95% CrI, 59%-70%) for the MRD-negative group and 25% (95% CrI, 20%-32%) for the MRD-positive group. The estimation for time-varying HRs for both OS and DFS are shown in eFigure 1 in the Supplement. The relative benefit of achieving MRD negativity was comparable for both OS and DFS (average HR, 0.36; 95% CrI, 0.33-0.39 for OS and average HR, 0.37; 95% CrI, 0.34-0.40 for DFS). The average HR for each study is shown in forest plots (eFigure 2 in the Supplement). The difference of 5-year restricted mean survival time of the MRD-negative and MRD-positive groups was 15.37 months (95% CrI, 13.58-17.19 months) for OS and 19.61 months (95% CrI, 17.33-21.92 months) for DFS.

Table. Included Studies by Subgroup

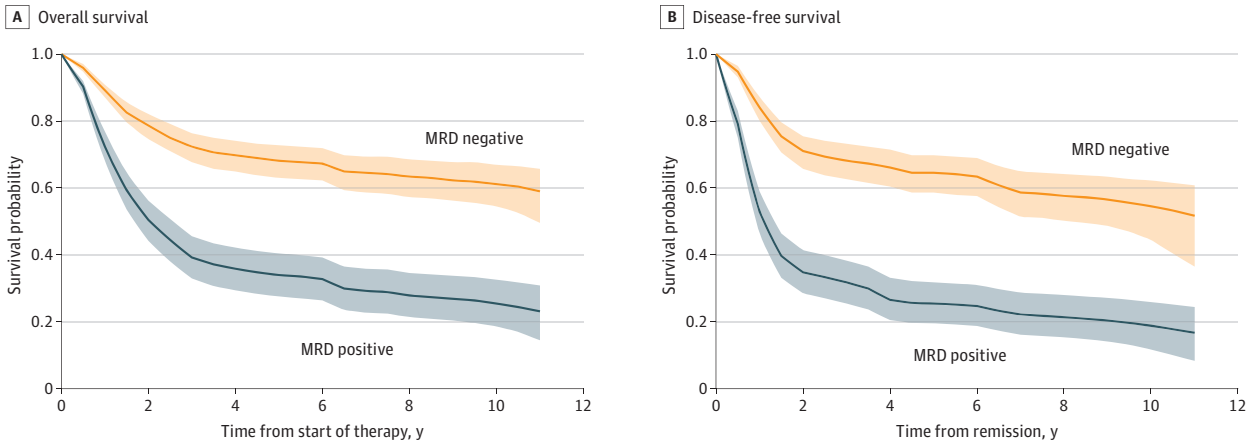
Subgroup	Studies included, No. (%)	
	In OS analysis	In DFS analysis
Age group	n = 61	n = 64
Adult	50 (82)	51 (80)
Pediatric	10 (16)	11 (17)
Mixed	1 (2)	2 (3)
MRD time point	n = 80	n = 85
Induction	53 (66)	54 (64)
During consolidation	11 (14)	15 (18)
After consolidation	16 (20)	16 (19)
MRD detection method	n = 63	n = 67
MFC	25 (40)	29 (43)
PCR (*WT1*)	7 (11)	8 (12)
PCR (gene/fusion)	22 (35)	21 (31)
NGS	4 (6)	4 (6)
Cytogenetics/FISH	2 (3)	2 (3)
Others	3 (5)	3 (5)
AML subtype	n = 61	n = 64
CBF	9 (15)	12 (19)
Non-CBF	52 (85)	52 (81)
Specimen source	n = 63	n = 67
Bone marrow	56 (89)	58 (87)
Peripheral blood	5 (8)	5 (7)
Mixed	2 (3)	4 (6)

Abbreviations: AML, acute myeloid leukemia; CBF, core-binding factor; DFS, disease-free survival; FISH, fluorescent in situ hybridization; MFC, multiparameter flow cytometry; MRD, measurable residual disease; NGS, next-generation sequencing; OS, overall survival; PCR, polymerase chain reaction; *WT1*, Wilms tumor 1.

Figure 3 presents the results of univariate analysis for different subgroups. In general, the MRD results showed a similar pattern for OS and DFS. Achievement of MRD negativity was associated with superior DFS and OS regardless of age group (adult or pediatric), MRD assessment time point (induction, during consolidation, or after consolidation), AML subgroup (CBF or non-CBF), or specimen source (bone marrow or peripheral blood). While most of the MRD detection methods were able to identify a difference in DFS and OS between groups with MRD negativity vs positivity, the MRD association using cytogenetics/FISH was not significant (average HR, 0.77; 95% CrI, 0.39-1.56 for OS and average HR, 0.65; 95% CrI, 0.34-1.23 for DFS). Among studies evaluating MRD by MFC, the impact of MRD was similar between studies using less than 6-color assays vs greater than or equal to 6-color assays (difference in HR, −0.02; 95% CrI, −0.54 to 0.49 for OS and −0.09; 95% CrI, −0.70 to 0.52 for DFS).

For AML subtypes, the association between MRD and survival outcomes was greater in studies reporting outcomes of

Figure 2. Estimated Survival Curves, Stratified by Measurable Residual Disease (MRD) Status



Overall survival (OS) (A) and disease-free survival (DFS) (B). The curves show the posterior means of survival distribution in the bayesian hierarchical analysis. The shadings of each curve show the 95% bayesian credible intervals (CrIs) for the survival proportion at the corresponding point in time of follow-up. The 5-year OS was 68% (95% CrI, 63%-73%) for the MRD-negative group and 34% (95% CrI, 28%-40%) for the MRD-positive group. The average hazard ratio for OS was 0.36 (95% CrI, 0.33-0.39), with a 5-year restricted mean survival time difference of 15.37 months (95% CrI, 13.58-17.19 months). The 5-year DFS was 64% (95% CrI, 59%-70%) for the MRD-negative group and 25% (95% CrI, 20%-32%) for the MRD-positive group. The average hazard ratio for DFS was 0.37 (95% CrI, 0.34-0.40), with a 5-year restricted mean survival time difference of 19.61 months (95% CrI, 17.33-21.92 months).

CBF AML compared with non-CBF AML, with a posterior probability of 0.999 for OS and 0.997 for DFS. Regarding the association of specimen source with survival outcomes, peripheral blood assessment of MRD better distinguished MRD-positive and MRD-negative groups compared with bone marrow assessment of MRD, with a posterior probability of 0.918 for OS and 0.999 for DFS.

Multivariate analysis results were consistent with univariate analysis results (eFigure 3 in the Supplement). All subgroups showed DFS and OS benefit to achievement of MRD negativity with the exception of MRD detection by cytogenetics/FISH. The differences of survival time by subgroup for 5-year survival rates and 5-year restricted mean survival times are summarized in eTable 2 in the Supplement.

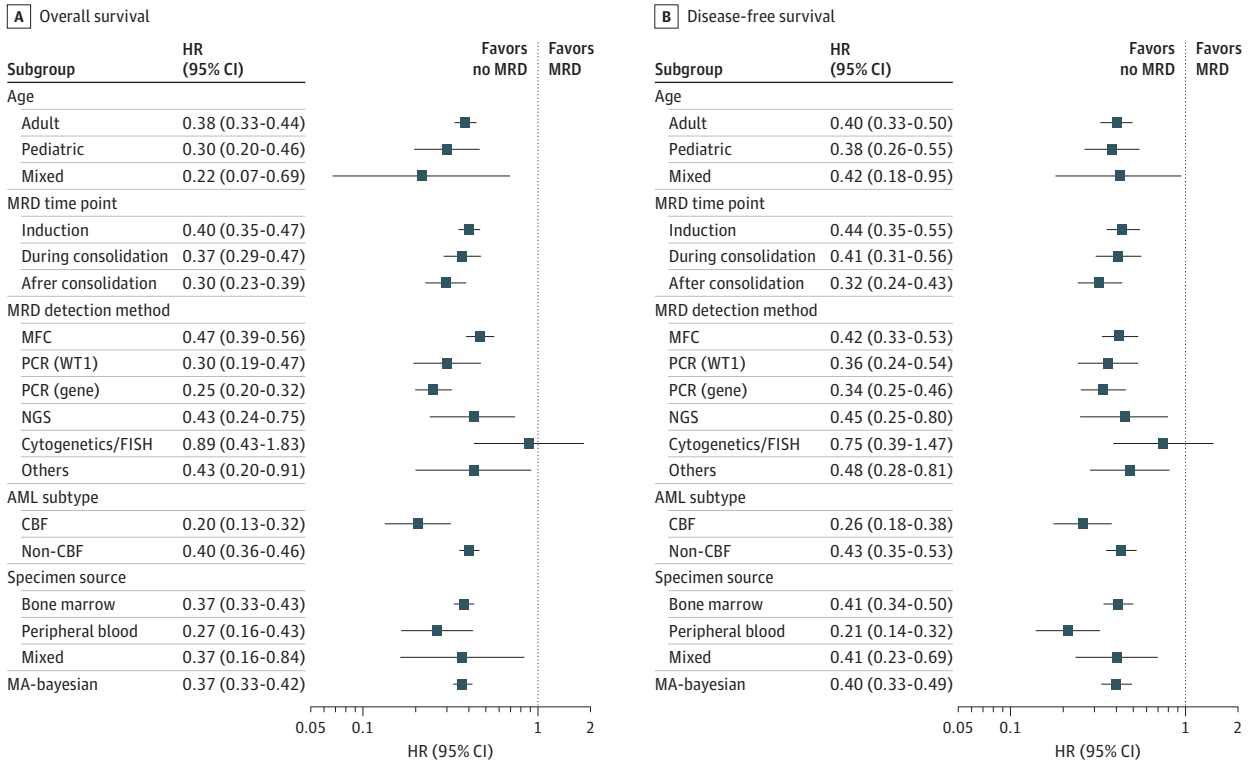
Discussion

This meta-analysis of 81 publications suggests that MRD status has prognostic importance in AML and may be a valid surrogate marker for both DFS and OS in AML clinical trials. The magnitude of benefit associated with achieving MRD negativity was substantial, corresponding to a 64% reduction in the risk of death for MRD-negative patients. The results of this meta-analysis thus provide quantitative support for consensus guidelines that consider achievement of complete remission without MRD as the optimal response in AML.[5]

The large number of studies considered in this meta-analysis allowed for relevant subgroup analyses. These subgroup analyses suggest that achievement of MRD negativity is associated with clinically relevant improvement in long-term survival outcomes in all subgroups evaluated, with the exception of MRD assessment by cytogenetics/FISH. The lack of significant association of cytogenetics/FISH with DFS and OS may be explained in part because only 2 studies using this method were included in this analysis (527 patients total) and because this MRD detection method has the lowest sensitivity among those considered.[23] The consistent impact of MRD across all other subgroups analyzed provides evidence that achievement of MRD negativity is an important end point across clinical contexts, including the most relevant MRD detection methods used in contemporary clinical practice and research (eg, MFC, PCR, and NGS). Multivariate analysis further supported the benefit of MRD negativity across these subgroups. Nonetheless, the optimal MRD assay and timing of assessment should be guided by the specific clinical scenario. For example, while PCR for *WT1* expression provided useful MRD information in our analysis, consensus recommendations advise against PCR for *WT1* as a routine marker of MRD owing to its low sensitivity and specificity unless no other MRD test is available.[7]

These data have several potential implications for both clinical practice and drug development in AML. In our analysis, the 5-year estimated OS for the MRD-negative group was 68% compared with only 34% for the MRD-positive group. In addition to supporting the use of MRD testing to provide prognostic information, the poor outcomes associated with the presence of MRD support the development of novel therapeutic approaches for these patients. Some studies suggested that the outcomes of MRD-positive patients may be improved with hematopoietic cell transplantation in first remission.[20,21,54,108,109] The use of hypomethylating agents (eg, azacitidine or decitabine) may also be beneficial.[110-113] In ALL, the CD3-CD19 bispecific T-cell–engaging antibody blinatumomab is effective in eradicating persistent or recurrent MRD and is approved by the US Food and Drug Administration for this use.[114] Similarly, in AML, well-designed prospective clinical trials using effective MRD-directed therapies should test

Figure 3. Hazard Ratios (HRs) for Subgroups



Overall survival (A) and disease-free survival (B). Each square represents the mean HR from bayesian hierarchical analysis, and the horizontal lines represent the 95% bayesian credible interval (CrI) for the subgroup's HR. AML indicates acute myeloid leukemia; CBF, core-binding factor; FISH, fluorescence in situ hybridization; MA, meta-analysis; MFC, multiparameter flow cytometry; MRD, measurable residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction; and WT1, Wilms tumor 1.

whether the outcomes of patients with MRD-positive disease could be improved with such an approach. The robust effect of MRD on both DFS and OS across studies also supports the consideration of MRD as a surrogate end point in clinical trial development that could lead to accelerated drug approval. An important caveat is that accelerated approval of any new drug based on an intermediate end point, such as MRD, would require eventual confirmation using traditional efficacy end points (eg, OS).

Strengths and Limitations

One strength of this analysis of pooled data from different publications is the advanced method used to generate the DFS and OS curves. Rather than converting survival information to study-level HR estimates, we reversely reconstructed survival data from published Kaplan-Meier curves to take advantage of the additional survival information, such that the baseline hazard function and time-varying HR can still be modeled without individual patient data. To use all of the available evidence, we applied 3 common types of survival information, including reconstructed survival data, HR estimates, and survival rates at particular points. A 1-stage bayesian hierarchical model to integrate different survival data was introduced to complete the information synthesis. Our model can assess the time-varying hazard rate for each treatment group, examine the proportional hazards assumption after controlling for the interstudy heterogeneity, and generate visual presentation of meta-analysis survival curves.

The study has several limitations. Inherent in any such meta-analysis is the potential for publication bias in that researchers are less likely to publish negative results. Because our meta-analysis was based on pooled data rather than patient-level data, we also cannot assess the association of MRD with survival outcomes in subgroups not reported within the individual publications that we selected. For example, while studies often restricted their analyses to CBF AML or to non-CBF AML, this latter group is composed of heterogeneous cytogenetic and molecular subgroups in which MRD status could have variable effects on long-term outcomes. Although none of the included studies prospectively altered consolidation strategies based on MRD status, we cannot account for how MRD information may have been used by individual clinicians (eg, to inform the decision to pursue allogeneic hematopoietic cell transplantation), and such real-time use of MRD information to guide treatment decisions may have led to imbalances between the MRD-negative and MRD-positive groups. Furthermore, most publications on MRD in AML included in this meta-analysis evaluated the impact of MRD in the context of first-line intensive chemotherapy with a cytarabine- and anthracycline-based induction regimen. Thus, owing to the

similarity of treatment across most of these studies, the generalizability of these findings to nonintensive regimens that do not use conventional cytotoxic chemotherapy is limited.

Conclusions

In this large-cohort meta-analysis, achievement of MRD negativity was associated with superior DFS and OS in patients with AML, an association that was observed across ages, disease subtypes, time of assessment, specimen source, and most MRD detection methods. Assessment of MRD in AML in cytomorphologic remission provides important prognostic information. Given the robustness of the association of MRD with long-term outcomes across studies, use of MRD status as an eligibility criterion and/or an end point in clinical trial design could lead to more efficient assessment of the efficacy of new drugs and combination therapies in AML.

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Conflict of Interest Disclosures: Dr Berry is co-owner of Berry Consultants LLC, a company that designs bayesian and adaptive clinical trials. Dr Freeman reported receiving personal fees from JAZZ outside the submitted work. Dr Hourigan reported receiving research funding from Sellas and Merck during the conduct of the study. No other disclosures were reported.

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Invited Commentary

Minimal Residual Disease in Acute Myeloid Leukemia

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The role of minimal disease testing in acute myeloid leukemia (AML) has been explored for many years. Based on the clear association with outcomes, measurable residual disease (MRD) has been incorporated into the consensus guidelines to reflect complete remission without MRD as an official AML response criterion. There are different methods for assessing MRD, including next-generation sequencing, polymerase chain reaction, and multicolor flow cytometry, all with varying levels of sensitivity. Multicolor flow cytometry is the more commonly used method in the US. However, the sensitivity of the multicolor flow cytometry assay can be dependent on the quality of the sample collected during bone marrow biopsy and on the experience of the laboratory; the latter is important in distinguishing the immunophenotype of the AML clone vs hematogone, which has traditionally been more difficult to distinguish in AML than in acute lymphoblastic leukemia.

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Measurable residual disease has routinely been used to determine consolidation therapies in pediatric patients with acute lymphoblastic leukemia. With the approval of blinatumomab, a particularly effective agent to eliminate MRD with low potential for toxic effects, MRD assessment has become standard of care for patients with acute lymphoblastic leukemia and is used to make treatment decisions.

In this issue of *JAMA Oncology*, Short et al[1] report on a meta-analysis that examined 81 relevant publications of studies including 11 151 patients with AML evaluating the role of MRD through various methods. Measurable residual disease positivity vs negativity appeared to result in significant differences in disease-free survival as well as overall survival in patients with AML. This publication reports the average HR for achieving MRD negativity for overall survival was 0.36 (95% bayesian credible interval [CrI], 0.33-0.39) and for disease-free survival was 0.37 (95% CrI, 0.34-0.40). Similarly, the estimated 5-year disease-free survival was 64% for MRD-negative and 25% for MRD-positive patients, with an estimated