Early death and intracranial hemorrhage prediction in acute promyelocytic leukemia: validation of a risk score in a cohort from an international consortium treated with chemotherapy plus all-*trans* retinoic acid

Acute promyelocytic leukemia (APL) is a distinctive subtype of acute myeloid leukemia characterized by excellent cure rates after frontline therapy, based on all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO).[1] In clinical practice, this disease usually presents with a peculiar coagulopathy, marked by primary hyperfibrinolysis and a high incidence of early fatal bleeding events.[2] Therefore, early death (ED), which is defined as death occurring within the first 30 days after diagnosis, is the most common cause of treatment failure.[3] Long-term survival rates reported in "real-world" retrospective studies range from 60 to 80%, while overall survival, reported in pivotal clinical trials of APL, usually exceeds 90%.[3-5] A recent publication by Österroos *et al.*[6] introduced a new risk score for ED in APL, based on three baseline parameters – age, platelet count, and white blood cell count. This study documented ED rates of 4.8%, 20.2%, and 50.9% in patients from a Swedish registry with low, high, and very high-risk ED scores, respectively. This cohort comprised patients treated with ATRA plus chemotherapy or ATO, depending on the time of diagnosis.[6] Here, we present an analysis in a cohort of patients from Latin America, treated prospectively with ATRA plus daunorubicin within the International Consortium on APL (IC-APL).[7]

The issue of early mortality in APL appears to be even more severe in resource-limited healthcare settings, where delayed recognition of APL and limited access to ATRA or blood transfusion in remote areas are reported.[4] Intracranial hemorrhage (ICH) is the most common site of bleeding in APL, and plays a significant role in early mortality.[4,8,9] In these cases, patients are commonly diagnosed in a poor clinical condition, unable to receive adequate antileukemic therapy, and frequently die from neurological complications.

In 2005, the IC-APL trial was initiated in Brazil, Mexico, Chile and Uruguay, aiming at increasing cure rates of APL in Latin America, as well as creating a cooperative diagnostic and therapeutic network of institutions in developing countries.[7] Among 183 patients previously reported, the ED rate was 15%, which was much lower than previous retrospective values reported by these centers.[5,7] Although ICH is already acknowledged as a frequent event in APL, there are few studies specifically evaluating this complication. Herein, we aimed to validate the ED risk score in our population, and to analyze the impact of ICH at diagnosis, and risk factors for its occurrence in a large cohort of APL patients enrolled into the IC-APL.

The data from the IC-APL registry include those for patients newly diagnosed with APL between March 2005 and March 2020. The IC-APL study protocol has been described elsewhere (*Online Supplementary Material, Online Supplementary Figure S1*).[7,10] Patients had their diagnosis confirmed by the presence of *PML-RARA* as previously described.[7] Laboratory data were collected at baseline. The protocol recommended that all patients undergo testing for renal and hepatic function (creatinine, urea, aminotransferases, bilirubin), coagulation parameters (fibrinogen, prothrombin time, and activated partial thromboplastin time), as well as a complete blood count, pregnancy test, and serology for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus. All ICH cases had their diagnosis confirmed by head computed tomography scan, indicated by the treating physician in case of clinical suspicion. Central nervous system (CNS) prophylaxis was not given. Local ethics committees from the participating institutions approved this study.

Among 1,004 subjects screened, 813 patients were eligible for the treatment protocol and were included in this analysis. The main reasons for ineligibility were treatment with other protocols (48.7%), negative *PML-RARA* (12.2%), and age (10.7%). Some patients died before receiving ATRA (N=13) and were also not included in the cohort (6.5%). Among these 13 patients, ten presented with severe ICH and did not receive any antileukemic treatment. Other reasons are detailed in the original publication.[10]

Overall, the median age was 35 years old (range, 15-74). Ten percent of patients presented with an Eastern Cooperative Oncology Group performance status >2. Most patients presented with symptoms that had been ongoing for more than 10 days (44.7%). Variant hypogranular morphology was reported in 10.4%, while Sanz[11] relapse risk score was low, intermediate, and high in 10.9%, 52.3%, and 36.8% of subjects, respectively. The ED rate was 14% (112/813, 95% confidence interval [95% CI]: 11.7-16.6). Bleeding was the major cause of ED in those patients (60.5%), followed by infection (25.4%). Differentiation syndrome occurred in 37% of patients who died within 30 days, but it was only registered as the cause of death in 5.3% of cases. ICH represented the most common site of hemorrhage (36% of ED patients), followed by bleeds at pulmonary (11.4%), and gastrointestinal sites (9.6%). All bleeding events occurred within 30 days of diagnosis. Acute kidney injury of any grade was detected in 13.1% during induction, being grade 3 or 4 in 5%.

When the aforementioned ED risk score was applied to the IC-APL cohort, it divided the cohort into three distinct categories, those with low (N=392, 48.5%), high (N=344, 42.6%), and very high risk (N=72, 8.9%), with ED rates of 5.9%, 18.3%, and 37.5%, respectively (Figure 1). The overall rate of ICH was 8.2% (67/813), with ICH rates being 4.8%, 12.8%, and 17.1% in patients with low, high, and very high ED risk scores (Figure 2). The ED rate in patients with ICH was 61.2%, with two more deaths occurring more than 30 days after diagnosis.

Univariate analysis for CNS bleeding in this cohort showed an association (P<0.05) with various parameters of severity, such as the variant morphological subtype, initial hemoglobin concentration, white blood cell count, and creatinine levels. The incidence of ICH in patients with a white blood cell count >10x10^9/L and variant morphology was 21.3%. A multivariable adjustment of these factors with the ED risk score is presented in Table 1. After excluding those patients who died within 30 days of diagnosis, ICH did not have an impact on overall survival (hazard ratio [HR]=1.55, 95% CI: 0.374-6.45; P=0.544) but did affect relapse-free survival (HR=2.23, 95% CI: 1.09-4.56; P=0.028). By competing risk analysis, an impact could be seen on relapse incidence (HR=2.43, 95% CI: 1.04-5.70; P=0.041), while there was no impact on non-relapse mortality after 30 days (HR=1.44, 95% CI: 0.34-6.02; P=0.62). This impact remained significant even after adjusting for Sanz relapse risk score (adjusted HR=2.47, 95% CI: 1.05-5.78; P=0.037). Out of 93 relapses, only nine presented concomitant CNS relapse. Among these nine CNS relapses, only one had presented with ICH at diagnosis. Long-term outcomes of the whole IC-APL cohort have been reported elsewhere.[10]

In this study, we validated the utility of the ED risk score

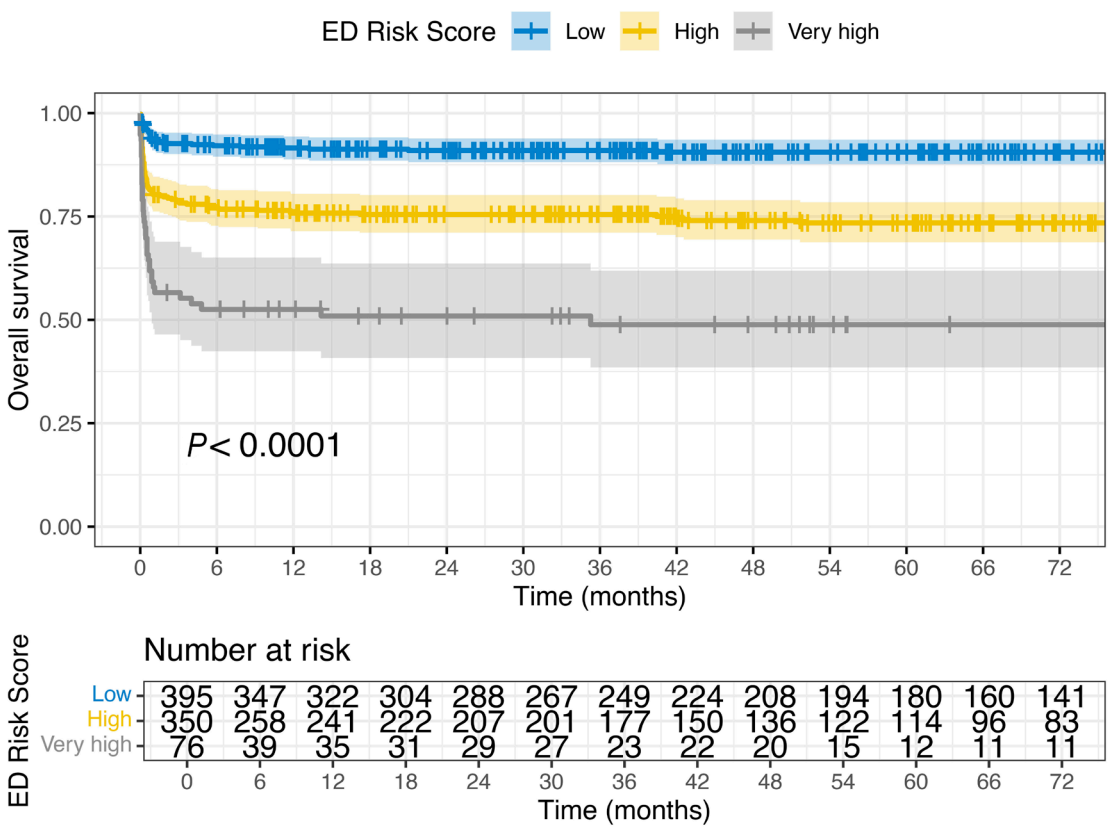

Figure 1. Overall survival according to low, high, and very high-risk early death risk score in patients from the International Consortium on Acute Promyelocytic Leukemia. ED: early death; ICH: intracranial hemorrhage.

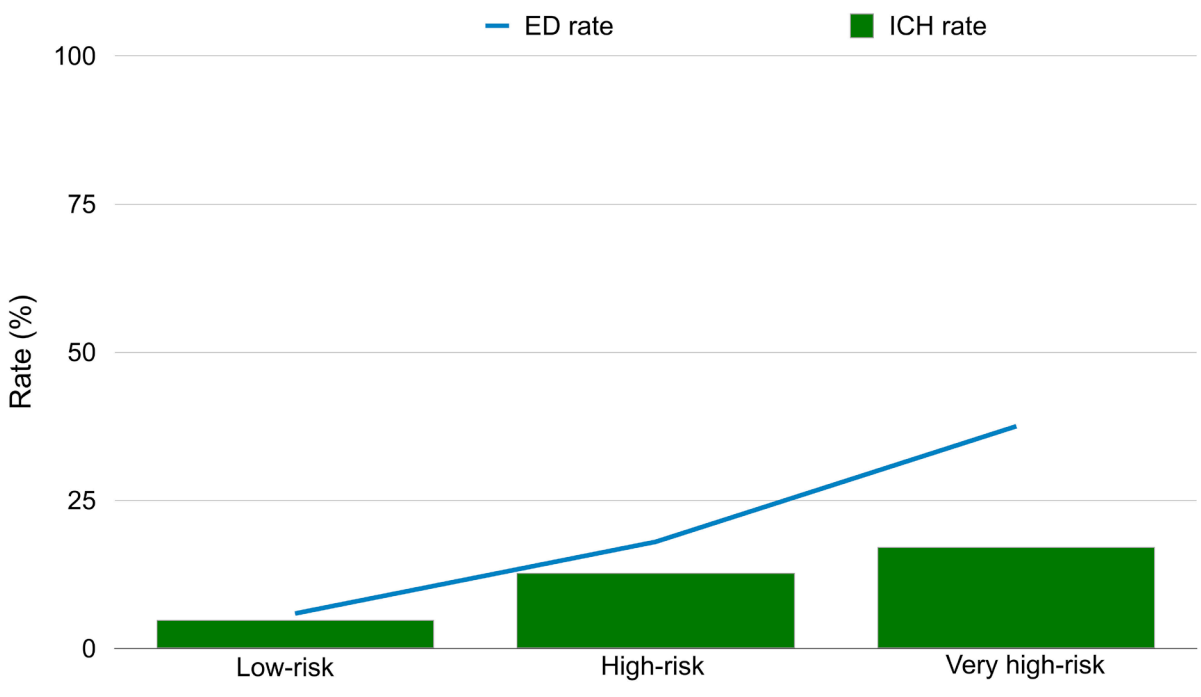

Figure 2. Proportions of intracranial hemorrhage and early death according to the early death risk score in patients from the International Consortium on Acute Promyelocytic Leukemia. ED: early death; ICH: intracranial hemorrhage.

Table 1. Multivariable adjustment of baseline variables for intracranial hemorrhage in acute promyelocytic leukemia.

Variable	Odds ratio	95% confidence interval	*P*
Variant morphology	1.330	0.458-3.290	0.5648
Hemoglobin, g/dL	0.926	0.801-1.068	0.2965
ED risk score Low High Very high	 reference 1.586 2.621	 0.752-3.426 0.930-6.951	 0.2284 0.0576
Creatinine	1.767	1.113-2.952	0.0171
WBC, x10^9/L	1.007	1.001-1.013	0.0284

ED: early death; WBC: white blood cells.

previously published in a large Latin American prospective cohort (IC-APL) for predicting early outcomes in APL.[6] Its validated utility in predicting early outcomes in APL strengthens its basis for facilitating tailored interventions to mitigate mortality risks, such as the implementation of differential transfusion triggers or newer agents in this early scenario. The increased prevalence of bleeding in high-risk patients may prompt early screening for ICH in patients with mild or no neurological symptoms, using cranial computed tomography, with the aim of diagnosing this complication early and enabling prompt intervention. Furthermore, it should be recognized that the incidence of ICH may be underestimated in prospective registry studies, as some patients arrive in the emergency room in such a critical condition that further therapy is not possible.

In the IC-APL, the multivariable logistic regression model showed that age ≥40 years, Eastern Cooperative Oncology Group performance status of 3, high-risk Sanz relapse category, bcr3 PML-RARA isoform, time interval from symptom onset to diagnosis longer than 48 hours, ICH, and pulmonary bleeding were statistically associated with ED.[10] Comparatively with the ED score just reported, in our cohort, only age and white blood count were predictive of ED, while platelet counts did not reach statistical significance in the reported model.[10] This also highlights that the Sanz relapse risk score was originally reported for predicting relapse after remission has been achieved, rather than ED. The PETHEMA group itself reported in prior publications on the LPA96 and LPA99 trials that creatinine level, white blood cell count, peripheral blood blast count, age, and male sex were associated with ED in these cohorts.[12] In children and adolescents with newly diagnosed APL, a multivariable model demonstrated that high white blood cell count and obesity were independently associated with ED.[13] In Latin America, the proportion of high-risk patients is greater, possibly due to delayed diagnosis and intrinsic biological differences.[4,5]

This study also demonstrated that ICH within 30 days of diagnosis may lead to APL relapses after induction therapy. This had already been demonstrated by the PETHEMA group regarding CNS relapses, where its incidence in patients who presented with ICH at diagnosis was 18.7%.[14] Kulkarni *et al.*[15] demonstrated that, when using an ATO-based approach, relapses did not increase in patients who presented with ICH, which might reflect the augmented disease control with ATO and increased CNS penetration of this drug.[1] The role of intrathecal chemotherapy and high-dose cytarabine in preventing CNS disease is unclear, especially in the current scenario of ATO-based regimens.[1] Guidelines still recommend intrathecal chemotherapy for patients with ICH at presentation.[1]

In conclusion, our study underscores the critical role of early mortality risk assessment in APL and highlights the significant impact of ICH on both short-term and long-term outcomes. These insights pave the way for future studies aimed at optimizing APL treatment approaches and improving patients' outcomes. The current IC-APL2020 employs ATRA plus oral ATO for frontline APL treatment, with the expectation of reducing early toxicity and disease relapses in the coming years.

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Disclosures

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Contributions

WFS acquired and interpreted data and performed the statistical analysis. HTK reviewed the statistical analyses. SU, JRN, VS, PM and EMR were the National Coordinators of ICAL in Chile, Peru, Paraguay, Uruguay, and Brazil, respectively, and contributed to the development of the clinical network, the supervision of laboratory and management procedures, data acquisition and interpretation. RAMM, ABFG, KP, ECN, RIB, NR, SQ, AAL, CO, LLFP, FT, FM, PM, EMF, BKLD, PD and JU were responsible for centers performing the diagnosis and treatment of patients and acquired data. MT, RR, AG, RD, PJMV, MS, BL, NB, HTK and EMR contributed to the conception and design of the work, interpreted data, and drafted the manuscript. All authors critically reviewed and approved the manuscript.

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Data-sharing statement

The data collected are available upon reasonable request to the authors.

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