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D Dimer and Prothrombin Time as a Prognotic Marker of Covid 19 Morbidity and Mortality: A Retrospective Analysis

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***Abstract:** To analyse the value of coagulation indicators D Dimer and PT. D Dimer and PT as a prognostic marker of covid 19 morbidity and mortality. A total of 230 patients with confirmed covid 19 at the time of admission between march 5 to June 19 2021 are included in the study. The changes in D Dimer and PT are tested with their clinical classification and disease prognosis are studied. Result showed that coagulation disorders occurs at early stages of infection with 78.3 % patients having D Dimer increased, PT analysis shows 10 abnormal value in 46 deceased patients. The level of D Dimer and PT are compared with clinical classification. Among 46 patients who died of covid 19 36 had increased DD levels at their 1st laboratory investigation, 44 had DD increased at 2nd and 3rd lab test. ROC analysis in predicting morbidity and mortality rate showed that DD levels were o.742.0.818 and 0.851 respectively. PT levels were 0.643,0.824 and 0.937 respectively. The probability value of DD (P<0.01) indicate the severeneous of DD levels and covid 19. The study concluded that coagulation dysfunction is severe in critically ill patients and patients who are having lifestyle disorders and aging.DD and PT values can be used as a significant tool for making predictions of morbidity and mortality rate in severe covid 19 infection*

***Keywords:** Include at least 5 keywords or phrases*
D Dimer, Prothrombin time, Covid 19, cardiac arrest, Fibrinogen

I. INTRODUCTION

Covid 19 which was emerged in Kerala on the mid of march 2020 on a medical student arrived from China. Kerala government had implemented strict lockdown measure's for controlling the pandemic, setting up of covid hospitals, mandatory vaccination drives, awareness programs. Closure of schools and universities to prevent the spread and to controll the disease.

Although so many steps to prevent covid. (wearing of masks, hand sanitization…) The Pandemic shows its real face with known cases are increasing and death toll is also rising. The scenario is worse, even the vaccinated people are also getting infected and possibilities existing for the emergence of new lethal strains. The new rapid spreading variant delta making havoc and confusion among health workers and researchers.

The disease cause widespread lung injury (1,2) that rapidly progress to severe and critical illness like respiratory disease, fatal pneumonia and cause the death of subject by respiratory failure. Disease appears with mild to moderate fever, throat pain, persistent dry cough later develops multiple organs failures, fungal infection and a verity of other disease depend on the strains of covid 19 (3 4)

Like the strain change the symptoms of the diseases also change, that shows the virus is capable of lethal mutations in a short period of time. Disease spread through respiratory droplets and through close contact with diseased persons.

Hospitals in Kerala work in accordance with WHO and health and family ministry to tackle the pandemic. So many studies are ongoing includes zero surveillance studies, sepsis markers, coagulation markers scanning process, D Dimer……. To evaluate the current situations.

Medical laboratories are playing a vital role in accessing the patient status. In addition to RT-PCR and other test for confirmation they are accessing multiple organ function test to access the severity and shock created by the disease in each organ. This include a wide verity of tests but most profound ones are D Dimer, PT, APTT, TT, Fibrinogen, and other panel tests.

Among the panel tests after preliminary assessment it is shown that D Dimer and prothrombin time are the most reliable indicators of predicting the disease severity and more research is needed to confirm the statement.

The values of DD, and PT are significant in severe and critically ill patients having coagulation dysfunction and high mortality rate.

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II. MATERIALS AND METHOD

A. Patients' Criteria for Disease Diagnosis

Patients with covid confirmation admitted to covid care center at Ernakulam district Kerala was selected.

They are admitted to this hospital between March 5 to June 19 2021.A total of 230 cases where selected for the study. 230 patients have positive RT-PCR. Lab information of these patients were collected. Clinical data sheet of each patient was received from hospital with discharge summaries, under treatment, death within the duration of hospitalization more than 15 days before June 19. 2021 were included in this study. Excluded indicate for those are hospitalized and discharged for shorter periods of 15 days. Data provision is authorized by the director board framed for covid intervention and treatment at the hospital.

B. Clinical Classification of Covid

1) Case Categorization: Based on the revised guidelines on clinical management covid 19, government of India. Ministry of health and family welfare.

Cases are categorized in to

a) Mild pneumonia
b) Moderate
c) Severe

This classification is wholly based on the instructions given from health and family welfare government of India and Covid Management policy. (AIIMS / ICMR Covid national task forces)

- Mild Disease: Upper respiratory tract symptoms and (or fever) without shortness of breath or hypoxia.
- Moderate disease

✓ Respiratory rate >=24/minute breathlessness.
✓ SpO_2 : 90% to <= 93% on room air.

- Severe disease

✓ Respiratory rate >30/minute, breathlessness.
✓ SpO_2 <90% on room air.

According to revised guidelines on clinical management of covid 19 government of India intended for clinicians in India the above classification of mild moderate and severe cases is classified as

1. Uncomplicated illness, mild, severe, and acute respiratory syndrome. This classification based on respiratory distress and pneumonia severely confirmed TB rough chest x ray and C.T.

Oxygenation. (adults)

Mild ARDS: 200mmHg < paO_2/FiO_2 <= 300mmHg
(with PEEP or CPAP >= 5cm H_2O or no ventilated)

Moderate ARDS: - 100mmHg < PaO_2/FiO_2 <= 200mmHg
(with PEEP >= 5cm H_2O or non-ventilated)

Severe ARDS: - PaO_2/FiO_2 <= 100mmHg with PEEP >= 5cm H_2O, or non-ventilated.

2) Clinical Progression of Illness and Outcome

a) Discharged
b) Improved
c) Exacerbation
d) Death

C. Data Report

Timely collection of data is significant.

3type collection method was used: -

1) At admission time
2) After 4 or 5 days of admission
3) At composite end point.

D Dimer and prothrombin time sample are collected from laboratory data.

The value obtained in clinical recorded are labeled as
DD1
DD2
DD3 and
PT1, PT2, and PT3 Respectively.

D. Statistical Methods of Evaluating patient Data Using SPSS 25 Software

Group difference are calculated using H test and independent chi square test.
Roc curve used to analyze the sensitivity and specificity of DD and PT in predicting mortality rate and hospital discharge. Spearman's rank correlation coefficient is used to measure variables that is the study.
Probability value less than 0.05 was statistically significant.

E. Sample Collection

Conducted study by retrospective method. Case series study. Study design excludes patient involvement at any stage.

III.RESULT AND DISCUSSION

A. The Median age of 230 Patients were 63.55+-13.86(27-96)

Male population were 132(57.4%) and female were 98(42.6%)
Above 60 years older patients were 156.
At admission time mild category patients were 78(33.9%). Moderate cases reported are 96(41.7%) and severe cases were 56(24.5%). (*Table1)*

Table 1 - patients clinical classification (Age & Gender)

Demographic Data	Mild	Severe	Critical	Total
Age, Years (X+-S)	57.08+-12.92	64.94+-12.75	70.18+-13.86	63.55+-13.86
Distribution n (%) <60	40(17.4%)	22(9.6%)	12(5.2%)	74(32.2%)
>=60	38(16.5%)	74(32.2%)	44(19.1%)	156(67.8%)
Total	78(33.9%)	96(41.7%)	56(24.3%)	230
Gender Male n (%)	40(17.4%)	58(25.2%)	34(14.8%)	132(57.4%)
Female n (%)	38(16.5%)	38(16.5%)	22(9.6%)	98(42.6%)
Total	78(33.9%)	96(41.7%)	56(24.3%)	230

Table 1(b) – Discharge improved critical and death of covid 19 patients data summary at composite end point

Demographic Data	Hospital discharge	improved	critical	death	total
Age, Years(X+-S)	59.42+-14.78	63.94+-12.24	67.75+-15.36	70.87+-10.01	63.55+-13.86
Distribution n(%) <60	48(20.9%)	16(6.9%)	2(0.8%)	8(3.5%)	74(32.2%)
>=60	56(24.3%)	48(20.9%)	14(6.1%)	38(16.5%)	156(67.8%)
Total					230
Gender Male n(%)	56(24.3%)	38(16.5%)	14(6.1%)	24(10.4%)	132(57.4%)
Female n(%)	48(20.9%)	26(11.3%)	2(0.8%)	22(9.6%)	98(42.6%)
Total	104(45.2%)	64(27.8%)	16(6.9%)	46(20.0%)	230

B. Relationship Between DD_1 and PT_1.

Significant variation among DD_1 and clinical stage of patients.

DD_1 increased with disease severity (P<0.05) 162. (*Table 2)*

Table 2 – first analysis of DD_1, PT_1 and their clinical classification (n%)

Parameter	Mild	Severe	Critical	Total
DD_1(M+-SD)	0.85+-1.68	1.78+-4.40	3.86+-7.93	1.97+-5.01
<0.55	56(24.3%)	52(22.6%)	22(9.6%)	130(56.5%)
0.55 - 1.10	8(3.4%)	16(6.9%)	6(2.6%)	30(13.0%)
>1.10	14(6.0%)	28(12.2%)	28(12.2%)	70(30.5%)
Total X^2, P	78(33.9%) x^2=9.505 r=0.268	96(41.7%) P<0.05 P<0.01	56(24.3%)	230

Normal Reference Value DD(<0.55mg/l)

P value – 2-sided test

Parameter	Mild	Severe	Critical	Total
PT_1(M+-SD)	12.34+-1.91	12.14+-1.16	13.70+-338	12.59+-2.21
<9.2	0(0%)	0(0%)	0(0%)	0(0%)
9.2 - 15.0	74(32.1%)	94(40.9%)	46(20.0%)	214(93.0%)
>15	4(1.7%)	2(0.8%)	10(4.3%)	16(7.0%)
Total	78(33.9%)	96(41.7%)	56(24.3%)	230
X^2, P	X^2 =7.013	P<0.05		
r, P	r =0.162	P>0.05		

Normal Value PT (9.20 – 15 second)

Calculated P value – 2-sided test

C. Relationship between the dynamic change of DD and PT and prediction of covid 19.

A P-value (P<0.05) shows significant difference and positive correlation existing between DD and PT and outcomes at composite end points correlation of third with second and first was stronger: -

A 46 patients who died with disease.

36(78.3%) had DD_1 high

24 of 36 had DD_1 2 times higher > 1.10mg/L

44 cases had DD_2 and DD_3 increased

42 of 44 had DD_2 and DD_3 twice higher > 1.10mg/L.

16 cases who met the ultimatum (exacerbated) had increased DD_2 and DD3 higher than 1.10mg/L.

Table 3(a) – Correlation between DD, PT and covid prognosis. outcome at composite end point(n)

Parameters	Hospital discharge	Improved	Exacerbation	Death	Total
DD_1(M+-SD)	0.87+-1.73	1.55+-3.93	6.51+-10.29	3.47+-7.41	1.97+-3.01
<0.35	76	36	8	10	130
0.35 - 1.11	6	12	0	12	38
>1.11	22	16	8	24	70
Total	104	64	16	46	230
X^2, P	X^2 = 20.82	P < 0.01			
r, P	r = 0.346	P < 0.01			

Parameters	Hospital discharge	Improved	Exacerbation	Death	Total
DD_2(M+-SD)	1.62+-3.29	4.73+-8.02	12.40+-13.21	8.08+-10.96	4.50+-7.99
<0.55	40	10	0	2	52
0.35 - 1.11	24	22	0	2	48
>1.11	40	32	16	42	120
Total	104	64	16	46	230
X^2, P	X^2 = 30.11	P < 0.01			
r, P	r = 0.439	P < 0.01			

Parameters	Hospital discharge	Improved	Exacerbation	Death	Total
DD_3(M+-SD)	1.27+-2.08	2.38+-4.27	6.22+-3.75	8.93+-10.91	3.40+-6.23
<0.55	52	22	0	4	78
0.35 - 1.11	22	18	0	0	40
>1.11	30	24	16	42	112
Total	104	64	16	46	230
X^2, P	X^2 = 36.86	P < 0.01			
r, P	r = 0.467	P < 0.01			

DD normal references value (<0.55mg/l), P value calculated by 2-sided test

Table 3(b) – Correlation between DD, PT and covid 19 prognosis. outcome at composite end point(n)

Parameters	Hospital discharge	Improved	Exacerbation	Death	Total
PT_1(M+-SD)	11.91+-0.99	12.56+-1.84	13.41+-2.37	13.86+-3.68	12.59+-2.21
<9.2	0	0	0	0	0
9.20 - 15.0	104	62	12	36	
>15	0	2	4	10	
Total	104	64	16	46	
X^2, P	X^2 = 16.403	P < 0.01			
r, P	r = 0.331	P < 0.01			

Parameters	Hospital discharge	Improved	Exacerbation	Death	Total
PT_2(M+-SD)	12.97+-2.29	13.74+-4.28	14.23+-2.13	16.63+-5.06	14.00+-3.50
<9.2	0	0	0	0	0
9.20 - 15.0	100	56	10	26	192
>15	4	08	06	20	38
Total	104	64	16	46	230
X^2, P	X^2 = 21.104	P < 0.01			
r, P	r = 0.399	P < 0.01			

Parameters	Hospital discharge	Improved	Exacerbation	Death	Total
PT_3(M+-SD)	12.72+-1.68	12.81+-2.45	16.56+-5.50	24.52+-15.20	15.37+-8.45
<9.2	0	0	0	0	0
9.20 - 15.0	100	60	10	10	180
>15	04	04	06	36	50
Total	104	64	16	46	230
X^2, P	X^2 = 58.66	P < 0.01			
r, P	r = 0.595	P < 0.01			

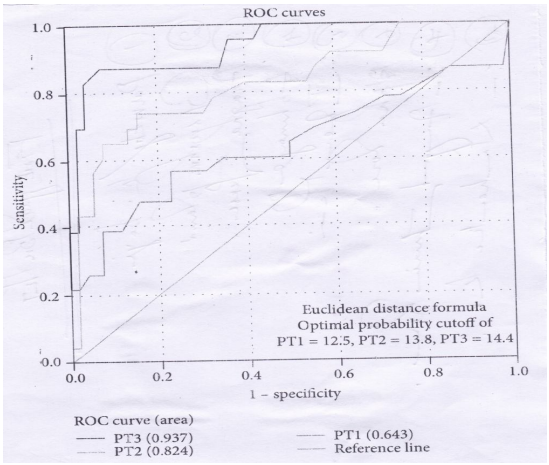
Reference value PT = (9.20 – 15 seconds)
P value calculations 2-sided test

D. DD and PT analysis is used to relation with patient discharge and mortality.

* ROC curve analysis is used to predict discharge and mortality role in 230 patients.

The area under the curve (AUCs) of DD_1, DD_2 and DD_3 to predict discharge and mortality were o.742.0.818 and 0.851 respectively

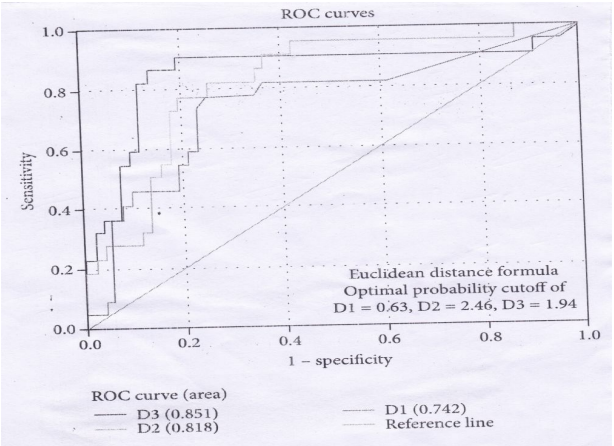
Fig 1 (a)



The AUC of PT_1 PT2 and PT_3 to predict the same

*were 0.643,0.824 and 0.937 respectively

(Fig1 (b))



IV. CONCLUSION

Covid 19 is an acute viral infection with the causative agent is corona virus (SARS-Cov2)

*The symptoms are marked with mild fever (4-6) loss of taste, abdominal discomfort and persistent dry cough. Some have developed fatal conditions leads to fatal pneumonia, cardiac failure and multiple organ failure, septic shock and death (7-10). The pattern of symptoms is complex, but so many disfunction with most prominent sepsis markers. Accompanied by cardiac arrest are shown at end stages. Coagulation dysfunction is also a major concern related with covid 19.

The viral entry to human body is through a receptor activated mechanism. Angiotensin converting enzyme 2$(ACE)_2$ receptor.

*Adsorbed on the surface of mucosal epithelial cells (7-8) and pathogen associated molecular pattern (PAMP) will recognize the virus quickly and onset of a sudden immune response occurs.

The response will trigger cytokine flux leads to vascular endothelial damage. In turn leads to coagulation system failure. This reaction cascade prohibits the fibrinolytic and anticoagulating systems by coagulation activation. Excessive thromboses in micro vascular system leads to disseminated intra vascular coagulation (DIC) micro circulatory disorder and multiple organ failure (11).

So, it is crucial to diagnose the coagulation disorder and timely correction will have definitive positive effect in reducing mortality.

Laboratory indicators of coagulate dysfunction are DD, PT, APTT and Fg:- liver is the central organ involved in coagulation process which include fibrinogen, which composed of intertwined polypeptide chains a, b, and g held together by disulfide linkages. Fibrin bound plasma degrade the fibrin network in to several soluble fragments of which will include D Dimer of the (DD)E complex instead of DD, Fg1, PT, APTT are most sensitive'

*Indicators of coagulation dysfunctions (12-15). DD and PT be used as sensitive indicators of coagulation dysfunction and this study was pointed to these 2 indicators related to covid severity.

When we analyzed DD,100 of 230 had abnormal DD (> 0.55 mg/l accounting 43.5% critically ill patients 34/50 (> 0.55 mg accounting for 60.7%.28 of critically ill patients have 2 time more than the average reference value of DD. So, this value is suggestive for clinical classification of covid.

There are significant correlation existing between DD and PT. So that shows the relationship of these two parameters with disease progression. 46 patients who deceased 36 had abnormal DD in first diagnosis (78.3%) and 24 of the 36 had DD levels 2 times more than reference value.

In prothrombin time analysis the first one shows we have 4 abnormalities in 8 critical patients. 10 abnormal value shown in 46 deceased patients. Second first shows 20 and third first of PT shows 36 abnormalities (>15sec) in 23 deceased patients. This sharp rise in PT values suggestive of high correlation of disease progression to end stages.

Based on discharged and deceased cases based on positive division.

ROC curve analysis shows the (AUC,s) for DD were 0.742,0.808 and 0.851 respectively.

The same (AUC, S) for PT are 0.643,0.824 and 0.937 respectively.

These two values have significance that is disease prediction and its severity.

Results of the analysis and its outcomes shows that D Dimer and PT are significantly increases with disease severity. This underline the complex coagulation process associated with covid 19. (12-15)

The results indicate that a hyper coagulating state due to fibrinolysis activation and its outcome was indicated by increased DD values in secondary and tertiary lab examinations (DD_2 and DD_3). (16)

[Limitations of the study]

Non-availability of control groups.

A. Conclusion

The major findings of this study proved the existence of a hyper coagulation state in covid 19 patients in early stages of disease. Data obtained and statistical analysis showed that DD and PT are the most reliable indicators to access and understand thrombotic complications and early and timely analysis of these parameters help the physicians to take interventions before being complicated by multiple organ failure and cardiac arrest. So many health workers and patients died in Kerala due to sudden onset of cardiac arrest. Problem lying behind that was the formation of thromboembolism and DIC secondary to coagulation disorder. It is better to evaluate these DD and PT as early and consistently throughout the disease period can reduce the morbidity and mortality by effective therapy measures before cardiac arrest. May this study will shed light on the project which was added with more coagulation factors like APTT, Fibrinogen and thromboplastin and CT studies for early intervention.

This will significantly reduce the morbidity and mortality of covid 19 infected patients.

B. Data Collection

Data availability of this study from one of the covid 19 treatment centers in central Kerala.

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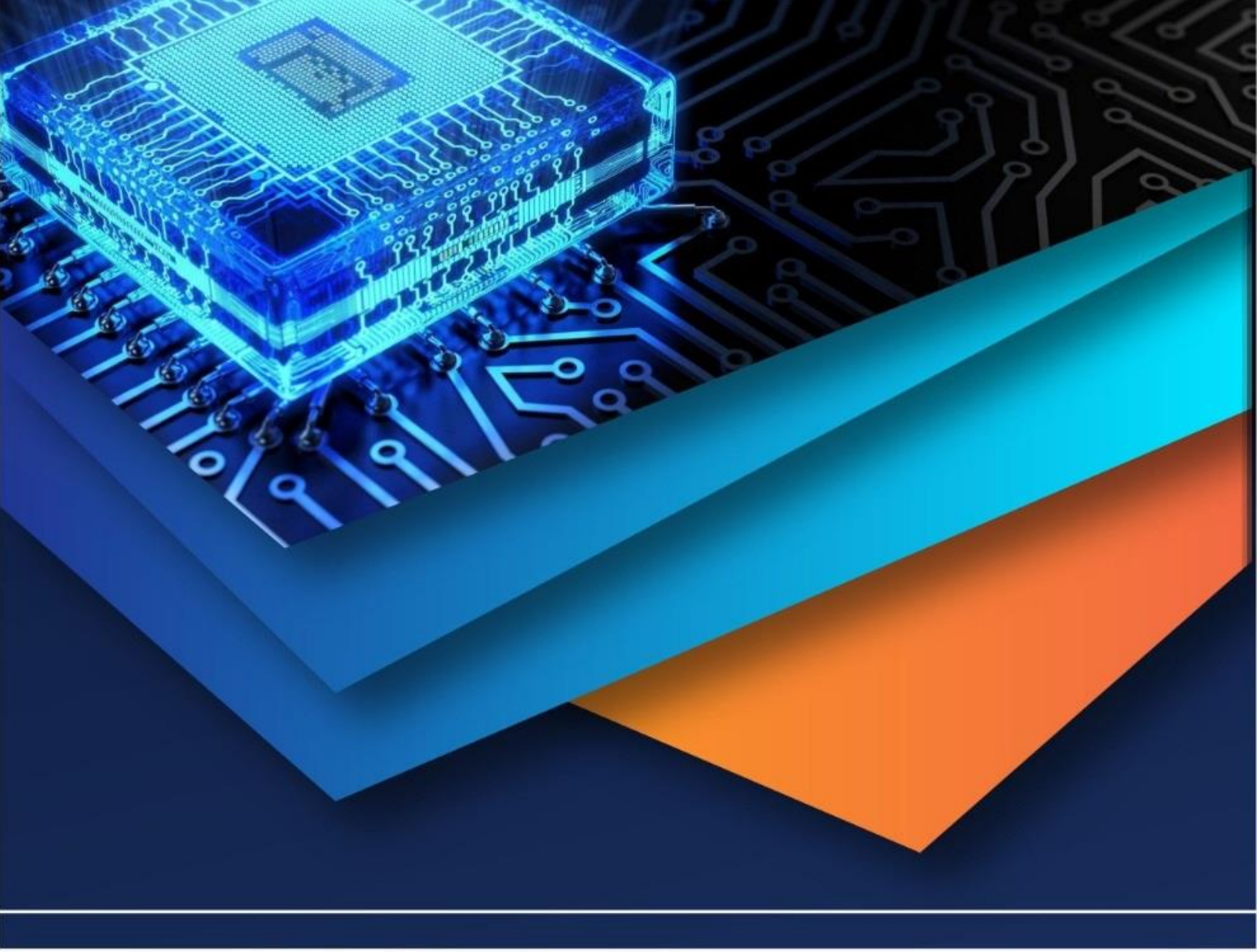

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