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Evaluation Of Soluble Fibrin Monomer Complex and D Dimer as Early Markers of Hypercoagulability in Patients with Acute Myeloid Leukemia

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ABSTRACT

Background: Hypercoagulability is a prominent feature in acute myeloid leukemia (AML), yet the underlying biomarkers and their relationship to disease burden remain incompletely characterized. D-dimer and soluble fibrin monomer complex (SFMC) are proposed as candidates for early detection of coagulopathy, but their distinct biological roles and clinical utilities require clarification.

Objective: This study aims to evaluate and compare plasma levels of D-dimer and SFMC in newly diagnosed AML patients versus healthy controls, and to investigate their correlations with disease parameters.

Methods: A cross-sectional analysis measured plasma D-dimer and SFMC in AML patients and controls. Correlations with leukocyte count, blast percentage, and platelet count were assessed. Receiver Operating Characteristic (ROC) curves evaluated diagnostic performance. Subtype-specific analyses, especially for M3, explored biomarker variability.

Results: AML patients had significantly higher D-dimer (median 1.2 µg/mL) and SFMC (median 7.3 µg/mL) than controls. D-dimer correlated with leukocyte count (ρ=0.39) and blast percentage (ρ=0.49); SFMC showed weak, non-significant correlations. ROC analysis revealed superior diagnostic performance for D-dimer (AUC=0.96) over SFMC (AUC=0.81). SFMC elevations were greatest in M3; neither marker correlated with platelet count.

Conclusion: Both biomarkers are elevated at AML diagnosis, with D-dimer reflecting overall fibrinolytic activity and SFMC identifying high-risk subgroups. Combined assessment could improve early risk stratification and guide prophylaxis; larger longitudinal studies should define cut-offs and validate prognostic value.

KEYWORDS: *AML, hypercoagulability, D-dimer, SFMC, thrombotic risk, biomarkers, leukemia subtypes, thrombosis, risk stratification, coagulation.*

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1. INTRODUCTION

Acute myeloid leukemia (AML) is a genetically and clinically heterogeneous hematopoietic malignancy characterized by clonal expansion and maturation arrest of myeloid progenitors in the bone marrow and, frequently, the peripheral blood. Beyond its primary impact of marrow failure, AML is increasingly recognized to confer a high risk of hemostatic derangements, with thrombotic events constituting a notable yet understudied contributor to morbidity and mortality compared with solid tumors [1]. Cancer broadly constitutes a prothrombotic state through tumor-driven activation of the coagulation cascade, tissue factor expression, fibrin deposition, and platelet aggregation. While elevated coagulation markers predict venous thromboembolism (VTE) in solid cancers, hematologic malignancies, especially AML, present distinct challenges: leukemic blasts possess procoagulant properties [3], yet thrombocytopenia and baseline coagulopathy complicate prophylaxis and obscure diagnosis. Reported AML-associated VTE incidence ranges from 2% to 22%, and existing risk models derived from solid tumors often lack predictive validity in this setting [4]. Even large AML cohorts reveal inconsistent biomarker associations, underscoring the need for sensitive and specific markers that identify hypercoagulability early in the disease course [5].

D-dimer, a fibrin degradation product generated during plasmin-mediated cleavage of cross-linked fibrin, reflects activation of both coagulation and fibrinolysis and is widely used to evaluate suspected VTE. In cancer, high baseline D-dimer correlates with increased thrombotic risk, tumor burden, and poorer survival [7]. Yet its specificity is limited because infection, inflammation, surgery, and malignancy itself elevate levels, reducing discriminatory power. Moreover, as a downstream marker it may indicate only later stages of thrombus formation rather than early procoagulant changes, a limitation compounded in AML by deranged fibrinogen and coagulation factor levels [2].

The soluble fibrin monomer complex (SFMC) represents an earlier intermediate in fibrin formation, reflecting thrombin activation before full clot polymerization. SFMC may therefore detect hypercoagulability at an earlier stage than D-dimer [8]. Although data in oncology are scarce, preliminary studies in acute leukemia suggest SFMC correlates positively with

D-dimer and von Willebrand factor and inversely with ADAMTS13, with higher levels seen in AML compared with controls, particularly the M3 subtype [9]. Evidence from non-oncologic populations also indicates SFMC may offer higher specificity than D-dimer at certain cutoffs, but findings remain inconsistent and methods unstandardized [6].

Against this backdrop, the present study aims to evaluate and compare SFMC and D-dimer as biomarkers of hypercoagulability in newly diagnosed AML patients relative to healthy controls, to explore their correlations with key hematologic and coagulation parameters, and to determine their potential as early predictors of thrombotic risk [10]. This approach addresses an important gap in AML management, where balancing thrombosis prevention and bleeding risk requires more reliable early markers than currently available [11].

2. MATERIALS AND METHODS

Study Design

This hospital-based case–control study was designed to assess soluble fibrin monomer complex (SFMC) and D-dimer as early hypercoagulability markers in acute myeloid leukemia (AML). A case–control approach allowed direct comparison between newly diagnosed AML patients and healthy volunteers under standardized conditions, minimizing laboratory variability and enhancing interpretability of biomarker levels [12]. Conducted at Al-Azhar University Hospitals, the study capitalized on a large referral base to recruit sufficient incident AML cases.

Ethical Considerations

The protocol received approval from the Institutional Review Board/Ethics Committee of the Faculty of Medicine, Al-Azhar University (Approval No. 2531). Written informed consent was obtained from all participants. Data confidentiality was ensured through coded identifiers and secure storage. All procedures adhered to the Declaration of Helsinki and Good Clinical Practice standards [19].

Study Population

Inclusion and Exclusion Criteria: Patients (≥14 years) with a first diagnosis of AML, confirmed by peripheral blood film, bone marrow aspirate, and flow cytometry, were enrolled. Exclusions were recurrent or previously treated AML, any history of venous/arterial thrombosis, or ongoing anticoagulant therapy [12].

Sample Size: Eighty participants (40 AML cases, 40 controls) were recruited. This sample, based on feasibility and prior research, provided 80% power to detect a moderate effect size (Cohen's d = 0.5) at $\alpha = 0.05$ [20].

Data Collection Procedures

Clinical and Demographic Data: Standardized interviews and physical examinations recorded age, sex, comorbidities, and thrombosis risk factors (smoking, obesity, immobility, cardiovascular disease). AML subtype (M0–M7) was classified per WHO criteria [21].

Comprehensive geriatric assessment for elderly participants.
Laboratory Assessments:

- Diagnosis: Circulating blast cells were identified on peripheral blood film; bone marrow aspirate and flow cytometry confirmed AML subtype.
- Coagulation Testing: Venous blood (4 mL) was drawn into 3.2% sodium citrate tubes for SFMC and D-dimer, centrifuged at 2,500 rpm for 15 min within 30 min of collection; plasma stored at –80 °C. CBC was performed on EDTA blood.
- Assays: D-dimer measured by immunoturbidimetric assay (FEU; intra-assay CV < 5%). SFMC determined by ELISA, run in duplicate with quality controls.

Variables Measured: Demographics, Hematologic indices (haemoglobin, leukocytes, as well as platelets, blast percentage), Coagulation variables (D-dimer, SFMC), and AML subtype.

Data Quality and Bias Control: The case-control study was blinded to the laboratory personnel. Such bias and errors in data entries were reduced by the same preanalytical protocols, dual entry checks, and random audits (10% of the data) [23].

Statistical Analysis

Data analysis and entry were done using SPSS version 26 and Microsoft Excel. Continuous variables were described using the mean ± SD or median (IQR); categorical data using frequencies/ percentages. Student t-test or Mann-Whitney U test was used to test between-group differences in SFMC, D-dimer and haematological indices; Chi-square or Fisher exact test was used to test categorical distributions. Correlations of coagulation markers and hematologic parameters were measured

by using Pearson or Spearman coefficients.

3. RESULTS

Demographic Comparability

In order to limit the confounding factor in case-control research, there is a need to make cases and controls comparable with respect to important population variables [2]. The current experiment consisted of 40 AML patients who had been diagnosed recently and 40 healthy controls. The clubs were well-age-matched, and this is one of the most important factors of coagulation activity and risk of thrombosis. The average age of the AML patients was 55.6 (+-8.8 SD), which was not significantly lower than the mean age of patients in the control group, 52.5 (+-5.9 SD) (p=0.060). This matching age augmented the internal validity of this study because a periodical age increment would raise the baseline D-dimer and fibrin degradation products regardless of the independent variables and otherwise would bias the comparisons of the coagulation biomarkers [14].

Conversely, the AML group showed a certain male preponderance over the controls, but this was not statistically significant. In particular, the AML population had 26 males (65.0 percent) and 14 females (35.0 percent), so the ratio between males and females was 1.9:1, whereas, in the control group, these numbers were 22 and 18, respectively, which was 1.2:1 (p=0.200)/ Although not statistically significant, male sex has been linked to a higher incidence of thromboembolic events in some cancer cohorts [21], likely due to differences in coagulation factor activity and platelet responsiveness. Consequently, this imbalance may introduce a subtle biological confounding effect, potentially amplifying the hypercoagulability signal observed in the AML group. This represents a recognized limitation of the recruitment process and must be acknowledged when interpreting subsequent biomarker findings [13].

Hematological Parameters and Disease Validation

Marked differences in hematological parameters between AML patients and controls confirm the profound biological impact of AML and validate the case–control construct. The AML patients exhibited the classical triad of bone marrow failure, severe anemia, thrombocytopenia and marked leukocytosis with circulating blasts, that underpins the disease's pathophysiology [17]. The mean hemoglobin level in the AML group was 8.7 g/dL, significantly lower than the 13.9 g/dL recorded in controls ($p<0.001$). Platelet counts were also dramatically reduced, with a median of 38.5 $\times 10^9$/L in AML patients compared to 314.5 $\times 10^9$/L in controls ($p<0.001$). In contrast, the total leucocytic count (TLC) in AML patients was markedly elevated, with a median of 34.1 $\times 10^9$/L and a median blast percentage of 73.5%, whereas controls had a median TLC of 6.5 $\times 10^9$/L and no circulating blasts ($p<0.001$ for both parameters). These highly significant differences in hematological indices not only reinforce the validity of the case–control design but also establish a robust platform for comparing coagulation biomarkers between the two groups [19]. Table 1

Baseline Characteristics and Subtype Distribution

Table 1 summarizes the demographic and hematological characteristics of the study population.

Characteristic	AML Patients (n=40)	Healthy Controls (n=40)	p-value	Test Used
Age (years) Mean ± SD	55.6 ± 8.8	52.5 ± 5.9	0.060	Independent t-test
Sex n (%) Male	26 (65.0%)	22 (55.0%)	0.200	Chi-square test
Female	14 (35.0%)	18 (45.0%)		
Total Leucocytic Count ($\times 10^9$/L) Median (IQR)	34.1 (21.8–53.4)	6.5 (5.1–8.2)	<0.001	Mann–Whitney U test
Blast Percentage (%) Median (IQR)	73.5 (30.8–87.3)	0.0 (0.0–0.0)	<0.001	Mann–Whitney U test
Hemoglobin (g/dL) Mean ± SD	8.7 ± 1.2	13.9 ± 2.3	<0.001	Independent t-test
Platelet Count ($\times 10^9$/L) Median (IQR)	38.5 (29.0–76.0)	314.5 (234.3–372.5)	<0.001	Mann–Whitney U test

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range.

Table 1: Baseline Demographic and Hematological Characteristics of the Study Population

In addition to demographic and hematological data, Table 2 provides the distribution of AML subtypes according to the French–American–British (FAB) classification.

FAB Subtype	Frequency (n)	Percentage (%)
M0/M1	8	20.0%
M2	13	32.5%
M3 (APL)	10	25.0%

M4/M5	8	20.0%
M7	1	2.5%
Total	40	100.0%

Table 2: Distribution of AML Subtypes (FAB Classification) within the Patient Cohort (n=40)

The heterogeneity of AML subtypes is of particular relevance to interpreting coagulation markers. The predominance of M2 (32.5%) and M3/ Acute promyelocytic Leukemia (25.0%) is notable, especially because the M3 subtype is strongly associated with disseminated intravascular coagulation and extreme hyperfibrinolysis [18]. This high representation of M3 cases may disproportionately influence baseline coagulation profiles and biomarker levels in the AML group, thereby justifying the need for stratified or sensitivity analyses in subsequent sections [21].

Magnitude of Differences and Effect Sizes

While p-values establish statistical significance, effect size indices and ratios deepen the interpretation of clinical relevance [22]. Ratios of AML to control values demonstrate the scale of hematological abnormalities: hemoglobin was reduced to 63% of control levels, platelets to just 12%, whereas TLC was more than fivefold higher in AML patients. Effect size estimates derived from these figures indicate very large differences, underscoring the profound biological divergence between groups and supporting the validity of comparing their coagulation markers [27].

Critical Interpretation

The demographic data thus confirm a high level of comparability between AML patients and controls in terms of age, thereby reducing one major source of bias. However, the male predominance in the AML group, although not statistically significant, represents a plausible biological confounder given the association between sex and thrombotic risk. The hematological findings strongly mirror the established pathophysiology of AML and provide confidence in the accuracy of case definitions [19]. Moreover, the relatively high proportion of M3 cases raises important considerations for interpreting coagulation marker data, as this subtype is uniquely prone to coagulopathy [27]. Combined, all of these findings leave a robust basis for the interpretation of the soluble fibrin monomer complex and D-dimer complex as early soluble hypercoagulability indicators in AML, but likewise indicate the necessity of contextualizing findings by sex and AML subtype [16].

Comparison of Coagulation Biomarkers Between AML Patients and Controls: A Marked Hypercoagulable State

One of the keys aims of the current research was to determine plasma SFMC and D-dimer as sensitive biomarkers of hypercoagulability in new acute myeloid leukemia (AML) patients relative to control subjects. The two markers have already been linked to the risk of thrombosis and the presence of hypercoagulability in cancer patients [30], yet the behaviour of the two markers in comparison with each other at the first AML diagnosis is not fully described. The existing evidence indicates a substantial and statistically significant overregulation of the two biomarkers.

Elevated D-dimer Concentrations: Evidence of Active Fibrinolysis

Table 3 indicates that the median plasma D-dimer level in the AML group (1.2 ug/mL, IQR: 0.7-1.8) was sixfold of that of 0.2 ug/mL (IQR: 0.1-0.3) under the control group ($p<0.001$). This dramatic difference is also depicted in Figure 1A, showing that there is almost total separation between the D-dimer distributions of AML patients and healthy people. The existence of the extreme outliers over five ug/mL in the AML cohort group implies that the group of patients with the extreme active coagulation and fibrinolysis processes might also be connected with the high number of leukocytes in the group or procoagulant types of AML, including acute promyelocytic leukemia (APL/M3) [23].

This pattern strongly supports the hypothesis that AML at diagnosis is accompanied by ongoing fibrin formation and breakdown. D-dimer is a stable fibrin degradation product and its elevation is therefore indicative of secondary fibrinolysis following widespread thrombin generation. The magnitude of this elevation is consistent with prior observations in malignancy-associated coagulopathy but exceeds typical levels reported in solid tumours suggesting that the pathobiology of AML generates an especially intense prothrombotic milieu [33].

Increased SFMC Levels: Early Marker of Thrombin Activity:

SFMC concentrations were also significantly higher in AML patients, with a median of 7.3 µg/mL (IQR: 4.6–13.0), compared to 3.8 µg/mL (IQR: 2.3–4.5) in controls ($p<0.001$) (Table 3). SFMC represents circulating soluble complexes of fibrin monomers before polymerization, reflecting early steps in the coagulation cascade and active thrombin generation [31]. However, compared to D-dimer, SFMC shows greater overlap between the groups, suggesting that while it captures early thrombin activity, it may be less discriminatory in distinguishing AML-associated hypercoagulability from physiological variation at the upper end of normal. This observation is clinically important: it highlights the possibility that D-dimer could outperform SFMC as a diagnostic or prognostic marker in AML-related coagulopathy.

Variability and Heterogeneity of Biomarker Distributions:
A critical observation emerging from Table 3 is the markedly different variability patterns between the two biomarkers. The IQR of D-dimer in the AML group (1.1) is nearly equal to its median (1.2), reflecting significant heterogeneity across patients, whereas in controls the IQR is narrow (0.2) with tight clustering. This pattern suggests that D-dimer levels may capture differences in disease burden, white cell count, or the presence of subclinical disseminated intravascular coagulation (DIC), a recognized complication in AML [39]. In contrast, SFMC's broader distribution with overlap across groups may indicate greater biological fluctuation in thrombin activity or differences in clearance mechanisms [28].

These findings align with established literature reporting that biomarker variability within AML populations often mirrors heterogeneity in disease biology, including leukemic subtype, blast burden, and endothelial activation [31]. Importantly, 25% of the AML cohort had the APL (M3) subtype, a form of AML uniquely associated with severe coagulopathy. This heterogeneity of subtypes may partly explain the distributional spread seen particularly for SFMC [35].

Biomarker	Category (Cut-off)	AML Patients (n=40) n (%)	Healthy Controls (n=40) n (%)	p-value (Chi-square)
D-dimer	High (>0.5 µg/mL)	29 (72.5%)	3 (7.5%)	<0.001
	Low (≤0.5 µg/mL)	11 (27.5%)	37 (92.5%)	<0.001
SFMC	High (>10.0 µg/mL)	16 (40.0%)	0 (0.0%)	<0.001
	Low (≤10.0 µg/mL)	24 (60.0%)	40 (100.0%)	<0.001

Table3: Comparison of Coagulation Biomarkers Between AML Patients and Healthy Controls

Interpretation and Implications
Taken together, these findings demonstrate a robust hypercoagulable state in treatment-naïve AML patients, characterized by markedly elevated D-dimer and SFMC levels relative to controls. D-dimer appears to show greater discriminatory capacity and may serve as a more sensitive biomarker of overt fibrinolysis, whereas SFMC reflects earlier upstream thrombin activity. The combination of these two biomarkers thus provides complementary insights into the coagulation disturbances in AML. This dual-marker approach parallels recent calls in the literature for multi-biomarker panels to better characterize cancer-related hypercoagulability [24].

The clinical implications are substantial. Elevated D-dimer at diagnosis has been associated with increased risk of venous thromboembolism and poorer prognosis in hematologic malignancies [28]. Likewise, high SFMC levels may predict impending clot formation even before fibrinolysis occurs, offering a potential window for pre-emptive risk stratification. Subsequent sections of this chapter will further explore correlations between these biomarkers and hematologic parameters, and evaluate their diagnostic performance through receiver operating characteristic (ROC) analysis [33].

Categorical Analysis of SFMC and D-Dimer Levels: Clinical Applicability and Diagnostic Thresholds
Although continuous biomarker levels provide a nuanced view of coagulation activation, clinical decision-making often depends on categorical thresholds to identify patients at elevated risk. Translating continuous variables into dichotomous "high" versus "low" states enables clearer diagnostic criteria and facilitates triage in clinical settings. This section therefore evaluates soluble fibrin monomer complex (SFMC) and D-dimer using predefined cut-offs (>10 µg/mL for SFMC and >0.5 µg/mL for D-dimer) to identify individuals with a "high-risk" hypercoagulable profile. This simplified categorical framework provides good information on the relative sensitivity and specificity of these biomarkers and their possible use in the diagnosis of acute myeloid leukemia (AML) [39].

D-dimer Categorical Analysis: High Sensitivity but Incomplete Capture
Table 4 also shows that 29/40 AML patients (72.5%) had the values exceeding the D-dimer cut-off of 0.5mg/mL compared to 3/40 controls (7.5%). These findings confirm that D-dimer is a very sensitive AML coagulation activation marker, which is in tandem with its predetermined capacity to reflect fibrin degradation and active fibrinolysis [34]. This extreme sensitivity is particularly required in the AML case, whereby the initial symptoms of coagulopathy may be observed, and as such, preventive action may be taken [40].

Nonetheless, a critical analysis shows that the study has a significant limitation: 11 out of the 40 AML patients (27.5%) had a D-dimer level below the threshold regardless of the diagnosis, which amounted to creating a false-negative rate of nearly one-third of the cohort. This observation highlights the ineffectiveness of a universal cut-off to be applied to an AML group with distinct hemostatic disturbances, having been created by exclusion of venous thromboembolism (0.5 ug/mL) [23]. In clinical terms, a "low" D-dimer in an AML patient does not equate to an absence of hypercoagulability; rather, it may reflect interpatient variability, early disease stage, or subtype-specific patterns of coagulation activation [32].

SFMC Categorical Analysis: High Specificity but Limited Sensitivity

Table 4 also shows the categorical analysis of SFMC reveals a distinct pattern. Sixteen of the 40 AML patients (40.0%) had SFMC levels above 10 µg/mL, while none of the healthy controls exceeded this threshold ($p<0.001$). This perfect specificity (100%) in the control cohort highlights SFMC's potential as a confirmatory marker of AML-associated hypercoagulability. Elevated SFMC represents circulating soluble fibrin monomers formed during intense thrombin generation and thus reflects a more upstream phase of coagulation activation than D-dimer [28].

Yet the high specificity is counterbalanced by low sensitivity: 24 of the 40 AML patients (60%) were classified as "low" SFMC despite their diagnosis. This divergence underscores the biological complementarity of the two biomarkers. Whereas D-dimer captures a broad fibrinolytic footprint, SFMC identifies a more select subset of patients with pronounced thrombin burst and fibrin formation. This difference mirrors the conceptual model proposed by (BEREZINA & FOMINA, 2021), who highlighted the need for multiple markers to comprehensively capture cancer-related coagulopathy [7].

Biomarker / Category	AML Patients(n40) n(%)	Healthy Controls (n=40) n (%)	p-value
D-dimer High (>0.5 µg/mL)	29 (72.5%)	3 (7.5%)	<0.001
D-dimer Low (≤0.5 µg/mL)	11 (27.5%)	37 (92.5%)	<0.001
SFMC High (>10.0 µg/mL)	16 (40.0%)	0 (0.0%)	<0.001
SFMC Low (≤10.0 µg/mL)	24 (60.0%)	40 (100.0%)	<0.001

p-value calculated using Chi-square test.

Table 4: Categorical Analysis of Biomarker Levels Based on Predefined Cut-offs

Sensitivity, Specificity and the Trade-off Between Markers

The inherent trade-off to be pointed out in the context of this categorical analysis is that D-dimer is characterised by high sensitivity and low specificity, whereas SFMC is characterised by high specificity and low sensitivity. This tendency suggests a two-process diagnosis. D-dimer could be clinically employed as a primary screening test to assist in identifying a majority of the patients in hypercoagulability status, and SFMC could be used as a confirmatory test to identify patients with highly active or clinically significant coagulation activation. The approach is similar to other fields of haematology, with an initial, general screening test being followed by a more specific test to confirm [37].

Clinical Implications of Categorical Analysis

These findings have two clinical implications. To begin with, risk stratification in AML will not be effective with only one biomarker cut-off. Second, the intense difference between sensitivity and specificity is an indication that the integration of D-dimer and SFMC in a composite model can be associated with better predictive accuracy [39]. As an example, patients who cross both of these thresholds can be considered a high-high group with a particularly high risk of thrombotic complications, and those who cross only one of the two markers can have intermediate risk profiles [34].

One of the limitations of the given analysis is the use of arbitrary cut-offs. The D-dimer cutoff of 0.5 µg/mL is based on non-cancer outpatient samples, and this may not be a true indicator of hypercoagulability in AML. In the same manner, the SFMC cut-off of 10 µg/mL does not have a universal standard and was selected pragmatically [23]. Such problems highlight why receiver operating characteristic (ROC) analyses are necessary to obtain data-driven cut-offs unique to AML, as will be discussed further in this chapter.

Interpretation and the Path Forward

This is a categorical study that supports the complementary nature of D-dimer and SFMC in the identification of AML-related coagulopathy. D-dimer is sensitive and is therefore a good first-line screening test, but not sensitive enough to eliminate hypercoagulability. High specificity of SFMC makes it a rare but strong indication of an abnormal coagulation state, especially one that would confirm a diagnosis of AML-related hypercoagulability or help to reveal high-risk subgroups [21]. Future research of ROC curves, longitudinal follow-up, and stratification by subtype of AML could potentially give the more precise thresholds required to enhance diagnostic accuracy [36].

Correlation of SFMC and D-Dimer with Disease Parameters in AML Patients

A simple comparison of biomarker levels between AML patients and controls, while statistically significant, fails to capture the multidimensional nature of hypercoagulability in acute myeloid leukemia. To address this, a comprehensive analysis was conducted to explore the interplay between soluble fibrin monomer complex (SFMC), D-dimer, and key hematologic parameters in AML patients. By moving beyond mean differences to examine correlations and stratified analyses, this section uncovers the mechanisms by which these biomarkers reflect disease pathophysiology [23].

Primary Correlation Analysis: Unveiling Divergent Pathways

Spearman's rank correlation analysis (Table 5) highlights a striking divergence between the biological roles of D-dimer and SFMC in AML-associated coagulopathy.

D-dimer as a Marker of Disease Burden: D-dimer levels demonstrated a statistically significant, moderate positive correlation with total leukocytic count (TLC) ($\rho = 0.39$, $p = 0.013$) and an even stronger positive correlation with blast percentage ($\rho = 0.49$, $p = 0.001$). This dual relationship positions D-dimer as a sensitive index of tumor burden and fibrinolytic activity. The stronger association with blast percentage is particularly revealing; it underscores that the immature proliferative blast cell population may be the principal driver of fibrinolytic cascade activation. This is presumably due to the overexpression of procoagulant factors on leukemic cells, such as Tissue Factor and Cancer Procoagulant factors, which have previously been demonstrated in previous studies to be the drivers of hypercoagulability in haematological malignancies [10].

Insensitivity of SFMC to Bulk Disease: SFMC, in contrast, had weak, non-significant relationships with TLC ($\rho = 0.24$, $p = 0.140$) and blast percentage (0.26, $p = 0.110$). It is to show that the genesis of initial generation soluble fibrin monomers is not merely an extension of leukemic cell load. This finding is pivotal because it suggests that SFMC elevations may be triggered by more specific biological contexts, such as the unique coagulopathy of acute promyelocytic leukemia (APL), localized endothelial injury, or episodes of disseminated intravascular coagulation, rather than reflecting systemic tumor mass alone [36].

Dissociation from Platelet Count: Importantly, neither D-dimer nor SFMC correlated with platelet count ($p > 0.6$ for both). This absence of association confirms that the plasma-based hypercoagulable state in AML is independent of platelet-mediated hemostasis. This observation provides a pathophysiological rationale for the clinical paradox of thrombosis occurring concurrently with thrombocytopenia and warns against using low platelet counts as a reassuring marker for low thrombotic risk in AML patients [33].

Parameter	D-dimer (ρ)	D-dimer (p-value)	SFMC (ρ)	SFMC (p-value)
Total Leucocytic Count	0.39	0.013*	0.24	0.140
Blast Percentage	0.49	0.001*	0.26	0.110
Platelet Count	-0.04	0.816	-0.08	0.622
D-dimer	,	,	0.66	<0.001*
SFMC	0.66	<0.001*	,	,

Statistically significant at $p < 0.05$; ρ = Spearman's rank correlation coefficient.
Table 5: Spearman's Correlation Analysis between Biomarkers and Disease Parameters in AML Patients (n = 40)

Stratified Analysis by Disease Burden: Testing the Correlation Hypothesis

To validate these findings visually and analytically, the AML cohort was stratified into two groups based on median blast percentage (73.5%). This stratification revealed a distinct pattern of biomarker elevation that reinforces the conclusions drawn from the correlation analysis.

Patients with high blast burden (>73.5%) had a significantly higher median D-dimer level (1.65 µg/mL) compared to those with low blast burden (0.80 µg/mL, $p = 0.005$). This finding offers compelling confirmatory evidence that fibrinolytic activity, as measured by D-dimer, scales directly with disease intensity [22].

Conversely, SFMC levels exhibited only a modest, non-significant difference between the two groups (8.95 µg/mL vs. 6.70 µg/mL, $p = 0.210$), which is consistent with its weaker correlation with blast burden. This further supports the hypothesis that SFMC reflects distinct biological processes or more proximal steps of thrombin generation rather than the overall tumor burden [21]. Table 6

Group	Blast%(Median,IQR)	D-dimer/SFMC (µg/mL, Median, IQR)	p-value
D-dimer Low Blast Burden (n = 20)	30.8 (18.5–61.0)	0.80 (0.58–1.20)	0.005*
D-dimer High Blast Burden (n = 20)	87.3 (82.0–91.0)	1.65 (1.10–2.70)	
SFMC Low Blast Burden (n = 20)	30.8 (18.5–61.0)	6.70 (4.35–9.80)	0.210
SFMC High Blast Burden (n = 20)	87.3 (82.0–91.0)	8.95 (5.15–18.25)	

Mann–Whitney U test; $p < 0.05$ considered statistically significant.
Table 6: Biomarker Levels Stratified by Disease Burden (Blast Percentage)

Investigating the SFMC–D-dimer Relationship: A Temporal Cascade?

The strong correlation between SFMC and D-dimer ($\rho = 0.66$, $p < 0.001$) confirms that both biomarkers participate in the

same pathological process. Most patients cluster in the lower-left quadrant (low SFMC, low D-dimer), but a subset diverges sharply into the high SFMC/high D-dimer quadrant [22].

This distribution is consistent with a temporal cascade model: SFMC elevation marks the upstream phase of thrombin generation and fibrin formation, while D-dimer reflects the downstream phase of fibrin degradation. In this framework, SFMC can be seen as a more specific but less sensitive biomarker, identifying a subset of AML patients with particularly aggressive or subtype-specific coagulopathy. Conversely, D-dimer functions as a sensitive but less specific biomarker, mirroring the overall fibrinolytic load [20].

Interpretation

This further examination shows that there are two biomarker profiles in AML patients.

To begin with, D-dimer is a sensitive, quantitative measure of both disease burden and fibrinolytic activity across the whole world. Its persistent high-level and association with the number of blasts make it an excellent candidate for regular screening and longitudinal tracking of thrombotic risk in AML [40].

Second, SFMC is a narrower, qualitative measure of severe thrombin burst. Its elevation is uncommon and is not directly proportional to leukemic burden, which may indicate that it identifies a subgroup of patients who are at a high risk of thrombotic event because of subtype-specific biology or localised endothelial injury [8].

This is sophisticated knowledge which has clinical importance. D-dimer might be used as an initial screening instrument to evaluate AML patients with an increased risk of thrombosis, and SFMC might be more appropriate to detect patients who need urgent and aggressive prophylaxis or treatment. Essentially, this is the reason why the interactive evaluation of these two biomarkers offers a more refined and multidimensional perspective of AML-related coagulopathy than either of the two markers [31].

The paper assessed the soluble fibrin monomer complex (SFMC) and D-dimer as early predictors of hypercoagulability in treatment-naive AML patients at diagnosis versus healthy controls. They tested three hypotheses, which included the following: 1) SFMC and D-dimer levels should be significantly increased in AML, and the two biomarkers should be correlated with haematological and coagulation parameters, and 3) SFMC should provide predictive value earlier or better than D-dimer does [31]. The results are a clear positive indication in favour of the first hypothesis since the median D-dimer (1.2 vs. 0.2 µg/mL) and SFMC (7.3 vs. 3.8 µg/mL) measured in AML patients are significantly greater than in controls ($p < 0.001$). Correlation analyses provide partial support for the second hypothesis, as D-dimer but not SFMC showed moderate, significant associations with leukocyte count and blast percentage. The third hypothesis was not fully confirmed; D-dimer achieved superior diagnostic performance (AUC 0.96 vs. 0.81 for SFMC) in distinguishing AML from controls. Stratified analyses revealed that the M3 (APL) subtype exerted a dominant influence on biomarker elevations, emphasizing the importance of subtype-aware interpretation [33].

The elevated D-dimer levels observed are consistent with its role as a downstream marker of fibrin degradation and fibrinolytic activity. They indicate that active fibrin turnover is present at AML diagnosis, likely driven by procoagulant expression on leukemic blasts and microthrombi formation [12]. SFMC elevation adds complementary insight by reflecting thrombin activation and fibrin monomer formation upstream of fibrinolysis, supporting the view that coagulation activation in AML spans the entire cascade from monomer generation to fibrin breakdown [12]. Yet the magnitude of SFMC elevation was less pronounced than that of D-dimer, suggesting that fibrinolysis amplifies the D-dimer signal. M3 patients displayed particularly high SFMC and D-dimer levels, consistent with the severe coagulopathy and hyperfibrinolysis characteristic of APL. These findings suggest that while both biomarkers identify hypercoagulability, their interpretation must account for AML heterogeneity [14].

The correlation patterns further refine our understanding. D-dimer correlated with leukocyte count and blast percentage, implying it tracks global disease burden and fibrinolytic activity. SFMC, in contrast, showed weak, non-significant correlations, which may indicate it reflects localized or subtype-specific thrombin generation rather than bulk leukemic burden [21]. Neither biomarker correlated with platelet count, underscoring that AML's hypercoagulability is primarily plasma-based and can occur despite thrombocytopenia. This dissociation reinforces the clinical paradox of thrombotic events in thrombocytopenic AML and supports a combined biomarker strategy [34].

The diagnostic analyses clarify the relative roles of the two markers. D-dimer's high AUC reflects its ability to capture the cumulative effect of fibrin formation and breakdown, making it a sensitive marker for AML-associated hypercoagulability at diagnosis [37]. SFMC measures an earlier stage of fibrin formation but appears more specific to high-risk subgroups such as M3 AML. This pattern supports a potential two-step model in clinical practice: D-dimer as a highly sensitive screening tool for hypercoagulability, followed by SFMC as a second-tier marker to identify patients at the greatest thrombotic risk. Thus, rather than being a universally stronger predictor, SFMC may be better suited to risk stratification

[38].

4. DISCUSSION

This study tested three hypotheses: that SFMC and D-dimer are elevated in newly diagnosed, treatment-naïve AML; that these biomarkers correlate with hematologic and coagulation parameters; and that SFMC might offer earlier or stronger predictive value than D-dimer. Results strongly support the first hypothesis: median D-dimer (1.2 vs. 0.2 µg/mL) and SFMC (7.3 vs. 3.8 µg/mL) were markedly higher in AML patients ($p < 0.001$), indicating active coagulation and fibrinolysis at diagnosis [11]. Correlation analyses partially support the second hypothesis: D-dimer correlated with total leukocyte count and blast percentage, whereas SFMC showed weaker, non-significant associations. The third hypothesis was not confirmed in a broad sense; ROC analysis yielded superior diagnostic performance for D-dimer (AUC 0.96) versus SFMC (AUC 0.81), although subtype effects complicate interpretation [40], [17].

The elevation of D-dimer aligns with its role as a downstream marker of fibrin degradation and reflects ongoing fibrin turnover driven by procoagulant activity of leukemic blasts and microvascular thrombus formation in AML [25]. SFMC, an upstream indicator of thrombin-mediated fibrin monomer formation, complements this picture by signalling earlier thrombin activity prior to full polymerization [29]. The greater magnitude of D-dimer elevation suggests amplification of the signal by fibrinolysis, consistent with prior observations that downstream markers can exceed upstream signals in settings of active clot turnover [32]. However, stratified analyses showed a pronounced effect of the M3 (APL) subtype—M3 patients had substantially higher D-dimer and SFMC—reflecting APL's well-known consumption coagulopathy and hyperfibrinolysis and indicating that subtype heterogeneity strongly influences biomarker distributions [26].

Correlation patterns refine the mechanistic interpretation. D-dimer's moderate correlation with leukocyte counts and stronger correlation with blast percentage suggest it tracks global disease burden and fibrinolytic activity; leukemic blasts express tissue factor and cancer procoagulant that accelerate thrombin generation and downstream fibrinolysis [32], [36]. SFMC's weak correlations imply it may capture localized or subtype-specific thrombin bursts not linearly related to bulk leukemic burden [35]. The lack of association between either biomarker and platelet count underscores that AML's hypercoagulability is primarily plasma-based and can coexist with thrombocytopenia, explaining the clinical paradox of thrombosis in thrombocytopenic patients [38]. These complementary patterns support using both markers rather than relying on one alone [12].

Diagnostic comparisons indicate that D-dimer, by integrating cumulative fibrin formation and breakdown, is a highly sensitive discriminator of AML-associated hypercoagulability at diagnosis, while SFMC—though theoretically more proximal—is more specific to high-risk subgroups (notably M3) and therefore less sensitive across an unselected cohort [40]. This suggests a pragmatic two-tier model: screen with D-dimer and apply SFMC selectively to identify those at greatest thrombotic risk [39].

Strengths of study and future direction

Among the strengths are concomitant assessments of the upstream (SFMC) and downstream (D-dimer) markers in a clearly defined treatment-naive AML cohort using healthy controls and stratified analyses that revealed significant subtype influences. Limitations encompass a small sample size, which restricts subgroup power, the cross-sectional design, which excludes time dynamics and the fact that no universally standardised SFMC assays exist, meaning that cut-offs are not optimised to AML. Further studies are required to aim at multicentre, longitudinal validation, correlating biomarkers with clinical thrombotic events and survival, and combining molecular subtypes profiling to clarify the mechanisms underlying extreme hypercoagulability and influence thromboprophylaxis approaches.

5. CONCLUSION

This study demonstrates that hypercoagulability is an early and widespread manifestation of newly diagnosed AML. Through the measurement of soluble fibrin monomer complex (SFMC) and D-dimer on a treatment-naive cohort with matched controls, we were able to show that both of the biomarkers were significantly higher at diagnosis, which supported the presence of a prothrombotic milieu early on. D-dimer was a reflection of the downstream fibrinolytic response to extensive fibrinogenesis and good association with leukemic burden, especially blood blast percentage, but reflected the upstream thrombin-initiated fibrinogenesis and was highly increased in the M3 (APL) subtype. This distinction indicates that the two markers assess complementary and not substitutable processes and advocate a complementary, as opposed to unique, use of biomarkers. ROC analysis proved the superiority of D-dimer as a general screening tool and placed SFMC as a useful risk-stratification criterion. The combination of the two in the diagnostic and risk models can lead to better predictions of the thrombotic complications and targeted prophylaxis, yet the more extensive longitudinal studies are needed to determine AML-specific cut-offs.

Declaration and statements
Conflict of interest: NON
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Ethical approval: The study protocol was reviewed and approved by the Institutional Review Board (IRB)/Ethics Committee of the Faculty of Medicine, Al-Azhar University (Approval No. 2531). Informed consent was obtained from the patients or their legal guardians before inclusion in the study.

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