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# A prediction model for central venous catheter-related thrombosis in patients with newly-diagnosed acute myeloid leukemia: A derivation cohort analysis

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ABSTRACT

*Background:* Catheter-related thrombosis (CRT) is a common complication in cancer patients, that may lead to chemotherapy deferral, elevated risk for systemic infections and pulmonary embolism. This study aimed to assess CRT incidence and risk factors in newly-diagnosed acute myeloid leukemia (AML) patients and create predictive models potentially allowing to decrease CRT occurrence in this population.

*Methods:* This retrospective single-center analysis included all AML patients treated at the Rambam Health Care Campus between 2006 and 2019. Patient clinical and laboratory data were collected to evaluate thrombosis occurrence and time from AML diagnosis to CRT development. Multivariate classification models were created using logistic regression (LR) and competing risk analyzes.

*Results:* The final analysis included 632 newly-diagnosed AML patients (mean age 54 ± 15 years). CRT incidence was 10.1% [confidence interval (CI) 7.7–12.9%], median time from AML diagnosis to CRT was 12.5 days [interquartile range 6–30]. In an LR multivariate model, prior history of venous thromboembolism [adjusted odds ratio (AOR) 12.046, $p < 0.0001$], acute promyelocytic leukemia (APL) (AOR 2.824, $p = 0.015$), a high body mass index and initial platelet counts <100 × 10E9/L (AOR 1.059 and 0.546; $p = 0.011$ and 0.040, respectively) were significantly associated with high CRT risk. Analysis of 587 non-APL patients demonstrated comparable results, with CRT incidence of 9.3% (CI 7.0%-12.1%) and emergence of chronic obstructive pulmonary disease (COPD) as a novel significant co-factor (AOR 34.491, $p = 0.004$). In both models, the area under curve (AUC) was ≥70%.

*Conclusions:* Significant CRT risk factors defined using the created model could be used for identification of high-risk newly-diagnosed AML patients requiring CRT prophylaxis.

## 1. Introduction

Venous thromboembolism (VTE) is a major cause of morbidity and mortality in cancer patients. In a large population-based cohort study from Denmark, the VTE incidence within the first 6 months after cancer diagnosis has been shown to significantly increase between 1997 and 2017 [1]. Acute leukemias are prothrombotic diseases, which is attributed to the induction of leukemic cell procoagulant activity, especially following treatment-mediated leukemia cell death [2,3]. Catheter-related thrombosis (CRT), defined as VTE associated with central venous catheters (CVCs), may occur shortly after catheter insertion [4] and its incidence varies between 3.0 and 11.7%, depending on the leukemia subtype [5,6]. Risk factors for CRT include age, type of cancer, prior VTE (especially CRT), thrombophilia and infection [5,7,8]. In acute myeloid leukemia (AML), the female gender, older age, the number of chronic co-morbidities, and CVC presence have been recognized as significant predictive factors for VTE development within one year following AML diagnosis [9]. Yet, there is scarcity of studies

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focusing on CRT in newly-diagnosed AML patients.

Given the complicated VTE management in leukemia patients due to concurrent thrombocytopenia and thrombosis requiring anti-coagulation, the current study has been designed to determine the CRT incidence and potential risk factors in newly-diagnosed AML patients as well as to develop predictive models that could be applied for personalized treatment of CRT in this vulnerable patient population.

## 2. Material and methods

### 2.1. Study design and population

This retrospective analysis incorporated all newly-diagnosed AML patients admitted to the Rambam Health Care Campus (RHCC; Haifa, Israel) between January 2006 and September 2019. RHCC is the tertiary leukemia referral center for northern Israel, providing services to over 1.5 million citizens. All the included patients underwent CVC insertion and were treated with the same therapeutic approaches consistent with established international treatment protocols [i.e., chemotherapy-based induction and consolidation for non-APL patients and all-trans retinoic acid (ATRA) based therapy for APL patients]. All centrally inserted lines were subclavian and all peripherally inserted lines were inserted in the upper extremities. Patients were followed from diagnosis until the occurrence of either CRT, death or the last follow-up. With regard to the date of CRT onset or death, the final follow-up date was December 01, 2019. This study was approved by the Rambam Institutional Review Board (IRB; approval #0483-18-RMB). The need for informed consent was waived by the IRB due to the retrospective nature of the study.

### 2.2. Patient characteristics and outcomes

Predictive models and analyzes were developed based on data derived from patients' electronic medical records, utilizing the MDClone (Beer Sheba, Israel) software. Clinical variables known to be associated with VTE, as well as potential risk factors, including patient demographics, body mass index (BMI), body surface area (BSA), comorbid conditions inclusive of history of solid tumors, lymphoma, myeloproliferative disorders, hypercoagulable conditions [e.g., antiphospholipid antibodies (APLA) and Factor V Leiden] and previous VTE were recorded. The information on the diagnosis of APLA syndrome or factor V Leiden deficiency was taken from the past medical history, documented in each patient's medical record. None of the patients underwent screening for these medical conditions at diagnosis. No information on other inherited risk factors for thrombosis was available due to the retrospective nature of this study. Additional medical conditions, such as myocardial infarction, congestive heart failure, atrial fibrillation, diabetes mellitus, hypertension and chronic obstructive pulmonary disease (COPD) were documented. Baseline laboratory variables at diagnosis, including complete blood count (CBC), coagulation studies, lactate dehydrogenase (LDH), serum creatinine and glomerular filtration rate (GFR; based on the Cockcroft-Gault equation) were also retrieved. Both peripherally and centrally inserted catheters were employed for treatment administration. CRT was diagnosed using Doppler ultrasound performed according to physician's suspicion. Patients were not screened systematically. The diagnosis of CRT was based on objective data observed on US Doppler examination. Findings consistent with thrombosis were vein non-compressibility and lack of blood flow in the suspected vein. US Doppler examinations were conducted by a trained technician and approved or repeated by a trained radiologist.

### 2.3. Study endpoints

Outcomes included: CRT occurrence, time from AML diagnosis to CRT development and a correlation between the CRT diagnosis and patient death.

### 2.4. Statistical analysis

The study database was analyzed using R software (version 4.0.3, The R Foundation for Statistical Computing). Comparisons between groups were performed with the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Predictive models for CRT were developed with univariate logistic regression (LR) and presented as odds ratios (OR) and *p*-values. Variables found to have statistical significance ($p$-value $< 0.050$) or trend ($p$-value $< 0.090$) in univariate analysis, were introduced into a multivariate LR model, in a backward stepwise fashion and presented as adjusted OR (AOR) with 95% confidence intervals (CI) and *p*-values. The multivariate model accuracy is presented with receiver operating characteristic (ROC) curves, including the area under the curve (AUC), with 95% confidence intervals (CI) based on bootstrapping method, as well as Hosmer and Lemeshow goodness-of-fit (HLGOF) *p*-value and overall model *p*-value. The ROC best threshold is presented utilizing Youden's J statistic to estimate the optimal cutoff values of sensitivity/specificity. Positive and negative predictive values were calculated based on logistic regression estimation of probability, taking into account 0.5 as the cut-off for positive probability. Platelet levels were assessed as both continuous and Boolean variables (i.e., platelet level $<100 \times 10E9/L$).

Time-to-thrombosis analysis was carried out as a competing risk analysis, with patient death considered a competing event. The cause-specific hazard regression model was calculated with Cox proportional hazards regression. The sub-distribution hazard model was determined using the Fine and Grey sub-distribution hazard function. Both univariate and multivariate regressions are presented, with a selection of parameters for the multivariate analysis according to univariate statistical significance or trend.

### 2.5. Theory

Risk factors for CRT in newly-diagnosed AML patients can be identified and may serve as a basis for the development of a prediction model.

## 3. Results

A total of 632 newly-diagnosed AML patients were included in this study (average age $54 \pm 15$ years; 54% − males). While in the majority of patients a peripherally inserted central catheter (PICC) was used, in 19 (3%) individuals, treatment was administered via a centrally-inserted central catheter (CICC; Hickman™ catheters). Eight patients received thrombosis prophylaxis in case of known atrial fibrillation with indication for stroke prevention. Two patients received thrombosis prophylaxis in case of prior VTE with a history of APLA or factor V Leiden. Main baseline characteristics of the patients, with the differentiation based on the CRT development, are presented in Table 1.

### 3.1. A predictive model for catheter-related thrombosis

The cumulative incidence of CRT was 10.1% (64/632 patients; CI 7.7–12.9%) for the entire AML cohort. Out of the 64 patients diagnosed with CRT, **c**atheter-related blood stream infection developed in 16 (25%) individuals. In univariate analysis, patients with APL and those with a prior history of VTE were found to be more likely to develop CRT (AOR 2.894 and 12.046; *p*-values 0.015 and <0.0001, respectively). In addition, a BMI increase of 1 $kg/m^2$ appeared to correlate with a 5.9% elevation in the CRT incidence. As to the platelet counts at diagnosis, while the absolute level showed a non-significant positive correlation with CRT (i.e., a platelet count increase of 1000/μL corresponded to a 0.1% increase in CRT incidence; *p*-value 0.101), initial platelet levels $<100 \times 10E9/L$ were associated with lower CRT occurrence (AOR 0.546; *p*-value 0.040). Notably, patient age and initial blood workup results (apart from low platelet counts) did not correlate with CRT. In

**Table 1**
Baseline clinical characteristics of study population (n = 632).

| | No CRT ($n$ = 568) | CRT ($n$ = 64) | $P$-value |
|---|---|---|---|
| Age (years) | 54.6(±15.7) | 57.4(±14.0) | 0.222 |
| Gender - Female | 261(46%) | 29(45%) | >0.999 |
| BMI (kg/m$^2$) | 27.8(±5.5) | 29.7(±6.2) | 0.042* |
| BSA (m$^2$) | 1.89(±0.23) | 1.95(±0.23) | 0.044* |
| APL | 36(6%) | 9(14%) | 0.036* |
| CICC (Hickman) only | 19(3%) | 0(0%) | 0.243 |
| **Hematological medical history** | | | |
| Coagulation disorder | 1(0%) | 1(1%) | 0.192 |
| Myelodysplastic syndrome | 44(8%) | 7(11%) | 0.338 |
| MPN | 6(1%) | 1(1%) | 0.528 |
| Lymphoma | 14(2%) | 1(1%) | >0.99 |
| Venous thromboembolism | 9(1%) | 11(17%) | <0.0001* |
| **Other medical history** | | | |
| Solid tumor | 32(6%) | 6(9%) | 0.261 |
| COPD | 3(1%) | 2(3%) | 0.083 |
| CHF | 1(0%) | 0(0%) | >0.999 |
| Atrial fibrillation | 31(5%) | 3(4%) | >0.999 |
| Diabetes mellitus | 80(14%) | 10(15%) | 0.708 |
| Myocardial infarction | 35(6%) | 5(8%) | 0.587 |
| CVA | 14(2%) | 0(0%) | 0.381 |
| Hypertension | 186(33%) | 23(36%) | 0.674 |
| **1st laboratory findings** | | | |
| WBC (x10$^3$/μL) | 24.7(±50.2) | 14.0(±25.9) | 0.154 |
| Neutrophils (x10$^3$/μL) | 3.7(±12.4) | 2.9(±4.3) | 0.763 |
| Blasts (%) | 28.6(±28.1) | 28.3(±31.8) | 0.707 |
| Hemoglobin (g/dl) | 9.5(±2.2) | 9.6(±1.8) | 0.796 |
| Platelets (x10E9/L) | 107.7(±148.4) | 146.7(±139.2) | 0.003* |
| PT (seconds) | 12.1(±2.5) | 11.8(±1.4) | 0.360 |
| APTT (seconds) | 30.7(±8.1) | 29.4(±6.9) | 0.211 |
| Fibrinogen (mg/dl) | 373.9(±149.8) | 375.4(±143.8) | 0.823 |
| LDH (U/L) | 481.1(±656.2) | 332.5(±339.0) | 0.011* |
| Creatinine (mg/dl) | 0.9(±0.4) | 0.9(±0.3) | 0.738 |
| GFR (mL/min/1.73m$^2$) | 100.9(±42.9) | 112.1(±59.8) | 0.333 |

* – statistically significant, Average (±standard deviation); absolute number (percentage of group), APL–Acute Promyelocytic Leukemia; APTT–Activated Partial Thromboplastin Time; BMI–Body Mass Index; BSA–Body Surface Area; CICC–Centrally Inserted Central Catheter; CRT–Catheter Related Thrombosis; CHF–Congestive Heart Failure; COPD–Chronic Obstructive Pulmonary Disease; CVA–Cerebrovascular Accident; GFR–Glomerular Filtration Rate; MPN–Myeloproliferative Neoplasm; PT–Prothrombin Time; LDH–Lactate Dehydrogenase; WBC–White Blood Cells.

addition, while none of the patients treated with CICC developed CRT, the catheter type was not found to be of predictive significance (Table 2).

The multivariate LR classification model, which included 4 parameters (APL, prior VTE, BMI and platelet counts <100 × 10E9/L), identified as significant or trending toward significance in the univariate analysis, demonstrated satisfactory performance, with an AUC of 69.8% (CI 62.6–77.1%) (Fig. 1). Overall, the model $p$-value <0.0001, HLGOF $p$-value 0.443 and ROC Youden's J statistic thresholds of 0.76 for sensitivity and 0.56 for specificity were shown. The positive predictive value (PPV) and the negative predictive value (NPV) were 0.687 and 0.913, respectively.

Among 587 non-APL patients, the cumulative incidence of CRT was 9.3% (CI 7.0–12.1%).

Univariate LR analysis revealed relatively similar results, with patient age and BMI (OR 1.021 and 1.046, respectively) as well as a prior history of VTE (OR 12.913) or COPD (OR 20.037) and an initial platelet level <100 × 10E9/L (OR 0.401), found to have significant statistical correlations. The multivariate LR model included the following 4 parameters: BMI (AOR 1.060, $p$-value 0.017), prior VTE (AOR 11.264, $p$-value < 0.0001), COPD (AOR 34.491, $p$-value 0.004) and an initial platelet count <100 × 10E9/L (AOR 0.498, $p$-value 0.028) (Table 3). This classification model demonstrated good performance, with an AUC of 71.1% (CI 63.5–78.9%) (Fig. 2). Overall, model $p$-value <0.0001, HLGOF $p$-value 0.469 and ROC Youden's J statistic thresholds of 0.61 for sensitivity and 0.72 for specificity were shown. The PPV and NPV were 0.666 and 0.920, respectively.

### 3.2. Time from AML diagnosis to CRT development

Median time between AML diagnosis and CRT for the entire study population was 12.5 days [interquartile range (IQR) 6–30; minimum 1 day, maximum 71 days], indicating that most patients developed CRT early during the treatment course (i.e., induction and consolidation periods). Eighty-eight percent of the patients were diagnosed with CRT within 56 days from AML diagnosis. Univariate hazard models, taking into account patient death as a competing risk event, are presented in Table 4. Notably, increased patient BMI, BSA, prior VTE and APL were associated with higher incidence of CRT over time, while platelet counts lower than 100 × 10E9/L correlated with decreased thrombosis incidence. COPD and a history of APLA syndrome or Factor V Leiden were found to have significant univariate associations. Results of multivariate analyzes of the time lapse between AML diagnosis and CRT occurrence are presented in Table 5. In Cox regression analysis, a prior history of VTE, patient BMI and APL were found to have significant hazard ratios (HR), whereas platelet counts lower than 100 × 10E9/L demonstrated a statistical trend correlation (HR 7.558, 1.069, 2.630, 0.609, respectively) (Fig. 3).

### 3.3. Mortality and CRT

Three hundred and ninety-three AML patients (62%) and 6 (13%) APL patients died within the study follow-up period [median 1.1 years (IQR 0.4–4.0 years)]. Occurrence of CRT was not found correlate with patient death (Fisher's exact test $p$-value > 0.999; univariate Cox regression $p$-value 0.635). Similar results were observed both in non-APL (Fisher's exact test $p$-value 0.656, Cox regression $p$-value 0.898) and APL subgroups (Fisher's exact test $p$-value 0.583, Cox regression $p$-value 0.390).

## 4. Discussion

VTE is recognized as a major complication in patients with hematological malignancies. In a large Danish population-based cohort trial evaluating the VTE risk in 32,141 patients with hematological cancers, the 10-year absolute risk for any thromboembolic event was reported to be 5.2% [10,11]. CVCs have long become critical for the delivery of intravenous therapy to cancer patients [12,13]. Despite recent advances in CVC techniques, the use of these devices remains being associated with a number of recognized complications, including such major ones as bloodstream infections and thrombosis [14,15].

A prospective observational multicenter study from Italy, including 416 patients with hematological malignancies, has reported an overall incidence of CVC-related venous thrombosis events of 12.0% (2.54 cases per 1000 catheter days) [16]. In acute leukemias in general, where the procoagulant nature of malignant cells is the major factor accounting for VTE risk at diagnosis, treatment regimens, including chemotherapy and steroids, as well as CVC and infections, further enhance this risk [3, 17–19]. Indeed, the thrombosis prevalence post-induction chemotherapy, evaluated among younger and older AML patients in a prospective trial from the Netherlands, has reached 8.7% and 10.4%, respectively [20].

Given the predisposition of AML patients to thrombosis as well as both disease- and therapy-related challenges associated with its management, the present study focused on a large homogenous cohort of AML patients, treated at the same tertiary medical center, with a similar approach. The cumulative CRT incidence was 10.1% and 9.3% for the entire study group and the non-APL subgroup, respectively. Patients diagnosed with CRT were more likely to have a history of VTE or COPD, present with APL and have a higher BMI. Initial platelet counts were the only laboratory parameter associated with CRT development, with low levels being more common in patients who did not develop CRT. While

**Table 2**
Analysis of risk factors for catheter-related thrombosis in all the evaluable patients ($n = 632$).

| | Univariate analysis | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|
| | OR | *P*-value | AOR | 95% Confidence Interval Low | High | *P*-value |
| Age (years) | 1.012 | 0.164 | | | | |
| Gender - Female | 0.974 | 0.923 | | | | |
| BMI (kg/m$^2$) | 1.055 | 0.012* | 1.059 | 1.012 | 1.107 | 0.011* |
| BSA (m$^2$) | 3.358 | 0.028* | | | | |
| APL | 2.418 | 0.026* | 2.824 | 1.160 | 6.348 | 0.015* |
| CICC (Hickman) only | $2 \times 10^{-7}$ | 0.986 | | | | |
| **Hematological medical history** | | | | | | |
| Coagulation disorder‡ | 8.999 | 0.122 | | | | |
| Myelodysplastic syndrome | 1.462 | 0.377 | | | | |
| MPN | 1.486 | 0.716 | | | | |
| Lymphoma | 0.628 | 0.656 | | | | |
| Venous thromboembolism | 12.890 | <0.0001* | 12.046 | 4.558 | 32.794 | <0.0001* |
| **Other medical history** | | | | | | |
| Solid tumor | 1.732 | 0.238 | | | | |
| COPD | 6.075 | 0.050 | | | | |
| CHF | $4 \times 10^{-6}$ | 0.989 | | | | |
| Atrial fibrillation | 0.851 | 0.796 | | | | |
| Diabetes mellitus | 1.129 | 0.738 | | | | |
| Myocardial infarction | 1.290 | 0.608 | | | | |
| CVA | $5 \times 10^{-7}$ | 0.982 | | | | |
| Hypertension | 1.152 | 0.607 | | | | |
| **1st laboratory findings** | | | | | | |
| WBC (x10$^3$/μL) | 0.992 | 0.113 | | | | |
| Neutrophils (x10$^3$/μL) | 0.989 | 0.587 | | | | |
| Blasts (%) | 0.999 | 0.958 | | | | |
| Hemoglobin (g/dl) | 1.004 | 0.942 | | | | |
| Platelets (x10E9/L) | 1.001 | 0.101 | | | | |
| Platelets <100 × 10E9/L | 0.483 | 0.006* | 0.546 | 0.304 | 0.972 | 0.040* |
| PT (seconds) | 0.909 | 0.232 | | | | |
| APTT (seconds) | 0.977 | 0.239 | | | | |
| Fibrinogen (mg/dl) | 1.000 | 0.939 | | | | |
| LDH (U/L) | 0.999 | 0.056 | | | | |
| Creatinine (mg/dl) | 0.730 | 0.432 | | | | |
| GFR (mL/min/1.73m$^2$ | 1.004 | 0.064 | | | | |

‡ APLA syndrome, Factor V Leiden.
* – statistically significant, AOR – Adjusted Odds Ratio; APL – Acute Promyelocytic Leukemia; APTT – Activated Partial Thromboplastin Time; BMI – Body Mass Index; BSA – Body Surface Area; CICC – Centrally Inserted Central Catheter; CHF – Congestive Heart Failure; COPD – Chronic Obstructive Pulmonary Disease; CVA – Cerebrovascular Accident; GFR – Glomerular Filtration Rate; LDH – Lactate Dehydrogenase; MPN - Myeloproliferative Neoplasm; OR – Odds Ratio; PT – Prothrombin Time; WBC – White Blood Cells.

the reported incidence of CRT in AML patients markedly varied across the studies, ranging from 3 to 18% [17,21–23], the values demonstrated in the present study fell within this range. In this study, the insertion location (peripheral versus central) of the CVC was not found to be related to the CRT incidence. Previous studies arrived at mixed conclusions regarding the use of PICC lines in comparison with CICCs [6,21,24,25]. Similar to our findings, some reports showed higher CRT incidence with PICCs, whereas the difference was not always significant. At the same time, studies on larger AML cohorts demonstrated higher CRT rates for PICCs [26].The very low rates of CICCs utilization in the present study may explain the lack of statistically significant difference in CRT incidence related to the device types.

Reduction of CRT occurrence in cancer patients remains challenging. Moreover, in AML, prophylactic approaches may be hazardous due to concomitant thrombocytopenia. In this context, predictive models designed to identify high-risk AML patients could be one of the key elements contributing to improved management of such individuals. The relative simplicity of the proposed models, based only on clinical and laboratory findings, can provide clinicians with a CRT risk stratification tool, allowing to identify the patients who might benefit from thromboprophylaxis.

Our current findings strongly validate the earlier reported evidence that patients with a previous episode of VTE are at an increased risk of its recurrence, especially during high-risk periods (e.g., major surgery or serious illness) [27] and this is also the case with CRT in cancer patients [28].

Obesity has long been considered a moderate risk factor for VTE in general [29,30] and CRT in particular [31]. This relation has been reported in patients with solid cancer [32] as well as in pediatric and adult ALL patients [33,34]. Our results are in line with these data and demonstrate that every addition of 1 kg/m$^2$ increases the occurrence of CRT by 6%. The risk for CRT development in APL patients is relatively high and well documented [6,22]. In the present study, comparable data were observed.

COPD is known to be associated with an increased risk of VTE, which appears to correlate to disease severity [35–37]. To the best of our knowledge, the present study is the first to identify COPD as a major risk factor for CRT in non-APL AML patients in a multivariate analysis, with an AOR being as high as 34.5.

Among the laboratory indices determined at AML diagnosis, platelet levels were the sole parameter with a significant classification power to be included in multivariate prediction models, with the counts below 100 × 10E9/L associated with lower CRT occurrence (LR AOR 0.546, sub-distribution HR 0.459). The relationship between platelet levels and VTE in other diseases is well established. For instance, patients with essential thrombocytosis are known to be more likely to develop VTE during COVID-19 infection [38]. The pre-cancer platelet count and the platelet to lymphocyte ratio, are reported to be associated with a risk of symptomatic VTE in cancer patients [39–41].

Unlike other hematological malignancies and solid tumors, where high platelet counts are recognized as risk factors for DVT, in leukemia patients, our data suggest that CRT occurrence is diminished in the

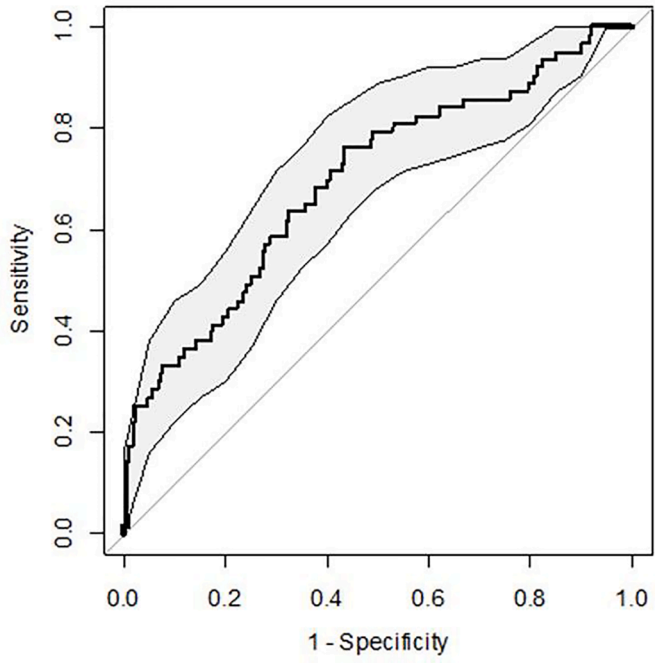


**Fig. 1.** Catheter-related thrombosis among all the evaluable AML patients ($n$ = 632): multivariate logistic regression analysis – ROC curve, ROC – Receiver Operating Characteristic.

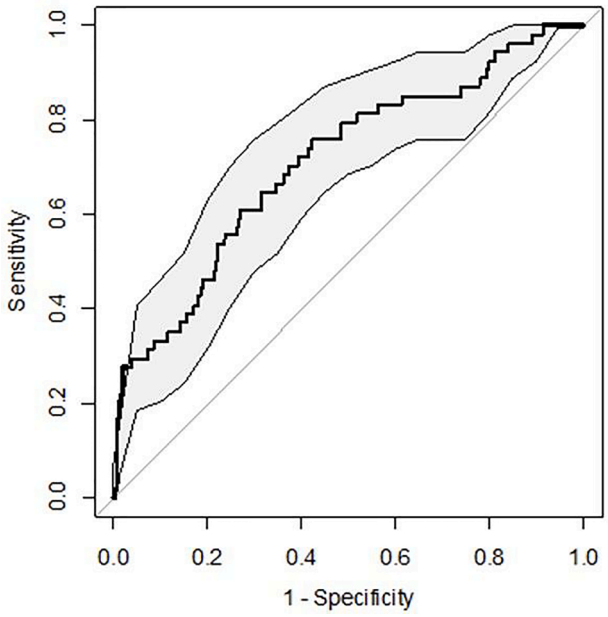


**Fig. 2.** Catheter-related thrombosis among non-APL patients ($n$ = 587): multivariate logistic regression analysis – ROC curve, APL – Acute Promyelocytic Leukemia; ROC – Receiver Operating Characteristic.

**Table 3**
Analysis of risk factors for catheter-related thrombosis in non-APL patients ($n$ = 587).

| | Univariate analysis | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|
| | OR | *P*-value | AOR | 95% Confidence Interval Low | High | *P*-value |
| Age (years) | 1.021 | 0.036* | | | | |
| Gender - Female | 0.804 | 0.449 | | | | |
| BMI (kg/m$^2$) | 1.046 | 0.054 | 1.060 | 1.009 | 1.112 | 0.017* |
| BSA (m$^2$) | 3.152 | 0.055 | | | | |
| CICC (Hickman) only | $6 \times 10^{-7}$ | 0.982 | | | | |
| **Hematological medical history** | | | | | | |
| Coagulation disorder‡ | 9.833 | 0.108 | | | | |
| Myelodysplastic syndrome | 1.617 | 0.268 | | | | |
| MPN | 1.623 | 0.657 | | | | |
| Lymphoma | 0.685 | 0.717 | | | | |
| Venous thromboembolism | 12.913 | <0.0001* | 11.264 | 4.112 | 31.462 | <0.0001* |
| **Other medical history** | | | | | | |
| Solid tumor | 1.978 | 0.147 | | | | |
| COPD | 20.037 | 0.015* | 34.491 | 3.123 | 771.022 | 0.004* |
| Atrial fibrillation | 1.000 | 0.999 | | | | |
| Diabetes mellitus | 1.192 | 0.648 | | | | |
| Myocardial infarction | 1.512 | 0.410 | | | | |
| CVA | $6 \times 10^{-7}$ | 0.984 | | | | |
| Hypertension | 1.076 | 0.804 | | | | |
| **1st laboratory findings** | | | | | | |
| WBC (x10$^3$/μL) | 0.993 | 0.161 | | | | |
| Neutrophils (x10$^3$/μL) | 0.990 | 0.616 | | | | |
| Blasts (%) | 0.997 | 0.640 | | | | |
| Hemoglobin (g/dl) | 1.018 | 0.775 | | | | |
| Platelets (x10E9/L) | 1.001 | 0.080 | | | | |
| Platelets <100 × 10E9/L | 0.401 | 0.002* | 0.498 | 0.264 | 0.923 | 0.028* |
| PT (seconds) | 0.908 | 0.274 | | | | |
| APTT (seconds) | 0.966 | 0.121 | | | | |
| Fibrinogen (mg/dl) | 1.000 | 0.639 | | | | |
| LDH (U/L) | 0.999 | 0.090 | | | | |
| Creatinine (mg/dl) | 0.926 | 0.837 | | | | |
| GFR (mL/min/1.73m$^2$) | 1.001 | 0.601 | | | | |

‡ APLA syndrome, Factor V Leiden.

* – statistically significant, AOR – Adjusted Odds Ratio; APL – Acute Promyelocytic Leukemia; APTT – Activated Partial Thromboplastin Time; BMI – Body Mass Index; BSA – Body Surface Area; CHF – Congestive Heart Failure; CICC – Centrally Inserted Central Catheter; COPD – Chronic Obstructive Pulmonary Disease; CVA – Cerebrovascular Accident; GFR – Glomerular Filtration Rate; LDH – Lactate Dehydrogenase; MPN - Myeloproliferative Neoplasm; OR – Odds Ratio; PT – Prothrombin Time; WBC – White Blood Cells.

**Table 4**
Time from AML diagnosis to CRT occurrence: univariate sub-distribution and proportional hazard regression analyzes (all patients, $n = 632$).

| | Sub-distribution hazard model HR (95% CI) | *P*-value | Cause-specific hazard model HR (95% CI) | *P*-value |
|---|---|---|---|---|
| Age (years) | 1.010(0.996–1.030) | 0.140 | 1.013(0.996–1.030) | 0.119 |
| Gender - Female | 0.994(0.608–1.620) | 0.980 | 1.008(0.616–1.650) | 0.974 |
| BMI (kg/m$^2$) | 1.060(1.010–1.100) | 0.008* | 1.055(1.015–1.098) | 0.007* |
| BSA (m$^2$) | 3.190(1.200–8.450) | 0.020* | 3.142(1.142–8.644) | 0.026* |
| APL | 2.330(1.140–4.780) | 0.020* | 2.273(1.124–4.600) | 0.022* |
| **Hematological medical history** | | | | |
| Coagulation disorder‡ | 7.500(0.835–67.400) | 0.072 | 7.513(1.041–54.230) | 0.045* |
| Myelodysplastic syndrome | 1.440(0.655–3.150) | 0.370 | 1.436(0.655–3.149) | 0.366 |
| MPN | 1.530(0.193–12.200) | 0.690 | 1.512(0.209–10.900) | 0.682 |
| Lymphoma | 0.634(0.090–4.450) | 0.650 | 0.638(0.088–4.602) | 0.656 |
| Venous thromboembolism | 8.460(4.510–15.900) | <0.0001* | 8.332(4.346–15.970) | <0.0001* |
| **Other medical history** | | | | |
| Solid tumor | 1.710(0.729–4.000) | 0.220 | 1.788(0.771–4.145) | 0.175 |
| COPD | 4.180(1.270–13.80) | 0.019* | 4.045(0.989–16.540) | 0.051 |
| Atrial fibrillation | 0.880(0.270–2.860) | 0.830 | 0.914(0.286–2.915) | 0.88 |
| Diabetes mellitus | 1.130(0.574–2.220) | 0.730 | 1.181(0.601–2.320) | 0.628 |
| Myocardial infarction | 1.250(0.510–3.060) | 0.630 | 1.318(0.529–3.286) | 0.553 |
| Hypertension | 1.140(0.687–1.900) | 0.610 | 1.168(0.701–1.947) | 0.550 |
| **1st laboratory findings** | | | | |
| WBC (x10$^3$/μL) | 0.992(0.983–1.000) | 0.110 | 0.992(0.982–1.002) | 0.116 |
| Neutrophils (x10$^3$/μL) | 0.990(0.967–1.010) | 0.400 | 0.989(0.954–1.026) | 0.585 |
| Blasts (%) | 1.000(0.988–1.010) | 0.960 | 0.999(0.989–1.010) | 0.979 |
| Hemoglobin (g/dl) | 1.000(0.913–1.100) | 0.950 | 1.000(0.895–1.118) | 0.990 |
| Platelets (x10E9/L) | 1.000(1.000–1.000) | 0.041* | 1.000(1.000–1.002) | 0.063 |
| Platelets <100 × 10E9/L | 0.503(0.306–0.827) | 0.006* | 0.518(0.314–0.854) | 0.009* |
| PT (seconds) | 0.917(0.810–1.040) | 0.170 | 0.920(0.795–1.065) | 0.265 |
| APTT (seconds) | 0.978(0.944–1.010) | 0.230 | 0.977(0.942–1.014) | 0.218 |
| Fibrinogen (mg/dl) | 1.000(0.998–1.000) | 0.930 | 1.000(0.998–1.002) | 0.941 |
| LDH (U/L) | 0.999(0.998–1.000) | 0.140 | 0.999(0.998–1.000) | 0.069 |
| Creatinine (mg/dl) | 0.757(0.389–1.470) | 0.410 | 0.769(0.369–1.602) | 0.483 |
| GFR (mL/min/1.73m$^2$) | 1.000(0.999–1.010) | 0.083 | 1.004(0.999–1.009) | 0.075 |

‡ APLA syndrome, Factor V Leiden.
* – statistically significant, APL – Acute Promyelocytic Leukemia; APTT – Activated Partial Thromboplastin Time; BMI – Body Mass Index; BSA – Body Surface Area; CI – Confidence Interval; COPD – Chronic Obstructive Pulmonary Disease; GFR – Glomerular Filtration Rate; HR – Hazard ratio; LDH – Lactate Dehydrogenase; MPN - Myeloproliferative Neoplasm; PT – Prothrombin Time; WBC – White Blood Cells.

**Table 5**
Time from AML diagnosis to CRT occurrence: multivariate sub-distribution and proportional hazard regression analyzes (all patients, $n = 632$).

| | Sub-distribution hazard model HR (95% CI) | *P*-value | Cause-specific hazard model HR (95% CI) | *P*-value |
|---|---|---|---|---|
| BMI (kg/m$^2$) | 1.054(0.996–1.116) | 0.068 | 1.069(1.008–1.134) | 0.025* |
| BSA (m$^2$) | 0.980(0.205–4.688) | 0.980 | 0.575(0.119–2.760) | 0.489 |
| APL | 2.283(0.999–5.217) | 0.050 | 2.630(1.208–5.722) | 0.014* |
| **Hematological medical history** | | | | |
| Coagulation disorder‡ | 13.569(2.654–69.375) | 0.001* | 5.627(0.721–43.871) | 0.099 |
| Venous thromboembolism | 2.188(0.755–6.335) | 0.150 | 7.558(3.590–15.909) | <0.0001* |
| **Other medical history** | | | | |
| COPD | 3.356(0.555–20.288) | 0.190 | 3.340(0.744–14.982) | 0.115 |
| **1st laboratory findings** | | | | |
| Platelets <100 × 10E9/L | 0.459(0.276–0.762) | 0.002* | 0.609(0.353–1.052) | 0.075 |
| GFR | 1.002(0.997–1.007) | 0.430 | 1.001(0.995–1.007) | 0.634 |

‡ APLA syndrome, Factor V Leiden.
* – statistically significant, APL – Acute Promyelocytic Leukemia; BMI – Body Mass Index; BSA – Body Surface Area; CI – Confidence Interval; COPD – Chronic Obstructive Pulmonary Disease; GFR – Glomerular Filtration Rate; HR – Hazard ratio.

presence of thrombocytopenia.

Notably, in our study, the CRT diagnosis is not found to result in higher mortality for either the entire cohort or any of its subgroups. These findings are in line with previous publications reporting no effect of thrombotic (catheter or non-catheter related) events on survival in AML patients [42–44]. Conversely, a large population-based study has demonstrated an association between VTE development and a 40% increase in the risk of dying within 1 year among patients with acute lymphoblastic leukemia (ALL) [9]. These differences could be related at least in part to the use of L-asparaginase in most regimens employed in the management of newly-diagnosed ALL patients.

The present study has a number of limitations, that are related to its retrospective and single-center nature. However, the study includes a large adult cohort of a newly-diagnosed AML patients, treated with a similar therapeutic strategy at a tertiary leukemia center. Furthermore, the CRT diagnosis was based on ultra-sonographic tests performed due to appearance of clinical signs or symptoms, which may lead to under-diagnoses of subclinical thrombosis, known to be more prevalent than symptomatic CRT [45]. In addition, most non-APL patients were treated with chemotherapy-based regimens. Currently, many non-APL patients are treated with a non-chemotherapy approach (i.e., vidaza and venetoclax), which might have an impact on the cumulative incidence of CRT. Furthermore, in our study APLA syndrome and factor V Leiden were documented as pre-diagnosis procoagulant factors and were

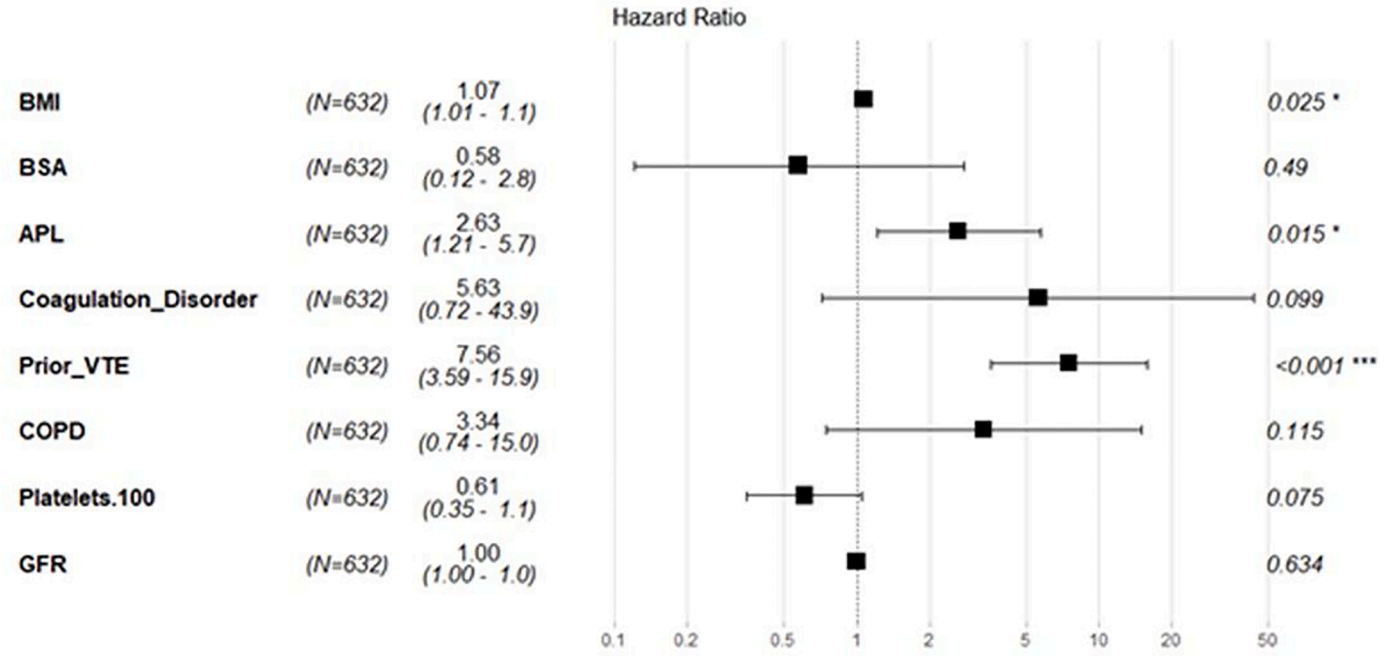


**Fig. 3.** Time from AML diagnosis to CRT occurrence in all the evaluable AML patients ($n = 632$): multivariate Cox regression analysis, Coagulation Disorder - APLA syndrome, Factor V Leiden, APL – Acute Promyelocytic Leukemia; BMI – Body Mass Index (kg/m$^2$); BSA – Body Surface Area (m$^2$); COPD – Chronic Obstructive Pulmonary Disease; GFR – Glomerular Filtration Rate; Platelets.100 – Platelets <100 × 10E9/L; VTE – Venous Thromboembolism.

retrieved from electronic medical records rather than updated laboratory analysis. Finally, our findings were not validated in another cohort of AML patients.

## 5. Conclusion

The current study demonstrated a relatively high rate of CRT in newly-diagnosed AML patients, reaching 10%. The majority of thrombotic events occurred early during induction therapy, which could lead to delays in anti-leukemic therapy and further complicate thrombosis management in such patients, that is primarily associated with their concurrent thrombocytopenia. This study proposes simple models based on anthropometric data (BMI, BSA), medical history (prior VTE or COPD), clinical (APL) and laboratory (platelet count) parameters obtained at diagnosis, permitting early identification of AML patients at high risk for CRT development. Moreover, patients at low risk for developing this complication may be identified with relatively high confidence. The very high NPVs with acceptable PPVs of these models may further support this notion.

After validating these models in other cohorts, they could be applied for designing personalized CRT prophylactic and treatment approaches in this challenging clinical scenario.

## Ethical statement

All the procedures involved in this study were in accordance with the ethical standards of the the Institutional Review Board of the Rambam Health Care Campus (Approval #0483-18-RMB) and with the 1964 Helsinki Declaration and its later amendments.

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## CRediT authorship contribution statement

**Shay Perek:** Conceptualization, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Alaa Khatib:** Data curation, Formal analysis, Data curation, Writing – review & editing. **Niv Izhaki:** Data curation, Writing – review & editing. **Ali Sleman Khalaila:** Data curation, Writing – review & editing. **Benjamin Brenner:** Writing – original draft, Writing – review & editing. **Netanel A. Horowitz:** Conceptualization, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing.

## Declaration of Competing Interest

S.P., A.K., N.I., A.S.K. and N.A.H. declare no conflict of interest., B.B. declares receiving honoraria for lectures and advisory board contributions from Sanofi, ROVI Laboratories, Johnson & Johnson and HORIBA Medical.

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