



ANALYSIS OF DIFFERENCES IN INR AND D-DIMER ON MORTALITY IN COVID-19 PATIENTS

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ABSTRACT

As of July 2022, COVID-19 has infected 565 million people, with 6.3 million deaths worldwide. The relationship between laboratory parameters with time to death and comorbidities has not been widely studied. This study determines the difference between INR and D-dimer on the mortality of COVID-19 patients at Dr. Hospitals. In a retrospective cohort study conducted in April 2020 - September 2021, 229 COVID-19 subjects were diagnosed with swab PCR. Data analysis included time to death from hospital admission divided into <7 days and >7 days, laboratory data, comorbidity data, and no comorbidity. Data were tested using Chi-Square for categorical data, Mann-Whitney, and Kruskal Wallis for numerical data. Overall, INR levels were significantly higher in subjects with comorbidities compared to those without ($p < 0.05$). This was based on the time to death of subjects <7 days without comorbidities. In addition, the change from hypercoagulation to hyperfibrinolysis due to excessive coagulant consumption factors, resulting in increased PT and INR in severe COVID-19 conditions. Overall, it was found that INR levels were significantly higher in subjects with comorbidities compared to subjects without comorbidities, as well as D-dimer in subjects with a time of death >7 days without comorbidities was significantly higher compared to other subject groups.

Keywords: COVID-19, time mortality, comorbidities, platelets, P.T., APTT, INR, D-dimer, ferritin

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INTRODUCTION

Since first identified at the end of 2019, Coronavirus Disease 2019 (COVID-19) has infected 565 million people worldwide since July 2022 (Ministry of Health, 2022). Number This shows the ability to infect high levels of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), declared as a pandemic in March 2020 infected 238 million people in October 2021 (Lau & Vadlamudi, 2022). In Indonesia, COVID-19 has spread rapidly, with 6.1 million cases identified, increasing drastically from the number of positive cases at the end of September 2020, namely 196,000 (Ministry of Health, 2022) (Nugraha et al., 2020).

Not only case high positivity, COVID-19 has resulted in 6.3 million case deaths all over the world, with 150 thousand cases originating from Indonesia (Ministry of Health, 2022). Various manifestation of clinical COVID-19 is associated with increased mortality, such as pneumonia, distress breath, and injury heart (Shi et al., 2020) (Yang et al., 2020). Many studies predict COVID-19 mortality wrong; the only one is a laboratory parameter (Simadibrata DM, 2020) (Lippi et al., 2020).

Providing knowledge about the difference between INR and D-dimer in the death of Covid-19 patients. This study aims to determine the difference between INR and D-dimer in the mortality of COVID-19 patients at Dr. Saiful Anwar General Hospital Malang.

Various laboratory parameters have proven to be related to the mortality of COVID-19. Available laboratory parameters Enough wide on various facility health like platelets, prothrombin time (P.T.), and activated prothrombin thromboplastin (APTT) is known related with degrees severity,

as well as a better prognosis bad (Barale & Russo, 2020) (Lippi et al., 2020) (Long et al., 2020). Other related laboratory parameters with coagulation, such as fibrinogen and D-Dimer, are known to be related to enhancement incident mortality (Simadibrata DM, 2020) (Listyoko et al., 2021) (Yorike et al., 2022). Known ferritin related to storm cytokines that occur during COVID-19, has proven to increase in COVID-19 patients with poor prognosis (Monica & Wulanjani, 2022). Relationship of laboratory parameters with time death And comorbidity Not yet Lots researched.

METHOD

A retrospective cohort study was conducted from April 2020 to September 2021 in the COVID-19 Inpatient Room at Dr. RSUD. Saiful Anwar Malang. Subject data was selected on condition that the medical record data was complete, there was an outcome (survive or non-survive), and a diagnosis of COVID-19 based on the results of the swab polymerase chain reaction (PCR). Data analysis consisted of time to death after hospital admission, which was divided into early (<7 days) and late (> 7 days), laboratory data, and comorbidity data. Laboratory parameters checked when the patient is admitted to the hospital are platelets, P.T., APTT, international normalized ratio (INR), D-Dimer, ferritin, and fibrinogen with average values according to the reference tool (XE-2100 et al.) (Sysmex, 2010) (W et al., 2021). According to CDC recommendations, comorbidities were included in comorbidities (hypertension, CAD, H.F., obesity, cancer, COPD, and CKD). Test the data with Chi-Square for categorical data and Mann-Whitney and Kruskal Wallis for numerical data. Data analysis used SPSS version 26.0 (IBM).

RESULTS AND DISCUSSION

There were a total of 229 subjects taking part in this study. Subject data were divided based on time to death <7 days (154 patients) and > 7 days (75 patients). There were 41 patients with a time to death of <7 days without comorbidities, <7 days with comorbidities, as many as 113 patients, >7 days without comorbidities, as many as 20 patients, >7 days with comorbidities, and as many as 55 patients. There were no significant differences in age, gender, and comorbidities in subjects with time to death <7 days and >7 days. (Table 1).

Table 1 Subject Characteristics

Variable (%)	Time Death		p
	≤ 7 days (n=154)	>7 days (n=75)	
Age (mean ± SD)	54.13 ± 13.36	55.77 ± 13.95	0.282
Type Sex			
Man	85 (37.1)	37 (16.2)	0.488
Woman	69 (30.1)	38 (16.6)	
Comorbidity			
Yes (H.T., D.M., CAD, CKD, CVA, COPD, T.B. Asthma, Malignancy)	113 (49.3)	55 (24.0)	1,000
No	41 (17.9)	20 (8.7)	

Platelet levels in the group with time to death > 7 days with comorbidities were significantly higher than the group with time to death <7 days without comorbidities. P.T. was found to be significantly longer in the group with time to death <7 days with comorbidities compared to the group with time to death <7 days without comorbidities. INR was significantly prolonged in the <7 days and > 7 days with the comorbidity group compared to <7 days without comorbidity. D-Dimer significantly increased in the >7 days group without comorbidities compared to all other groups. Ferritin levels were significantly lower in the group > 7 days with comorbidities than without comorbidities (Table 2).

Table 2 Table category platelets, P.T., APTT, INR, D-dimer, ferritin, and fibrinogen based on time death at a time comorbidity.

Group Platelets (N)	≤ 7hK(-) (n=41)	≤ 7hK(+) (n=113)	>7hK(-) (n=20)	>7hK(+) (n=55)
≤ 216000	21	42	6	19
216000 - 451000	17	62	13	33
>451000	3	9	1	3
P.T. (N)				
≤ 9.4	2	4	0	4
9.4 – 11.3	32	78	15	39
>11.3	7	31	5	12
APTT (N)				
≤ 24.6	10	27	5	11
24.6 – 30.6	24	61	12	27
>30.6	7	25	3	17
INR (N)				
≤ 1.5	41	112	20	54
≥ 1.5	0	1	0	1
D-Dimer (N)				
≤ 0.5	4	2	0	4
> 0.5	37	111	20	51
Ferritin (N)				
≤ 150	1	2	1	0
>150	40	111	19	55
Fibrinogen (N)				
≤ 154.3	0	2	0	1
154.3 – 397.9	8	27	3	14
>397.9	33	84	17	40

In subjects without comorbidities, D-Dimer levels were significantly higher in subjects with time to death >7 days compared to <7 days. In subjects with time to death <7 days, P.T. and INR levels were significantly higher in subjects with comorbidities than without comorbidities. In subjects with time to death >7 days, D-Dimer and ferritin levels were significantly lower in subjects with comorbidities than without comorbidities. Overall, INR levels were found to be significantly higher in subjects with comorbidities than in subjects without comorbidities ($p < 0.05$) (Table 3).

Table 3 Analysis of Differences in Platelet, P.T., APTT, INR, D-Dimer, Ferritin, and Fibrinogen Categories based on Time of Death and Comorbidities

Variable (mean ± SD)	≤ 7 days without comorbid (n=41)	≤ 7 days with comorbid (n=113)	>7 days without comorbid (n=20)	>7 days with comorbid (n=55)	p
Platelets	227243.90 ± 86097.56	257256.64 ± 108523.02	255800.00 ± 102843.57	287527.27 ± 123792.22	0.073
PT	10.57 ± 1.07	10.87 ± 1.11	10.89 ± 1.07	10.82 ± 1.16	0.214
APTT	27.22 ± 5.27	27.54 ± 4.62	26.96 ± 3.98	28.18 ± 5.71	0.717
INR	1.00 ± 0.11	1.04 ± 0.11	1.05 ± 0.11	1.05 ± 0.18	0.020
D-Dimer	5.06 ± 9.36	6.78 ± 9.93	13.18 ± 12.77	3.27 ± 5.20	0.003
Ferritin	1417.84 ± 1580.23	1557.34 ± 1201.94	1771.63 ± 1298.48	1335.83 ± 1122.83	0.131
Fibrinogen	485.66 ± 100.91	489.84 ± 183.63	604.29 ± 352.97	469.41 ± 142.43	0.602

In studies, laboratory parameter abnormalities exist on the part of the significant subject. Abnormality of platelets was experienced by 104 subjects (45.3%), P.T. abnormalities in 65 subjects (28.3%), and APTT abnormalities in 105 subjects (47.1%). Number high abnormality D-Dimer was found in 219 subjects (95.6%), ferritin in 225 subjects (98.3%), and fibrinogen in 177 subjects (76.0%). Subject to studies This is a patient with outer non-survivor, so findings studies by various studies previously proved that various laboratory parameters on is factor risk independent as well as mortality prognosis on COVID-19 (Yang et al., 2020) (Long et al., 2020) (Yao et al., 2020) (Mehrdad et al., 2021) (Barrett et al., 2021) (Mahroum et al., 2022). Findings are shown differently on INR, with

a percentage abnormality of only 0.8 %. Studies previously show a difference in significant INR among survivors compared to COVID-19 non-survivors. However, studies show a median INR of 1.20 as a healthy distance interquartile 1.03-1.32 on non-survivors who have not included high INR (≥ 1.5) (Paliogiannis P, Zinellu A Mangoni AA, Pazzola A Bandiera FL, 2022).

D-dimer analysis in studies shows significant D-dimer levels in groups with time death > 7 days without comorbidity compared to other groups. Various studies show exciting findings. They found high D-Dimer without followed activity, high fibrinolysis, also (Ibañez et al., 2021) (Wright et al., 2020). The group with high D-Dimer levels This No showed significant prolongation of P.T., APTT, and INR compared to group another, which shows activity fibrinolysis too no significantly tall compared to other groups. D-dimer is a product that results in normal fibrin metabolism and is used as a marker of various disease-related thromboembolisms. In COVID-19 patients, there can be an increase in D-dimer without accompanying enhancement of fibrinolysis systemic. According to researchers this can happen due to focused fibrin metabolism in COVID-19 on network lungs. Fibrin metabolism is done by the fibrinolytic mechanism in local lungs To remove fibrin and network necrotic around parenchyma-affected lung injury. This thing causes high amounts of various product fibrin metabolism, such as D-dimer, to be in the internal plasma. Fibrin metabolism occurs locally. This happens especially in stages of progressiveness early, so it is not accompanied by the enhancement of fibrinolysis systemic (Barale & Russo, 2020) (Tural Onur et al., 2021) (Nielsen et al., 2022). Theory This can explain findings on studies here, where time D-dimer analysis was performed in subjects with time death > 7 days is at in progressiveness more disease early.

There are several areas for improvement in this study. First, the study is monocenter, only involving Dr. Hospital. Saiful Anwar Malang as a source of patient data. Second, the number of research subjects was only 229 patients, who were then divided into subgroups based on time of death and comorbidities, indicating a lack of data in this study. Third, patient data is available only after hospital admission. Looking at the results of this study, knowing the progress of the patient's disease before entering the hospital is essential to know more clearly regarding the results of the laboratory parameter analysis obtained. Studies with a more significant number of subjects, as well as data regarding disease progression before hospital admission, are expected to clarify the relationship between the various laboratory parameters studied and the time of death in COVID-19 patients. (Alroomi et al., 2021) (Lino K et al., 2021) .

CONCLUSION

Overall, it was found that INR levels were significantly higher in subjects with comorbidities than without comorbidities, and D-dimer in subjects with time to death >7 days without significant comorbidities was higher than in other groups of subjects.

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