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The ISTH DIC-score predicts early mortality in patients with non-promyelocitic acute myeloid leukemia

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ABSTRACT

Coagulation disorders frequently complicate the clinical course of acute myeloid leukemia (AML) patients. This study examined the frequency and prognostic significance, with regards of early mortality, of the presence of overt disseminated intravascular coagulation (DIC) at AML diagnosis and its correlation with clinical and biological characteristics.

A retrospective analysis of 351 newly diagnosed non-promyelocytic AML patients was conducted, utilizing the 2018 ISTH DIC-Score criteria to evaluate the presence of overt DIC at AML onset. The study cohort had a median age of 65 years with a predominance of male gender (59 %). Overt DIC was present in 21 % of cases and was associated with advanced age, comorbidities, poor performance status, hyperleukocytosis, LDH levels, *NPM1* mutations, expression of CD33 and CD4, and lack of expression of CD34. With a median follow-up of 72 months (3–147 months), the 6-year overall survival (OS) was 17.4 %, with patients having overt DIC showing significantly poorer outcomes (7.2 % compared to 20.3 % of those without DIC, $p < 0.001$). Patients with overt DIC showed markedly high early mortality rates at 30 (42.5 % vs 8 %), 60 (49.3 % vs 16.9 %), and 120 days (64.4 % vs 25.6 %) from disease onset. In multivariate analysis overt DIC retained its independent prognostic value for early mortality.

In conclusion, the prevalence and clinical relevance of DIC in non-promyelocytic AML is not negligible, underlining its potential as an unfavorable prognostic marker. In newly diagnosed patients with AML, early recognition and measure to counteract coagulation disturbances might help mitigate the elevated mortality risk associated with DIC.

1. Introduction

Coagulation disorders are a common complication in patients with newly diagnosed acute myeloid leukemia (AML) and may be caused by a variety of factors [1]. Blasts overexpress tissue factor (TF), which activates the coagulation cascade, representing one of the main mechanisms implicated in the pathophysiology of such a hemostatic disturbance. Furthermore, leukemic blasts release pro-inflammatory and pro-coagulant cytokines such as IL-1b and TNF-alpha, which, in turn, activate endothelial cells promoting the production of TF, cytokines, and platelets-activating growth factors [2].

Platelets also play a key role in both physiological and pathological conditions associated with perturbance of coagulation. After activation, they divide into two subpopulations: the first can aggregate through various molecular interactions, such as the binding of P-selectin to phosphatidylserine; and the other, so-called “super activated”, externalizes P-selectin, promoting the activation of the coagulation cascade. These “super activated” platelets have a higher pro-coagulant activity

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than the normal platelets [2].

Cytolysis induced by antineoplastic treatments is another factor that contributes to coagulation disorders in AML patients. This results in the release of circulating free DNA, which can interfere with the processes of inhibition of fibrinolysis and alteration of primary and secondary hemostasis. Circulating free DNA can promote coagulation activation, inhibit fibrinolysis, and alter clot stability. A related phenomenon is the release of intracellular histones as part of the neutrophils extracellular traps (NET), which in turn accelerates the coagulation cascade. NET secretion is one of the postulated processes that, like platelets-produced polyphosphates, activates the coagulation cascade [3]. This also entails changes in fibrinogen, factors VII (FVII), FVIII, FIX, and FXII levels and activation, resulting in prolonged coagulation time [4,5].

Concomitant infections may also contribute to the pathogenesis of hemorrhagic and thromboembolic complications by i) increasing levels of circulating inflammatory cytokine and subsequently TF, ii) decreasing of thrombomodulin levels, and iii) increasing plasminogen activator inhibitor levels. Furthermore, gram-negative bacteria may stimulate the production of TF, TNF-alpha, and IL-1b, whilst gram-positive bacteria can degrade mucopolysaccharides that directly activate FXII [6].

These factors may generate a hemostatic imbalance resulting in disseminated intravascular coagulation (DIC), which can then lead to organ dysfunction and become a life-threatening condition. Because of the intrinsic heterogeneity of acute leukemias and the differences in patients' characteristics across studies, the actual prevalence of DIC in such diseases has not been established yet [7–9]. DIC is present in most patients with acute promyelocytic leukemia (APL) at presentation [10,11], while the prevalence in AML and acute lymphoblastic leukemia (ALL) varies from 3 to 25 % [12–14]. The cytogenetic and molecular characteristics appear to influence the prevalence and severity of DIC in AML. Several investigations have found a correlation between the development of DIC at disease presentation, and concomitance presence of *FLT3-ITD* and *NPM1* mutations, in patients with a normal karyotype [12,14]. The clinical presentation is variable: most studies report mainly hemorrhagic signs, but thromboembolic complications may also occur.

The aim of this study was to analyze the frequency and prognostic significance of DIC assessed by means of the 2018 revision of the International Society of Thrombosis and Hemostasis (ISTH) scoring system for overt DIC at the time of diagnosis in a large cohort of AML patients. Furthermore, we investigate the relationship between clinical and laboratory features of AML and DIC.

2. Materials and methods

We retrospectively examined data from 351 adult patients (≥18 years) with newly diagnosed non-promyelocytic AML, admitted to the Hematology Department of the Policlinico Tor Vergata (Rome, Italy), between January 2010 and December 2022. The following characteristics were evaluated at baseline: date of diagnosis of AML, age, gender, performance status, fitness for treatment, body mass index (BMI), immunophenotypic and genetic/cytogenetic profile, blood count and coagulation profile. Information on chemotherapy regimens, date of complete remission (CR)/resistance, date of relapse, date of death or last follow-up were also collected. We also gathered information on thrombotic events (TE) and major bleeding occurred within 30 days from AML onset. TE were defined as a composite of first deep vein thrombosis or arterial thrombosis at any site, diagnosed by Doppler ultrasonography, computed tomography, or magnetic resonance imaging. Myocardial infarction was diagnosed according to clinical, enzymatic and electrocardiographic criteria as per well established guidelines [15]. Major bleeding events were defined as a grade 4 bleeding according to the WHO bleeding assessment scale [16]: bleeding with severe hemodynamic instability requiring transfusion over routine transfusion needs, retinal bleeding with visual impairment, central nervous system bleeding with or without neurologic dysfunction, fatal bleeding.

Performance Status was assessed according to the criteria proposed by the Eastern Cooperative Oncology Group (ECOG) scale [17], while the presence of comorbidities was assessed using the Charlson Comorbidity Index (CCI) [18]. The fitness for treatment was assessed by applying the SIE/SIES/GITMO criteria (F-Fitness) [19], according to the three categories provided by the score: fit for intensive chemotherapy, unfit for intensive chemotherapy, and unfit for non-intensive chemotherapy regimens (frail). Routine blood tests, including hemoglobin, white blood cells (WBC) and platelet count (PLTc), were performed on blood samples anticoagulated with ethylenediaminetetraacetic acid (EDTA). The evaluation of coagulation parameters, such as PT, aPTT, fibrinogen (Clauss method) and D-dimer (immunoturbidimetric method) were performed on citrate plasma tubes. The presence of overt DIC was assessed according to the 2018 revision of the ISTH DIC-score [20] as described in Table 1. A score of ≥4 was defined as an overt DIC. All patients at onset underwent bone marrow aspiration for morphological, immunophenotypic, cytogenetic and molecular evaluation of the disease characteristics as per routine clinical practice. Accordingly, patients were stratified based on the 2017 update of the ELN guidelines [21]. Depending on age and fitness, patients underwent induction treatment with intensive chemotherapy regimens (anthracycline + cytarabine-based regimens), non-intensive therapies (mainly hypomethylating drugs or hypomethylating+venetoclax association) or supportive therapy only. All patients underwent transfusion support as per international guidelines [22]. Generally, the cut-offs used for prophylactic use of transfusions of red blood cells, platelet concentrates, fresh frozen plasma, human ATIII and human fibrinogen were: Hb <8 g/dL, PLTc $<10 \times 10^9$/L, fibrinogen<100 mg/dL, ATIII<65 %. For patients with active bleeding and/or sepsis the PLTc threshold used was 20×10^9/L. The study was approved by the Ethics Committee of the Policlinico Tor Vergata and conducted in accordance with the standards established by the Declaration of Helsinki.

2.1. Statistical analysis

Descriptive analyses were performed on the total population and stratified by study group. Each continuous variable was assessed using the Shapiro-Wilks test.

Continuous variables were expressed as mean ± standard deviation (SD); categorical variables were expressed as numbers and percentages. Differences between groups were assessed by univariate analysis using parametric and non-parametric tests: chi-squared test and Fisher's exact test for categorical variables, *t*-test and Wilcoxon rank-sum test for continuous variables.

Overall survival (OS) and Cumulative Overall Mortality were estimated using the Kaplan-Meier product-limit estimator. Differences in curves were assessed using log-rank tests. Cox regression models were used in univariate and multivariate analysis to assess the effect of variables on 30-days mortality. Hazard ratios (HRs) and 95 % confidence intervals (CIs) were calculated. A p-value <0.05 was considered statistically significant.

All analyses were performed using RStudio 2021.09.0 + 351 (RStudio Team (2020)). RStudio: Integrated Development for R, RStudio, PBC, Boston.

Table 1
ISTH-DIC score 2018 calculation.

Points	0	1	2	3
Platelet ($\times 10^9$/L)	≥100	50–99	<50	
Fibrinogen (mg/dL)	≥100	<100		
Prothrombin Time (seconds)	<16	16–19	>19	
D-Dimer (ng/mL)	<3000		3000–7000	>7000

A score of ≥4 was defined as an overt DIC.

3. Results

3.1. Patient characteristics

Overall, median age at AML onset was 65 years (range 21–90), with a male predominance (59 %). Based on the ELN 2017 guidelines, patients were classified as follows: 56 (16 %) favorable, 137 (39 %) intermediate, 103 (29 %) unfavorable, and 55 (16 %) were not categorizable due to incomplete genetic/cytogenetic data. Main clinical and laboratory features of our study cohort are summarized in Table 2 and Table 3.

Approximately 13 % of patients had an ECOG >2, and 23 % had a CCI > 4. With regards to treatment fitness (F-fitness), 204 (58 %) patients were judged "fit" for intensive chemotherapy, 64 (18 %) "unfit" for intensive chemotherapy and 83 (24 %) were "frail". As for the first-line therapy, 195 (56 %) patients received intensive chemotherapy, 71 (20 %) non-intensive therapies and 85 (24 %) received only supportive therapy. Out of 266 patients receiving active treatment, 162 (60.1 %) achieved CR.

3.2. ISTH DIC-score and association with clinical and laboratory characteristics

At the time of AML onset, 73 patients (21 %) had a DIC-score ≥ 4. We found that the presence of a DIC-score ≥ 4 was associated with advanced age (>65 years, $p = 0.004$), higher comorbidity burden (CCI >4, $p < 0.001$), ECOG >2 ($p < 0.001$), F-fitness frail ($p < 0.001$), a WBC count >50 × 10^9/L ($p = 0.001$), LDH values >380 U/L ($p < 0.001$), ATIII values lower than 70 % ($p < 0.001$), presence of *NPM1* mutations ($p = 0.09$), expression of CD33 ($p = 0.003$) and CD4 ($p = 0.011$) and lack of expression of CD34 ($p = 0.012$) The early (within 30 days from AML onset) major bleeding and TE rate was 5,7 % and 10,5 %, respectively. Whereas no correlation was found with TE, overt DIC significantly associated with a higher risk of major bleeding episodes, as compared to patients with a DIC score < 4 (15/73 vs 5/278, OR 14.121, 95 % CI: 4.936–40.394; $p < 0.001$) (Tables 2 and 3).

3.3. ISTH DIC-score and AML outcomes

At a median follow-up of 72 months (3–147 months), the 6-year OS of the study cohort was 17.4 % (95 % CI 15.2–19.6). Patients with overt DIC had a substantially poorer OS as compared to those without overt coagulation disturbances (7.2 % vs 20.3 %, respectively, log-rank test $p < 0.001$, HR 2.40, 95 % CI: 1.81–3.17) (Fig. 1).

Next, we explored the relationship between DIC and early mortality. In our cohort, the death rates at 30, 60, and 120 days were 14.7 %, 24.1 %, and 32.1 %, respectively. Patients with overt DIC at the onset of disease had mortality rates of 42.5 %, 49.3 %, and 64.4 % at 30, 60, and 120 days, respectively, whereas patients without overt DIC had mortality rates of 8 %, 16.9 %, and 25,6 %. ($p < 0.001$; HR 2.42, 95 % CI:1.83–3.20, Fig. 2). In the univariate analysis, we found that DIC score ≥ 4, age > 65, ECOG performance status >2, CCI > 4, F-fitness assessed as "frail", concomitant infection at the time of AML presentation, WBC count >50 × 10^9/L, LDH values>380/L were associated with early mortality in patients with AML (Table 4). In the multivariate analysis, DIC score (HR 3.95, 95 % CI: 2.00–7.78), F-Fitness "frail" (HR 15.26, 95 % CI: 5.97–39.04), WBC count >50 × 10^9/L (HR 2.14, 95 % CI: 1.06–4.34) remained statistically significant (Table 4).

Results were similar even when considering only patients aged up to 65 years. In this category, the presence of overt DIC still impacted on mortality rates, with a 30, 60 and 120 mortality rates of 41.7 %, 45.8 % and 54.9 % vs 2.7 %, 10.3 %, 15.1 %, (log-rank test $p < 0.001$; HR 2.43, 95 % CI: 1.90–3.95, Fig. 3). Of the 14 patients who died within 30 days from diagnosis, 5 presented a fatal bleeding before being able to start an active treatment for AML, despite being eligible for active therapy (all had overt DIC), 4 from complications related to disease progression before starting any active treatment for AML (3 with overt DIC), and 5

Table 2
Characteristics of patients.

Characteristic	N (missing)	Overall. $N = 351$	DIC score < 4; $N = 278$ (79 %)	DIC score ≥ 4; $N = 73$ (21 %)	p-Value*
Age	351				0.004
<65 years		179/351 (51 %)	153/278 (55 %)	26/73 (36 %)	
≥65 years		172 (49 %)	125/278 (45 %)	47/73 (64 %)	
Gender	351				0.430
F		144/351 (41 %)	117/278 (42 %)	27/73 (37 %)	
M		207/351 (59 %)	161/278 (58 %)	46/73 (63 %)	
CCI	351				<0.001
<4		270/351 (77 %)	228/278 (82 %)	42/73 (58 %)	
≥4		81/351 (23 %)	50/278 (18 %)	31/73 (42 %)	
ECOG	351				<0.001
0–2		304/351 (87 %)	253/278 (91 %)	51/73 (70 %)	
3–4		47/351 (13 %)	25/278 (9.0 %)	22/73 (30 %)	
F-Fitness	351				<0.001
Fit		204/350 (58 %)	176/277 (64 %)	28/73 (38 %)	
Unfit to intensive		64/350 (18 %)	52/277 (19 %)	12/73 (16 %)	
Unfit to not intensive		83/350 (23 %)	50/277 (18 %)	33/73 (45 %)	
Infection at the time of AML onset	351	14/351 (4.0 %)	9/278 (3.2 %)	5/73 (6.8 %)	0.180
Thrombosis within 30 days from AML onset	351	37/351 (11 %)	32/278 (12 %)	5/73 (6.8 %)	0.250
Major bleeding within 30 days from AML onset	351	20/351 (5.7 %)	5/278 (1.8 %)	15/73 (21 %)	<0.001
BMI	331 (20)				0.710
<30		305/331 (92 %)	244/264 (92 %)	61/67 (91 %)	
≥30		26/331 (7.9 %)	20/264 (7.6 %)	6/67 (9.0 %)	
Smoking habits	330 (21)	141/330 (43 %)	113/263 (43 %)	28/67 (42 %)	0.860
ELN	296 (55)				0.870
Favorable		56/296 (19 %)	46/237 (19 %)	10/59 (17 %)	
Intermediate		137/296 (46 %)	110/237 (46 %)	27/59 (46 %)	
Adverse		103/296 (35 %)	81/237 (34 %)	22/59 (37 %)	
s_AML	328 (23)	91/328 (28 %)	73/261 (28 %)	18/67 (27 %)	0.860
CBF	308 (43)	11/308 (3.6 %)	10/246 (4.1 %)	1/62 (1.6 %)	0.700
FLT3	315 (36)	65/315 (21 %)	47/253 (19 %)	18/62 (29 %)	0.068
NPM1	315 (36)	64/315 (20 %)	44/253 (17 %)	20/62 (32 %)	0.009
CD34	328 (23)	236/328 (72 %)	194/258 (75 %)	42/70 (60 %)	0.012
CD33	328 (23)	291/328 (89 %)	222/258 (86 %)	69/70 (99 %)	0.003
CD2	328 (23)	18/328 (5.5 %)	15/258 (6 %)	3/70 (4 %)	0.770
CD7	328 (23)	94/328 (29 %)	79/258 (31 %)	15/70 (21 %)	0.130
CD19	328 (23)	20/328 (6 %)	17/258 (7 %)	3/70 (4 %)	0.580
CD15	328 (23)	133/328 (41 %)	105/258 (41 %)	28/70 (40 %)	0.920

(continued on next page)

Table 2 (*continued*)

Characteristic	N (missing)	Overall. $N = 351$	DIC score < 4; $N =$ 278 (79 %)	DIC score ≥ 4; $N =$ 73 (21 %)	p-Value*
CD117	328 (23)	280/328 (85 %)	224/258 (87 %)	56/70 (80 %)	0.150
CD14	328 (23)	85/328 (26 %)	61/258 (24 %)	24/70 (34 %)	0.072
CD64	328 (23)	116/328 (35 %)	87/258 (34 %)	29/70 (41 %)	0.230
CD13	328 (23)	300/328 (91 %)	234/258 (91 %)	66/70 (94 %)	0.340
HLA-DR	328 (23)	292/328 (89 %)	234/258 (91 %)	58/70 (83 %)	0.063
CD4	327 (24)	190/327 (58 %)	140/257 (54 %)	50/71 (71 %)	0.011
CD56	327 (24)	97/327 (30 %)	73/257 (28 %)	24/70 (34 %)	0.340

Abbreviation: F, female; M, male; CCI, Charlson Comorbidity index; ECOG, Eastern Cooperative Oncology Group performance status scale; F-Fitness, Società Italiana di Ematologia/ Società Italiana di Ematologia Sperimentale/Gruppo Italiano Trapianti di Midollo criteria for fitness for treatment; AML, acute myeloid leukemia; BMI, body mass index; CBF, core binding factor; FLT-3, Fms-related tyrosine kinase 3; NPM1, Nucleophosmin-1; ELN, European LeukemiaNet; CD, cluster of derivation; Hb, hemoglobin; WBC, white blood cells; ATIII, antithrombin III; LDH lactate dehydrogenas.

* A *p*-value <0.05 is to consider statistically significant.

Table 3
Laboratory characteristics of patients.

Characteristic	Overall. $N =$ 351	DIC score < 4; $N = 278$ (79 %)	DIC score ≥ 4; $N = 73$ (21 %)	p-Value*
Hb (g/dl)	8.77 (1.70)	8.80 (1.75)	8.68 (1.49)	0.750
WBC ($\times 10^9$/L)	34.91 (62.70)	26.27 (45.27)	67.85 (99.19)	0.001
PLTc (x 10^9/L)	84.01 (123.25)	93.45 (1315.47)	48.08 (74.92)	<0.001
aPTT (sec)	14.95 (2.42)	14.49 (1.77)	16.68 (3.56)	<0.001
PT (sec)	1.30 (5.25)	1.38 (5.90)	1.01 (0.24)	0.60
LDH (U/L)	531.00 (599.15)	455.06 (530.85)	821.06 (744.47)	<0.001
D-Dimer (ng/mL)	4749.61 (13,917.11)	1053.09 (1197.63)	18,826.78 (26,121.51)	<0.001
ATIII (ng/mL)	119.44 (517.26)	129.01 (580.60)	82.77 (21.77)	<0.001
Fibrinogen (mg/dL)	387.88 (164.63)	405.78 (157.82)	319.71 (173.12)	<0.001

Abbreviations: Hb, Hemoglobin; WBC, white blood cells; PLTc, platelets count; aPTT, activated Partial Thromboplastin Time; PT, Prothrombin Time; LDH lactate dehydrogenase; ATIII, Antithrombin.
All data are expressed in mean (SD).

* A p-value <0.05 is to consider statistically significant.

died during the period of aplasia post chemotherapy (2 with overt DIC), of which 3 from infectious complications and 1 from other causes. Similarly, when considering only the 204 fit individuals, we found a 30-day mortality rate of 4.4 % (9/204), with patients with DIC-score ≥ 4 having a mortality rate of 17.9 % vs 2.3 % ($p = 0.004$, HR 1.93, CI 1.23–3.02).

4. Discussion

Recent advances have resulted in improved response and survival rates for patients with newly diagnosed AML [23]. However, early (<30 days) mortality in AML has been found to be as high as 15–30 % [24,25]. Several factors related to patient, disease, and treatment can cause have a role into this. Although some scoring systems have been developed to estimate the overall risk of early death during AML treatment, they are not able to foresee specific life-threatening complications or inform on

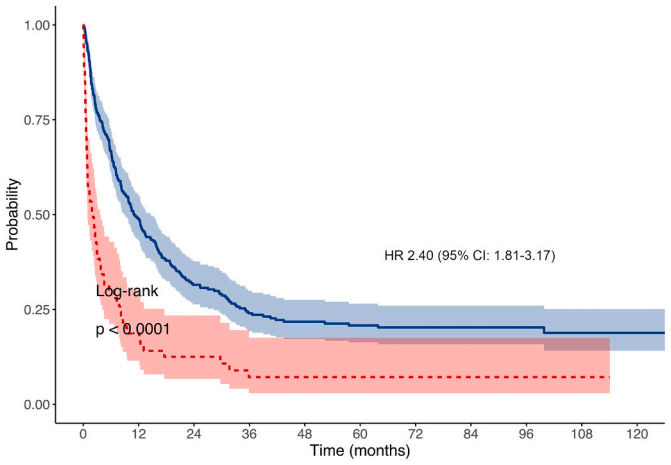

Fig. 1. Overall Survival according to DIC score.
Kaplan-Meier curves show overall survival based on DIC Score at baseline. Curves are color-coded with blue indicating DIC Score < 4 and red indicating DIC Score ≥ 4 ($p < 0.001$ by Log-rank test). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

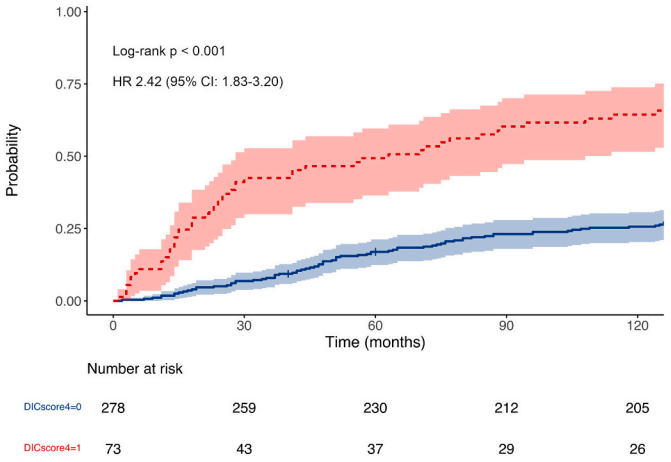

Fig. 2. Cumulative Overall Mortality at 30, 60, 100 days according to DIC score.
Kaplan-Meier curves show cumulative overall mortality based on DIC Score at baseline. Curves are color-coded with blue indicating DIC Score < 4 and red indicating DIC Score ≥ 4 ($p < 0.001$ by Log-rank test). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

how to prevent them [19,26,27]. In particular, major bleeding and infections remain major causes associated with early mortality in AML [24,28,29]. Indeed, bleeding events pose challenges as to the initial therapeutic approach, which together with other factors such as thrombocytopenia and anticoagulation, leukemia treatment start, and concomitant infections, generate a clinical scenario of extreme frailty. Coagulation disorders have been reported to be a predictor of major bleeding in AML patients [28]. Considering all this, the aim of our retrospective-observational study, involving 351 adult patients consecutively diagnosed with non-promyelocytic AML, was to evaluate the frequency and prognostic significance of overt DIC at disease onset.

The incidence and the clinical impact of DIC have been widely analyzed in the context of APL, while data on its frequency and significance in non-promyelocytic AML are more limited [5,30]. According to the literature, the reported frequency of DIC, based on the ISTH criteria, in patients with non-promyelocytic AML at diagnosis ranged from 6.4 %

Table 4
Risk factors for early (30-days) mortality.

Predictive variables		Univariate analysis		Multivariate analysis	
		HR (95 % CI)	p value	HR (95 % CI)	p value
Sex (male)		1.60 (0.88–2.88)	0.121		
Age (>65 years)		2.96 (1.59–6.46)	**0.001**	0.60 (0.27–1.31)	0.198
ISTH-DIC score ≥ 4		7.49 (4.26–13.15)	**<0.001**	3.95 (2.00–7.78)	**<0.001**
CCI >4		3.03 (1.75–5.27)	**<0.001**		
ECOG >2		10.52 (6.05–18.28)	**<0.001**		
F-Fitness	Fit	–	–		
	Unfit to intensive	0.70 (0.15–3.22)	0.644		
	Frail	14.91 (7.22–30.78)	**<0.001**	15.26 (5.97–39.04)	**<0.001**
Infection at the time on AML onset		3.99 (1.70–9.3789)	**0.001**	0.99 (0.38–2.59)	0.990
BMI >30		1.20 (0.43–3.36)	0.725		
Smoking habits		0.81 (0.44–1.52)	0.515		
s-AML		1.17 (0.61–2.25)	0.638		
FLT3		1.54 (0.74–3.20)	0.244		
NPM1		1.37 (0.65–2.92)	0.409		
ELN	Favorable	–	–		
	Intermediate	0.96 (0.34–2.73)	0.943		
	Adverse	1.76 (0.64–4.79)	0.272		
CD34		0.73 (0.40–1.33)	0.308		
CD33		6.44 (0.89–46.71)	0.065	2.72 (0.36–20.48)	0.330
CD4		1.67 (0.91–3.07)	0.100	1.04 (0.54–2.04)	0.918
WBC >50 × 10^9/L		3.32 (1.91–5.78)	**<0.001**	2.14 (1.06–4.34)	**0.034**
LDH >380 U/L		2.12 (1.22–5.68)	**0.008**	0.59 (0.29–1.22)	0.153
Hb < 10 g/dL		1.89 (0.81–4.44)	0.142		

Abbreviations: AML, acute myeloid leukemia; HR, hazard ratio; CI, confidence interval; ISTH-DIC score, International Society of Thrombosis and Hemostasis-disseminated intravascular coagulation score; ECOG, Eastern Cooperative Oncology Group performance; CCI, Charlson Comorbidity index; F-Fitness, Società Italiana di Ematologia/Società Italiana di Ematologia Sperimentale/Gruppo Italiano Trapianti di Midollo criteria for fitness for treatment; BMI, body mass index; FLT-3, Fms-related tyrosine kinase 3; NPM1, Nucleophosmin-1; ELN, European LeukemiaNet; CD, cluster of derivation; WBC, white blood cells; LDH lactate dehydrogenase; Hb, hemoglobin.
p-value: Cox Regression, a *p* value <0.05 is to consider statistically significant.

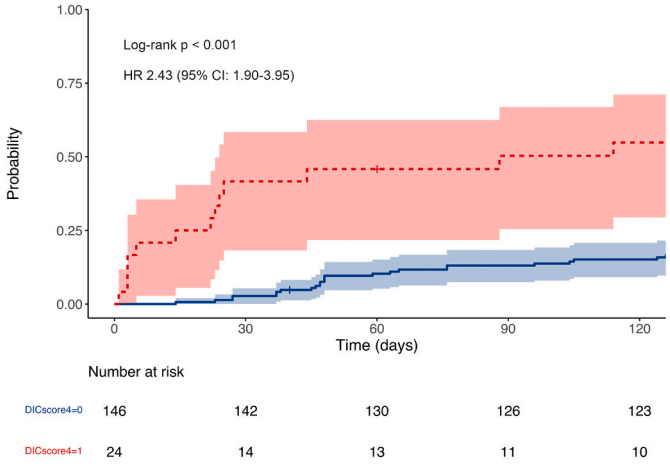

Fig. 3. Cumulative overall mortality at 30, 60, 100 days for patients aged < 65 years according to DIC Score.
Kaplan-Meier curves show cumulative overall mortality based on DIC Score at baseline for patients aged <65 years. Curves are color-coded with blue indicating DIC Score < 4 and red indicating DIC Score ≥ 4 ($p < 0.001$ by Log-rank test). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[31] to 25.2 % [14]. In a study conducted by Libourel et al. [12] the rate of overt DIC in non-promyelocytic AML patients reached 7 %, with a higher frequency in younger individuals (8.5 %). The unfavorable prognostic value of DIC has been evaluated in several studies, although it is not included in the main prognostic scores used for risk stratification in AML patients [19,32–34].

Using the ISTH DIC-score criteria, we found a frequency of overt DIC of 21 %, which is consistent with what has been reported in the literature [7,12–14]. Overt DIC was associated with clinical factors such as advanced age, the presence of comorbidities, poor performance status (all factors also associated with unfitness to treatments), hyperleukocytosis, and increased LDH. It is noteworthy that patients with overt DIC were significantly older and had a greater number of comorbidities than patients without DIC. Advanced age by itself is considered a state of chronic inflammation [35], although comorbidities can also favor the emergence of DIC. Conversely, it is uncertain what causes the increased prevalence of DIC in patients with poor performance status, and its pathogenesis in such cases is most likely multifactorial. One could speculate that, in some instances, the performance status and fitness to treatments is altered as a result of other factors that favor the development of DIC, such as age and comorbidities. Moreover, patients' fitness can also be impacted by DIC-related complications such as bleeding, thromboembolic complications, and organ damage, thereby generating a vicious circle. As observed in other studies [7,12,14,31,36,37], leukocytosis at onset is closely associated with the presence of DIC. Leukemic blasts, unlike erythrocytes, are not elastic and flexible cells, and can cause microcirculation stasis, resulting in vascular blockage, endothelial damage, and release of cytokines, microparticles, and intranuclear proteins from blasts [36]. In addition to hyperleukocytosis (WBC > 50 × 10^9/L), significantly higher levels of LDH were also found in our patients with overt DIC. High LDH levels have been reported to be a predictor of major bleeding [28,38] and poor disease prognosis [24], as well as a parameter of cell proliferation and cytolysis reflecting disease burden [39]. In terms of the biological aspects of AML involved in the development of DIC, we found a higher frequency of overt DIC in patients with *NPM1* mutations, and, although not statistically significant, in patients with *FLT3* mutation, which is consistent with what observed by Guo et al. [14]. Furthermore, Libourel et al. [12], reported a higher frequency of overt DIC in the FAB M5 subtype (monoblastic/monocytic forms), which exhibit a mature myeloid phenotype (CD34-/CD33+/CD4+), as observed in our patients with overt DIC. It is worth noting that *NPM1* and *FLT3-ITD* mutations, as well as monoblastic/monocytic forms, are associated with hyperleukocytosis, and thus coagulation disturbances, as ascertained by our

results and literature evidence [40,41].

Finally, our findings show that the presence of overt DIC at the onset of the disease is associated with an unfavorable prognosis, with a high rate of early mortality, regardless of patients' age, performance status or fitness. DIC can result in hemorrhagic and thrombotic complications, with negative impact on quality of life and survival. However, in our cohort, overt DIC did not associate with thrombosis, while morbidity and mortality where mainly driven by hemorrhagic complications. Indeed, while DIC may be associated with both thrombosis and hemorrhage, we previously showed [42] that commonly-used thrombosis risk scores do not perform well in AML, since the main acknowledged risk factor are higher platelets count and previous history of thrombosis. In our cohort, major bleeding rate was 5,7 %, with a 14-fold increased risk in patient with overt DIC. This data are consistent with other literature reports [28,43]. DIC perturbs the hemostatic balance via a systemic activation of coagulation cascade and endothelial damage, both of which can contribute to the leukemia pathogenesis and progression, perhaps been the initial event generating a fertile soil to infectious and metabolic complications. This situation is reminiscent of the APL form of AML, whereby early death is mainly due to such coagulation disturbances, which are accounted for in the disease risk assessment and taken into consideration for clinical management [38,44]. Although reporting on a retrospective series, our study suggest that patients with an ISTH DIC-score ≥ 4 might be candidates for a more aggressive support therapy aimed at reversing the coagulopathy, similarly to what recommended for APL, and a more tempestive antileukemic treatment initiation in order to promptly mitigate the leukemia-associated coagulopathy and decrease the incidence of life-threatening bleeding events, thereby reducing the risk of early mortality [45]. Prospective studies are needed to confirm the prognostic value of the ISTH DIC-score, and to establish more accurately which patients might be considered for more assertive supportive care.

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This study was conducted as part of our routine work.

Data sharing statement

All data are presented in the paper and supplemental requests for additional information should be sent to the corresponding author.

CRediT authorship contribution statement

Giovangiacinto Paterno: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Raffaele Palmieri:** Writing – original draft, Methodology, Conceptualization. **Cristiano Tesei:** Formal analysis, Data curation. **Andrea Nunzi:** Data curation. **Giorgia Ranucci:** Data curation. **Flavia Mallegni:** Data curation. **Federico Moretti:** Data curation. **Elisa Meddi:** Data curation. **Ilaria Tiravanti:** Data curation. **Massimiliano Marinoni:** Data curation. **Camilla Page:** Data curation. **Solaria Fagiolo:** Data curation. **Elisa Buzzatti:** Data curation. **Roberto Secchi:** Data curation. **Carmelo Gurnari:** Writing – original draft, Methodology, Conceptualization. **Luca Maurillo:** Writing – review & editing. **Francesco Buccisano:** Writing – review & editing. **Adriano Venditti:** Writing – original draft, Methodology, Conceptualization. **Maria Ilaria Del Principe:** Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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