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Indication for FLT3 and CD34 Among Acute Myeloid Leukemia in Sudanese Patients

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Abstract: Background: Multiparametric flow cytometry (MPFC) is an effective method for AML diagnosis, classification, characterization, and MRD monitoring. Abnormal surface and cytoplasmic antigen patterns can form leukemia-associated immunophenotypes (LAIPs), enabling sensitive MRD detection. MPFC is applicable to more than 90% of AML cases, offering broad utility compared with PCR-based molecular MRD testing. AML outcomes vary widely, and prognosis is influenced by age, performance status, and cytogenetic abnormalities. CD34 is an important cell-surface glycoprotein used in AML immunophenotyping. CD34 contributes to cell adhesion and may facilitate interactions between hematopoietic stem/progenitor cells and the bone marrow stromal microenvironment. The FLT3 protein is primarily expressed on early hematopoietic progenitor cells, especially CD34-positive cells in the bone marrow, highlighting its important role in the initial stages of blood cell formation. Although FLT3 is also present in various other tissues, its major function is to act as an important regulatory receptor in hematopoiesis. This study aimed to detect CD34 and FLT3 among Sudanese patients with AML in order to assist in diagnosis and prognosis.

Methodology: 100 AML patients were enrolled in this study, they were 40% males and 60 females. Complete blood count was assessed via Beckman Coulter device and CD34 was detected through flow cytometer assessment and FLT3 was detected through molecular detection through PCR. Data analysis was conducted by statistical package of social science. Patients were recruited from Khartoum center for Nuclear and Isotope therapy -Sudan.

Result: Out of collected data of patients' files, CD34 detection, which was conducted via flow cytometer, it showed 21% with no CD34 and 79% with presence of CD34. FT3 mutation also detected 18% with wild type and 82% as mutant.

Conclusion: Males were less than females, CD34 was detected among 21% and FLT3 mutation detected among 18% as wild, those considered as poor prognosis phase.

Key word: flow cytometer, prognosis.

I. INTRODUCTION

The clonal growth of immature myeloid precursors (blasts and blast equivalents) is the hallmark of acute myeloid leukemia (AML), a broad category of hematological malignancies. AML has a diverse etiology, with a number of established risk factors linked to the development of the disease, such as exposure to ionization radiation and/or chemotherapy (especially alkylating agents and topoisomerase II inhibitors), which can result in therapy-related AML; occupational and environmental exposures, such as benzene; and genetic predispositions, such as Down syndrome, inherited bone marrow failure syndromes, and germline mutations in DDX41, CEBPA, and RUNX1), antecedent myelodysplastic neoplasms (MDSs) or myeloproliferative neoplasms (MPNs), presence of clonal hematopoiesis of indeterminate potential (CHIP) mutations in IDH1, IDH2, TP53, DNMT3A, TET2, and spliceosome genes, and lifestyle factors. (1-2).

In acute myeloid leukemia (AML), immunophenotyping using multiparametric flow cytometry (MPFC) is a useful and efficient diagnostic method for minimal residual disease (MRD) monitoring, classification, and characterization. Surface and cytoplasmic markers that are abnormally expressed on AML blasts at diagnosis have actually been identified by a number of studies; these combinations may establish leukemia-associated immunophenotypes (LAIP), which enable sensitive monitoring of MRD during follow-up. MPFC has the benefit of being applicable to the great majority (>90%) of cases when compared to molecular evaluation of MRD using PCR amplification of hereditary AML abnormalities (3).

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Patients with AML have a wide range of prognoses, from a few days of survival to full recovery. Age, performance status, and cytogenetics can all be used to predict the outcome. One surface marker that has been identified as a cell-surface glycoprotein is CD34. It serves as a promoter of cell-to-cell adhesion. It might act as a mediator in the attachment of bone marrow stem cells to stromal cells or the extracellular matrix of the bone marrow. In the late 1980s and early 1990s, CD34's prognostic function was thoroughly investigated. Numerous investigations have found it to be an undesirable prognostic sign. However, additional research disproved similar findings and questioned CD34's potential predictive significance (4-5).

The FLT3 protein is primarily expressed on early hematopoietic progenitor cells, especially CD34-positive cells in the bone marrow, highlighting its important role in the initial stages of blood cell formation. Although FLT3 is also present in various other tissues, its major function is to act as an important regulatory receptor in hematopoiesis. Its ligand (FLT3L) occurs in both membrane-bound and soluble forms and is produced by cells within the bone marrow microenvironment. Under normal physiological conditions, binding of the FLT3 ligand promotes receptor dimerization and autophosphorylation, thereby initiating several downstream signaling pathways, including PI3K/AKT, MAPK/ERK, and STAT. These signaling cascades regulate cell proliferation, survival, and differentiation, contributing to the controlled production of mature and functional blood cells. In addition to its essential role in hematopoiesis, FLT3 is involved in immune regulation by promoting the development of dendritic cells and natural killer cells. FLT3 ligand also works synergistically with cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-4 (IL-4) to enhance dendritic cell differentiation and expansion, highlighting its contribution to immune system development and adaptive immune responses (6-7).

When activated, the transmembrane tyrosine kinase receptor FMS-like tyrosine kinase 3 promotes cell division. AML is frequently caused by mutations in the FLT3 gene, which result in internal tandem duplications (FLT3-ITD) and activation of the FLT3 receptor tyrosine kinase, particularly in patients with normal karyotypes. In individuals with AML undergoing intense chemotherapy, it has been linked to poorer outcomes. The primary indicator of prognosis in patients with intermediate-risk AML is FLT3-ITD mutational status (8-9). Although approximately 60–70% of patients achieve complete remission following induction therapy, a substantial proportion subsequently experience relapse, often within three years. Relapse has been associated with the emergence and persistence of $CD34^{+}/CD38^{-}$ acute myeloid leukemia (AML) leukemic stem cells (LSCs), which possess self-renewal capacity and can continuously generate immature leukemic cells. These LSCs frequently carry genetic mutations that disrupt normal hematopoietic differentiation pathways, representing a characteristic feature of AML. Therefore, identifying and characterizing these functionally distinct $CD34^{+}$ cell populations is important for monitoring disease progression and improving the prediction of relapse (10-11).

II. MATERIAL AND METHOD

This cross sectional study was conducted in Khartoum center for nuclear and isotopic therapy. 100 of patients were diagnosed with acute myeloid leukemia (AML). From their files information were agreed to be collected from, their ages, type of classification according to FAB and extra medullary involvement. The patients were undergoing investigations of complete blood count by Beckman Coulter device, detection of FLT3 mutation was performed by polymerase chain reaction (PCR) and CD34 detection was conducted by follow cytometer Beckman Coulter device, reagents used were suitable for the purpose. Blood film were used for detection of blast percentage in blood samples and bone marrow as well as to grading type of leukemia. Data analysis was conducted by statistical package of social science (SPSS) version 20.

III. RESULT

Samples were 100 AML patients with age between 16-67 years old, they were 40 male (40 %) and 60 female(60%) as in figure 4-1, their mean age of (49.4+11.1) years old. Parameters measured included hemoglobin concentration, white blood cell and platelet counts, beside peripheral blast cell (52.8+2.89%) and blast in bone marrow (63.2+2.1%) as in table 1.

Participants AML patients sorted according to sub-types of AML according to FAB characteristics of blood picture, M4 was the most frequent, then M5, then M3, M1 and M2 then M7 and lower frequency was for M0 as in table 4-2 and figure 1.

Presence of complications among AML patients involved extra medullary infiltration showed it occurred among 60% of patients as positive result and among the 40% negative or not occurred. Lymphadenopathy as in table 3 and figure 2

Out of collected data of patients' files, CD34 detection, which was conducted via flow cytometer, it showed 21% with no CD34 and 79% with presence of CD34. FT3 mutation also detected 18% with wild type and 82% as mutant as in figure 3.

Table 1: mean±SD of age &WBC, Hb and platelet counts in PBP and BM

	Age	WBC	Hb	Platelet	Blast % Blood	Blast % BM
No						100
Mean±SD	49.35±11.1	35.36±7.1	9.01±0.23	55.4±8.89	52.8±2.89	63.2+2.1

Table 2 Classification of study population according to FAB classification:

FAB	Frequency	Percent
M0	1	1.0
M1	12	12.0
M2	12	12.0
M3	16	16.0
M4	24	24.0
M5	19	19.0
M6	7	7.0
M7	9	9.0
Total	100	100.0

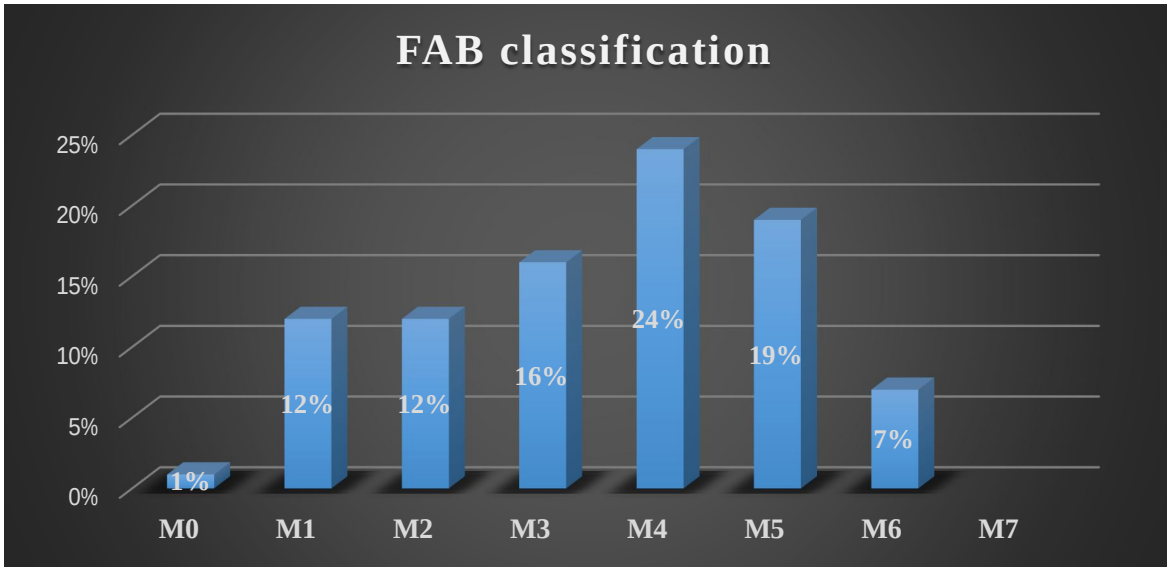

Figure 1: Classification of study population according to FAB classification

Table 3: complications among AML patients

Complications	Presence	Frequency	
Extra medullary infiltration	Positive	60%	100%
	Negative	40%	
BM cellular	Normal cellular	20%	
	Hyper cellular	80%	
Lymphadenopathy	Present	27%	
	Absent	73%	
Splenomegaly	Present	28%	
	Absent	72%	
Hepatomegaly	Present	23%	
	Absent	77%	

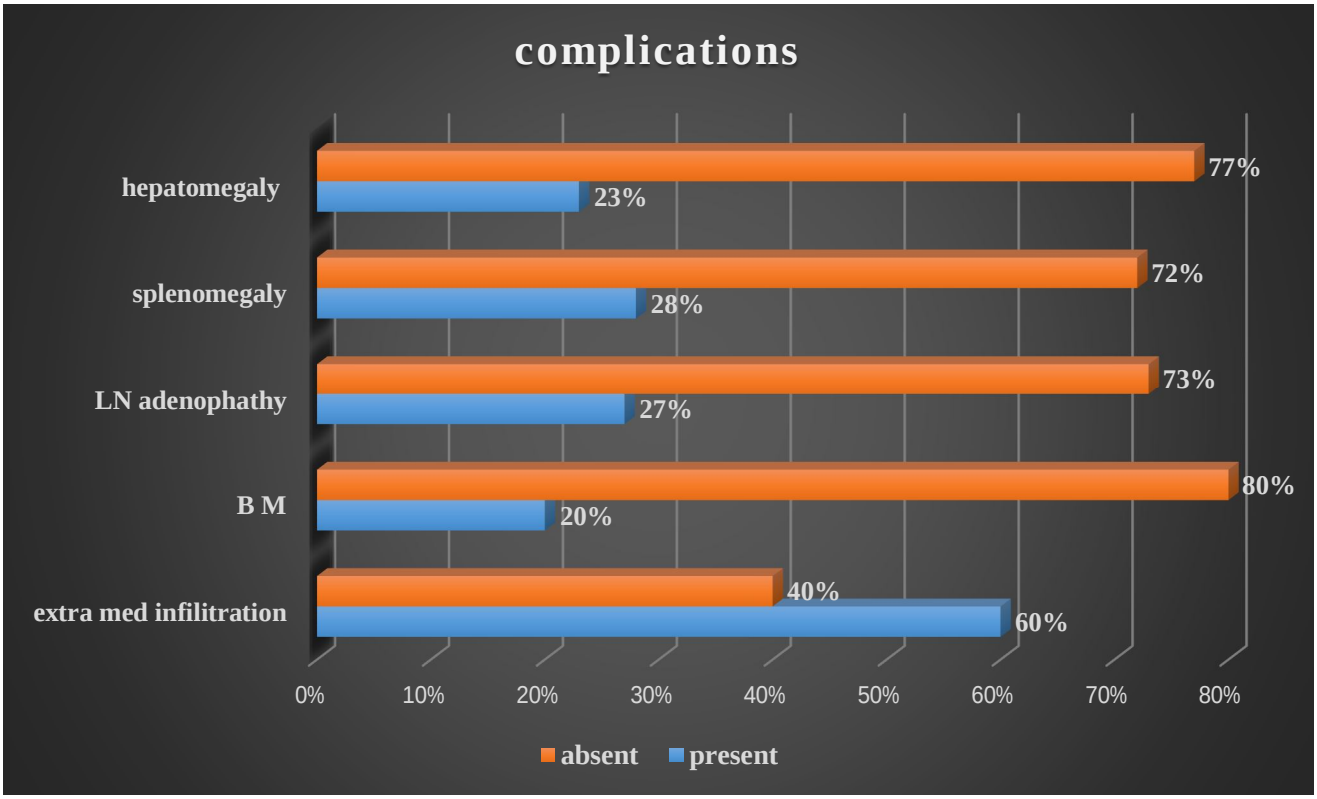

Figure 2: complications among AML patients

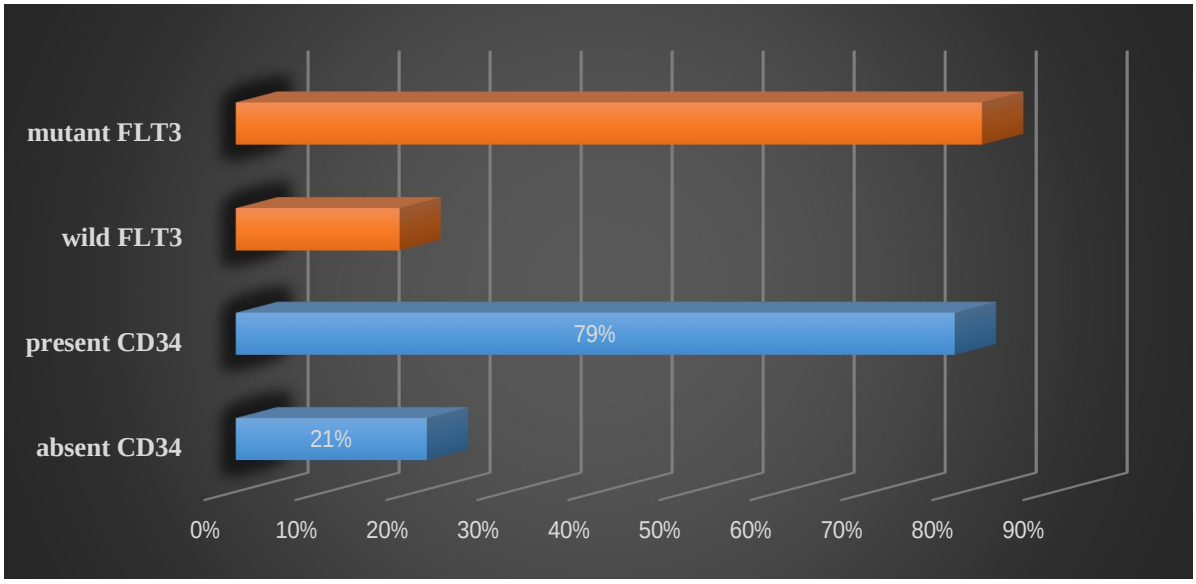

Figure 3: expression of CD34 marker in study population.

IV. DISCUSSION

The study included 100 patients diagnosed with acute myeloid leukemia (AML), ranging in age from 16 to 67 years, with a mean age of 49.35 ± 11.1 years. Of the study participants, 40 (40%) were males and 60 (60%) were females. The hematological parameters assessed included hemoglobin (Hb) concentration, white blood cell (WBC) count, platelet count, and blast cell percentages in peripheral blood and bone marrow. The mean WBC count was 35.36 ± 7.1 × 10^9/L, while the mean Hb concentration and platelet count were 9.01 ± 0.23 g/dL and 55.4 ± 8.89 × 10^9/L, respectively. The mean blast cell percentage was 52.8 ± 2.89% in peripheral blood and 63.2 ± 2.1% in bone marrow.

Our findings can be compared with published AML studies, particularly with respect to CD34 immunophenotypic expression and FLT3 mutation frequency by (Ihsan M. Osman et al) [12]. One important point is that your reported 82% FLT3-mutant frequency is substantially higher than the frequency generally reported when FLT3-ITD/TKD mutations are specifically measured, so the exact FLT3 assay and mutation type should be clearly stated in the thesis.

The close similarity between the two Sudanese studies (79.0% versus 78.7%) suggests that CD34 expression is relatively frequent among AML patients in the Sudanese population. The present finding is also comparable with earlier international observations. A study of AML immunophenotyping reported CD34 expression in 71% of cases overall and 77% when acute promyelocytic leukemia (APL) cases were excluded (Brian A Webber et al 2008)[13].

Similarly, 83% of patients in a previous flow-cytometric investigation of AML had CD34-positive leukemic cells, which is comparable to the 79% found in our study. Other research, however, has found much lower frequencies. For instance, only 42% of AML cases had CD34, according to a study conducted by the Australian Leukemia Study Group (K Bradstock et al 1994)[14].

Such differences may reflect variation in the distribution of FAB subtypes, particularly the proportion of APL and monocytic AML, because CD34 expression varies considerably among AML subtypes. This is relevant to the present study because M4 and M5 were the predominant FAB subtypes, whereas CD34 expression is generally less frequent in monocytic differentiation and particularly low in APL. The 79% CD34 positivity observed in the present study is also supported by the biological role of CD34 as a marker of immature hematopoietic progenitor cells. CD34 expression is frequently observed in AML blasts and can assist in identifying immature leukemic populations by flow cytometry. Nevertheless, CD34 is not expressed uniformly across AML, and its diagnostic interpretation should therefore be integrated with other markers such as CD117, HLA-DR, MPO, CD13 and CD33 rather than being used as an isolated diagnostic marker. Regarding FLT3, the present study found that 82% of patients were classified as FLT3-mutant and 18% as wild type. This proportion is markedly higher than that reported in most published AML cohorts. The generally accepted frequency of FLT3 mutations in AML is approximately 30%, with FLT3-ITD accounting for approximately 25% and FLT3-TKD mutations for approximately 5% of AML cases (Naval Daver et al 2019)[15].

A recent systematic review and meta-analysis provides more specific estimates, reporting a weighted prevalence of 20% for FLT3-ITD and 7% for FLT3-TKD, although individual studies showed substantial variation.Therefore, the 82% frequency in the present

study is considerably higher than the approximately 27% combined FLT3-ITD/TKD frequency expected from the recent literature. Regional studies similarly report substantially lower frequencies. For example, a Saudi Arabian study involving 97 newly diagnosed AML patients found FLT3 mutations in 18.56%, comprising 14.4% FLT3-ITD and 4.1% FLT3-TKD (Ghaleb Elyamany et al 2014)[16].

The close agreement between these two Sudanese studies suggests that CD34 expression is frequently observed among AML patients in the Sudanese population. The present result was also consistent with previous international studies, including a flow-cytometric investigation in which CD34-positive leukemic cells were identified in 83% of AML patients (L W Terstappen et al 1992) [17].

These variations may be related to differences in FAB subtype distribution, particularly the proportion of AML-M3 and monocytic subtypes, in which CD34 expression is often lower. In the present study, M4 and M5 were the predominant FAB subtypes, which may have influenced the overall CD34 expression pattern. Therefore, the 82% FLT3-mutant frequency observed in the present study is substantially higher than frequencies reported internationally and regionally. This discrepancy may be explained by differences in the definition of FLT3 mutation, the molecular method used for detection, patient selection, FAB subtype distribution, or population-specific genetic characteristics. It is therefore important to specify whether the present study evaluated FLT3-ITD alone, FLT3-TKD, or both types of mutation. If the 82% represents FLT3-ITD/TKD positivity specifically, the finding is unusually high and warrants careful methodological verification. Nevertheless, the high prevalence of CD34 expression and FLT3 abnormalities observed in this Sudanese AML cohort emphasizes the potential importance of immunophenotypic and molecular characterization for AML diagnosis, classification, and prognostic assessment. Previous research has also demonstrated that combined CD34 expression and FLT3-ITD may be associated with adverse clinical outcomes, including treatment resistance and shorter disease-free and overall survival (Mona S Abdellateif et al 2020) [18].

V. CONCLUSION

Patients showed significant hematological abnormalities, including high WBC counts, low hemoglobin and platelet levels, and increased blast percentages.

Bone marrow blasts (63.2%) were higher than peripheral blood blasts (52.8%), indicating substantial bone marrow involvement.

AML-M4 (24%) was the most frequent FAB subtype, followed by M5 (19%) and M3 (16%); M0 (1%) was the least frequent.

Extramedullary infiltration was present in 60% of patients.

The major clinical manifestations included splenomegaly (28%), lymphadenopathy (27%), and hepatomegaly (23%).

Bone marrow hypercellularity was observed in 80% of patients.

CD34 expression was detected in 79% of patients, while 21% were negative.

FLT3 mutation was detected in 82% of patients, compared with 18% who were wild type.

Overall, AML patients demonstrated considerable clinical, hematological, morphological, and molecular heterogeneity.

The findings emphasize the importance of combining hematological, morphological, immunophenotypic, and molecular investigations for comprehensive AML characterization and clinical assessment.

VI. RECOMMENDATION

Conduct larger multicenter studies to validate the findings and improve generalizability.

Perform routine hematological evaluation, including CBC and peripheral/bone marrow blast assessment.

Maintain bone marrow examination as an essential component of AML diagnosis and evaluation.

Combine FAB classification with immunophenotypic and molecular investigations for better AML characterization.

Incorporate flow cytometry, including CD34 and other relevant myeloid markers, into AML diagnosis.

Implement FLT3 mutation testing where resources permit for risk assessment and therapeutic planning.

Conduct careful assessment for extramedullary involvement, including lymphadenopathy, hepatomegaly, and splenomegaly.

Expand cytogenetic and molecular testing to include NPM1, CEBPA, RUNX1, and other relevant AML markers.

Investigate associations between CD34, FLT3 mutations, FAB subtypes, clinical features, treatment response, and survival.

Conduct prospective and longitudinal studies to evaluate prognostic significance and treatment outcomes.

Strengthen access to flow cytometry and molecular diagnostic facilities in healthcare institutions.

Further investigate the high frequency of AML-M4, extramedullary infiltration, and FLT3 mutations in the studied population.

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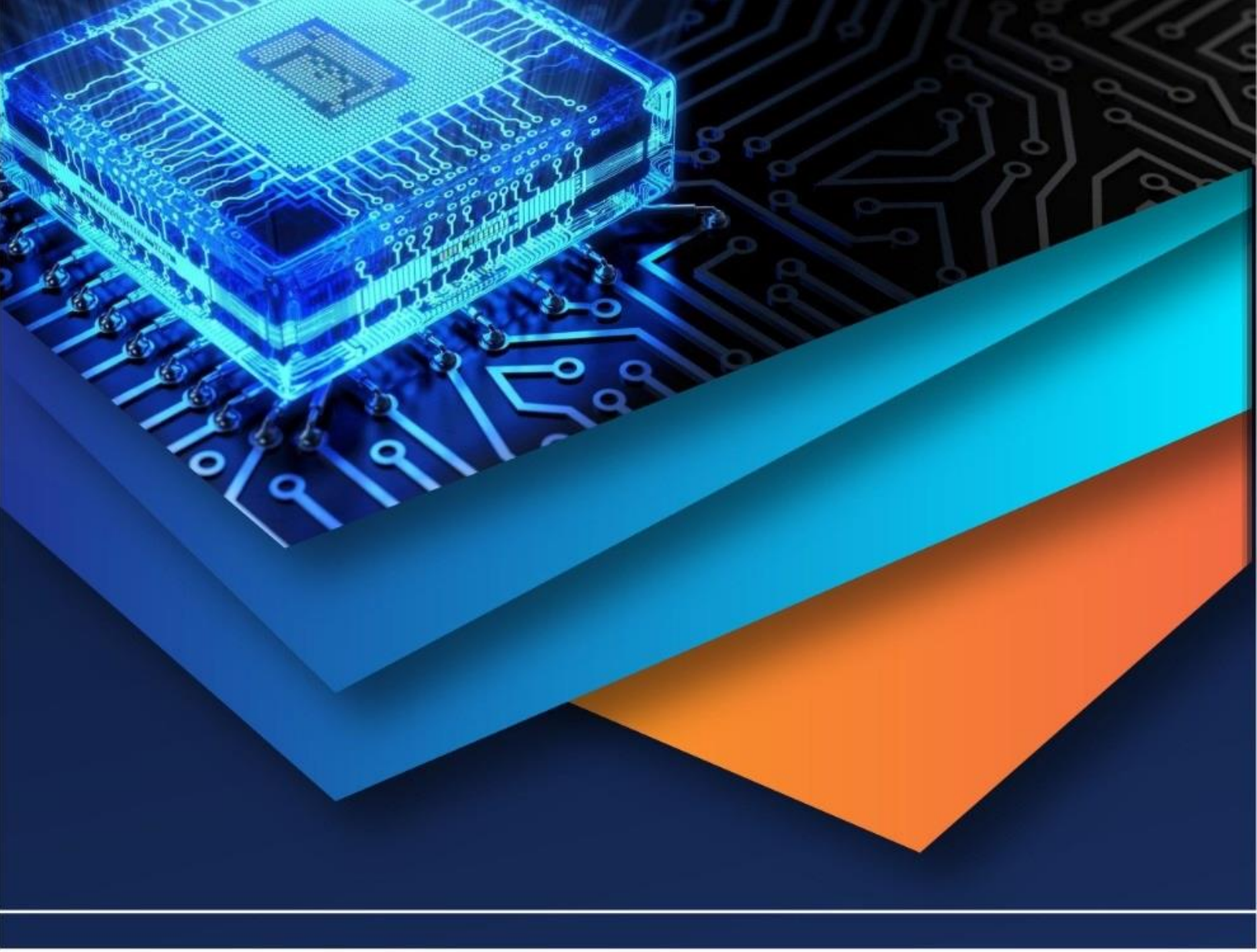

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