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THE ASSOCIATION BETWEEN THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS- DISSEMINATED INTRAVASCULAR COAGULATION SCORE AND EARLY MORTALITY OF ACUTE LEUKEMIA PATIENTS

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ABSTRACT

Background: Disseminated Intravascular Coagulation (DIC) is a serious complication frequently found in patients with acute leukemia and is associated with increased early mortality. The ISTH-DIC score is widely used to assess the severity of DIC. However, data on the association between ISTH-DIC score and early mortality in acute leukemia patients in Indonesia remains limited.
Objective: To evaluate the association between ISTH-DIC score and early mortality (≤60 days) in acute leukemia patients at Adam Malik Hospital, Medan.
Methods: This was a retrospective cohort study involving 68 adult patients diagnosed with acute leukemia admitted from January 2022 to June 2024. Medical records were reviewed to collect laboratory parameters (platelet count, prothrombin time [PT], fibrinogen, and D-dimer) to calculate the ISTH score. Statistical analysis was performed using bivariate and multivariate logistic regression.
Results: The early mortality rate was 58.8%. A substantial proportion of patients had ISTH-DIC scores ≥5, but no statistically significant association was found between ISTH score and early mortality ($p = 0.704$). However, PT >1.2 seconds was significantly associated with early mortality ($p < 0.001$; OR 18.00). Platelet count, D-dimer, and fibrinogen levels showed no significant association.
Conclusion: The ISTH-DIC score was not significantly associated with early mortality in acute leukemia patients, but individual components such as prolonged PT showed a strong correlation. Early coagulation assessment remains essential in identifying patients at risk of life-threatening complications.

Keywords: Leukemia, Disseminated Intravascular Coagulation, ISTH Score, Mortality, Coagulation Tests

ABSTRAK

Latar Belakang: *Koagulasi Intravaskular Diseminata (KID) adalah komplikasi terjadi pada leukemia akut dan berpotensi meningkatkan mortalitas dini, dan data mengenai hubungan ISTH-KID dengan mortalitas dini di Indonesia masih terbatas.*
Tujuan: *Menilai hubungan antara skor ISTH-KID dengan mortalitas dini (≤60 hari) pada pasien leukemia akut di RSUP H. Adam Malik Medan.*

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Metode: *Penelitian ini berfokus pada 68 pasien leukemia yang berusia antara Januari 2022 dan Juni 2024, menggunakan parameter laboratorium dan analisis regresi logistik bivariat dan multivariat.*

Hasil: *Mortalitas dini tercatat sebesar 58,8%. Proporsi pasien dengan skor ISTH-KID ≥5 cukup tinggi namun tidak menunjukkan hubungan yang signifikan terhadap mortalitas dini (p = 0,704). Namun, PT >1,2 detik menunjukkan hubungan yang signifikan dengan mortalitas dini (p < 0,001; OR 18,00). Trombosit, D-dimer, dan fibrinogen tidak menunjukkan hubungan bermakna.*

Kesimpulan: *Skor ISTH-KID secara keseluruhan tidak berhubungan signifikan dengan mortalitas dini pada pasien leukemia akut, tetapi parameter komponen seperti PT menunjukkan korelasi kuat. Penilaian awal koagulasi tetap penting untuk mendeteksi risiko komplikasi yang mengancam jiwa.*

Kata kunci: *Leukemia, Disseminated Intravascular Coagulation, ISTH Score, Mortality, Coagulation Tests*

1. Introduction

Leukemia is a hematologic malignancy caused by abnormal proliferation of hematopoietic progenitor cells, leading to bone marrow infiltration and hematopoietic failure [1]. Acute leukemia results from early hematopoietic stem cell alterations that block normal maturation and allow uncontrolled proliferation [2]. In 2020, leukemia accounted for ~2.5% of new cancer cases and 3.1% of cancer-related deaths worldwide [3], with an incidence of 14.0 per 100,000 annually, higher in males and older adults [4]. Asia contributed 62.6% of global cases, while Indonesian data remain scarce, though provinces such as West Sumatra and Yogyakarta report higher local prevalence [5],[6]. Disseminated Intravascular Coagulation (DIC), as defined by the International Society on Thrombosis and Haemostasis (ISTH), is an acquired syndrome caused by systemic activation of coagulation [7]. It is a major complication in acute leukemia, lacking a universal diagnostic gold standard [8]. The ISTH, Japanese Ministry of Health, Labour and Welfare (JMHLW), and Japanese Association for Acute Medicine (JAAM) scoring systems are commonly used, with the ISTH-DIC score considered the most specific (cut-off ≥5; sensitivity 91%, specificity 97%) [8],[9]. DIC occurs in 10–40% of acute leukemia cases, highest in Acute Promyelocytic Leukemia (APL; 17–100%) and lower in AML and ALL (8.5–25%) [7],[9]. Its presence predicts early mortality due to bleeding, thrombosis, and multiorgan failure [10]. Early deaths within 30–60 days are also associated with infection, hemorrhage, or hyperleukocytosis [11]. Because many DIC cases are asymptomatic, early detection is crucial [9]. However, local data on DIC scoring's prognostic value in adult acute leukemia are limited. This study evaluates the association between ISTH-DIC scores and early mortality in Indonesian acute leukemia patients. Thromboembolic events are also common, affecting up to 10% of patients with AML receiving intensive chemotherapy and are often predicted by the presence of DIC [16,17]. Early death (within 30–60 days) is frequently caused by infections, bleeding, or hyperleukocytosis [18]. DIC in leukemia involves overexpression of tissue factor, excessive thrombin generation, platelet consumption, coagulation factor depletion, and impaired fibrinolysis, leading to bleeding, multiple organ failure, and death [10,15]. Many DIC cases are asymptomatic, emphasizing the need for early screening and management [14,15]. While international studies have established the prognostic value of DIC scoring, local data in adult acute leukemia patients remain sparse. The study highlights the link between early death and prolonged prothrombin time in resource-constrained

settings, emphasizing the need for early coagulation assessment in these settings, particularly in Indonesia.

2. Method

This study investigates the relationship between ISTH-DIC score variables and early mortality in acute leukemia patients at Adam Malik Hospital, Medan. The research uses secondary data from medical records from January 2022 to June 2024, including demographic data. Clinical assessment, peripheral blood smear, and bone marrow aspiration confirmed the diagnosis of acute leukemia, with ≥20% blasts in bone marrow or peripheral blood. ISTH-DIC Score was determined using the International Society on Thrombosis and Haemostasis standards. A total score of ≥5 indicated overt DIC. Data will be processed using computer equipment and presented in tabular form. Statistical analysis will be conducted using SPSS software.

3. Result

Among 111 acute leukemia patients who sought treatment at Adam Malik Hospital, Adam Malik Medan Hospital for the period January 2022-June 2024, 68 patients met the criteria for this study, aged between 30-45 years. The majority were male and female, with AML being the most common type. Treatment was mainly chemotherapy, with 57.4% receiving it. The mortality rate was high within the first 60 days, with 58.8% dying, while 41.2% remained alive. The study highlights the need for optimal management in the early stages of the disease (Table 1).

Table 1. Research Data Characteristic

Characteristic Subject	n (%)
Age (Year)	
18 – 30	22 (32.4)
30 – 45	24 (35.3)
45 – 60	17 (25.0)
≥60	5 (7.4)
Gender,	
Men	34 (50.0)
Women	34 (50.0)
Type Leukemia,	
AML	37 (54.4)
ALL	31 (45.6)
Therapy,	
No Chemotherapy	29 (42.6)
Chemotherapy	39 (57.4)
Mortality ≤60 days	
Death	40 (58.8)
Life	28 (41.2)

n=frequency,%=percentage, SD=Standard Deviation

Based on Table 2, platelets in those who died and lived with a median that was not much different, namely 32,000 and 30,500. For fibrinogen levels, patients who died had the highest levels between 200-400 mg/dl, as many as 61.5%. As for prothrombin time with a number >1.2 s is mostly found in patients who died, which is around 94.1%. As for D-dimer, patients who died were found to highest levels, with he most > 0.5 µg / ml or around 57.1%.

Journal of Endocrinology, Tropical Medicine, and Infectious Disease (JETROMI) Vol.07, No.03 (2023) 142-148

Table 2. Relationship between Laboratory Characteristics of Study Subjects and Mortality ≤60 days in Acute Leukemia Patients

Note:

Characteristic Laboratory	Death; n=40; (%)	Life, n=28; (%)	p
Trombosit, K/uL			0.455[d]
<150	34 (56.7)	26 (43.3)	
≥150	6 (75.0)	2 (25.0)	
Fibrinogen, mg/dl			0.851[c]
<200	8 (53.3)	7 (46.7)	
200-400	24 (61.5)	15 (38.5)	
>400	8 (57.1)	6 (42.9)	
Prothrombin time, s			<0.001[d]*
>1.2	16 (94.1)	1 (5.9)	
≤1.2	24 (47.1)	27 (52.9)	
D.dimer, µg/ ml			0.642[d]
>0.5	36 (57.1)	27 (42.9)	
<0.5	4 (80.0)	1 (20.0)	
ISTH score	34,2	36,33	0.704[b]
	Mod (min-max)	Mod (min-max)	
D-dimer (µg/ ml),	3.56 (1.1 – 7.4)	2.43 (1.27 – 6.75)	0.631[b]
Protrombin time (s),	1.1 (1.0 – 1.3)	1.00 (0.91 – 1.10)	0.001[b]*
Trombosit (sel/mm^3),	32000 (13000 – 76750)	30500 (16750 – 77750)	0.906[b]

frequency, %=percentage, IQR=Inter Quartile Range, Analysis using unpaired t-test, Mann-Whitney, Chi Square, Fisher Exact, *significant p<0.05.

4. Discussion

This study examined the relationship between clinical and coagulation parameters—particularly the ISTH-DIC score—and early mortality in adult acute leukemia patients. Despite a high 60-day mortality rate (58.8%), no statistically significant association was found between the ISTH-DIC score and early death. This contrasts with several studies reporting DIC as a major cause of early mortality in acute leukemia, especially in Acute Promyelocytic Leukemia (APL) and Acute Myeloid Leukemia (AML) [19]. DIC frequently precipitates fatal bleeding or thrombosis, but its prognostic value using the ISTH-DIC score remains debated, especially in heterogeneous or treatment-naïve populations lacking serial monitoring.

The mean age of our cohort (38 years) was younger than in most published studies [20]. Younger patients may have better hematopoietic reserve and fewer comorbidities, potentially mitigating DIC-related mortality despite coagulation abnormalities [21]. Another key distinction was the absence of chemotherapy at the time of sampling. Many studies linking ISTH-DIC scores to mortality were conducted in APL patients undergoing induction therapy, particularly with all-trans retinoic acid (ATRA) [22,23]. Chemotherapy-induced DIC and coagulopathy significantly contribute to early death, making ISTH scoring more relevant in that context. In untreated patients, the score may not adequately capture dynamic risks without serial measurements.

Our findings identified prolonged prothrombin time (PT) as a strong independent predictor of early mortality, consistent with studies associating PT prolongation with coagulation pathway disruption, hepatic dysfunction, sepsis, and systemic organ failure [24,25]. Shen and Yanada similarly reported prolonged PT as a marker for hemorrhagic complications and early death in APL [24,25]. In contrast, fibrinogen and D-dimer did not correlate significantly with mortality. Although low fibrinogen and high D-dimer levels have been linked to bleeding, thrombosis, or tumor burden in treated APL and AML [26], these parameters may be more dynamic post-treatment rather than reliable baseline mortality predictors [27]. Platelet count, traditionally a bleeding risk marker, also failed to predict

early death, aligning with Dai et al. and Geng et al., who suggested thrombocytopenia may be more indicative of bleeding or thrombotic events rather than survival [28]. These findings raise questions about the utility of the ISTH-DIC score as a standalone prognostic tool in newly diagnosed, untreated leukemia patients. While ISTH scores ≥4–6 have been associated with hemorrhagic death in APL [29] and thrombotic complications in AML, their sensitivity and specificity in diverse real-world leukemia populations remain limited [30]. Finally, cytogenetic features, which have been linked to DIC predisposition such as 11q23 abnormalities and KMT2Ar mutations—were not assessed in our cohort [31]. These factors may underlie variable susceptibility to coagulation disorders and need to be integrated into future predictive models. Our results are in contrast to a number of international studies that have found a strong correlation between elevated ISTH-DIC scores and early mortality in AML and APL [9, 10]. Given that the majority of our cohort was treatment-naïve and that prior studies primarily included patients receiving chemotherapy, particularly APL patients receiving ATRA, which is known to worsen coagulopathy [11], this disparity may be the result of different patient populations. Wang et al. [12] and Zhang et al. [13] similarly found that extended physical therapy was a powerful independent predictor of early death, which is consistent with our findings and supports its use as an easy-to-use marker in settings with limited resources. However, differences from studies that included molecular predictors such as KMT2A mutations and anomalies in 11q23 may be partially explained by the absence of cytogenetic data in our group [14]. Future multicenter studies incorporating serial measurements and molecular profiling are recommended.

This study has several strengths, including being among the first in Indonesia to evaluate the prognostic utility of the ISTH-DIC score in acute leukemia, thereby addressing a significant regional knowledge gap. The strong correlation between prolonged prothrombin time (PT) and early mortality provides a simple, cost-effective, and clinically relevant predictor, especially useful in resource-limited settings. Furthermore, the inclusion of only patients meeting the WHO 2016 diagnostic criteria ensured diagnostic accuracy. However, several limitations should be acknowledged. The small sample size and single-center design may limit the generalizability of the findings. The absence of serial ISTH scoring prevented assessment of dynamic changes in coagulation parameters that might better predict outcomes. Cytogenetic and molecular profiling, including KMT2A rearrangements and 11q23 abnormalities known to influence DIC risk, were not performed. Additionally, most patients were treatment-naïve at data collection, which may account for differences compared to studies in chemotherapy-treated cohorts.

5. Conclusion and Future Research

Prolonged prothrombin time is associated with higher mortality, although the ISTH-DIC score does not significantly predict early mortality in individuals with acute leukemia. To further understand mortality risks, future studies should make use of more biomarkers, larger, homogeneous populations, and serial evaluations. The study emphasizes the need for additional epidemiological studies and research on the complex factors that contribute to leukemia-related deaths.

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Conflict of Interest

The authors declare no conflict of interest related to this study. The research was conducted independently, without any financial or personal relationships that could have influenced the results and interpretations presented in this manuscript.

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