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Association of Early Chemotherapy With Reduced In-Hospital Mortality and Complications in Acute Promyelocytic Leukemia: Insights From a Nationwide Cohort

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Abstract

Background/Aim: Prompt treatment in acute promyelocytic leukemia (APML) is critical due to high risk of early mortality. Early initiation of chemotherapy has been associated with favorable outcomes. The purpose of this study was to investigate differences in inpatient outcomes of APML based on time to chemotherapy initiation.

Patients and Methods: The National Inpatient Sample (NIS) was queried between the years 2016 and 2020 to identify all patients with APML who were administered chemotherapy inpatient. These patients were stratified into an early cohort if chemotherapy was given within 24 hours of admission and late cohort if it was after 24 hours. Baseline characteristics were compared amongst cohorts using independent sample *t*-tests and Chi-squared tests.

Results: Among 5,155 APML patients, 1,300 (25.2%) received early treatment and 3,855 (74.8%) late. Early treated patients were younger (45.4±19.4 *vs.* 47.6±18.9 years; $p<001$) with comparable sex distribution (50.8% *vs.* 48.0% female; $p=0.083$). Racial distribution was similar but statistically different due to sample size: White (58.9% *vs.* 58.7%) and Black (13.3% *vs.* 12.6%) ($p<0.001$). Early treated patients had lower Charlson Comorbidity Index (CCI) scores (3.9 *vs.* 4.2; $p<0.001$), shorter hospital stays (18.0 *vs.* 29.5 days; $p<0.001$), lower hospital charges ($262,436 *vs.* $405,537; $p<0.001$), lower rates of neutropenia (14.2% *vs.* 21.8%), sepsis (9.6% *vs.* 14.3%), disseminated intravascular coagulation (DIC) (23.8% *vs.* 35.8%), and mortality (4.6% *vs.* 6.7%) ($p<0.01$ for all).

Conclusion: Early chemotherapy was associated with lower rates of DIC, sepsis and mortality despite similar demographics and comorbidity burden in APML patients. These findings support immediate initiation of chemotherapy upon presentation.

Keywords: Acute promyelocytic leukemia, early chemotherapy, treatment delay, in hospital mortality, nationwide inpatient sample.

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Introduction

Acute promyelocytic leukemia (APML) is a distinct subtype of acute myeloid leukemia characterized by the chromosomal translocation t(15;17), which creates the PML-RARα fusion gene (1). This oncogene halts myeloid differentiation, leading to the accumulation of malignant promyelocytes and a life-threatening coagulopathy marked by disseminated intravascular coagulation (DIC) and hyperfibrinolysis (1, 2). Historically, this severe bleeding tendency, particularly intracranial hemorrhage, contributed to a "rapid downhill course," making APML one of the most fatal leukemias with high early mortality before modern therapies were introduced (3-5).

The management of APML was revolutionized by the introduction of all-trans retinoic acid (ATRA) and later arsenic trioxide (ATO), which induce the differentiation of leukemic cells and rapidly resolve the associated coagulopathy (6, 7). These targeted agents have transformed APML into a highly curable malignancy, with combination regimens achieving long-term survival rates of 90-95% in clinical trials, often without the need for conventional chemotherapy (7, 8). Despite these remarkable successes, early mortality remains the most significant challenge in APML care. Population-based studies report that 20-30% of patients die within the first few weeks of presentation, a stark contrast to the less than 10% early death rates seen in controlled trials (8-10). This discrepancy is further supported by recent real-world data from Byun *et al*., which confirmed high early mortality rates in nationwide cohorts outside of clinical trial settings (11). This discrepancy highlights a critical gap between ideal treatment outcomes and real-world clinical practice.

The primary driver of this mortality gap is a delay in the initiation of therapy. Most early deaths are due to hemorrhagic complications that occur before treatment has been administered or has taken effect (10). Recognizing this, major clinical guidelines from the NCCN and ELN stress that APML is a medical emergency and recommend starting ATRA immediately upon suspicion, even before genetic confirmation is available (7, 12). However, real-world adherence to this crucial recommendation is inconsistent. Factors such as clinician unfamiliarity with this rare disease, systemic inefficiencies, and lack of immediate ATRA availability can lead to dangerous treatment delays, particularly in non-specialized centers (7, 13, 14). Studies have repeatedly shown that a significant portion of early fatalities occur in patients who never received ATRA, underscoring that these deaths are often preventable (10, 15, 16).

To address these preventable deaths, some institutions have implemented rapid-response protocols that have successfully reduced early mortality rates by ensuring prompt treatment (17). Building on this evidence, our study aims to evaluate the impact of timely therapy on a national scale. Using the Nationwide Inpatient Sample (NIS), we sought to compare clinical outcomes between APML patients who received immediate therapy (within 24 hours of admission) and those who experienced a delay. We hypothesized that early treatment initiation would be associated with lower in-hospital mortality, fewer complications, shorter hospital stays, and reduced healthcare costs. By analyzing real-world data from diverse hospital settings, this study aimed to quantify the benefits of prompt intervention and reinforce the critical importance of adhering to treatment guidelines to improve APML survival nationwide.

Patients and Methods

Data source. We conducted a retrospective cohort analysis using the NIS database for the years 2016-2020. The NIS is part of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality. It is the largest publicly available all-payer inpatient database in the United States, designed to produce nationally representative estimates of hospitalizations. Each year's NIS contains information from approximately 7 million hospital stays, which can be weighted to represent about 35 million discharges nationwide. The NIS draws from 97% of the U.S. population

and, since 2012, is constructed as a 20% stratified sample of all discharges from non-federal acute-care hospitals in participating states. For each discharge record, the NIS provides data on patient age, sex, race, insurance payer, median income of residential ZIP code, hospital characteristics (teaching status, bed size, region, urban/rural location), up to 40 diagnosis codes, procedure codes, length of stay, discharge disposition, and total charges, among other variables. This broad scope enabled us to identify APML cases and analyze their clinical outcomes and resource use on a national scale. Because the NIS is a de-identified dataset available for public use, this study was deemed exempt from institutional review board review.

Study population. We identified hospitalizations for APML using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code C92.40 ("Acute promyelocytic leukemia, not having achieved remission") as the principal diagnosis. This code specifically denotes newly diagnosed or active APML. We limited the cohort to adult patients age ≥18 years, since pediatric APML is managed differently and is not the focus of this study. Patients with secondary or therapy-related APML were included if coded as such, but the vast majority were presumed de novo cases. We excluded any encounters where APML was not the primary reason for admission (to focus on initial treatment hospitalizations) or where key outcome data were missing. Each APML admission was categorized into one of two groups based on the timing of induction chemotherapy initiation, determined by ICD-10 procedure codes for systemic chemotherapy administration. Early treatment was defined as administration of induction therapy (which in practice would be ATRA with or without adjunctive chemotherapy/ATO) on the same day of admission or the next calendar day (within 24 hours of hospital arrival). Late treatment was defined as induction chemotherapy initiated more than 24 hours after admission. This cutoff was chosen to reflect guideline recommendations to start ATRA immediately; in essence, the early group represents patients who received urgent therapy at presentation, whereas the late group experienced a delay of at least one day. We recognize that some patients in both groups may have received ATRA empirically even before a formal chemotherapy billing code (for an anthracycline or arsenic) appears; however, using the procedure codes provides a standardized proxy for treatment timing across the dataset.

Variables and definitions. For each patient, we extracted demographic variables (age at admission, sex, and race/ethnicity as recorded). Socioeconomic status was approximated by the median household income quartile of the patient's ZIP code and by insurance payer (Medicare, Medicaid, private, or uninsured). Clinical severity and comorbid conditions were assessed using the Charlson Comorbidity Index (CCI), a validated summary score of 17 chronic conditions (excluding the APML diagnosis itself) derived from secondary diagnosis codes. We identified key complications of interest using ICD-10-CM diagnosis codes present during the hospital stay, focusing on those complications most relevant to APML induction: DIC/coagulopathy, severe neutropenia (agranulocytosis), and sepsis. DIC was defined by codes indicating acute DIC or hemorrhagic disorder due to intrinsic circulating anticoagulants; neutropenia was defined by codes for febrile neutropenia or agranulocytosis; and sepsis by standard sepsis or bacteremia codes. While we expected most APML patients to have some coagulopathy at baseline, we coded DIC as present only if it was explicitly diagnosed/treated during the hospitalization (which would correspond to more severe coagulopathy). Hospital-level variables included location (urban *vs.* rural), teaching status (academic teaching hospital *vs.* community hospital), bed size, and geographic region, as provided by the NIS.

Outcomes. The primary outcome was in-hospital mortality, defined as death (or not) during the hospitalization. This captures early mortality in the sense of induction death, since APML induction typically requires inpatient care.

Secondary clinical outcomes were the occurrence of the major complications mentioned above: DIC, neutropenia, and sepsis during the admission (all coded as binary indicators). These complications were chosen because they reflect the key life-threatening issues in early APML management—coagulopathy and infections—which might be mitigated by prompt therapy. We also examined two key healthcare utilization outcomes: hospital length of stay (LOS), measured in days, and total hospital charges, as reported in the NIS (adjusted to 2020 U.S. dollars using the medical care component of the Consumer Price Index). These serve as proxies for the intensity and cost of care, and we hypothesized that delays in therapy (late treatment group) could lead to prolonged hospitalizations and higher costs due to managing complications of APML.

Statistical analysis. We first performed descriptive analyses comparing patient characteristics and hospital factors between the early treatment and late treatment groups. Categorical variables were compared using chi-square tests (or Fisher's exact test when cell counts were small), and continuous variables (like age, LOS, charges) were compared using Student's *t*-test or the nonparametric equivalent as appropriate. We then assessed univariate outcomes: the rates of in-hospital death, DIC, neutropenic complications, and sepsis in each group, as well as average LOS and costs, comparing early vs. late therapy using the same statistical tests. To adjust for potential confounding, we built multivariable logistic regression models for the binary outcomes (mortality and complications), including covariates that were clinically relevant or statistically different between groups. Covariates in the models included: age, sex, race, Charlson Comorbidity Index, hospital teaching status, and insurance type (as a surrogate for socioeconomic status and access to care). We specifically included hospital teaching status and patient insurance because we suspected (a priori, and based on literature) that these factors might influence both the likelihood of early treatment and the outcomes (for example, academic centers may treat sooner and have better support protocols). For continuous outcomes LOS and cost, we used multivariable linear regression on log-transformed values (to account for right-skewed distribution of days and dollars), adjusting for the same covariates. From the logistic models, we reported adjusted odds ratios (OR) with 95% confidence intervals (CI) for early treatment vs late treatment, and from the linear models we derived percentage differences in geometric mean LOS/cost associated with early treatment (back-transforming the beta coefficients). Statistical significance was defined as $p<0.05$ (two-tailed). All analyses were conducted using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) and accounted for the complex survey design of NIS (using discharge-level weights) to derive national estimates.

Results

Between 2016 and 2020, a total of 5,155 adults were hospitalized for APML. Of these, 1,300 patients (25.2%) received induction chemotherapy within 24 hours of admission (early treatment group), while 3,855 (n=74.8%) had a delay beyond the first day (late treatment group). Baseline characteristics differed somewhat between the groups. On average, early treatment patients were slightly younger than those treated later (mean 45.4 *vs.* 47.6 years, $p<0.001$). There was no significant difference in sex distribution (overall male: 50.8%; female: 49.2%; $p=0.083$). Urban teaching hospitals were more likely to initiate early therapy (75% of early-treatment cases), compared to Rural nonteaching hospitals ($p<0.001$) while Urban non-teaching hospitals were more likely to initiate late chemotherapy ($p<0.001$). In contrast, hospital bed size showed no significant effect on treatment timing ($p=0.171$). Patients in the early treatment cohort were more often covered by Medicare or private insurance (≈46%), while Medicaid patients were somewhat underrepresented compared to the late group ($p=0.038$). Similarly, patients from lower-income ZIP codes were slightly more likely to receive early therapy than those from higher-income quartiles ($p<0.001$). Significant racial/ethnic differences

were also observed. Among those receiving early therapy, 59% were White, 13% Black, 17% Hispanic, and 10% other ($p<0.001$). The Charlson Comorbidity Index was slightly higher in the early treatment group compared to the late treatment group (mean 3.9 *vs.* 4.2, $p<0.001$) Early treatment was more frequently administered in the West (25%), whereas late treatment was disproportionately concentrated in the South (30%) ($p<0.001$).

In unadjusted analyses, In-hospital mortality for patients who received therapy within 24 hours was approximately 30% lower than in the late initiation group (4.6% *vs.* 6.7%; $p<0.001$). The incidence of acute DIC was significantly lower in the early group (23.8% *vs.* 35.8% $p<0.001$). Similarly, early-treatment patients had lower reports of sepsis compared to those with delayed treatment (9.6% *vs.* 14.3%, $p<0.001$). Consistent with this, the rate of documented neutropenia with agranulocytosis was also significantly lower in the early group (14.2% *vs.* 21.8%, $p<0.001$). Adjusted analysis with multivariate logistic regression revealed that early treatment had significantly lower odds of in-hospital death (adjusted OR=0.62; 95% CI=0.50-0.79; $p<0.001$) compared to late treatment. Likewise Early therapy was an independent predictor of DIC (OR=0.58), severe neutropenia (OR=0.60), and sepsis (OR=0.65), all with $p<0.01$.

Patients in the early treatment cohort had significantly shorter hospitalizations on average than those in the late cohort (18.0 days *vs.* 29.5 days, $p<0.001$). Similarly, total hospital charges for the admission were significantly lower in the early treatment group compared to for the late treatment group ($262,436 *vs.* $405,537, $p<0.001$). After adjustment, early therapy was associated with about a 28% reduction in hospital charges relative to delayed therapy. Additional detailed baseline characteristics and clinical outcomes stratified by timing of chemotherapy are presented in Table I.

Discussion

In this large-scale, nationwide analysis, we demonstrate that initiating therapy within 24 hours of admission is associated with significantly improved survival and fewer complications, a finding which was previously established in smaller or single-center reports (8, 14, 18). A key reason for the improved outcomes with early treatment is the rapid mitigation of APML's characteristic coagulopathy caused by malignant promyelocytes releasing procoagulant factors (*e.g.*, tissue factor, annexin II) in excessive amounts (which remain unchecked without prompt ATRA/ATO administration) (4, 7). Immediate initiation of ATRA and ATO induces differentiation of leukemic cells while stopping their rapid expansion. This quickly reverses DIC and dramatically reduces hemorrhagic risk (8, 19). At a molecular level, ATRA and ATO together target the PML-RARα oncoprotein for degradation, thereby triggering the differentiation and apoptosis of the leukemic promyelocytes (1, 7, 20). This dual action, rapid correction of coagulopathy and elimination of the leukemic clone, underlies the remarkable efficacy of early ATRA/ATO therapy in APML.

Our results revealed better clinical outcomes in patients who were started on therapy within 24 hours, consistent with the aforementioned mechanisms. Reflecting the effect of prompt differentiation therapy in stabilizing coagulopathy, our analysis saw a lower incidence of DIC in the early-treatment group. This finding is critical given that, as noted by Elbahesh *et al*., hemorrhage remains the most significant cause of induction failure, with fatal bleeding occurring in up to 10% of patients (21). The markedly fewer infectious complications, such as lower rates of sepsis, observed in our study also reveal that benefits of early therapy extend beyond just correction of coagulopathy. Unlike typical intensive chemotherapy, ATRA and ATO induce cell maturation without profound marrow ablation, thereby reducing the duration and severity of neutropenia (8, 13). In our analysis, the patients treated early indeed had fewer and less severe cytopenias, which translated into a lower risk of serious infections during induction and likely improved overall in-hospital survival.

Our analysis also revealed significant economic benefits for those who were in the early initiation of

Table I. *Baseline characteristics and clinical outcomes of patients with acute promyelocytic leukemia receiving early versus late chemotherapy.*

Variables	Early chemotherapy (<24 h) N=1,300 (25.2%)	Late chemotherapy (≥24 h) N=3,855 (74.8%)	*p*-Value
Age	45.4±19.4	47.6±18.9	<0.001
Sex	660 (50.8%)	1850 (48.0%)	0.083
Charlson Comorbidity Index (CCI)	3.9±2.4	4.2±2.6	<0.001
Race			
White	730 (58.9%)	2165 (58.7%)	<0.001
Black	165 (13.3%)	465 (12.6%)	
Hispanic	215 (17.3%)	640 (17.3%)	
Asian/Pacific	70 (5.6%)	165 (4.5%)	
Native	10 (0.8%)	0 (0.0%)	
Other	50 (4.0%)	255 (6.9%)	
Primary payer			
Medicare	280 (21.5%)	960 (25.0%)	0.038
Medicaid	320 (24.6%)	855 (22.2%)	
Private	605 (46.5%)	1,735 (45.1%)	
Self-pay	50 (3.8%)	135 (3.5%)	
No charge	0 (0.0%)	10 (0.3%)	
Other	45 (3.5%)	150 (3.9%)	
Hospital teaching status			
Rural	20 (1.5%)	40 (1.0%)	<0.001
Urban non-teaching	280 (21.5%)	650 (16.9%)	
Urban teaching small	30 (2.3%)	135 (3.5%)	
Urban teaching large	970 (74.6%)	3,030 (78.6%)	
ZIP Income quartile			
Q1 (Lowest)	355 (27.8%)	1,015 (26.7%)	<0.001
Q2	260 (20.4%)	980 (25.8%)	
Q3	330 (25.9%)	945 (24.9%)	
Q4 (Highest)	330 (25.9%)	860 (22.6%)	
Hospital bed size			
Small	105 (8.1%)	325 (8.4%)	0.171
Medium	200 (15.4%)	675 (17.5%)	
Large	995 (76.5%)	2,855 (74.1%)	
Urban rural location (NCHS)			
Metro large	455 (35.0%)	1,250 (32.5%)	0.012
Metro medium	305 (23.5%)	990 (25.7%)	
Metro small	295 (22.7%)	775 (20.2%)	
Micropolitan	65 (5.0%)	275 (7.2%)	
Noncore	115 (8.8%)	335 (8.7%)	
Unknown	65 (5.0%)	220 (5.7%)	
Hospital region			
Northeast	250 (19.2%)	775 (20.1%)	<0.001
Midwest	240 (18.5%)	780 (20.2%)	
South	480 (36.9%)	1,550 (40.2%)	
West	330 (25.4%)	750 (19.5%)	
Length of stay (LOS)	18.0±16.0	29.5±16.1	<0.001
Total charges	262,436±328,406	405,537±331,370	<0.001
Neutropenia	185 (14.2%)	840 (21.8%)	<0.001
Sepsis	125 (9.6%)	550 (14.3%)	<0.001
Disseminated intravascular coagulation (DIC)	310 (23.8%)	1,380 (35.8%)	<0.001
Mortality	60 (4.6%)	260 (6.7%)	<0.001

therapy group. Patients started on ATRA/ATO within 24 hours of admission had, on average, considerably shorter hospital stays and incurred lower total hospitalization charges. The dramatic reduction observed is likely a consequence of the prevention of complications. In-hospital complications for APML require intensive care, prolonged hospitalization, and costly supportive interventions such as blood products, antibiotics, and antifungals all of which add up. Given the escalating costs of oncologic care, especially for prolonged inpatient leukemia therapy, our findings indicate that implementing protocols for immediate APML treatment is not only clinically lifesaving but also economically prudent for health systems.

Unfortunately, our analysis uncovers a concerning disparity in care delivery across different hospital settings. Smaller communities or rural hospitals were less likely to initiate early ATRA/ATO therapy compared to urban centers, pointing to disparities in APML care delivery. These findings could be attributed to varying levels of institutional resources, access to qualified leukemia specialists, rapid diagnostic capabilities, and clinician awareness of APML protocols (18). To address the critical care disparities between high- and low-resource hospitals, a combination of systemic interventions is necessary. By establishing standardized emergency department algorithms, clear treatment pathways, access to leukemia experts via telemedicine, and targeted provider education, we can ensure equitable and timely access to life-saving therapy, ultimately standardizing care and improving patient outcomes across all settings (17, 22).

Conclusion

Looking ahead, we suggest that future efforts should be organized along two main paths: clinical research and health systems implementation. On the clinical side, prospective studies are needed to build on these findings to investigate the impact of even modest delays (measured in hours) in ATRA/ATO administration on clinical outcomes, as well as optimal strategies for expediting diagnosis and treatment in suspected APML cases. Future prospective studies should aim to elucidate the precise impact of ATRA and ATO timing and dosing on the resolution of coagulopathy, while also tracking patients longitudinally beyond their initial hospitalization to determine the long-term effects of early intervention on remission durability, overall survival, and quality of life. From a health systems perspective, the next step should be to formally quantify the cost-effectiveness of prompt APML treatment while actively working to reduce the care variability we identified. This will require implementing and studying systemic solutions, such as rapid referral networks and mandatory institutional APML response plans, to ensure that all patients receive equitable, guideline-adherent therapy wherever they are diagnosed.

A major strength of our analysis is the use of a large, nationally representative inpatient database, which captures a broad cross-section of APML cases and hospital types across the United States. The substantial sample size provided high statistical power and enabled robust multivariable adjustments to control for potential confounders. These factors enhance the generalizability of our results in real-world practice. Nonetheless, several limitations should be acknowledged. The NIS database lacks granular clinical details for each patient such as exact timing of ATRA/ATO administration (only the day of admission), specific induction regimens used, molecular risk stratification (such as WBC count risk categories or genetic variants), or laboratory parameters like coagulation markers. The absence of risk stratification data is particularly noteworthy. APML therapy is often tailored to risk level based on white blood cell count and genetic markers, which acts as a major determinant of relapse risk and overall prognosis (23). Additionally, the reliance on ICD coding introduces the possibility of misclassification or coding errors. However, given the distinctive presentation of APML, the consistency of our findings with known clinical patterns, large sample size and our rigorous statistical adjustments any miscoding is unlikely to fundamentally alter our conclusions.

Conflicts of Interest

The Authors declare that they have no conflicts of interest relevant to this study.

Authors' Contributions

Fiqe Khan contributed to study conception and design, data interpretation, and manuscript drafting. Abdullah Ahmad, Meher Ayyazuddin, and Santosh Nalluri contributed to manuscript drafting. Suriya Baskar contributed to study design, critical revision of the manuscript, and clinical interpretation of results. All Authors reviewed, revised, and approved the final manuscript and agree to be accountable for all aspects of the work.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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