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

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Running title: Thrombotic risk fin acute promyelocytic leukemia

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AUTHORSHIP
Rebeca Rodríguez-Veiga and Pau Montesinos conceived the study, analyzed, and interpreted the data; Pau Montesinos, Rebeca Rodríguez-Veiga, and Marta Sobas wrote the paper; Pau Montesinos and Pilar Lloret performed the statistical analyses; Cristina Gil, Laura Torres-Miñana, Carmen Botella, Javier de la Serna, Teresa Bernal, Olga Salamero, Cristina Otero, Irene Navarro-Vicente, Carlos de Miguel, Ana Garrido, Susana Vives, Juan Bergua, Manuel Pérez-Encinas, Lorenzo Algarra, José González-Campos, Mª del Mar Caballero Gómez, Mª Virginia Prates, Celina Benavente, Mar Tormo, Marta Cervera, Patricia Fazio, Mª Elena Amutio, Raimundo García, Helena Pomares, Belén Vidriales, Josefina Serrano, Mª Luz Amigo, Vicente Rubio, Ágata Almela, Manuel Barrios, Claudia Lucia Sossa-Melo, Monika Paluszewska, Andrés Novo, Tomasz Gromek, Gabriela Rodríguez-Macías, Jolanta Oleksiuk reviewed the manuscript and contributed to the final draft.

Statements relating to our ethics and integrity policies:

- ethics approval statement: this study was approved by the Research Ethics Board of the institution according to the Declaration of Helsinki (Registry 2024-0499-1).
- patient consent statement: Informed consent was obtained from all patients, according to the Declaration of Helsinki, the registry and treatments protocols were approved by Research Ethics Committees.

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Data sharing statement:

Data could be shared under reasonable request, contacting the registry coordinator, montesinos_pau@gva.es

Abstract

Acute promyelocytic leukemia (APL) is a highly curable leukemia characterized by life-threatening coagulopathy leading to hemorrhagic and thrombo-ischemic events. We analyzed the incidence, outcomes and risk-factors of thrombo-ischemic events in a large series of 1210 patients with newly diagnosed APL reported to the PETHEMA registry. Therapy consisted on ATRA and chemotherapy (AIDA-based). Median age of patients was 46 years (range 2-90 years). Fifty-eight patients (5%) did not start AIDA regimen as they were unfit for chemotherapy, or they died early before initiating ATRA. A total of 195 (16%) patients developed thrombo-ischemic events, the most frequent being superficial-vein and/or central catheter-related (6.9%) followed by central nervous system (2.2%), deep-vein thrombosis (2.1%), pulmonary embolism (2.1%), acute myocardial infarction (1.6%), or other locations (1.2%). Thrombo-ischemic events mostly occurred at diagnosis and during induction (4.0%, and 9.3%, respectively). Patients developing life-threatening thrombo-ischemic events (i.e, excluding superficial and/or catheter-related) at diagnosis/induction had 31% early death rate. Prolonged aPTT, age >40 years, ECOG more than 1, platelets > 25 x 10^9/L, and absence of bleeding at presentation were independent risk factors for life-threatening thrombo-ischemic events. Using these variables (1 point each) we developed and validated the Thromb-On risk score, identifying a high-risk group (3 to 5 points). The Thromb-On risk score was validated in a cohort of 585 patients treated since 2017 with arsenic trioxide plus ATRA (<10x10^9 leukocytes) or AIDA (≥10x10^9 leukocytes). This study could help to improve prevention and management of life-threatening thrombo-ischemic events, through risk-adapted guidance, potentially leading to decrease early mortality in APL.

Key words: thrombosis, acute promyelocytic leukemia, risk factors,

Introduction

Acute promyelocytic leukemia (APL), is a highly curable leukemia characterized by the t(15;17) translocation. However, there is still a 10 to 15% of pre-treatment and induction mortality, mostly due to haemorrhages and a frequent association with life threatening coagulopathy[1–4]. Coagulopathy in APL is not only associated to haemorrhage but to a procoagulant state that could lead to thrombotic and ischemic events, which could be also a fatal complication. The real incidence of thrombosis in APL ranges between 0.5 to 20.6%[5–13], with prospective studies reporting the higher incidence. Different risk factors for thrombosis development in APL have been proposed, such as differentiation syndrome (DS)[7,12], higher white blood cells (WBC) count[11–14], bcr-3 type PML/RARA[9,13], FLT3-ITD mutation[9,13], CD2 and CD15[13] expression, tranexamic acid prophylaxis, low fibrinogen and M3 variant subtype[12]. Establishing the incidence and risk-factors for thrombo-ischemic events could help to design supportive care guidelines aiming to prevent this life-threatening complication.

The aim of this study is to prospectively analyze the incidence, outcome and risk-factors of thrombo-ischemic events in a large series of patients diagnosed with APL and treated with PETHEMA LPA2005 and LPA2012 protocols based on ATRA and chemotherapy. In addition, we aim to analyze the incidence of thrombo-ischemic complications in a large series of patients treated with modern APL regimens (LPA2017 protocol), which included ATO+ATRA for low- and intermediate-risk patients, and AIDA-based regimen for high-risk patients. This study could help to improve prevention and management of these events, through risk-adapted guidance (i.e, based on a validated scoring system) for the management of thrombo-ischemic complications, potentially leading to decrease early mortality in APL.

Methods

Study design and population

The study comprises adult and pediatric newly diagnosed APL patients that were enrolled in the PETHEMA APL and acute myeloid leukemia registry (NCT02607059) between June 2005 and April 2017. To validate the scoring system, we used an external cohort of patients treated with modern protocols

since May 2017 with arsenic trioxide (ATO) plus ATRA (if <$10x10^9$ leukocytes at APL diagnosis) or AIDA (≥$10x10^9$ leukocytes). All patients with demonstration t(15;17) and/or *PML/RARA* rearrangements and intention to treat were included, regardless of the performance status, and whether they were *"de novo"* or secondary. Informed consent was obtained from all patients, according to the Declaration of Helsinki, the registry and treatments protocols were approved by Research Ethics Committees (2024-0499-1).

Therapy of APL

Therapy for APL was given according to PETHEMA LPA2005[15] and LPA2012 trials[16] (ethics approval code 2012/00050/EO). The LPA2017 protocol included ATO+ATRA according to Lo Coco schedule for low-intermediate risk APL, and AIDA-based for high risk patients. See supplementary material.

Data collection

The following variables were prospectively collected, among others, in a specific form: sex, age, performance status using Eastern Cooperative Oncology Group (ECOG) scale, de novo vs. secondary, baseline fever, body mass index (BMI), body surface, liver and spleen enlargement, thrombosis at diagnosis (yes/no/ location); hemorrhage at diagnosis (yes/no/location); fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrin degradation products or D-dimers, albumin, serum lactate dehydrogenase (LDH), creatinine, blood urea nitrogen (BUN), uric acid, alkaline phosphatases, transaminases, cholesterol, triglycerides. total bilirubin; WBC and platelets, peripheral blood blast count and bone marrow blast percentage; bone marrow aspirate cellularity, peroxidase reactivity; local diagnostic laboratory parameters CD13, CD56, CD15, CD34, CD7, CD14, CD117, CD2, CD9, CD19, and CD33 surface antigen markers; *PML/RARA* bcr3 isoform, FLT3-*ITD* mutation, M3 variant, and karyotype. Induction outcome, cause of death, and the occurrence and severity of DS were captured. Data concerning thrombo-ischemic events during induction and consolidation cycles were also collected (yes/no/location/outcome).

Definitions and Study Endpoints

The primary endpoint was the overall incidence of thrombo-ischemic events during diagnosis, induction, and consolidation phases, including superficial vein and catheter-related thromboses (i.e, non-life-threatening events) and other thrombo-ischemic complications (i.e, life-threatening events). Thrombo-ischemic events were diagnosed by clinical signs or symptoms, based on routine practice. Thrombosis in active APL was considered when patients developed a thrombosis at diagnosis and/or during induction before achieving a CR. For risk factors and predictive model analyses superficial-vein and catheter related thrombosis were not considered events as the presence of vein access was supposed as the main risk factor itself.

Coagulopathy was defined as a prolonged PT and/or aPTT in addition to hypofibrinogenemia and/or increased levels of fibrin degradation products or D-dimers, as well as hypofibrinogenemia with increased levels of fibrin degradation products or D-dimers.

DS diagnosis was made according to previously published criteria[17] after ruling out other causes. Severe DS was considered when 4 or more of these symptoms were present: fever, dyspnea, pleural or pericardial effusion, pulmonary infiltrates, renal failure, hypotension, weight increase (≥5kg) and other diagnoses were rule out. Risk of relapse was assessed according to Sanz predictive model, as reported previously[18].

The primary end-point of the study was to assess the overall incidence of thrombosis and its incidence at different time-points (diagnosis, induction, and consolidation). Secondary end-points were to analyze risk factors for thrombosis development, overall survival (OS) and early mortality (i.e, mortality before starting therapy and during induction).

Statistical analysis

See supplementary material.

Results

Patient characteristics

A total of 1210 consecutive patients with full data set on thrombo-ischemic events were registered in the PETHEMA protocols LPA 2005 (n=941, 77.8%)

and LPA 2012 (n=269, 22.2%). Fifty-eight patients (5%) did not start AIDA regimen as they were considered unfit for chemotherapy due to underlying comorbidity/ECOG 4 or because they died early before initiating ATRA. Median age of patients was 46 years (range 2-90), secondary APL was diagnosed in 11% (n=133), and ECOG was 0-1 in 76% (n=829) of patients. The Sanz risk score distribution was as follow: low 22%(n=270), intermediate 49% (n=593) and high 29% (n=345). Out of all, 166 (13.7%) patients died early before starting therapy or during induction.

Incidence, site, and timing of thrombo-ischemic events

A total of 195 (16%) patients developed thrombo-ischemic events, 171 (14%) had one episode and 24 patients (2%) developed more than one episode. Overall, the most frequent thrombotic event was superficial-vein and/or central catheter-related thrombosis (SCVT), affecting 84 (6.9%) patients, followed by central nervous system ischemic stroke (CNS) in 27 (2.2%), deep-vein thrombosis (DVT) in 26 patients (2.1%), pulmonary embolism (PE) in 25 (2.1%), acute myocardial infarction (AMI) in 19 (1.6%), and other locations such as Budd-Chiari syndrome or corticorenal or splenic ischemia in 14 (1.2%) (Table 1).

Incidence of thrombo-ischemic events was higher during active APL phases, affecting 162 out of 1210 patients (13.4%), 49 (4.0%) at diagnosis before starting ATRA, and 113 (9.3%) during induction. During consolidation phase, 33 (3.2%) patients out of 1044 developed thrombo-ischemic events.

The site and type of thrombo-ischemic event differed between the diagnosis, induction and consolidation phase (Figure 1 and Table 1). At diagnosis the type of thrombosis was distributed as follow: CNS 13 (24%), DVT 11 (22%), PE 10 (20%), AMI 9 (18%), and other sites 6 (14%). During induction: SCVT 58 (51%), CNS 14 (12%), DVT 13 (12%), PE 13 (12%), AMI 9 (8%), and other sites 6 (5%). In the course of consolidations: SCVT 26 (79%), DVT 2 (6%), PE 2 (6%), AMI 1 (3%), and other sites 2 (6%).

Risk factors for life-threatening thrombosis in active APL phase

There were 104 (9%) of episodes of life-threatening thrombo-ischemic events during active APL (i.e, at diagnosis and/or induction and excluding SCVT). The

Table 2 shows univariate analyses comparing patients in active APL phase with and without life-threatening thrombosis. The following factors were related to a higher incidence of life-threatening thrombosis at diagnosis and/or during induction phase: older age (p=0.004), higher BMI (p=0.02), higher weight (p=0.007), Sanz low-risk (p=0.01), higher ECOG (p<0.001), higher platelet counts (p<0.001), hypoalbuminemia (p=0.001), prolonged aPTT (p<0.001), triglycerides ≥220 mg/dL (p=0.03), higher creatinine levels (p=0.02), >20% blasts CD56 expression (p=0.005) and absence of hemorrhagic signs or symptoms at diagnosis (p<0.001). A trend was observed with cholesterol ≥ 200 mg/dl (p=0.07), and higher urea levels (p=0.06). No significant relation was observed with CD2 or other surface markers, as well as FLT3 mutations or any other characteristic.

The multivariate analysis showed the following independent risk factors: age older than 40 years (p=0.03), platelet count > 25 x 10^9/L (p=0.03), absence of hemorrhage at diagnosis (p=0.005), prolonged aPTT (p=0.02), and ECOG ≥2 (p=0.03), remained as independent prognostic factors (Table 3).

Testing and validation of the predictive model (Thromb-On score)

Based on the odds ratio for each independent risk factor, we assigned 1 point to each factor to build the Thromb-On score system to predict life-threatening thrombosis. Patients were grouped into the following categories: low risk (0 points), intermediate risk (1-2 points), and high risk (3–5 points). The study population where all risk factors were available (n=1010, 83.5%) was divided into two cohorts using a 1:1 random function. The evaluable population was distributed in low (13.3%), intermediate (63.4%) and high risk (23.3%). The training cohort, that was used to test the score system, showed 9% of life-threatening thrombosis, and the validation cohort (used for internal validation) showed 8.8%. The risk of life-threatening thrombosis for low, intermediate, and high risk groups was 1.4%, 4.9%, and 23.2%, respectively, in the training cohort, and was 3%, 5.8%, and 16.5%, respectively, in the validation cohort (Table 4). The area under the ROC curve was 0.69 when applying the low-intermediate-high risk categories, and 0.70 when applying the sum score categories (0 to 5 points) in the whole cohort (Figure 3A and 3B, respectively).

Outcomes in patients with life-threatening thrombosis in active APL phase

Early death (during induction and/or in the first month since diagnosis) was more frequent in patients developing life-threatening thrombo-ischemic complications as compared with those who did not (n=32/104 [31%] vs n=134/1106 [12%], respectively, p<0.001). In this group, death was mostly caused by thrombosis (n=19, 18%), followed by hemorrhagic transformation of the thrombosis (n=4, 4%), and other hemorrhages (n=2, 2%), (Figure 2A). Bleeding (n=76, 7%) was the main cause of early death among patients without life-threatening thrombosis in active APL phase (Figure 2B). Patients who developed life-threatening thrombosis had longer duration of hospitalizations during induction (more than 30 days stay, 9% vs. 2%: p=0.01). No difference was observed in the incidence of severe DS (85% vs. 88%; p=0.43) and use of intravenous antibiotic therapy (Table 5).

External validation of the Thromb-On score in patients treated with LPA2017 protocol

A total of 585 consecutive patients with full data set on thrombo-ischemic events were registered in the PETHEMA LPA2017 protocol. Twenty-seven patients (4.6%) did not start regimen as they were considered unfit for chemotherapy due to underlying comorbidity/ECOG 4 or because they died early before initiating ATRA. Median age was 48 years (range, 1-88), secondary APL was diagnosed in 9% (n=51), and ECOG performance status was 0-1 in 87% (n=508) of patients. Median leukocyte count at diagnosis was 2.0 $x10^9$/L (range, 0.14-418.7), with 18% of patients presenting with WBC counts >20 $x10^9$/L. Median platelet count was 30 $x10^9$/L (range, 2-269), with 69% presenting with counts >20 $x10^9$/L. According to the Sanz risk score, 75% (n=438) of patients were classified as low-intermediate risk, and 25% (n=147) as high risk. Overall, 76% (n=425) received an ATO+ATRA schedule, whereas 24% (n=135) were treated with an AIDA regimen. Other baseline characteristics are described in Supplementary Table 1. Out of all, 82 (14%) patients died early before starting therapy or during induction. A total of 81 (13.8%) patients developed thrombo-ischemic events, being the most frequent SCVT (6.2%), followed by CNS (3.1%), PE (2.7%), and DVT (1.2%) (Supplementary Table 2). Incidence of thrombo-ischemic events was higher during active APL phases, affecting 75 out of 585 patients (12.8%), 28 (4.7%) at diagnosis before starting

ATRA, and 47 (8%) during induction. Among the subgroup of patients who received the ATO-ATRA regimen (n=425), 49 (11.5%) experienced a thrombotic event at some point during treatment, with 15 events (31%) occurring at diagnosis, 29 (59%) during induction, and 5 (10%) during consolidation. At diagnosis in this subgroup, the most frequent thrombotic events were PE (47%) and CNS events (33%), whereas during induction and consolidation, SCVT predominated (69% and 80%, respectively). A detailed description of the site and frequency of thrombo-ischemic events in the ATO-ATRA cohort is provided in Supplementary Table 3.

There were 43 (7.4%) of episodes of life-threatening thrombo-ischemic events during active APL (i.e, at diagnosis and/or induction and excluding SCVT). The external validation cohort was distributed in low (10.9%), intermediate (66.5%) and high risk (22.6%), according to the Thromb-On score. The risk of life-threatening thrombosis for low, intermediate, and high risk groups was 1.6%, 7.2%, and 10.6%, respectively (Supplementary Table 3). The area under the ROC curve was 0.69 when applying the sum score categories (0 to 5 points) and 0.58 when applying the low-intermediate-high risk categories, in the external validation cohort (Supplementary Figure 1A and 1B, respectively).

Early death (during induction and/or in the first month since diagnosis) was more frequent in patients developing life-threatening thrombo-ischemic complications as compared with those who did not (n=13/43 [30.2%] vs n=70/542 [12.9%], respectively, p=0.009).

Discussion

This study shows that thrombo-ischemic events are frequent at diagnosis, during induction and consolidation phase in APL patients treated with ATRA-based schedules. Thrombotic complications were mostly life-threatening when occurring before starting ATRA or during induction phase (i.e, with active APL), and their incidence and severity decreased during consolidation phase (where they were mostly catheter-related). The development of life-threatening thrombosis at diagnosis or during induction leads to prolonged hospitalization and increased early death rate. We identified 5 independent risk factors that have helped to build and internally validate a simple scoring system (Thromb-

On score). The Thomb-On score could be useful for prevention and management of life-threatening thrombo-ischemic events in APL.

Despite the survival improvement in APL patients since the introduction of ATRA based regimens, early death remains as the unsolved issue for APL patients and the more challenging cause of treatment failure. The reported early death rate in real world ranges between 10% and 18%,[15,19,20] with bleeding as the most frequent cause of death. So far, the incidence and morbi-mortality of thrombo-ischemic complications has been analyzed in relatively small and/or retrospective studies, reporting a wide range of thrombosis from 0.5 to 20.6%[5–13]. We identified only one prospective study that included 31 APL patients and showed 9.6% of thrombosis[21]. On the other hand, two recent retrospective studies including 248 and 364 patients treated with ATO+ATRA studies showed an incidence of thrombosis of 5% and 0.5% respectively[8,22]. To date the largest study included 759 patients, data were retrospectively collected in the context of PETHEMA LPA96 and LPA99 protocols, and the reported incidence was 5.1%[12]. The present study has collected data prospectively and it has included a large series of patients treated homogenously in LPA2005 and LPA2012 PETHEMA trials. In addition, we have investigated the incidence of thrombo-ischemic complications in a large series of 585 patients treated with modern APL protocols (i.e, LPA2017, incorporating ATO+ATRA for patients with $<10x10^9$ WBC).

Catheter related thrombosis is a well-known risk factor for thrombosis development[23,24]. In our study, 43% of thrombotic events were associated with a venous line. Interestingly, a study performed in 25 patients reported 32% of catheter-related thrombosis in APL[25]. In case of catheter-related thrombosis, the risk of thrombosis was attributed to the catheter itself and therefore they were ruled out from the analysis of risk factors. Additionally, patients that developed thrombosis during consolidation were not considered as events for the risk factor analyses, assuming that, in this phase thrombosis was not related to APL itself, but instead with general population risk factors (e.g, prolonged hospitalization, or catheter-related). Another well-known risk factor for thrombosis is thrombophilia[26], and it has been also associated with thrombosis

in one study that included 34 patients[6], but in our real world series we have not collected thrombophilia studies as they are not routinely performed in APL.

Herein, we focused on the analysis of risk factors for developing life-threatening (i.e, no superficial vein or catheter-related) thrombosis, which included CNS, DVT, PE, AMI, and other severe complications at diagnosis or during induction, affecting 9% out of 1210 patients. Indeed, we found that these life-threatening thrombo-ischemic events were related with morbidity (prolonged hospitalization) and higher early death rate (up to 31%). Interestingly, in the LPA2017 cohort, we found similar rates of life-threatening thrombo-ischemic events (7.4%), leading also to higher mortality rate (30.2%) in this group, suggesting that the switching to ATO+ATRA therapy, at least for patients with $<10x10^9$ WBC, did not impact on the incidence and severity of this complication.

The introduction of ATRA into the APL therapy has produced a high rate of CR with a rapid resolution of the coagulopathy. It has been postulated that the imbalance caused by ATRA between procoagulant and fibrinolytic forces, may induce a prothrombotic effect,[7,27] but there seem to be additional risk factors for thrombosis in APL active phase. In this regard, it is important to highlight that we have found up to 4% of thrombosis at diagnosis, prior to the onset of ATRA, confirming that there are stronger biological factors than the procoagulant state induced by differentiating agents. Another risk factor that has been related to the exacerbation of the procoagulant state is the development of DS, as suggested in a study performed on 31 patients,[7] and in a study analyzing DS in 780 patients in which severe DS was associated with higher incidence of thrombotic events[12]. However, this PETHEMA study analyzed retrospective data of thrombosis. In this larger and specifically designed study we could not confirm and association between sever DS and life-threatening thrombosis.

There are other factors that have been associated with thrombosis, such as leukocytosis ATRA syndrome and some laboratory data specific to this disease: higher platelet count[9], ISTH DIC score[9], APL variant M3[12], PAI 4G/4G[9], CD2 and CD15[13]. However, most of these factors have not been confirmed by others. The following prognostic factors were identified in at least two studies leukocytosis, hypofobrinogenemia, PT, aPTT, D-dimers, FLT3-*ITD* and the bcr3 isoform[8,9,12–14,22]. In the present study none of those factors were confirmed in

the multivariable analysis with the exception of prolonged aPTT, identified in two previous studies[9,22]. Other independent risk factors were age >40 years, ECOG > 1, platelets > 25 x 10^9/L, and absence of bleeding at APL presentation. Based on these parameters we could identify a high risk population for life-threatening thrombosis, and we built and validated a simple scoring system with acceptable AUC of the ROC curve (0.7 in the whole LPA2005 and LPA2012 cohort, and 0.69 in the modern LPA2017 cohort). To our knowledge, no risk scores for thrombosis in APL have been published to date. We identified 23.3% of APL population with high risk for development of life-threatening thrombo-ischemic events, where we could recommend for frequent monitoring and high suspicion of thrombosis with compatible signs or symptoms, and even anticoagulant prophylactic strategies could be used in the context of well-designed protocols. Also, platelet and plasma products transfusion policies could be more restrictive in this setting. For low Thromb-On score patients management should focus on bleeding prevention, and for intermediate group we would suggest to follow the current supportive measures adopted by the ELN expert panel [28].

Limitations in our study are: 1) not all registered patients had full data-set regarding thrombosis events, and selection bias cannot ruled out, 2) we did not include patients with ≥10x10^9 WBC treated with ATO in front-line, potentially harnessing the applicability of our score system as chemotherapy free regimens become the standard also in this population, and 3) the score system should be validated in additional external cohorts.

In conclusion, in this large study analyzing real world APL patients, thrombo-ischemic events were frequent, mostly occurring in life-threatening locations, developing at diagnostic and induction phase, and leading to increased early death rate. The simple Thromb-On score identifies patients with high risk of life-threatening thrombosis, and it could offer guidance for prevention and early management. Further investigation to reduce early death in APL patients is warranted.

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Table 1. Location of all thrombo-ischemic events according to treatment phase

	Overall	At diagnosis	Induction	Consolidation
	n (%)	n (%)	n (%)	n (%)
Overall thrombosis	195 (100)	49 (100)	113 (100)	33 (100)
Central nervous system	27 (14)	13 (27)	14 (12)	0 (0)
Myocardial Infarction	19 (10)	9 (18)	9 (8)	1 (3)
Pulmonary embolism	25 (13)	10 (20)	13 (12)	2 (6)
Deep vein thrombosis	26 (13)	11 (22)	13 (12)	2 (6)
Surface vein or catheter-related	84 (43)	0 (0)	58 (51)	26 (79)
Other sites	14 (7)	6 (12)	6 (5)	2 (6)

Table 2. Patients and APL characteristics in patients with or without life-threatening thrombosis in active APL phase (i.e, at diagnosis or during induction).

Characteristic	Patients without life-threatening thrombosis		Patients with life-threatening thrombosis		P
	Mean (range)	n (%)	Mean (range)	n (%)	
Overall; n=1210		1106 (91)		104 (9)	
Sex					
Female		563 (51)		45 (43)	0.17
Male		543 (49)		59 (57)	
Type					
De novo		986 (89)		91 (88)	0.73
Secondary		120 (11)		13 (13)	
Age, years; n=1206	45 (2-90)		51 (9-82)		0.002
≤ 18		71 (6)		3 (3)	0.006
19-40		380 (34)		21 (20)	
41-60		412 (37)		51 (50)	
61-70		155 (14)		15 (15)	
>70		85 (8)		13 (13)	
BMI, n=1066	27 (13-58)		29 (19-48)		0.02
Weight, kg; n=1077	75.4 (12.3-166)		81.9 (42-160)		0.007
<70		611 (62)		43 (50)	0.045

≥70		380 (38)		43 (50)	
Relapse Risk; n=1208					
Low		236 (21)		34 (33)	0.004
Intermediate		557 (51)		36 (34)	
High		311 (28)		34 (33)	
ECOG; n=1089					
0-1		774 (78)		55 (60)	<0.001
2		116 (12)		23 (25)	
3		63 (6)		8 (9)	
4		44 (4)		6 (7)	
PETHEMA trial					
LPA 2005		857 (77)		84 (81)	0.52
LPA 2012		249 (23)		20 (19)	
Leukocytes, $x10^9$/L; n=1209	2.90 (0.1-217)		2.95 (0.5-198.6)		0.39
≤20		908 (82)		81 (78)	0.28
>20		197 (18)		23 (22)	
Platelets count, 10^9/L; n=1207	35 (1-290)		51 (1-208)		<0.001
≤20		478 (43)		30 (29)	0.006
>20		625 (57)		74 (71)	
Hemoglobin, g/dL; n=1205	9.3(1.9-17.7)		9.6 (4.1-14.5)		0.30
Albumin, g/dL; n=978	4.1 (2-6)		4.1 (1.8-5.1)		0.002

≤3.5	178 (20)		30 (36)		0.001
>3.5	716 (80)		54 (64)		
aPTT; n=1095					
Normal		877 (87)		70 (76)	<0.001
Prolonged		126 (13)		22 (24)	
Triglycerides, mg/dL; n=706	182 (117-218)		225 (56-1309)		0.2
<220		476 (75)		45 (63)	0.03
≥220		158 (25)		27 (38)	
Cholesterol, mg/dL; n=779	179 (150-205)		184 (155-215)		0.2
<200		498 (71)		45 (60)	0.07
≥200		206 (29)		30 (40)	
Creatinine n=1145	0.86 (0.25-6.17)		1.02 (0.3-6.17)		0.02
<1.3		1002 (96)		87 (90)	0.02
≥ 1.3		46 (4)		10 (10)	
Urea, mg/dL; n=860					
<40		187 (24)		9 (13)	0.06
≥40		604 (76)		60 (87)	
CD56 positive >20% over blast population n= 771					
<20%		631 (89)		46(77)	0.005
≥20%		76 (11)		15 (23)	

Bleeding at diagnosis; n=1169					
Present		808 (76)		44 (44)	<0.001
Absent		260 (24)		57 (56)	

BMI: Body mass index; aPTT: activated partial thromboplastin time.

Table 3. Multivariate analyses of risk factors for development of life-threatening thrombosis in APL

Characteristic	Total number of patients	Life-threatening thrombo-ischemic events		
	n (%)	n (%)	Odds ratio (95% CI)	P value
Overall	1210	104		
Age (years)				
≤40	475 (39)	24 (23)		0.03
>40	731 (61)	79 (77)	2.5 (1.1-5.6)	
Platelet count, $\times 10^9$/L				
≤ 25	732 (61)	47 (45)		0.03
>25	475 (39)	57 (55)	2.3 (1.1-4.7)	
ECOG				
0-1	829 (76)	55 (60)		0.005
≥ 2	260 (24)	37 (40)	2.8 (1.4-5.7)	
aPTT				
Normal	947 (86)	70 (76)		0.02
Prolonged	148 (14)	22 (24)	2.6 (1.2-5.9)	
Bleeding at diagnosis				
Present	865 (74)	57 (56)		0.03
Absent	304 (26)	44 (44)	2.4 (1.2-4.9)	

Relapse Risk				
Low	270 (22)	34 (33)		0.20
Intermediate-High	938 (78)	70 (67)	1.6 (0.8-3.4)	
Creatinine, mg/dl				
<1.3	1089 (95)	87 (90)		0.81
≥ 1.3	56 (5)	10 (10)	1.1 (0.4-3.3)	
Albumin, g/dL				
≤3.5	208 (21)	30 (36)		0.07
>3.5	770 (79)	54 (64)	1.7 (0.9-3)	
Weight, kg				
<70	654 (61)	43 (50)		0.58
≥70	423 (39)	43 (50)	1.2 (0.7-2)	
BMI	27 (13-58)	29 (19-48)	1 (0.9-1)	0.26

BMI: Body mass index; aPTT: activated partial thromboplastin time.

Table 4. Distribution of Thromb-On score risk sum and categories and performance in training and validation cohorts.

Characteristic	All evaluable patients	Training cohort n=505		Validation cohort n=505	
	n (%)	No thrombosis n	Thrombosis n (%)	No thrombosis n	Thrombosis n (%)
Overall	1010 (100)	463	42 (9)	464	41 (8.8)
Sum score					
0 point	135 (13.3)	69	1 (1.4)	63	2 (3.1)
1 point	325 (32.2)	157	6 (3.7)	153	9 (5.6)
2 points	315 (31.2)	154	10 (6.1)	142	9 (6.0)
3 points	186 (18.4)	66	19 (22.3)	84	17 (16.8)
4 points	48 (4.8)	17	6 (26.1)	22	3 (12.0)
5 points	1 (0.1)	0	0 (NA)	0	1 (100.0)
Risk group					
Low (0 points)	135 (13.3)	69	1 (1.4)	63 (97.0)	2 (3.0)
Intermediate (1-2 points)	640 (63.4)	311	16 (4.9)	295 (94.2)	18 (5.8)
High (3-5 points)	235 (23.3)	83	25 (23.2)	106 (83.5)	21 (16.5)

NA: not applicable

Table 5. Outcomes of APL patients with and without life-threatening thrombo-ischemic events at diagnosis or during induction.

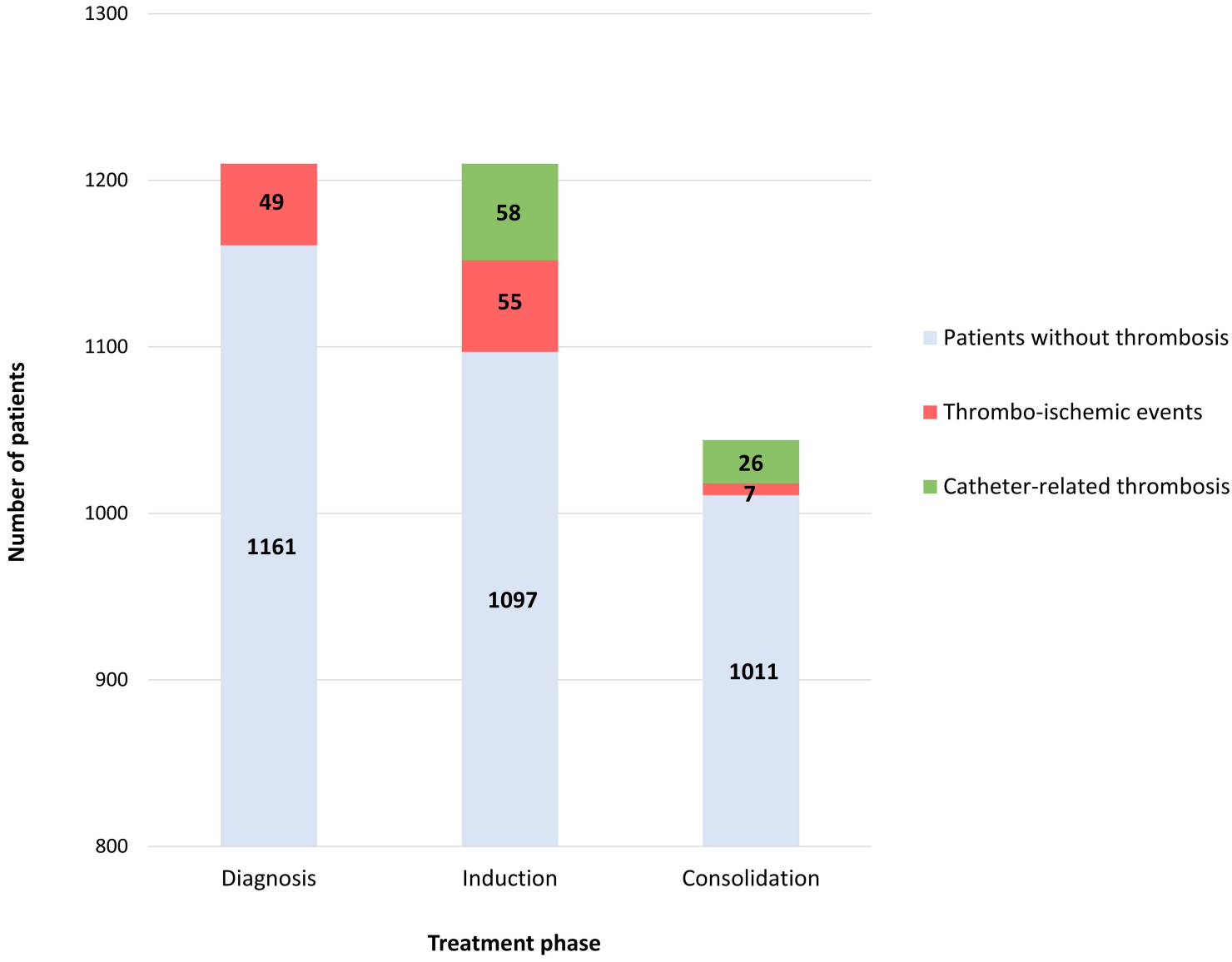
Characteristic	Patients without thrombosis		Patients with thrombosis in active APL		P
	Median (range)	n (%)	Median (range)	n (%)	
Overall; n=1210		1106 (91)		104 (9)	
Death during induction; n=1209					
No		972 (88)		61 (69)	<0.001
Yes		134 (12)		32 (31)	
Hospitalization during induction (days) n=871					
≤30		796 (98)		51 (91)	0.01
>30		19 (2)		5 (9)	
Days under intravenous antibiotics during induction; n=947	19 (1-161)		18 (2-59)		
≤15		426 (49)		37 (45)	0.55
>15		439 (51)		45 (55)	
Differentiation Syndrome; n=1148					
Severe		119 (11)		14 (15)	0.43
No/moderate		993 (88)		82 (85)	

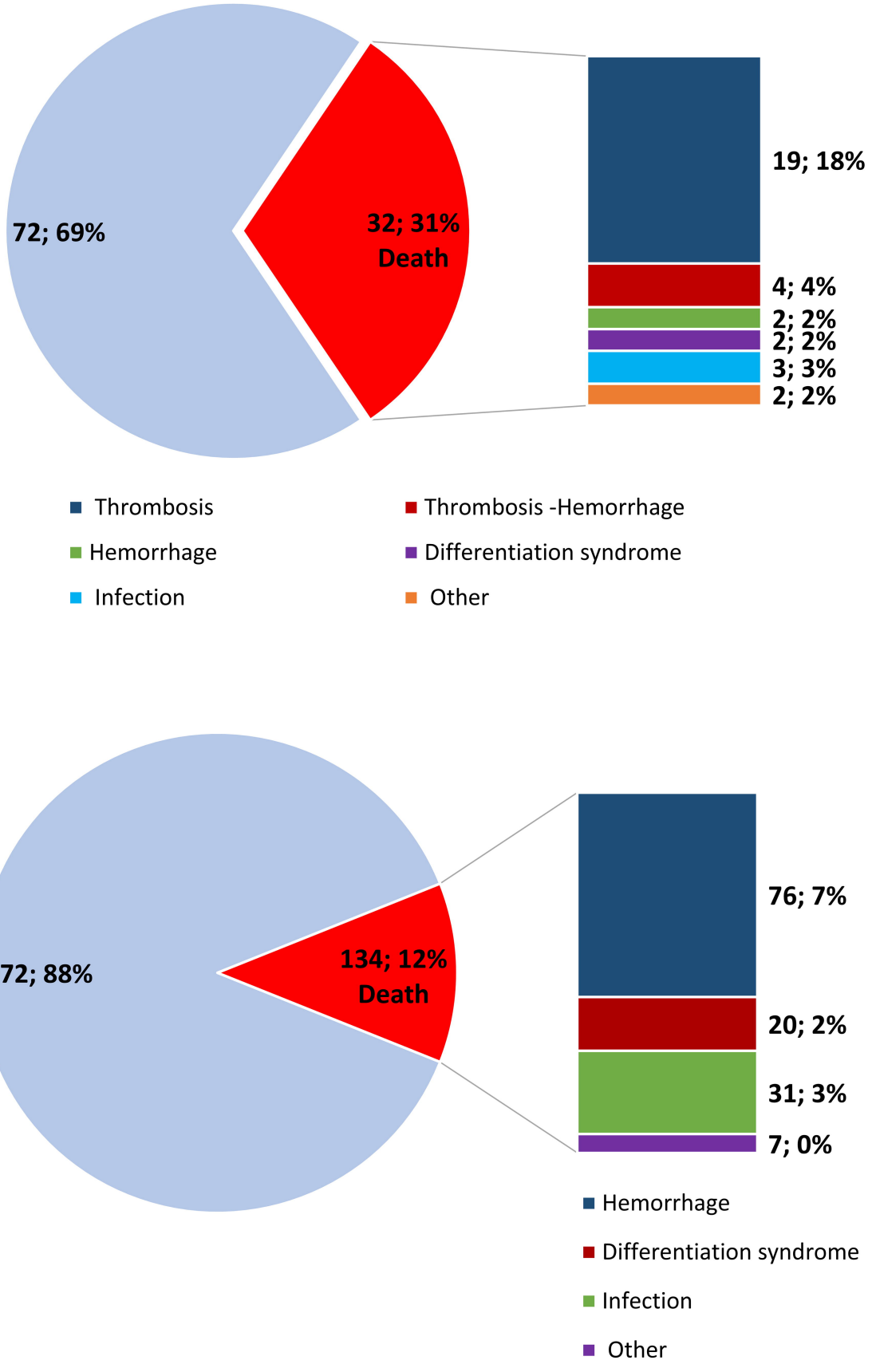
APL: acute promyelocytic leukemia

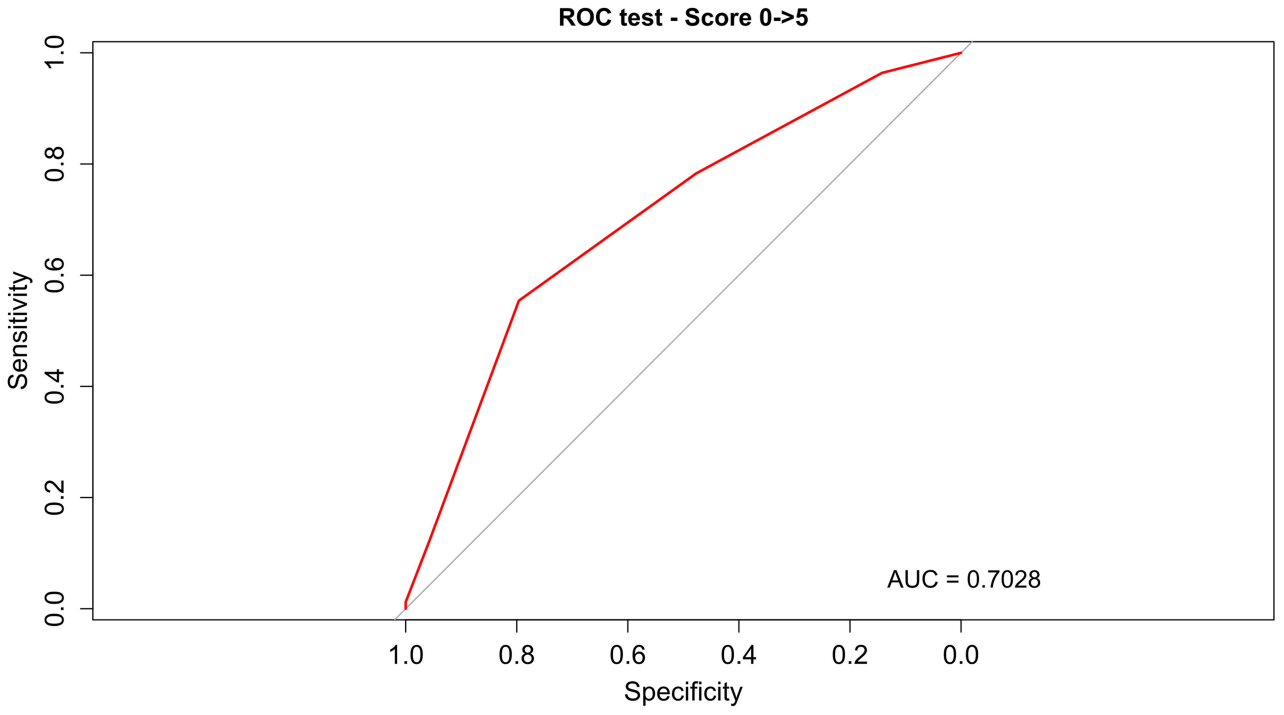
Figure 1. Incidence of thrombosis according to treatment phase (diagnosis, induction, consolidation) and type of thrombosis (catheter-related/surface vein thrombosis vs. life-threatening thrombo-ischemic events).
Data refer to patients treated with AIDA-based regimen.

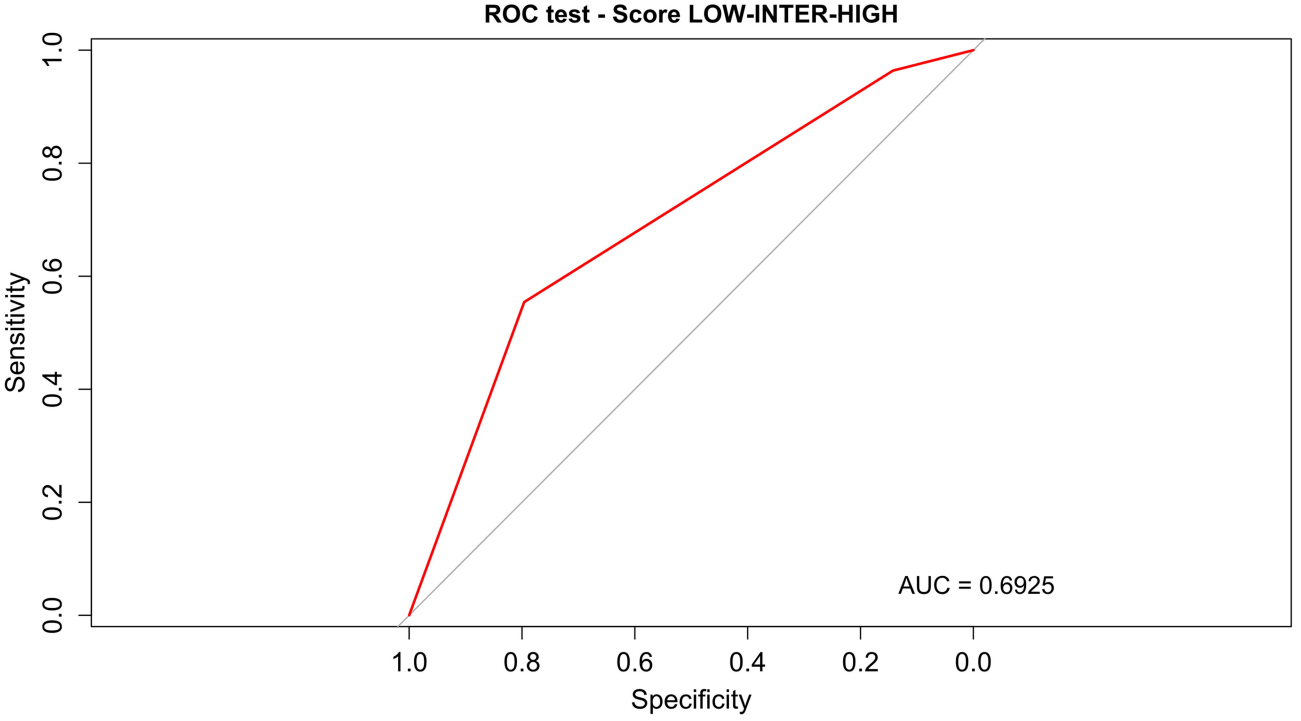
Figure 2. Early death rate and causes of death in APL patients: panel A) patients who developed life-threatening thrombosis at diagnosis or during induction; panel B) patients who did not develop life-threatening thrombosis at diagnosis or during induction.
Data refer to patients treated with AIDA-based regimen.

Figure 3. Receiver operator curve (ROC) according to the Thromb-On score: A) using the sum score 0 to 5, AUC 0.70; and B) using the 3 risk categories (low 0 points, intermediate 1-2 points, and high risk 3 to 5 points, AUC 0.69).
Data refer to patients treated with AIDA-based regimen.


1300
1200
1100
1000
900
800
Number of patients
49
1161
58
55
1097
26
7
1011
Diagnosis
Induction
Consolidation
Treatment phase
Patients without thrombosis
Thrombo-ischemic events
Catheter-related thrombosis


72; 69%
32; 31%
Death
19; 18%
4; 4%
2; 2%
2; 2%
3; 3%
2; 2%
Thrombosis
Thrombosis -Hemorrhage
Hemorrhage
Differentiation syndrome
Infection
Other
972; 88%
134; 12%
Death
76; 7%
20; 2%
31; 3%
7; 0%
Hemorrhage
Differentiation syndrome
Infection
Other


ROC test - Score 0->5
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
AUC = 0.7028
1.0
0.8
0.6
0.4
0.2
0.0
Specificity


ROC test - Score LOW-INTER-HIGH
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
AUC = 0.6925
1.0
0.8
0.6
0.4
0.2
0.0
Specificity

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

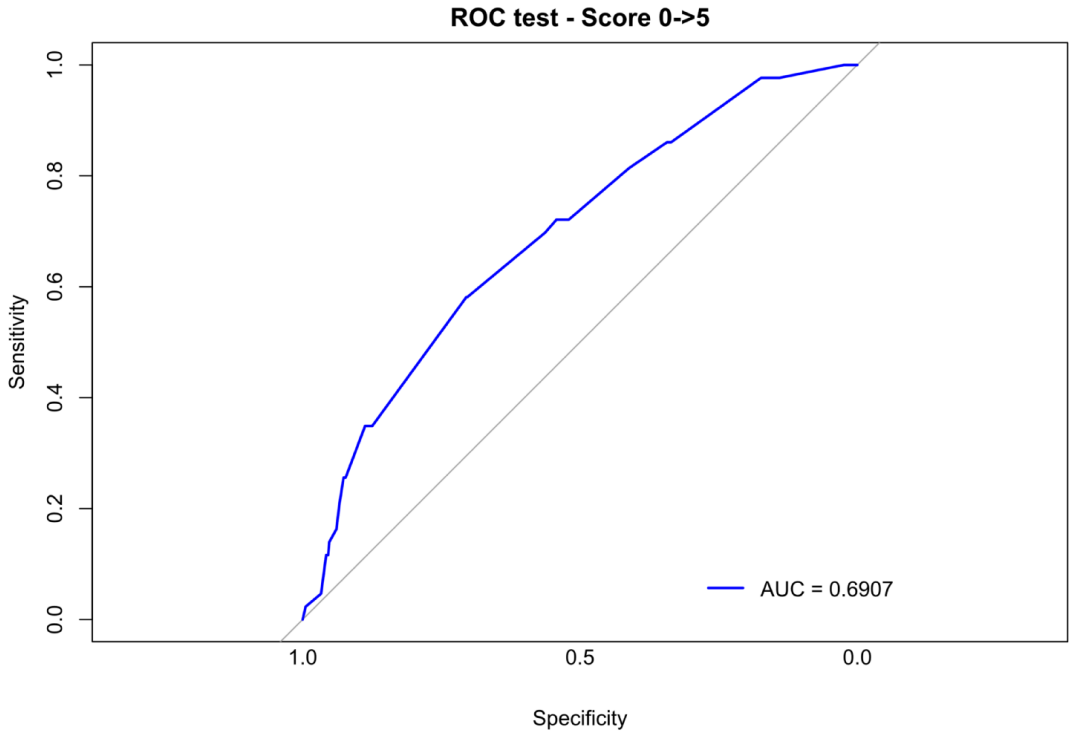
Supplementary Table 4. Distribution of Thromb-On score risk sum and categories and performance in external validation cohort (LPA2017 protocol).

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

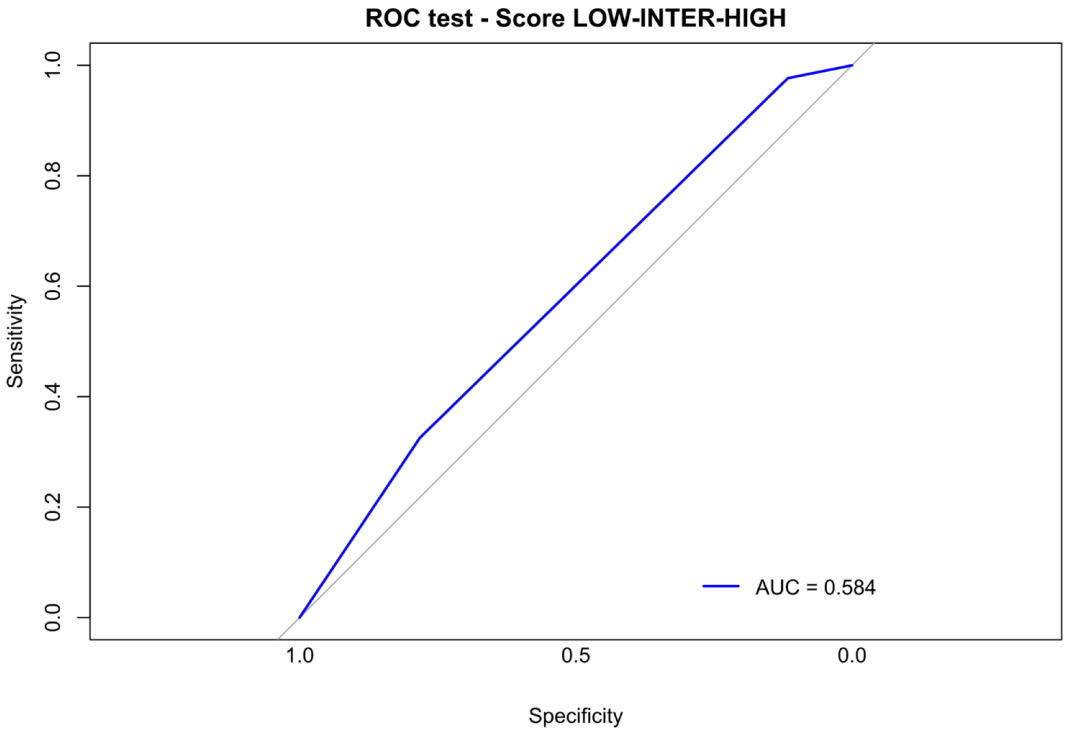
Supplementary Figure 1A and 1B. Receiver operator curve (ROC) and ANOVA according to the Thromb-On score in validation cohort (LPA2017 protocol): A) using the sum score 0 to 5, AUC 0.69; and B) using the 3 risk categories (low 0 points, intermediate 1-2 points, and high risk 3 to 5 points, AUC 0.58.

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	