Comparison of the Effectiveness of Risk Models Used in Acute Promyelocytic Leukemia

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ABSTRACT

Newly diagnosed acute promyelocytic leukemia (APL) patients were evaluated, and the effectiveness of the Sanz risk model was compared with other risk models developed for early mortality. To determine a simple, reliable, and highly effective risk model used in clinical practice for earlier recognition of high-risk patients at high risk of mortality. This is a retrospective analysis of 57 patients diagnosed with APL in our clinic between January 2002 and June 2019. Patients were grouped under the risk models of Sanz score, modified Sanz risk score, the International Society on Thrombosis and Haemostasis (ISTH), and other scores by Österroos et al. and Cai et al. We found higher white blood count (WBC) is independently associated with 30-day mortality [Odds ratio (OR): 1.030, 95% confidence interval (CI): 1.005 - 1.055, p= 0.017]. Albumin, another variable included in the multivariable model, was found non-significant (p= 0.055). The modified Sanz risk score had a sensitivity of 77.78% and specificity of 66.67% to predict 30-day mortality for high and ultra-high-risk patients [Area under the curve (AUC): 0.727, 95% CI: 0.514 - 0.939, p= 0.032]. Additionally, the AUC of the modified Sanz risk score was significantly higher than the Sanz risk score (p= 0.028). We found no significant difference between the AUC of the Sanz risk score and Österroos et al.'s, Cai et al.'s, and ISTH risk scores. Timely recognition of high-risk patients, taking appropriate protective measures, and administering more aggressive supportive care can help reduce the early mortality of APL patients. Sanz risk score and other scoring systems have been guiding the identification of high-risk APL patients. However, the most effective scoring system could not be determined at the end of the study. There is still a need for standardized scoring systems to identify high-risk patients more effectively, including comorbidities.

Keywords: Acute promyelocytic leukemia, Early mortality, Modified Sanz risk score, Risk scores

INTRODUCTION

Acute promyelocytic leukemia (APL) is a subtype of myeloid leukemia characterized by leukemic cells that are blocked at the promyelocytic stage of granulocytic differentiation. APL accounts for approximately 5-8% of all acute myeloid leukemia (AML) cases and is often characterized by active hemorrhagic manifestations. Hemorrhagic complications are the most common cause of morbidity and mortality.[1,2] The balanced reciprocal translocation t(15;17) (q22;q11-12), leading to the fusion of the promyelocytic (PML) gene on chromosome 15 and the retinoic acid receptor α (RARA) gene on chromosome 17, is responsible for the formation of the disease. The discovery of the cytogenetic defect in APL has led to the understanding of the role of the all-trans retinoic acid (ATRA) in the treatment and performing therapeutic research.[3,4] Recent clinical studies show that approximately 90% of patients can be cured with molecular-targeted therapies thanks to ATRA and arsenic trioxide (ATO).[5-9]

Despite all the positive developments in the course of APL, the incidence of early hemorrhagic complications leading to deaths due to the presence of coagulopathy, such as disseminated intravascular coagulation (DIC), fibrinolysis and proteolysis remains high.[10] Evidence obtained from population-based studies suggests that early deaths (EDs) continue affecting 10 to 32% of APL patients.[11-13] Therefore, current studies focus on the factors requiring to be taken into consideration to reduce EDs in APL, and various risk models have been developed to recognize high-risk patients; the Sanz risk model is the most widely used of such risk models.[14] The Sanz risk model, which was originally used for estimating the risk of the relapses of APL, is a recognized method to predict the prognosis of APL. Although the Sanz risk model has been widely adopted in daily practice, the role of the model in predicting EDs requires to be validated. In their studies, for this reason, Lou et al., Österroos et al., and Cai et al. have developed some risk models to detect EDs.[3,15,16] The International Society of Thrombosis and Haemostasis (ISTH) scoring system for disseminated intravascular coagulation has also been developed to detect EDs in APL patients.[17,18] However, there is currently no widely used, clinically useful, and proven standard risk model to predict EDs in APL.

In contrast to the high-mortality initial phase in APL, patients surviving within the initial period have superior outcomes characterized by a lower risk of recurrence and high 2-year survival rates of up to 75-84%, compared to other AML subtypes 19,20. Therefore, for this patient group with a high cure rate, the determination, disease course, and possible risk factors of clinical features of mortality, early mortality, and relapse tendencies, recognizing those at risk and creating general management strategies are extremely important for the successful treatment of APL patients. In the present study, newly diagnosed APL patients treated in a single center for 17 years have been evaluated, and the effectiveness of the Sanz risk model and other risk models developed for EDs have been compared. It has been aimed to determine a simple, reliable, and highly effective risk model health professionals can use in practical life for recognizing high-risk patients with a high probability of mortality at an earlier period.

PATIENTS AND METHODS

Patients and Data Collection

The present study is a retrospective analysis of 57 patients diagnosed with APL in our clinic between January 2002 and June 2019. The diagnoses of APL were carried out under the presence and specific morphological changes at (15;17) translocation and/or promyelocytic leukemia/RARA (PML/RARA) rearrangement. With the use of the MIA-Med system, data related to the patients such as complete blood count, coagulation, laboratory parameters, pathology, findings of flow cytometry, clinical characteristics on admission, initial date of treatment, regimen, and responses to treatment, side effects, EDs, and rates of disease-free and overall survivals were evaluated from the hospital database.

The Treatment

The treatment of ATRA was launched rapidly at a dose of 45 mg/m^2 for correcting the coagulopathy and inducing the remission treatment. Due to the treatment given to induce remission, idarubicin (IDA) at a dose of 12 mg/m^2 was administered concomitantly with ATRA on days 2, 4, 6, and 8. Supportive measures, such as platelet (PLT) transfusion, fresh frozen plasma, and/or fibrinogen transfusion were administered by targeting the PLT count to be >30×10^9/L and serum fibrinogen to be >150 mg/dL.

Upon deciding the preemptive use of corticosteroids by the attending physicians, those in remission were administered three courses of consolidation therapy with ATRA and anthracycline. To maintain the treatment, ATRA (45 mg/m^2/day) for 15 days every three months, 6-mercaptopurine (6 MP) (50 mg/m^2/day), and methotrexate (MTX) (15 mg/m^2/week) for two years were performed.

Definitions

Patients were grouped under the Sanz score, the modified Sanz risk score, and other risk models created by Österroos et al. and Cai et al., and the ISTH risk model. The scores and their definitions used in the study are presented in Table 1.[3,14-17]

EDs were defined as deaths due to any reason within 30 days after the diagnosis. The primary end-

Table 1. Distribution of risk scores of different models

Sanz risk score	Modified Sanz risk score	Österroos et al.'s risk score	Cai et al.'s risk score	ISTH risk score
Low-risk WBC ≤ $10x10^9$/L, PLT > $40x10^9$ /L	Low-risk WBC ≤ $10x10^9$/L, PLT > $40x10^9$/L	**Age at diagnosis** < 50 50-59 60-69 ≥ 70	**Age > 52** 1.5 point	**Thrombocyte count**, 10^9/L > 100; 0 point 50–100;1 point < 50; 2 points
Intermediate WBC ≤ $10x10^9$/L, PLT ≤ $40x10^9$ /L	**Intermediate** WBC/PLT < 0.2, and age ≤60, (not in low-risk)	**WBC count** WBC <$3x10^9$/L, WBC 3.0-5.0x10^9 /L	**WBC count** ≥ $10x10^9$/L, 2 points **PLT count** ≤ $10x10^9$/L, 1 point	**PT or aPTT** PT < 3 sec ULN 0 point PT 3–6 sec ULN 1 point PT > 6 sec ULN 2 points
High-risk WBC >$10x10^9$/L	**High-risk** WBC/PLT ≥ 0.2 or age >6 0, (not in low and ultra-high risk)	**PLTs** ≥ $30x10^9$ /L ≤ $30x10^9$ /L	**LDH level** > 500 U/L 1 point	**D-dimer level** < 0.5 µg/mL 0 point 0.5–5 µg/mL 2 points > 5 µg/mL 3 points
	Ultra-high risk WBC >$50x10^9$/L	**Low-risk** 0-2 points	**Low-risk** 0 point	**Fibrinogen** g/dL > 1 0 point < 1 1 point
		High-risk 3-4 points	**Intermediate** 1–2 points	**Interpretation of results** ≥ 5 points DIC
		Ultra-high risk 5-7 points	**High-risk** 2.5–4 points	
			Ultra-high risk 4.5 point	

aPTT: Activated Partial Thromboplastin Time, DIC: Disseminated intravascular coagulation, LDH: Lactate dehydrogenase, PLT: Platelet, PT: Partial thromboplastin, sec: Second, ULN: Upper limit normal, WBC: White blood count

point of our study was to evaluate the superiority and effectiveness of these scores in predicting EDs and prognosis in newly diagnosed APL patients.

Ethical approval: This research was carried out under the 1961 Declaration of Helsinki and its later amendments. Uludag Technical University Ethics Committee approved the study protocol (Date: February 2020, Approval number: 2020-3/9; 2011-KAEK-26/84).

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences for Windows, version 25.0 (SPSS, IBM Corp., Armonk, NY, U.S.) and MedCalc Statistical Software, Version 15.8 (MedCalc Software bvba, Ostend, Belgium). For checking the normality, the Shapiro-Wilk test was used. The data are given as mean±standard deviation (SD) or median (min-max) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. Recurrence and mortality rates concerning risk categories were analyzed with the chi-square test, Fisher's exact test, or Fisher-Freeman-Halton test. Pairwise comparisons were adjusted by the Bonferroni correction method, and logistic regression analyses were performed to determine the prognostic factors of recurrence and mortality. Variables were also analyzed with the univariable logistic regression analysis, and statistically significant variables were included in the multivariable logistic regression analysis through the forward conditional selection method. The prediction performance of the risk scores was assessed by using the Receiver Operating Characteristic (ROC) curve analysis. The comparisons of the area under the ROC curves were performed with the Hanley & McNeil approach, and the two-tailed p-values of ≤ 0.05 were considered statistically significant.

RESULTS

Fifty-seven patients (36 females and 21 males) were included in the study, and the mean age at diagnosis was measured as 40.77±12.15 (range between 18-68 years). While two (3.51%) patients had diabetes mellitus (DM), four (7.02%) patients were detected to be with hypertension, and one (1.75%) patient was with both DM and hypertension. Additionally, while one (1.75%) and 39 (68.42%) patients were determined to have hypogranular variant and hemorrhage at diagnosis respectively, six (10.53%) and three (5.26%) had thrombosis and both hemorrhage and thrombosis at diagnosis, respectively. The characteristics, laboratory findings, and risk scores of APL patients are presented in Table 2.

Considering the Sanz risk score, 19 (33.33%), 22 (38.60%), and 16 (28.07%) patients were found to be with low, intermediate and high risk, respectively. Given the modified Sanz risk score, however, 19 (33.33%), 15 (26.32%), 18 (31.58%), and 5 (8.77%) patients were seen to be with low, intermediate, high, and ultra-high risks, respectively. Compared in terms of Österroos et al.'s risk score, 32 (56.14%), 23 (40.35%), and two (3.51%) patients were found to be with low, high, and ultra-high risk, respectively. Even so, when compared the patients in terms of Cai et al.'s risk score, 28 (49.12%) were low risk, 11 (19.30%) were intermediate risk, 17 (29.82%) were high risk, and one (1.75%) patient was with ultra-high risk. Concerning the ISTH score, 31 (54.39%) and 26 (45.61%) were found to be low and high-risk patients (Table 2).

Data are given as mean±standard deviation or median (minimum - maximum) for continuous variables according to normality of distribution and as frequency (column percentage) for categorical variables. aPTT: Activated partial thromboplastin time, ATRA: All-trans retinoic acid, DM: Diabetes mellitus, Hgb: Hemoglobin, HF: Hearth failure, Ht: Hypertension, INR: International normalized ratio, ISTH: International Society on Thrombosis and Haemostasis, PLT: Platelet, WBC: White blood count

The median follow-up time was measured as 46.60 (range between 0.13-175.83 months). While nine (15.79%) patients had ATRA syndrome, 44 (77.19%) and six (10.53%) patients were seen to

Table 2. Summary of the characteristics, laboratory measurements, and risk scores of acute promyelocytic leukemia patients

	n (%)
Age (years)	40.77±12.15
Sex	
Female	36 (63.16)
Male	21 (36.84)
Comorbidity	
None	50 (87.72)
DM	2 (3.51)
Ht	4 (7.02)
DM&Ht	1 (1.75)
HF	0 (0.00)
Variants	
Classic	56 (98.25)
Hypogranular	1 (1.75)
Complication	
None	9 (15.79)
Thrombosis	6 (10.53)
Hemorrhage	39 (68.42)
Thrombosis&Hemorrhage	3 (5.26)
WBC (x109)	2.17 (0.49-164.00)
Hgb	95.42±20.45
Lymphocyte (x109)	0.73 (0.10-18.40)
Total cholesterol	198.60±48.50
Albumin	41.89±6.12
PLT (x10^9)	33.9 (4.21-232.0)
INR	1.16 (0.90-1.80)
D-dimer	20 (1.5-400)
Fibrinogen	176.5 (60-543)
aPTT	24.0 (19.3-43.8)
Sanz risk score	
Low	19 (33.33)
Intermediate	22 (38.60)
High	16 (28.07)
Modified Sanz risk score	
Low	19 (33.33)
Intermediate	15 (26.32)
High	18 (31.58)
Ultra-high	5 (8.77)
Österroos et al.'s risk score	
Low	32 (56.14)
High	23 (40.35)
Ultra-high	2 (3.51)
Cai et al.'s risk score	
Low	28 (49.12)
Intermediate	11 (19.30)
High	17 (29.82)
Ultra-high	1 (1.75)
ISTH score	
Low	31 (54.39)
High	26 (45.61)
Follow-up time, months	46.60 (0.13-175.83)
ATRA syndrome	9 (15.79)
Complete remission	44 (77.19)
Recurrence	6 (10.53)
Mortality	14 (24.56)
30-day mortality	9 (15.79)

Table 3. Recurrence, mortality, and 30-day mortality rates for risk scores

	Recurrence n (%)	p	Mortality n (%)	p	30-day Mortality n (%)	p
Sanz risk score						
Low	2 (10.53)	0.869	4 (21.05)	0.131	2 (10.53)	0.539
Intermediate	3 (13.64)		3 (13.64)		3 (13.64)	
High	1 (6.25)		7 (43.75)		4 (25.00)	
Modified Sanz risk score						
Low	2 (10.53)	1.000	4 (21.05)	0.016	2 (10.53)	0.014
Intermediate	2 (13.33)		1 (6.67)		0 (0.00)	
High	2 (11.11)		5 (27.78)		4 (22.22)	
Ultra-high	0 (0.00)		4 (80.00)#		3 (60.00)#	
Österroos et al.'s risk score						
Low	1 (3.13)	0.095	4 (12.50)	0.011	3 (9.38)	0.138
High	5 (21.74)		8 (34.78)		5 (21.74)	
Ultra-high	0 (0.00)		2 (100.00)*		1 (50.00)	
Cai et al.'s risk score						
Low	2 (7.14)	0.274	5 (17.86)	0.005	3 (10.71)	0.026
Intermediate	3 (27.27)		0 (0.00)		0 (0.00)	
High	1 (5.88)		8 (47.06)#		5 (29.41)	
Ultra-high	0 (0.00)		1 (100.00)#		1 (100.00)#	
ISTH risk score						
Low	4 (12.90)	0.678	4 (12.90)	0.026	2 (6.45)	0.065
High	2 (7.69)		10 (38.46)*		7 (26.92)	

*Data are given as frequency (row percentage). * Significantly different from Low risk. # Significantly different from Intermediate risk. ISTH: International Society on Thrombosis and Haemostasis*

have complete remission and recurrence, respectively. Among six patients having complete recurrence, while one received no treatment for recurrence, one patient was treated with ATO plus IDA (AIDA) treatment, one with ATRA, one with ATO+allogeneic stem cell transplant (AlloSCT), and two patients with ATO+ATRA+AlloSCT for the recurrence. Unfortunately, 14 (24.56%) patients were exitus. Given the reasons leading to mortality, the culprits were as follows: hemorrhage for seven patients, sepsis for three, pneumonia for one, aspiration for one, malignant arrhythmia for one, and hemorrhage+sepsis for one patient. Nine (15.79%) patients died within 30 days (Table 3), and the deaths of these patients took place on days 4, 4, 10, 12, 13, 17, 17, 22 and 22, respectively.

When we evaluated recurrence rates concerning the risk scores, we found no significant difference between the risk groups in all scores. When we evaluated mortality rates in terms of risk scores, we also observed no significant difference between the risk groups of the Sanz risk score. Mortality percentage was significantly seen to be higher among those with ultra-high risk than in the intermediate risk group in terms of the modified Sanz risk score (p= 0.016). Given Österroos et al.'s risk score, mortality percentages were found significantly higher in those with ultra-high risk than in the low-risk group (p= 0.011). Mortality percentages were also significantly higher in the high-risk and ultra-high-risk groups than in those with intermediate risk regarding Cai et al.'s risk score (p= 0.005). Mortality percentages were detected to be significantly higher among those with the high risk than in the low-risk group in terms of ISTH score, as well (p= 0.026). When we evaluated the 30-day mortality rates as to risk scores, no significant difference was seen between the risk groups of the Sanz, Österroos et al., and ISTH risk scores. The 30-day mortality percentages were significantly higher in the ultra-high-risk group than in the intermediate-risk group under the modified Sanz risk score (p= 0.014) and Cai et al.'s risk score (p= 0.026) (Table 3).

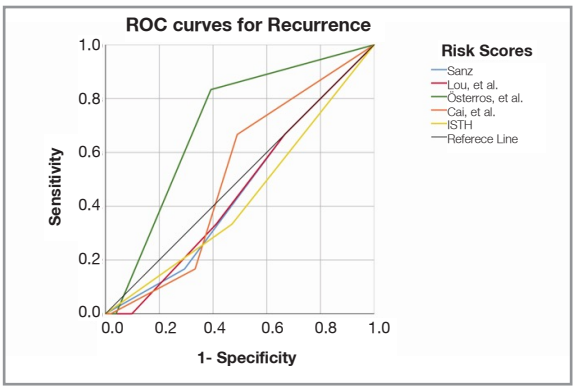

Figure 1. ROC curves of risk scores to predict recurrence ISTH: *International Society on Thrombosis and Haemostasis, ROC: Receiver Operating Characteristic*

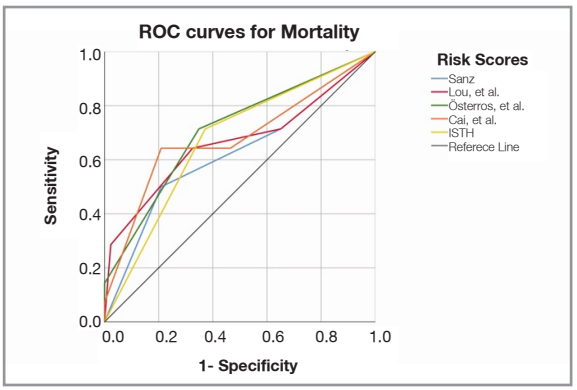

Figure 2. ROC curves of risk scores to predict mortality, *ISTH: International Society on Thrombosis and Haemostasis, ROC: Receiver Operating Characteristic*

When we evaluated the performance of risk scores to predict the recurrence, no scores were found to be significant, and no significant difference was found between the performance (AUC) of the Sanz risk score and other risk scores (Figure 1).

After performing logistic regression analysis to determine prognostic factors of mortality, we found that high WBC was independently associated with mortality (OR: 1.033, 95% CI: 1.004-1.061, p= 0.023), and another variable included in the multivariable model, albumin (p= 0.084) was also detected to be non-significant.

When we evaluated the performances of risk scores to predict mortality (Figure 2), it was found that the Sanz and modified Sanz risk scores, and the ISTH score were non-significant, and also that Österroos et al.'s risk score had a sensitivity of 71.43% and specificity of 65.12% in predicting mortality for high and ultra-high risk groups (AUC: 0.708, 95% CI: 0.544-0.871, p= 0.020). However, the sensitivity and specificity of Cai et al.'s risk score were detected as 64.29 and 79.07% to predict mortality for high and ultra-high-risk groups, respectively (AUC: 0.679, 95% CI: 0.496-0.861, p= 0.046). On the other hand, we found no significant difference between the AUC of the Sanz risk score and other risk scores (Table 4).

Upon performing logistic regression analysis to determine the prognostic factors of 30-day mortality, we revealed that high WBC was independently associated with 30-day mortality (OR: 1.030, 95% CI: 1.005-1.055, p= 0.017), and another variable included in the multivariable model, albumin (p= 0.055) was found to be non-significant.

The risk scores of Österroos et al., Cai et al., and ISTH were found to be non-significant (Figure 3). The sensitivity and specificity of the modified Sanz risk score were detected as 77.78 and 66.67% to predict 30-day mortality for high and ultra-high-risk groups (AUC: 0.727, 95% CI: 0.514-0.939, p= 0.032). In addition, the AUC of the modified Sanz risk score was significantly higher than in the Sanz risk score (p= 0.028), and no significant difference was found between the performances (AUC) of the Sanz, Österroos et al.'s, Cai et al.'s, and ISTH risk scores (Table 5).

DISCUSSION

In our study, we aimed to determine the most effective risk score in predicting mortality and prognosis in APL. It has also been observed that the Sanz risk score can be used as effectively as other scores in predicting EDs. To our knowledge, our study is one of the few reports comparing the performances of the Sanz risk score and other risk scores in APL. In a study performed in 2000, Sanz et al. proposed a simple risk model named the Sanz risk score in assessing the WBC and PLT counts for APL. The Sanz risk model was developed to predict post-treatment relapses with ATRA and IDA.[14] In the updated Swedish population-based report, the prognostic role of the Sanz risk score was further shown as 12% in low, 22% in interme-

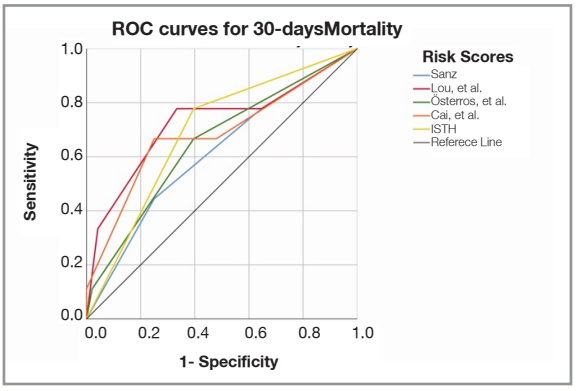

Figure 3. ROC curves of risk scores to predict 30-day mortality,
ISTH: International Society on Thrombosis and Haemostasis, ROC: Receiver Operating Characteristic

diate, and 44% in high-risk groups.[13] Several studies have also revealed that the Sanz score also has a prognostic value for EDs.[3,19,21] In another study by McClellan et al., the Sanz risk stratification values were reported as 0, 15, and 33% in predicting mortality rates in the low, intermediate, and high-risk groups by day 7, respectively.[22] In our study, we also found no significant difference between the performance of the Sanz risk score and other risk scores in predicting mortality.

Thanks to increasingly effective treatments, EDs have become the most significant cause of therapeutic failures in patients with APL. Clinical studies often underestimate the accurate rate of EDs, mainly due to the exclusion of patients presenting with advanced age, poor performance status, major hemorrhage, or life-threatening coagulopathy, resulting in differences in the rate of EDs between clinical studies and population-based reports.[6,23,24]

In our study, the rate of EDs was found to be 15.79%. Although some studies display slight differences in terms of risk factors for EDs, there are similar factors, such as WBC, PLT, and age in most studies.[19,25,26] Reducing the rate of EDs should undoubtedly be the most important goal, and so researchers have developed various risk models to achieve this goal. However, a widely accepted risk model with proven effectiveness in predicting the risk of premature death has yet to be developed.

In their study by Lou et al., the modified Sanz risk score was reported to divide patients into four risk categories based on age, WBC, and PLT, and this is the first report to show that the WBC/PLT ratio is a good indicator of EDs in patients with APL. While patients having WBC below 3×10^9/L had the lowest observed rate of EDs (1.6%), those presented with ultra-high WBC (above 50×10^9/L) were stated to have the highest ED rate (41.2%) 3. The current rate of EDs of 7.2% was close to that (9.6%) reported by the French study carried out by Rah-

Table 4. Performance of risk scores to predict mortality

	Sanz risk skor (%)	Modified Sanz risk score (%)	Österroos et al.'s risk score (%)	Cai et al.'s risk score (%)	ISTH risk score (%)
Cut-off	**High**	**High or above**	**High or above**	**High**	**High**
Sensitivity	50.00	64.29	71.43	64.29	71.43
Specificity	79.07	67.44	65.12	79.07	62.79
Accuracy	71.93	66.67	66.67	75.44	64.91
PPV	43.75	39.13	40.00	50.00	38.46
NPV	82.93	85.29	87.50	87.18	87.10
AUC (95% CI)	0.620 (0.435-0.804)	0.664 (0.475-0.852)	0.708 (0.544-0.871)	0.679 (0.496-0.861)	0.671 (0.509-0.833)
p for AUC (1)	0.182	0.068	0.020	0.046	0.056
p vs Sanz risk score (2)	–	0.416	0.243	0.358	0.629

(1) Analysis of AUC under the null hypothesis of H0: AUC=0.500, (2) Comparison with AUC of Sanz risk score under the null hypothesis of H0: AUC1=AUC2. AUC: Area under the ROC curve, CI: Confidence intervals, NPV: Negative predictive value, PPV: Positive predictive value

Table 5. Performance of risk scores to predict 30-day mortality

	Sanz risk skor (%)	Modified Sanz risk score (%)	Österroos et al.'s risk score (%)	Cai et al.'s risk score (%)	ISTH risk score (%)
Cut-off	High	High or above	High or above	High or above	High
Sensitivity	44.44	77.78	66.67	66.67	77.78
Specificity	75.00	66.67	60.42	75.00	60.42
Accuracy	70.18	68.42	61.40	73.68	63.16
PPV	25.00	30.43	24.00	33.33	26.92
NPV	87.80	94.12	90.63	92.31	93.55
AUC (95% CI)	0.612	0.727	0.650	0.684	0.691
	(0.407-0.817)	(0.514-0.939)	(0.449-0.852)	(0.466-0.902)	(0.510-0.872)
p for AUC(1)	0.289	0.032	0.155	0.082	0.071
p vs Sanz risk score(2)	-	0.028	0.640	0.338	0.459

(1) Analysis of AUC under the null hypothesis of H0: AUC= 0.500, (2) Comparison with AUC of Sanz risk score under the null hypothesis of H0: AUC1= AUC2. AUC: Area under ROC curve, CI: Confidence intervals, ISTH: International Society on Thrombosis and Haemostasis, NPV: Negative predictive value, PPV: Positive predictive value

mé et al.[12] However, the rate reported in the study by Rahmé et al. is lower than the rates found in most population-based studies in developed countries.[19,22,24] It was also seen in our study that high WBC was independently associated with 30-day mortality (OR: 1.030, 95% CI: 1.005-1.055, p= 0.017). In our study, the modified Sanz risk score was detected to have a sensitivity of 77.78% and specificity of 66.67% to predict 30-day mortality for high and ultra-high risk groups (AUC: 0.727, 95% CI: 0.514-0.939, p= 0.032). As a result, the modified Sanz score was found to be more effective in predicting 30-day mortality than the Sanz score and other risk scores in our study.

Österroos et al. carried out a study in 2022 on newly diagnosed APL patients in light of the population-based Swedish AML Registry (n= 301) and the Portuguese hospital-based registry (n= 129) as training and validation cohorts to develop a prediction model for EDs.[15] Based on univariate and multivariate logistic regression analyses, a model was developed by Österroos et al. to identify the most important risk factors and their optimal threshold values. In the model, patients were divided into three risk groups based on their total score points, and the risk scores for EDs were identified as <10, 10-30, and >30% in the low-risk, high-risk and ultra-high-risk patients, respectively. WBC, PLT, and age were also identified as the most significant risk factors in the model, based on these parameters. However, in contrast to the commonly used $10x10^9$/L cut-off value for WBC, Österroos et al. found that the risk of EDs already increased at subnormal WBC levels from approximately $2x10^9$/L and then continued to increase steeply within the normal WBC range. Such a situation indicates that health professionals should be more alert to patients with WBC values already at or below the normal reference range for EDs. Although Österroos et al. stated that their model demonstrated a better performance than the modified Sanz and Cai et al.'s risk scores in the study, such superiority was not observed in our study.

In another study, Cai et al. also developed a model, internally validated at the time of publication, to predict the risk score based on age, WBC, PLT, and LDH. In the study, it was observed that the ED risk gradually enhanced with increasing WBC, and the early mortality rate was found to be 7.54%.[16] However, the effect of PLT count was controversial in the study. Also, in the multivariate analysis of Cai et al.'s study, it was validated that lower PLT count was associated with increased early mortality.[16] However, in our study, PLT count was not found to be a significant risk factor in mortality and early mortality.

DIC is an important challenge to cope with early mortality in APL. The coagulopathy of APL is unique since the activation of the coagulation cascade exists due to the expression of tissue factor and other procoagulants with concomitant increase in primary and secondary fibrinolysis due to expression of Annexin II on the APL blasts.[27] The ISTH scoring system has been widely acknowledged as a reliable screening tool to detect DIC, regardless of the cause, and in ISTH, four parameters are evaluated at diagnosis: PLT level, fibrinogen, D-dimer, and PT.[28] In previous studies, the role of the ISTH score was also evaluated in predicting EDs in APL patients. A study revealed that while a score of ISTH ≥ 5 was not associated with DIC, a score of ≥ 6 was associated with EDs.[29] In another retrospective study, an ISTH score ≥ 6 was reported to be correlated with hemorrhagic ED.[30,31] In our study, patients were grouped as high and low-risk under the ISTH score, and no significant superiority was detected between the ISTH score and other scores. However, the percentage of mortality was significantly higher in the high-risk group than in the low-risk group in terms of the ISTH score (p= 0.026).

There are also various limitations in our study. Two primary limitations are that our study has a retrospective design and a relatively small sample size. Unrecognized bias might also have influenced the findings. Due to a substantial proportion of missing data in the patient's charts, we were unable to analyze other potential factors, such as the performance status, severity of hemorrhage, and other complications. Therefore, it is necessary to compare our findings with those in studies with prospective designs and larger populations that are performed in multiple centers to reach more accurate results.

In conclusion, EDs, mortality, and recurrences occurring from the initial of the treatment to the end of induction emerge as the largest challenges against the success of the treatment. Timely recognition of high-risk patients, taking appropriate protective measures, and administering more aggressive supportive care to such patients may help reduce EDs. The Sanz risk score and other scoring systems have guided identifying high-risk patients. However, the most effective scoring system could not be determined at the end of the study. We consider that there is still a requirement for standardized scoring systems, also including comorbidities, to identify high-risk patients more effectively.

REFERENCES

1. Sanz MA, Montesinos P. Open issues on bleeding and thrombosis in acute promyelocytic leukemia. Thromb Res 125 Suppl 2: S51-4, 2010.
2. Naymagon L, Moshier E, Tremblay D, Mascarenhas J. Predictors of early hemorrhage in acute promyelocytic leukemia. Leuk Lymphoma 60: 2394-2403, 2019.
3. Lou Y, Ma Y, Sun J, et al. Effectivity of a modified Sanz risk model for early death prediction in patients with newly diagnosed acute promyelocytic leukemia. Ann Hematol. Nov 96: 1793-1800, 2017.
4. Hassan IB, Zaabi MRA, Alam A, Hashim MJ, Tallman MS, Kristensen J. Characteristics features and factors influencing early death in acute promyelocytic leukemia; Experience from United Arab Emirates (UAE). Int J Hematol 106: 90-98, 2017.
5. Iland HJ, Collins M, Bradstock K, et al. Use of arsenic trioxide in remission induction and consolidation therapy for acute promyelocytic leukaemia in the Australasian Leukaemia and Lymphoma Group (ALLG) APML4 study: a non-randomised phase 2 trial. Lancet Haematol 2: e357-66, 2015.
6. Burnett AK, Russell NH, Hills RK, et al. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. Lancet Oncol 16: 1295-1305, 2015.
7. Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. J Clin Oncol 27: 504-510, 2009.
8. Lo-Coco F, Cicconi L, Breccia M. Current standard treatment of adult acute promyelocytic leukaemia. Br J Haematol 172: 841-854, 2016.
9. Platzbecker U, Avvisati G, Cicconi L, et al. Improved Outcomes With Retinoic Acid and Arsenic Trioxide Compared With Retinoic Acid and Chemotherapy in Non-High-Risk Acute Promyelocytic Leukemia: Final Results of the Randomized Italian-German APL0406 Trial. J Clin Oncol 35: 605-612, 2017.
10. Yanada M, Matsushita T, Asou N, et al. Severe hemorrhagic complications during remission induction therapy for acute promyelocytic leukemia: incidence, risk factors, and influence on outcome. Eur J Haematol 78: 213-219, 2007.
11. Paulson K, Serebrin A, Lambert P, et al. Acute promyelocytic leukaemia is characterized by stable incidence and improved survival that is restricted to patients managed in leukaemia referral centres: a pan-Canadian epidemiological study. Br J Haematol 166: 660-666, 2014.

12. Rahmé R, Thomas X, Recher C, et al. Early death in acute promyelocytic leukemia (APL) in French centers: a multicenter study in 399 patients. Leukemia 28: 2422-2424, 2014.

13. Lehmann S, Deneberg S, Antunovic P, et al. Early death rates remain high in high-risk APL: update from the Swedish Acute Leukemia Registry 1997-2013. Leukemia 31: 1457-1459, 2017.

14. Sanz MA, Lo Coco F, Martín G, et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. Blood 96: 1247-1253, 2000.

15. Österroos A, Maia T, Eriksson A, et al. A risk score based on real-world data to predict early death in acute promyelocytic leukemia. Haematologica 107: 1528, 2022.

16. Cai P, Wu Q, Wang Y, Yang X, Zhang X, Chen S. An effective early death scoring system for predicting early death risk in de novo acute promyelocytic leukemia. Leuk Lymphoma 61: 1989-1995, 2020.

17. Bakhtiari K, Meijers JC, de Jonge E, Levi M. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. Crit Care Med 32: 2416-2421, 2004.

18. Baysal M, Gürsoy V, Hunutlu FC, et al. The evaluation of risk factors leading to early deaths in patients with acute promyelocytic leukemia: a retrospective study. Ann Hematol 101: 1049-1057, 2022.

19. Park JH, Qiao B, Panageas KS, et al. Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. Blood 118: 1248-54, 2011.

20. Sanz MA, Montesinos P, Vellenga E, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans retinoic acid and anthracycline monochemotherapy: long-term outcome of the LPA 99 multicenter study by the PETHEMA Group. Blood 112: 3130-3134, 2008.

21. Rashidi A, Goudar RK, Sayedian F, et al. All-trans retinoic acid and early mortality in acute promyelocytic leukemia. Leuk Res 37: 1391-1392, 2013.

22. McClellan JS, Kohrt HE, Coutre S, et al. Treatment advances have not improved the early death rate in acute promyelocytic leukemia. Haematologica 97: 133-136, 2012.

23. Avvisati G, Lo-Coco F, Paoloni FP, et al. AIDA 0493 protocol for newly diagnosed acute promyelocytic leukemia: very long-term results and role of maintenance. Blood, The Journal of the American Society of Hematology 117: 4716-4725, 2011.

24. Lehmann S, Ravn A, Carlsson L, et al. Continuing high early death rate in acute promyelocytic leukemia: a population-based report from the Swedish Adult Acute Leukemia Registry. Leukemia 25: 1128-1134, 2011.

25. Lehmann S, Deneberg S, Antunovic P, et al. Early death rates remain high in high-risk APL: update from the Swedish Acute Leukemia Registry 1997–2013. Leukemia 31: 1457-1459, 2017.

26. Song Y-h, Peng P, Qiao C, et al. Low platelet count is potentially the most important contributor to severe bleeding in patients newly diagnosed with acute promyelocytic leukemia. Onco Targets Ther 10: 4917-4924, 2017.

27. Kutny MA, Rajpurkar M, Alonzo TA, et al. Evaluation of ISTH DIC score to predict significant bleeding and thrombosis events in pediatric acute promyelocytic leukemia; a report from the children's oncology group AAML0631 trial. Blood 124: 3669, 2014.

28. Taylor Jr FB, Toh C-H, Hoots KW, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 86: 1327-1330, 2001.

29. Chu T, Wang H, Lv X, et al. Investigation of fibrinogen in early bleeding of patients with newly diagnosed acute promyelocytic leukemia. Platelets 32: 677-683, 2021.

30. Mitrovic M, Suvajdzic N, Bogdanovic A, et al. International Society of Thrombosis and Hemostasis Scoring System for disseminated intravascular coagulation≥ 6: a new predictor of hemorrhagic early death in acute promyelocytic leukemia. Med Oncol 30: 1-7, 2013.

31. Rajpurkar M, Alonzo TA, Wang Y-C, et al. Risk markers for significant bleeding and thrombosis in pediatric acute promyelocytic leukemia; report from the children's oncology group study AAML0631. J Pediatr Hematol Oncol 41: 51, 2019.

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