A scoring system to predict life-threatening thrombo-ischemic events in patients with acute promyelocytic leukemia: the PETHEMA/PALG study

Rebeca Rodríguez-Veiga,[1] Cristina Gil,[2] Marta Sobas,[3°] Laura Torres-Miñana,[1] Carmen Botella,[2] Javier de la Serna,[4] Teresa Bernal,[5] Olga Salamero,[6] Cristina Otero,[7] Irene Navarro-Vicente,[1] Carlos de Miguel,[8] Ana Garrido,[9] Susana Vives,[10] Juan Bergua,[11] Manuel Pérez-Encinas,[12] Lorenzo Algarra,[13] José González-Campos,[14] Maria del Mar Caballero Gómez,[15] Maria Virginia Prates,[16] Celina Benavente,[17] Mar Tormo,[18] Marta Cervera,[19] Patricia Fazio,[20] Maria Elena Amutio,[21] Raimundo García,[22] Helena Pomares,[23] Belén Vidriales,[24] Josefina Serrano,[25] Maria Luz Amigo,[26] Vicente Rubio,[27] Ágata Almela,[28] Manuel Barrios,[29] Claudia Lucia Sossa-Melo,[30] Monika Paluszewska,[31] Andrés Novo,[32] Tomasz Gromek,[33] Gabriela Rodríguez-Macías,[34] Jolanta Oleksiuk,[35] Pilar Lloret-Madrid[1] and Pau Montesinos;[1] on behalf of the PETHEMA, PALG, and GATLA co-operative groups

[1]Hematology Department, Hospital Universitari i Politécnic-IIS La Fe, Valencia, Spain; [2]Hematology Department, Hospital General Universitario Dr. Balmis, Alicante, Spain; [3]Hematology Department, Wroclaw Medical University, Wroclaw, Poland; [4]Hematology Department, Hospital Universitario 12 de Octubre, CNIO, Complutense University, Madrid, Spain; [5]Hematology Department, Hospital Universitario Central de Asturias, Instituto Universitario (IUOPA), Instituto de investigación del Principado de Asturias (ISPA), Oviedo, Spain; [6]University Hospital Vall d'Hebron, and Experimental Hematology, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [7]Hematology Department, Hospital Maciel, Montevideo, Uruguay; [8]Hematology Department, Hospital Puerta de Hierro, Madrid, Spain; [9]Hematology Department, Hospital de la Sant Creu i Sant Pau, Barcelona, Spain; [10]Hematology Department, ICO-Hospital Universitari Germans Trias i Pujol, Institut de recerca Josep Carreras, Badalona, Spain; [11]Hematology Department, Hospital Universitario San Pedro de Alcántara, Cáceres, Spain; [12]Hematology Department, Hospital Clínico Universitario, Santiago de Compostela, Spain; [13]Hematology Department, Hospital General Universitario de Albacete, Albacete, Spain; [14]Hematology Department, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina (IBIS / CSIC / CIBERONC), Universidad de Sevilla, Sevilla, Spain; [15]Hematology Department, Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain; [16]Hematology Department, Hospital Italiano de La Plata (HILP), La Plata, Argentina; [17]Hematology Department, Hospital Clínico San Carlos, Madrid, Spain; [18]Hematology Department, Hospital Clínico Universitario-INCLIVA, Valencia, Spain; [19]Hematology Department, Hospital de Tarragona "Joan XXIII" (ICO-Tarragona), Tarragona, Spain; [20]Hematology Department, Hospital General San Martín, La Plata, Argentina; [21]Hematology Department, Hospital Universitario Cruces Barakaldo, Bizkaia, Spain; [22]Hematology Department, Hospital General de Castellón, Castellón, Spain; [23]Hematology Department, Institut Catala d'Oncologia, Hospitalet del Llobregat, Llobregat, Spain; [24]Hematology Department, Hospital Universitario de Salamanca (HUS/IBSAL), CIBERONC and Center for Cancer Research-IBMCC (USAL-CSIC), Salamanca, Spain; [25]Hematology Department, IMIBIC, Hematology, Hospital Universitario Reina Sofía, UCO, Córdoba, Spain; [26]Hematology Department, Hospital Morales Meseguer, Murcia, Spain; [27]Hematology Department, Hospital General Jerez de la Frontera, Cadiz, Spain; [28]Hematology Department, Hospital Universitario de León, León, Spain; [29]Hematology Department, Hospital Carlos Haya (COMPLEJO HOSPITALARIO REGIONAL DE MÁLAGA), Málaga, Spain; [30]Hematology Department, Fundación Oftalmológica de Santander-FOSCAL Facultad de Ciencias de la Salud, Universidad Autónoma de Bucaramanga-UNAB, Santander, Colombia; [31]Hematology Department, Medical University of Warsaw, Warsaw, Poland; [32]Hematology Department, Hospital Son Espases, Palma de Mallorca, Spain; [33]Hematology Department, Medical University Lublin (SPSK1), Lublin, Poland; [34]Hematology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain and [35]Hematology Department, Medical University Bialystok, Białystok, Poland

°Current address: Department of Hematology, Faculty of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-168 Bydgoszcz, Poland

Correspondence: P. Montesinos
montesinos_pau@gva.es

Received: June 26, 2025.
Accepted: November 4, 2025.
Early view: November 13, 2025.

https://doi.org/10.3324/haematol.2025.288112

Therapy of APL

Briefly, induction therapy consisted of oral ATRA 45 mg/m^2 per day and idarubicin 12 mg/m^2 per day given as an intravenous bolus on days 2, 4, 6 and 8 (AIDA regimen). Patients older than 70 years of age received only the three first doses of idarubicin. All patients in complete remission (CR) received 3 monthly risk-adapted consolidation courses with ATRA plus idarrubicine or mitoxantrone with or without cytarabine. After completion of consolidation, patients who tested negative for PML/RARA started maintenance therapy, as described elsewhere, with intermittent ATRA (45 mg/m^2 per daily for 15 days, every 3 months) and low-dose chemotherapy with 6-mercaptopurine (50 mg/m^2 per day) and methotrexate (15 mg/m^2 per day, weekly) for 2 years.

Neither of the two protocols indicated anti-hemorrhagic nor anti-thrombotic pharmacological prophylaxes. Transfusion policies recommended maintaining platelet count above 30 to 50 x 10^9/L and fibrinogen levels above 150 mg/dL during induction and until CR and/or resolution of coagulopathy. Central-venous lines were used at physician´s discretion.

Statistical analysis

Analysis was made on an intent-to-treat principle. Chi square test were used to analyze differences in the distribution of variables between patient subsets. The development of life-threatening thrombosis with active APL was the event studied in the univariate and multivariate analyses, and to raise a predictive model. The characteristics selected for inclusion in the multivariate analysis were those for which there was some indication of a significant association in the univariate analysis ($p<0.1$). Variables with more than 15% missing data were not considered for inclusion in the multivariable model. Missing data were substituted by the mean values from patients for whom data were available (19). The variables remaining significant ($P<0.05$) in the multivariate analysis were used to build a scoring system in a random training cohort to classify the patients in groups according to their risk of life-threatening thrombosis in active APL. For internal validation we used a validation cohort, and for external validation an external cohort of LPA2017

protocol form the same registry. A receiver operating curve (ROC) was performed to check the accuracy of the model. Computations were performed using the R 4.2.2 software package.

Supplementary Table 1. Patients and APL characteristics in external validation cohort (LPA2017 protocol)

	Overall (n = 585)	
Characteristic	Mean (range)	n (%)
Gender; n=585		
Female		280 (48)
Male		305 (52)
Type; n=585		
De novo		534 (91)
Secondary		51 (9)
Age, years; n=585	48 (1–88)	
≤ 18		50 (9)
19-40		169 (29)
41-60		206 (35)
61-70		90 (15)
>70		70 (12)
Relapse Risk; n=585		
Low		179 (31)
Intermediate		259 (44)
High		147 (25)
ECOG; n=585		
0-1		508 (87)
2		44 (8)
3		20 (3)
4		13 (2)
Scheme; n=558		
ATRA+ATO		425 (76)
AIDA		133 (24)
Leukocytes, $x10^9$/L; n=585	2.0 (0.14–418.7)	
≤20		482 (82)
>20		103 (18)
Platelets count, $x10^9$/L; n=585	30 (2–269)	
≤20		183 (31)

>20		402 (69)
Hemoglobin, g/dL; n=585	9.3 (1.07–17.9)	
Bone marrow blasts, %; n=489	82 (3-100)	
Albumin, g/dL; n=411	4.1 (1.8–5.6)	
≤3.5		78 (19)
>3.5		333 (81)
TTPA; n=585		
Normal		541 (92)
Prolonged		44 (8)
Triglycerides, mg/dL; n=252	166.5 (28–639)	
<220		197 (78)
≥220		55 (22)
Cholesterol, mg/dL; n=287	166 (56–319.3)	
<200		214 (75)
≥200		73 (25)
Creatinine, mg/dL; n=556	0.80 (0.21-9)	
<1.3		513 (92)
≥ 1.3		43 (8)
Urea, mg/dL; n=344	29 (3.70–116)	
<40		258 (75)
≥40		86 (25)
Uric acid, mg/dL; n=402	4.5 (0.1–10.6)	
LDH, U/L; n=522	316 (15-10061)	
Alkaline phosphatase, U/L; n=430	74.5 (12-586)	
Bilirubin, mg/dL; n=476	0.70 (0.2-18)	
Fibrinogen, mg/dl; n=562	177 (33-768)	
CD56 positive >20% over blast population; n= 318		
<20%		286 (90)
≥20%		32 (10)
Bleeding at diagnosis; n=585		
Present		412 (70)
Absent		173 (30)
Thrombosis in active APL; n=585		
No life-threating event		542 (93)
Life-threating event		43 (7)
Induction response; n=584		
Complete remission		502 (86)
Death		82 (14)

Supplementary Table 2. Location of all thrombo-ischemic events according to treatment phase in external validation cohort (LPA2017 protocol).

	Overall	At diagnosis	Induction	Consolidation
	n (%)	n (%)	n (%)	n (%)
Overall thrombosis	81 (100)	28 (100)	47 (100)	6 (100)
Central nervous system	18 (22)	12 (43)	6 (13)	0
Myocardial Infarction	1 (1)	1 (4)	0	0
Pulmonary embolism	13 (16)	9 (32)	3 (6)	1 (17)
Deep vein thrombosis	7 (9)	1 (4)	5 (11)	1 (17)
Surface vein or catheter-related	36 (44)	2 (7)	30 (64)	4 (66)
Other sites	6 (8)	3 (10)	3 (6)	0

Supplementary Table 3. Location of all thrombo-ischemic events according to treatment phase in the ATO-ATRA cohort (LPA2017 protocol).

	Overall	At diagnosis	Induction	Consolidation
	n (%)	n (%)	n (%)	n (%)
Overall thrombosis	49 (100)	15 (100)	29 (100)	5 (100)
Central nervous system	8 (16)	5 (33)	3 (10)	0
Myocardial Infarction	0	0	0	0
Pulmonary embolism	9 (19)	7 (47)	1 (4)	1 (20)
Deep vein thrombosis	3 (6)	0	3 (10)	0
Surface vein or catheter-related	25 (51)	1 (7)	20 (69)	4 (80)
Other sites	4 (8)	2 (13)	2 (7)	0

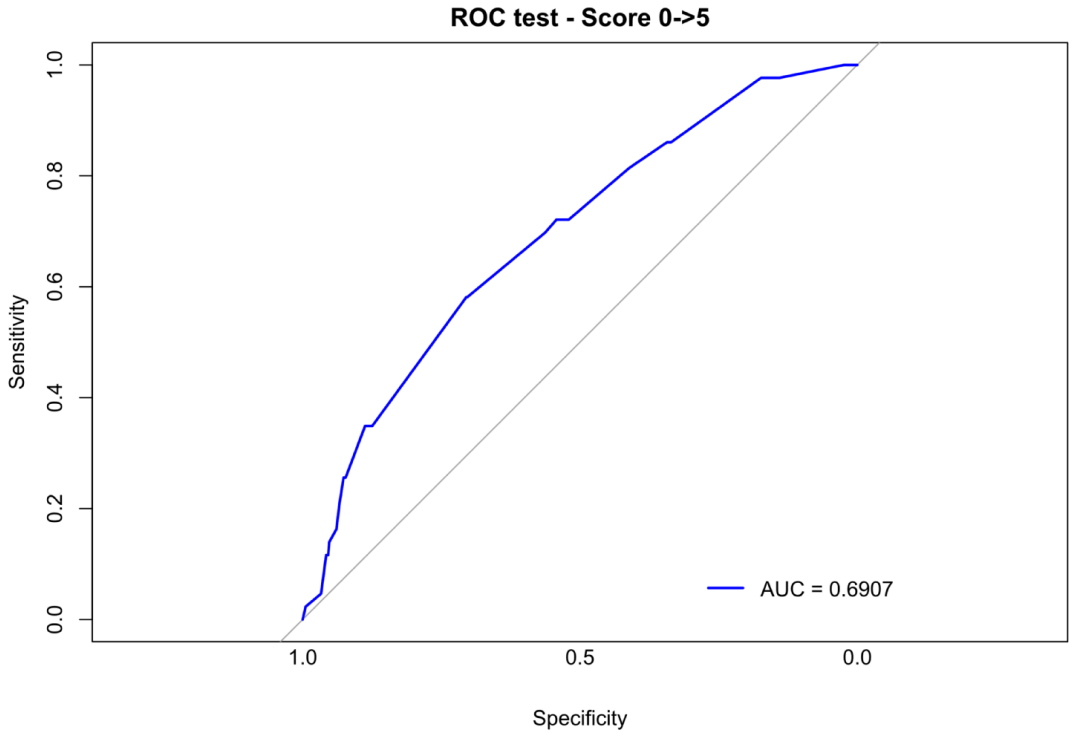
Supplementary Table 4. Distribution of Thromb-On score risk sum and categories and performance in external validation cohort (LPA2017 protocol).

Characteristic	Overall (n=585)	
	No thrombosis n	Thrombosis n (%)
Overall	542	43 (7.4)
Sum score		
0 point	63	1 (1.6)
1 point	174	9 (4.9)
2 points	187	19 (9.2)
3 points	106	7 (6.2)
4 points	12	7 (36.8)
5 points	0	0 (NA)
Risk group		
Low (0 points)	63	1 (1.6)
Intermediate (1-2 points)	361	28 (7.2)
High (3-5 points)	118	14 (10.6)

NA: not applicable

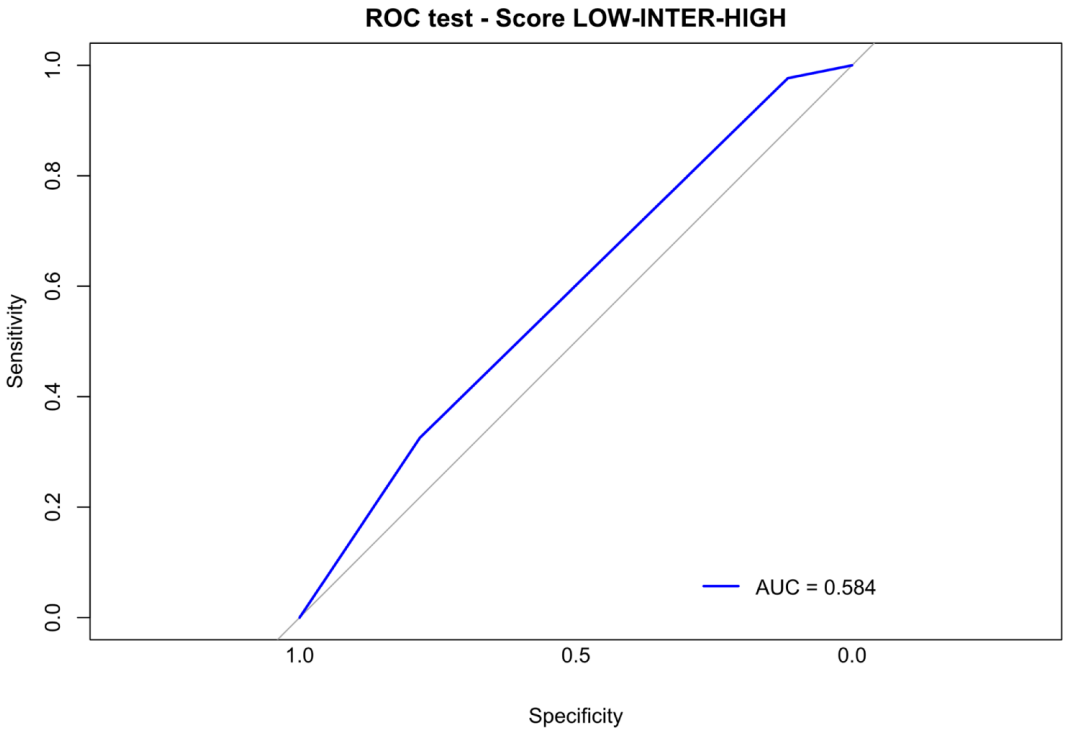
Supplementary Figure 1A and 1B. Receiver operator curve (ROC) and ANOVA according to the Thromb-On score in validation cohort (LPA2017 protocol): A) using the sum score 0 to 5, AUC 0.69; and B) using the 3 risk categories (low 0 points, intermediate 1-2 points, and high risk 3 to 5 points, AUC 0.58.

1 A)



Sum score	n	Thrombosis (%)	p-value (ANOVA)
0	64	1.6	0.0000032
1	183	4.9	
2	206	9.2	
3	113	6.2	
4	19	36.8	
5	0	0	

1 B)



Risk group	n	Thrombosis (%)	p-value (ANOVA)
Low (0)	64	1.6	0.074
Intermediate (1-2)	389	7.2	
High (3-5)	132	10.6	