# Relationship between Initial CT Value, Inflammatory Markers, and Onset of Clinical Symptoms with Outcomes of Treatment Outcomes of COVID-19 Patients at Dr. M. Djamil General Hospital Padang

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**A B S T R A C T**

**Background:** Treatment given for COVID-19 includes the provision of antiviral, anti-inflammatory, immunomodulatory, anticoagulant, and treatment of comorbidities and complications. The success of treatment in COVID-19 patients does not only depend on the drug given but is also influenced by clinical manifestations, clinical phase, and the presence or absence of complications and comorbidities. This study aims to assess the relationship between initial CT values, inflammatory markers, and symptom onset on treatment outcomes for COVID-19 patients at Dr. M. Djamil General Hospital Padang. **Methods:** This study is an observational analytic study with a retrospective cohort approach in confirmed COVID-19 patients treated at Dr. M. Djamil General Hospital Padang between 1st January – and 31st May 2021. The sample is the population that meets the inclusion criteria; confirmed COVID-19 from the results of RT PCR/TCM SARS-CoV-2, aged > 18 years, including the clinical degree of moderate, severe, critical illness. Exclusion criteria were patients with incomplete medical record data. Univariate analysis is intended to describe each research variable so that the distribution and percentage of each variable are presented in tabular form. Bivariate analysis using Chi-Square statistical test to see the relationship between variables. **Results:** COVID-19 patients being treated at Dr. M. Djamil General Hospital Padang were mostly in the age group above 50 years, namely 59.6%, and the female sex was treated more than the male, namely 55.5%. The moderate clinical grade is the highest proportion of hospitalized patients, namely 64.3%, followed by critical clinical 30.0% and severe clinical 5.6%. There is no relationship between the initial CT value and the outcome of COVID-19 patients. There is a relationship between IL-6 levels (initial) with the outcome of Covid-19 patients at Dr. M. Djamil General Hospital Padang. There is no relationship between the onset of clinical symptoms and the outcome of Covid-19 patients at Dr. M. Djamil General Hospital Padang. **Conclusion:** There is a relationship between IL-6 levels (initial) with patient outcomes, need for oxygen therapy, ferritin levels with the incidence of sepsis, initial albumin levels with initial D-Dimer levels, and IL-6 levels with D-dimers in COVID-19 patients at Dr. M. Djamil General Hospital Padang.

## 1. Introduction

Coronavirus Disease 19 (COVID-19) is a disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov 2). The latest report on the number of cases of COVID-19 in the world on 4th March 2021 was reported to have reached 114,790,763 confirmed cases with 2,560,074 deaths. Case Fatality Rate (CFR) 2.2% as many as 222

countries have reported where there is no difference between men and women and the most are in terms of productive age.[1-4] Clinical manifestations of COVID-19 can be asymptomatic, mild, moderate, severe, and critical. The main clinical symptoms that appear are fever, cough, difficulty breathing, other respiratory symptoms, and non-respiratory symptoms such as diarrhea, anosmia, ageusia, delirium, nausea, vomiting, and others. These symptoms depend on the clinical phase of COVID-19 when the patient arrives.[5,6] Polymerase Chain Reaction (PCR) swab examination is the gold standard to ensure that COVID-19 is confirmed. The results of the PCR examination that are declared positive are followed by the Cycle Threshold (CT) value which describes the concentration of virus that can be detected at the time of the swab examination.[1-4]

Treatments given to COVID-19 include the provision of antiviral, anti-inflammatory, immunomodulatory, anticoagulant, and treatment of comorbidities and complications, such as the use of antibiotics in cases accompanied by secondary infection. The success of treatment in COVID-19 patients does not only depend on the drug given but is also influenced by clinical manifestations, clinical phase, and the presence or absence of complications and comorbidities. The use of drugs in COVID-19 patients must be used according to clinical conditions and the predictive stage of the disease according to the phase. If given not at the right time, it may be useless or even potentially harmful. Giving aggressive anti-inflammatory drugs too early has the potential to depress the immune system and is also less useful if given after irreversible tissue damage has occurred. For this reason, researchers are interested in researching the relationship between initial CT values, inflammatory markers, and symptom onset on treatment outcomes for COVID-19 patients at Dr. M. Djamil General Hospital Padang.

## 2. Methods

This study is an observational analytic study with a retrospective cohort approach in confirmed COVID-19 patients treated at Dr. RSUP. M. Djamil Padang between 1st January – 31st May 2021. A total of 373 research subjects participated in this study, of which the research subjects had met the inclusion criteria; confirmed COVID-19 from SARS-CoV-2 RT PCR results taken from nasal/nasopharyngeal swabs, aged > 18 years, including moderate, severe, critical clinical disease degrees. Exclusion criteria were patients with incomplete medical record data. Observations were made on the characteristics of research subjects, laboratory descriptions of research subjects, and the relationship between laboratory results and outcomes of COVID 19 patients.

Data analysis was carried out with the help of SPSS 25 software. Univariate analysis was intended to describe each research variable so that the distribution and percentage of each variable were presented in the form of tables and graphs. Bivariate analysis to see the relationship between variables using Chi-square statistical test.

## 3. Results

Table 1 shows the COVID-19 patients who were treated at Dr. M. Djamil General Hospital Padang were mainly in the age group above 50 years, as much as 59.6%, and the female sex was treated than the male, namely 55.5%. The moderate clinical grade is the highest proportion of hospitalized patients, namely 64.3%, followed by critical clinical 30.0% and severe clinical 5.6%.

Table 1. Characteristic of COVID-19 patients treated at Dr. M. Djamil General Hospital Padang.

| Patient characteristics | Number of patients | Percentage (%) |
|---|---|---|
| **Age (Years) (n = 373)** | | |
| 18 – 49 years | 151 | 40.5 |
| 50 – 59 years | 92 | 24.7 |
| 60 – 69 years | 79 | 21.2 |
| ≥ 70 years | 51 | 13.7 |
| **Gender (n = 373)** | | |
| Male | 166 | 44.5 |
| Female | 207 | 55.5 |
| **Clinical degree of disease (n = 373)** | | |
| Moderate | 240 | 64.3 |
| Severe | 21 | 5, 6 |
| Critical | 112 | 30.0 |
| **Length of treatment (n = 373)** | | |
| ≤21 Days | 276 | 74.0 |
| > 21 Days | 97 | 26.0 |
| **Parameters of laboratory (mean/median):** | | |
| **Routine blood:** | | |
| - Leukocytes (n = 373) | | |
| <4,000 mm³ | 373 | 100 |
| 4,000 – 10,000 mm³ | 0 | 0 |
| >10,000 mm³ | 0 | 0 |
| **Faal hepar** | | |
| - SGOT (n = 373) | | |
| ≤38 U/L | 229 | 61.4 |
| > 38 U/L | 144 | 38.6 |
| - SGPT (n = 373) | | |
| ≤ 41 U/L | 274 | 73.5 |
| > 41 U/L | 99 | 26.5 |
| - Initial albumin (n = 232) | | |
| < 3 gr/dL | 84 | 36.2 |
| ≥ 3 gr/dL | 148 | 63.8 |
| - Serial albumin (n = 123) | | |
| < 3 gr/dL | 63 | 51.2 |
| ≥ 3 gr/dL | 60 | 48.8 |
| **Kidney faal** | | |
| - Urea (n = 373) | | |
| ≤ 50 mg/dL | 287 | 76.9 |
| > 50 mg/dL | 86 | 23.1 |
| - Creatinine (n = 373) | | |
| ≤ 1,2 mg/dL | 306 | 82.0 |
| > 1,2 mg/dL | 67 | 18.0 |
| **Inflammatory markers:** | | |
| - Initial D-Dimer (n = 372) | | |
| <500 ng/dl | 55 | 14.8 |
| >500 ng/dl | 317 | 85.2 |
| - Serial D-Dimer (n = 203) | | |
| <500 ng/dl | 29 | 14.3 |

| | | |
|---|---|---|
| >500 ng/dl | 174 | 85.7 |
| - Initial procalcitonin (n = 373) | | |
| < 0 ,5 ng/ml | 295 | 79.1 |
| > 0.5 ng/ml | 78 | 20.9 |
| - Serial procalcitonin (n = 101) | | |
| < 0.5 ng/ml | 49 | 48.5 |
| > 0.5 ng/ml | 52 | 51.5 |
| > | | |
| - Interleukins -6 initial (n = 373) | | |
| 7 pg/ml | 54 | 14.5 |
| > 7 pg/ml | 319 | 85.5 |
| - Interleukin-6 serial (n = 78) | | |
| ≤ 7 pg/ml | 14 | 17.9 |
| > 7 pg/ml | 64 | 82,1 |
| - Ferritin (n = 373) | | |
| < 500 ng/ml | 188 | 50.4 |
| 500 - 1000 ng/ml | 71 | 19.0 |
| > 1000 ng/ml | 114 | 30.6 |
| **CT initial value** | | |
| ● < 20 | 253 | 67.8 |
| ● 20 – 29 | 112 | 30.02 |
| ● ≥ 30 | 8 | 2.1 |
| **Outcome** (n = 373) | | |
| Recovered | 243 | 65.1 |
| Recovered with sequelae | 36 | 9.7 |
| Died | 94 | 25.2 |
| **Need for oxygen therapy (n=362)** | | |
| Free air | 103 | 28.5 |
| Required oxygen therapy | | |
| Nasal cannula | 47 | 13.0 |
| NRM | 61 | 16.9 |
| HFNC | 81 | 22.4 |
| Ventilator | 70 | 19.3 |
| **Number of comorbidities (n=373)** | | |
| No comorbidity | 116 | 31.1 |
| 1 comorbid | 45 | 12.1 |
| >1 comorbid | 212 | 56.8 |
| **Steroid use, anti-IL-6 (n=159)** | | |
| Steroids | 127 | 79.9 |
| Non-steroid | 5 | 3.1 |
| Combination of steroid-non-steroidal | 27 | 17.0 |
| **Complications of sepsis (n=373)** | | |
| No | 319 | 85.5 |
| Yes | 54 | 145.5 |

For the duration of treatment, the most are ≤21 days which is 74%. The parameters of the laboratory picture are leukopenia, 100%. The faal hepar profile shows 61.4% has a normal SGOT value (≤38 U/L) and a normal SGPT (≤41U/L) of 73.5%. The patient's initial albumin value <3 gr/dL was found in 51.2% of patients. The patient's kidney function picture was 76.9% with a normal ureum value and 82.0% with a normal creatinine value. For inflammatory markers 85.2% had an initial D-Dimer of ≥500 ng/dl, procalcitonin >0.5 ng/ml of 51.5%, an increase in interleukin-6 >7 pg/ml of 85.5%, and an increase in ferritin >500 ng/ml of only 49.6%. 82.0% with normal creatinine values.

A total of 68.9% of COVID-19 patients treated had comorbidities. Based on comorbid numbers 56.8% of patients have >1 comorbid. The patient's externalization showed that the majority (65.1%) of patients recovered, only 9.7% recovered with sequelae and 25.5% died. Initial CT value <20, 48% recovered, 2.1% recovered with sequelae and 17.7% died. Initial CT value 20-29, amounting to 21.7% cured, 1.3% cured with sequelae, 7% died. While the initial CT value of ≥30 of 1.3% healed no one recovered with symptoms of the remaining 0.8% died, as seen in table 2.

Table 2. Initial CT value relationship with COVID-19 patient externalities

|  | Recovered | | Recovered with sequelae | | Died | | p-value* |
|---|---|---|---|---|---|---|---|
|  | N | F(%) | N | F(%) | N | F(%) | |
| < 20 | 179 | 48.0 | 8 | 2.1 | 66 | 11.7 | |
| 20 – 29 | 81 | 21.7 | 5 | 1.3 | 26 | 7.0 | 0.764 |
| ≥ 30 | 5 | 1,3 | 0 | 0.0 | 3 | 0.8 | |

The proportion of patients recovering tends to decrease according to the high CT value seen in table 3, as well as the proportion of patients recovering with sequelae, as well as patients who died. Fisher's exact test results obtained a p-value of 0.764 (p>0.05)

meaning that there is no CT-value relationship with the external COVID-19 patients at shows the COVID-19 patients who were treated at Dr. M. Djamil General Hospital Padang.

Table 3. Relationship of IL-6 with COVID-19 patient outcomes

| IL-6 level | Recovered | | Recovered with sequelae | | Died | | p-value* |
|---|---|---|---|---|---|---|---|
|  | N | F(%) | N | F(%) | N | F(%) | |
| ≤ pg/ml | 44 | 81,5 | 7 | 13.0 | 3 | 5.6 | 0.002 |
| >7 pg/ml | 199 | 62.4 | 29 | 9.1 | 91 | 28.5 | |

* chi-square test

Table 3 shows the proportion of recovered patients with initial IL-6 levels 7 pg/ml higher (81.5%) than in patients with IL-6 levels above 7 pg/ml (62.4%). Recovery with sequelae was also the case, in patients with baseline IL-6 levels 7 pg/ml higher (13.0%) than

in patients with IL-6 levels above 7 pg/ml (9.1%). The proportion of deaths was higher (28.5%) in patients with IL-6 levels above 7 pg/ml compared to 7 pg/ml. The results of the chi-square test obtained a p-value of 0.002 (p <0.05) indicating that there is a relationship

between IL-6 levels (initial) with the outcome of COVID-19 patients at Dr. M. Djamil General Hospital Padang.

Table 4 shows that the proportion of cures in patients with an onset of 21 days and > 21 days was relatively similar, namely 65.6% and 63.9%, respectively. The outcome of recovery with sequelae between the two onsets also had a proportion that was not much different (10.5% and 7.2%), as well as the outcome of patients who died, namely 23.9% for onset 21 days and 28.9% for onset > 21 days. The results of the chi-square test obtained a p-value of 0.464 (p>0.05) indicating that there is no relationship between onset and outcome of COVID-19 patients at Dr. M. Djamil General Hospital Padang.

Table 4. Relationship between onset and outcome of COVID-19 patients

| Onset | Recovered | | Recovered with sequelae | | Died | | p-value* |
|---|---|---|---|---|---|---|---|
| | N | F(%) | N | F(%) | N | F(%) | |
| ≤ 21 days | 181 | 65.6 | 29 | 10.5 | 66 | 23.9 | 0.464 |
| 21 days | 62 | 63.9 | 7 | 7.2 | 28 | 28.9 | |

Table 5 shows that patients with IL-6 levels of 7 pg/ml tend not to require oxygen therapy, whereas patients with IL-6 levels above 7 pg/ml tend to require oxygen therapy. The results of the chi-square test obtained a p-value of 0.000 (p <0.05), meaning that the level of IL-6 is related to the need for oxygen therapy. IL-6 levels above 7 pg/ml increase the risk of needing oxygen therapy in COVID-19 patients at Dr. M. Djamil General Hospital Padang.

Table 5. Relationship of IL-6 with the possible risk of oxygen therapy needs of COVID-19 patients

| IL-6 level | Free air | | Nazal cannula | | NRM | | HFNC | | Ventilator | | p-value* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | F(%) | N | F(%) | N | F(%) | N | F(%) | N | F(%) | |
| ≤7pg/ml | 24 | 46.2 | 8 | 15.4 | 6 | 11.5 | 13 | 25 | 1 | 1.9 | 0.000 |
| >7pg/ml | 79 | 15.5 | 39 | 12.6 | 55 | 17.7 | 68 | 21.9 | 69 | 22.3 | |
| Total | 103 | 28.5 | 47 | 13 | 61 | 16.9 | 81 | 22.4 | 70 | 19.3 | |

* chi-square test

Table 6 shows that the incidence of sepsis in patients with ferritin levels <500 ng/ml is lower (7.4%) compared to the incidence of sepsis in patients with ferritin levels of 500-1000 ng/ml (12.7%) and in patients with ferritin levels of 500-1000 ng/ml (12.7%). with ferritin levels >1000 ng/ml (27.2%).

Table 6. The relationship between ferritin and the incidence of sepsis in COVID-19 patients

| Ferritin level | Sepsis | | Not sepsis | | p-value* |
|---|---|---|---|---|---|
| | N | F(%) | N | F(%) | |
| <500 ng/ml | 14 | 7.4 | 174 | 92.6 | |
| 500 – 1000 ng/ml | 9 | 12.7 | 62 | 87.3 | 0.000 |
| >1000 ng/ml | 31 | 27.2 | 83 | 72.8 | |
| Total | 54 | 14.5 | 319 | 85.6 | |

* chi-square test

The results of the chi-square test obtained a p-value of 0.000 (p<0.05) and showed that ferritin levels were related to the incidence of sepsis in Covid-19 patients at Dr. M. Djamil General Hospital Padang. Table 7 shows that in patients of moderate and severe clinical degrees there is an association between initial albumin levels and initial d-dimer levels, which can be seen from the acquisition of a chi-square test p-value of 0.000 (p<0.05). Hypoalbuminemia is at higher risk resulting in increased levels of d-dimer in non-critical COVID-19 patients at Dr. M. Djamil General Hospital Padang.

Table 7. Relationship between albumin and early D-dimer levels in COVID-19 patients

| D-dimer levels | | | | | |
|---|---|---|---|---|---|
| Initial rate Albumin | Normal (<500 ng/ml) | | Increased (>500 ng/ml) | | p-value* |
| | N | % | N | % | |
| Normoalbunemia | 29 | 38.7 | 46 | 61.3 | |
| Hipoalbunemia | 2 | 3.1 | 63 | 96.9 | 0.000 |
| Total | 31 | 22.1 | 109 | 77.9 | |

* chi-square test

Table 8 shows that both patients with normal albumin values and hypoalbuminemia all (100%) had d-dimer levels > 500 ng/ml; and because the data clustered in only one column, it can be stated that initial albumin levels were not related to initial d-dimer levels in critically ill Covid-19 patients at Dr. M. Djamil General Hospital Padang.

Table 8. Relationship between initial albumin and D-dimer levels in critical COVID-19 patients

| D-dimer levels | | | | | |
|---|---|---|---|---|---|
| Initial rate Albumin | Normal (<500 ng/ml) | | Increased (>500 ng/ml) | | p-value* |
| | N | % | N | % | |
| Normoalbunemia | 0 | 0.0 | 18 | 100.0 | |
| Hipoalbunemia | 0 | 0.0 | 74 | 100.0 | - |
| Total | 0 | 0.0 | 92 | 100.0 | |

Based on table 9, it can be seen that patients with IL-6 levels of 7 pg/ml Most (72.2%) had SGOT levels of 38 U/L. However, in patients with IL-6 levels above 7 pg/ml, the proportion of patients who had SGOT levels <38 U/L and > 38 U/L. were not much different, namely 59.6% and 40.0%. The results of the chi-square test obtained a p-value of 0.077 (p>0.05) indicating that IL-6 levels were not associated with SGOT levels in COVID-19 patients at Dr. M. Djamil General Hospital Padang.

Table 9. Relationship of IL-6 with SGOT in COVID-19 patients

| IL-6 levels | SGOT levels | | | | p-value* |
|---|---|---|---|---|---|
| | ≤38 U/L | | >38 U/L | | |
| | N | % | N | % | |
| ≤7pg/ml | 39 | 72.2 | 15 | 27.8 | 0.077 |
| >7pg/ml | 190 | 59.6 | 129 | 40.0 | |
| Total | 229 | 61.4 | 144 | 38.6 | |

* chi-square test

Based on Table 10 it appears that patients with IL-6 levels <7 pg / ml who have d-dimer levels <500 ng / ml more (34.0%) than in patients with IL-6 levels >7 pg / ml (11.6%).

Table 10. Relationship of IL-6 with D-dimer in COVID-19 patients at Dr. M. Djamil General Hospital Padang.

| IL-6 levels | D-dimer levels | | | | p-value* |
|---|---|---|---|---|---|
| | < 500 ng/ml | | ≥ 500 ng/ml | | |
| | N | % | N | % | |
| ≤7pg/ml | 18 | 44.0 | 35 | 66.0 | 0.000 |
| >7pg/ml | 37 | 11.6 | 282 | 88.4 | |
| Total | 55 | 14.8 | 317 | 85.2 | |

* chi-square test

Patients with IL-6 levels <7 pg/ml who had fewer d-dimer levels >500 ng/ml (66.0%) than patients with IL-6 levels >7 pg/ml (88.45). The results of the chi-square test obtained a p-value of 0.000 (p<0.05) and showed that IL-6 levels were associated with d-dimer levels in Covid-19 patients at Dr. M. Djamil General Hospital Padang.

## 4. Discussion

### Patient characteristics

The results showed that most COVID-19 patients were treated at Dr. M. Djamil General Hospital Padang in the age group 50 years as much as 59.5% while the age group <50 years as much as 40.5%. This result is in line with Shayan Khan's research, which found the most age in the >50 years group, as many as 74% (43.4% >50 years old and 46.5%>70 years old).[18] Age causes major changes in immune system responses and chronic inflammatory processes.[20] Jin et al. showed that older age is a major risk factor for severity and morbidity in Covid-19 patients.[21]

Based on gender, more women were treated than men, namely 55.5% compared to 44.5%. The results of this study are in line with research by Shayan Kahn,

which found that more female patients were 52.3% and male patients were 47.6%.[18]

Based on the results of routine blood tests, 100% of COVID-19 patients with a leukocyte count <4000 mm3. On examination of liver function, SGOT, SGPT, initial albumin, and serial albumin were examined. The results of liver function examination showed that most of the patients (61.4%) had SGOT levels of ≤38 U/L, and 73.5% of patients had SGPT levels of ≤41 U/L. Research by Ali stated that there was a significantly lower mean value of leukocytes (x10³ mm⁻³), a number of lymphocytes (x10³ mm⁻³), total protein (g/dL), and albumin (g/dL) (3,9 ± 1.5, 0.85 ± 0.3, 6.06 ± 0.4 and 2.5 ± 0.2, respectively) among severely infected patients than those who were light–moderately infected with COVID- 1 (5.6 ± 1.7, 1.12 ± 0.4, 6.9 ± 0.3, and 2.9 ± 0.1), p<0.05 for all. In addition, there were significantly higher mean values of CRP (mg/dL), ESR, ferritin (ng/mL), ALT (IU/L), and AST (IU/L) among patients with severe COVID-19. /critical (119.8 ± 39, 78.7 ± 20.4, 440.3 ± 87.3, 41.5 ± 6.7, and 44.5 ± 4.5, respectively) when compared with those who had mild to moderate COVID-19 (51.1 ± 9.5, 50.8 ± 21.3, 268.6 ± 57.5, 33.3 ± 8.03, and 32.8 ± 7.2, respectively), p<0.05 for all.[22] Regarding the analysis of abnormalities in hematological and biochemical parameters measured as categorical data, there was no difference (p>0.05) between COVID-19 severity categories in terms of the percentage frequency of anemia, leukopenia, elevated ESR or serum creatinine, low serum total protein, or albumin. And there was a significantly higher frequency of lymphopenia, elevated CRP, ALT, and AST among severe COVID-19 compared with mild to moderate COVID-19, p<0.05.[22]

Of the 232 patients who had data on initial albumin levels, 148 patients (63.8%) had albumin levels of ≥3 g/dL, while out of 123 patients who had serial albumin data, 51.2% had serial albumin < 3 g. /dL and the rest (48.8%) had serial albumin levels ≥3 g/dL. The results of this study are in line with research conducted by Kheir, namely the average albumin level was 3.17 g/dL (SD: 0.66 g/dL), and a total of 109 patients (60.2%) had hypoalbumin. Based on our univariate analysis,

patients were more likely to have higher albumin levels if they were younger (p < 0.001). Higher albumin levels were also associated with in-hospital mortality (p = 0.020) and fewer total adverse outcomes (p < 0.001). Mean albumin levels were higher in patients who were not admitted to the ICU (3.25 g/dL) compared to patients who were admitted to the ICU (2.93 g/dL) (p = 0.008). Patients admitted to the ICU were more likely to have higher adverse outcomes (p < 0.001) including incidence of VTE (p = 0.032), ARDS (p < 0.001), and in-hospital death (p < 0.001).[23]

## Relationship between initial CT values and outcomes of COVID-19 patients

Cycle threshold (CT) values correlate with the amount of viral nucleic acid in the sample and can be obtained from several qualitative real-time polymerase chain reaction tests used for the diagnosis of the majority of patients with respiratory syndrome coronavirus. Severe acute 2 (SARS-CoV-2). However, CT scores cannot be directly compared across tests, and they should be interpreted with caution as they are affected by sample type, sample collection time, and test design. Currently, the correlation between CT scores and clinical outcomes is not well understood. In this study, there was no correlation between CT-value and the outcome of Covid-19 patients at Dr. M. Djamil General Hospital Padang. Other investigators have conducted a systematic review and meta-analysis of the association between CT scores and hospitalization, disease severity, and mortality in elderly patients with SARS-CoV-2. A meta-analysis of 7 studies showed no significant difference in mean CT scores between hospitalized and non-hospitalized patients. Among hospitalized patients, those with CT scores <25 had a higher risk of more severe disease and death than patients with CT scores >30 (odds ratio [OR], 2.31; 95% CI, 1.70 to 3.13; and OR, 2.95; 95% CI, 2.19 to 3.96; respectively). The likelihood of increasing disease severity and death is less pronounced in patients with CT scores of 25-30 compared with >30.[24]

## The relationship of IL-6 with the outcome of Covid-19 patients

The results of this study showed that the proportion of cures in patients with initial IL-6 levels of ≤7 pg/ml was higher (81.5%) than in patients with IL-6 levels above 7 pg/ml (62.4%). Recovery with sequelae was also the case in patients with baseline IL-6 levels 7 pg/ml higher (13.0%) than in patients with IL-6 levels above 7 pg/ml (9.1%). The proportion of deaths was higher (28.5%) in patients with IL-6 levels above 7 pg/ml compared to ≤7 pg/ml. The results of the chi-square test obtained a p-value of 0.002 (p <0.05), indicating that there is a relationship between IL-6 levels (initial) with the outcome of Covid-19 patients at Dr. M. Djamil General Hospital Padang.

This is supported by research by Xiaohui, who reported the value of IL-6 is useful for predicting the severity of COVID-19 patients. The combined area under the curve (AUC) was 0.85 (95% CI 0.821 to 0.931). 5 studies described the predictive value of IL-6 on mortality. The aggregated sensitivity, specificity and AUC were 0.15 (95% CI 0.13 to 0.17, I 2 = 98.9%), 0.73 (95% CI 0.65 to 0.79, I 2 = 91.8%) and 0.531 (95% CI 0.451 to 0.612), respectively.[25] Research by Abdul et al. also showed the same result, namely that there was a correlation between IL-6 and the severity of COVID-19 patients.[26] This is because IL-6 is an adequate predictor of disease severity in patients infected with COVID-19.[25] In addition, a study in Munich stated that high IL-6 could predict critical illness. This study found elevated IL-6 (>80 pg/ml) was strongly associated with a 22 times higher need for mechanical ventilation compared with patients with lower IL-6 levels in a cohort involving 40 patients.[27]

IL-6 is an important cytokine whose production is associated with various inflammatory diseases.[28] Subjects with SARS-CoV-2 had high levels of IL-6, which correlated with patient symptoms, including pulmonary inflammation and extensive lung damage.[29] In addition, patients with SARS-CoV-2 infection, have low levels of the suppressor signaling-3 cytokine, which regulates and stimulates the negative feedback mechanism of IL-6.[30] Another study reported that IL-6 levels were higher in severe COVID-19 patients, and this could be used as a basis for predicting the transition from mild to severe infection. In particular, Diao et al. showed that COVID-19 patients in intensive care had lower CD8+ T cell counts, and their total CD4+ and CD8+ T cell counts were also negatively correlated with TNF-α and IL-6 concentrations. In addition, recent studies have shown significantly higher levels of IL-6, CRP, and also IL-10 than other cytokines in a critical group of COVID-19 patients.[28]

## Relationship between onset and outcome of COVID-19 patients.

The chi-square test results obtained a p-value of 0.464 (p>0.05), indicating that there was no relationship between onset and outcome for Covid-19 patients at Dr. M. Djamil General Hospital Padang.

The proportion of recovery in patients with onset of 21 days and > 21 days was relatively similar, namely 65.6% and 63.9%, respectively. The outcome of recovery with residual symptoms between the two onsets also had a proportion that was not much different (10.5% and 7.2%), as well as the outcome of patients who died, namely 23.9% for onset 21 days and 28.9% for onset > 21 days. This is in accordance with the research of Christel et al., which stated that there was no relationship between onset and outcome of Covid-19 patients (p = 0.633). The median length of stay for patients who recovered varied from 5 days (in the young population) to 15.7 days (in the elderly), the median length of stay for patients who died varied between 5.7 days (in the elderly) and 12.2 days (in the elderly population). Work). In general, it was observed that the duration of hospital stay for recovered patients increased with age, and males took a slightly longer time to recover compared to females. In contrast, the time between hospitalization and death was the longest for the working-age population, with shorter survival times for seniors and seniors. The length of hospital stay for patients who died was longer for patients presenting from nursing homes compared with patients of the same age group of the

general population. A similar trend was observed for the length of ICU stay.[31]

**Relationship of IL-6 with the possible risk of oxygen therapy needs of COVID-19 patients**

This study found a significant relationship between IL-6 and the need for oxygen therapy in COVID-19 patients. The results of this study indicate that IL-6 levels of 7 pg/ml tend not to require oxygen therapy, whereas patients with IL-6 levels above 7 pg/ml tend to require oxygen therapy. The results of the chi-square test obtained a p-value of 0.000 (p <0.05), meaning that the level of IL-6 is related to the need for oxygen therapy. IL-6 levels above 7 pg/ml increase the risk of needing oxygen therapy in Covid-19 patients at Dr. M. Djamil General Hospital Padang.

Research conducted by Theresa et al. found that hemoglobin levels decreased in patients with high oxygen demand. Consistently, COVID-19 patients showed significantly increased levels of IL-6 and hepcidin, and there was a correlation between these two parameters. The IL-6 cytokine activates the expression of the peptide hormone hepcidin, which can cause hypoferremia by blocking iron export from macrophages. Although hepcidin was unable to distinguish between the low and high oxygen demand groups, the pro-inflammatory cytokine IL-6 and the inflammatory marker CRP increased to a higher degree in patients on high oxygen than in patients on low oxygen. Ferritin levels vary widely and therefore do not significantly differ between patients with high and low oxygen demand. Overall, serum iron levels showed high negative correlations with inflammatory parameters IL-6 and PCT from d0 to d6, while correlations with CRP increased over time. As expected, iron was positively correlated with transferrin and hemoglobin saturation.[35]

**The relationship between ferritin and the incidence of sepsis in COVID-19 patients.**

The results of the chi-square test obtained a p-value of 0.000 (p<0.05), indicating that ferritin levels were associated with the incidence of sepsis in Covid-

19 patients at Dr. M. Djamil General Hospital Padang. The incidence of sepsis in patients with ferritin levels <500 ng/ml was lower (7.4%) compared to the incidence of sepsis in patients with ferritin levels of 500-1000 ng/ml (12.7%) and in patients with ferritin levels >1000 ng /ml (27.2%)

Ferritin acts as an iron binder and plays a role in the inflammatory process and the immune system.[36] The increase in ferritin after viral infection may be due to the release of iron from the reticuloendothelial, the increased release of ferritin from the cell, and decreased transport of ferritin to the liver and spleen.[22] The mechanism of hyperferritinemia in COVID-19 patients can be explained based on 3 emerging theories. First, the increase in ferritin synthesis was caused by an increase in pro-inflammatory cytokines such as IL-1β, TNF-, and IL-6. Second, cellular damage due to the inflammatory process can lead to leakage of intracellular ferritin, thereby increasing serum ferritin. Third, acidotic conditions and increased ROS in COVID patients with ARDS can liberate ferritin from the cell.[37]

Research on clinical features and laboratory biomarkers shows COVID-19 as part of the hyperferritinemia syndrome.[38] Hyperferritinemia syndrome is a collection of several diseases that exhibit hyper inflammation and hyperferritinemia, which are partly life-threatening. Hyperferritinemia is a body condition characterized by serum levels of more than 500 µg/ml.[39]

**The relationship between albumin levels and initial D-Dimer in COVID-19 patients at Dr. M. Djamil General Hospital Padang**

In this study, it was found that Hhpoalbuminemia is at higher risk resulting in increased levels of d-dimer in non-critical Covid-19 patients at DR M Djamil Hospital, Padang. The relationship between the initial albumin level and the initial d-dimer level, which can be seen from the acquisition of the chi square test p value of 0.000 (p<0.05).

Research by Kheir et al. stated that as many as 109 patients (60.2%) had hypoalbuminemia (albumin

levels < 3.3 g/dL). Patients with higher albumin levels at admission had a 72% reduced risk of developing venous thromboembolism (adjusted relative risk [RR]: 0.28, 95% confidence interval [CI]: 0.14–0.53, p<0.001 for each 1 g/dL increase in albumin. In addition, higher albumin levels on admission were associated with a lower risk of developing ARDS (adjusted RR: 0.73, 95%CI: 0.55–0.98, p = 0.033), was admitted to the ICU (adjusted RR: 0.64, 95% CI: 0.45–0.93, p = 0.019), and was less likely to be readmitted within 90 days (adjusted RR: 0.37, 95%CI: 0.17–0.81, p = 0.012. Furthermore, higher albumin levels were associated with fewer total adverse events (adjusted RR: 0.65, 95% CI: 0.52–0, 80, p<0.001) [23].

Hypoalbuminemia may be a contributing factor to the high incidence of VTE of about 11% to 70% seen in COVID-19 patients. Therefore, in addition to previously known biomarkers (e.g., procalcitonin, CRP, total lymphocytes, D-dimer, troponin I, AST, ALT, among others) are associated with COVID-19, serum albumin levels might be helpful in prognostic risk stratification.[23]

**Relationship of IL-6 with SGOT in COVID-19 patients at Dr. M. Djamil General Hospital Padang**

This study showed that there was no significant relationship between IL-6 levels and final SGOT levels in Covid-19 patients at Dr. M. Djamil General Hospital Padang. It was found that patients with IL-6 levels ≤ 7 pg/ml mostly (72.2%) had SGOT levels ≤ 38 U/L. However, in patients with IL-6 levels above 7 pg/ml, the proportion of patients with SGOT levels ≤ 38 U/L and > 38 U/L was not much different, namely 59.6% and 40.0%.

This result is different from the study of Maria et al., who found that there was a strong relationship between IL-6 levels and AST levels (r2= 0.481, p<0.001) in both ICU and non-ICU patients treated at the University Hospital of Innsbruck, Austria. This was reported due to significant histological and biochemical damage in Covid-19 patients. There are still few studies that discuss this, but it can be expected due to systemic inflammation, viral replication, or drug-induced liver injury. Cytokine storm is a pathophysiological feature of COVID-19 and is characterized by high levels of inflammatory markers, including IL-1 and IL-6, which trigger thrombosis by activating the platelet, endothelium, monocyte, and factor VIIa pathways.[40,41] Systemic inflammation (increased IL-6) in Covid-19 patients is produced by immune cells, fibroblasts, endothelial cells, and hepatocytes that regulate the acute inflammatory response of the liver, which results in an increase in AST as an acute inflammatory response in the liver. Parallel analysis revealed increased IL-6 was associated with increased mortality in COVID-19 patients.[42]

**Relationship of IL-6 with D-Dimer in COVID-9 patients at Dr. M. Djamil General Hospital Padang**

This study showed that there was a significant relationship between IL-6 levels and D-dimer levels in Covid-19 patients at Dr. M. Djamil General Hospital Padang. It was found that patients with IL-6 levels < 7 pg/ml had D-dimer. Levels <500 ng/ml more (34.0%) than in patients with IL-6 levels >7 pg/ml (11.6%). However, in patients with IL-6 levels < 7 pg/ml who had d-dimer levels > 500 ng/ml less (66.0%) than in patients with IL-6 levels > 7 pg/ml (88.4%).

These results are consistent with the study of Tao et al in China which stated that a significant increase in IL-6 was also associated with an increase in CRP levels (r=0.781, P=0.001), LDH (r=0.749, P=0.001), ferritin (r=0.606, P=0.001) and D-dimer (r=0.679, P=0.001). Increased levels of IL-6 suggest that there may be a positive correlation with the severity of COVID-19. The patient's IL-6 level also significantly decreased the levels of D-dimer, CRP and LDH.[41] D-dimer is a fibrin degradation product that is increased in thrombotic events, indicating fibrinolysis in Covid-19 patients. Such high D-Dimer values could be associated with activation of the coagulation cascade Secondary to the Systemic Inflammatory Response Syndrome (SIRS) in COVID-19 patients.[42,43]

## 5. Conclusion

Characteristics of COVID-19 patients treated at Dr. M. Djamil General Hospital Padang are mostly female, More are >50 years old, clinical degree of moderate disease, length of treatment ≤21 days, require oxygen therapy, recovered externals, comorbid amounts >1, using steroids and no complications of sepsis. There is a relationship between IL-6 (initial) levels with the patient's external, oxygen therapy needs, ferritin levels with sepsis incidence, initial albumin levels with initial D-Dimer levels, and IL-6 levels with D-Dimer in COVID-19 patients at Dr. M. Djamil General Hospital Padang. There was no onset relationship with the patient's external, steroid administration with changes in IL-6 levels, age with changes in IL-6 levels, gender with IL-6 levels, IL-6 levels with D-Dimer levels in COVID-19 patients at Dr. M. Djamil General Hospital Padang.

## 6. References

1. Ministry of Health of the Republic of Indonesia. Guidelines for the Prevention and Control of Coronavirus Disease (COVID-19). July 2020. Listiana A, Adistikah A, Maulidiah I, editors. Vol. 5. Jakarta: Ministry of Health of the Republic of Indonesia; 2020. 1–214.

2. World Health Organization. COVID-19 Weekly Epidemiological Update 22. World Health Organization. Geneva; 2021

3. Ministry of Health of the Republic of Indonesia. The Latest Situation of the Development of COVID-19. Jakarta; 2021.

4. Ministry of Health of the Republic of Indonesia. Latest Official Information Media of Emerging Infectious Diseases. Downloaded on January 13, 2021 on the https://infectionemerging.kemkes.go.id/dashboard/covid-19 page

5. Guan W, Ni Z, Hu Y, Liang W, Ou C, et al. Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv. 2020; 10: 1–30.

6. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect. 2020/03/27. 2020; 80(6): e14–8

7. Liu Y, Gayle AA, Wilder-smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020; 27(2): 1–4.

8. Cunha LL, Perazzio SF, Azzi J, Cravedi P, Riella LV. Remodeling of the immune response with aging: Immunosenescence and Its Potential Impact on COVID-19 Immune Response. Front Immune. 2020; 11: 1–11.

9. Burhan E, Dwi Susanto A, Isbaniah F, Aman Nasution S, Ginanjar E, et al. COVID-19 management guidelines. 3rd ed. Burhan E, Dwi Susanto A, Isbaniah F, Aman Nasution S, Ginanjar E, Wicaksono Pitoyo C, editors. Jakarta: PDPI, PERKI, PAPDI, PERDATIN and IDAI; 2020; 3–45.

10. Jin Y, Haiyan Yang, Ji W, Wu W, Chen S, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. MDPI J Viruses. 2020; 12(372): 1–17.

11. Machi J, Herkovitz J, Senan M. Ahmed, et al. The Natural history, pathobiology, and clinical manifestations of SARS-CoV-2 Infections. USA. J Neuroimmune Pharmacol.2020; 15: 359–86.

12. Khan M, Adil SF, Alkhathlan HZ, Tahir MN, Saif S, et al. COVID-19: A Global Challenge with Old History, Epidemiology, and Progress So Far. Molecules. 2020; 26(1): 1–25

13. Tu H, Tu S, Gao2 S, Shao A, Sheng J. The epidemiological and clinical features of COVID-19 and lessons from this global infectious public health event. J Infect. 2020; 10: 44–53

14. Pietrobon AJ, Teixeira FME, Sato MN. Immunosenescence and Inflammaging: Risk Factors of Severe COVID-19 in Older People. Front Immune. 2020; 11: 1–18.

15. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, et al. COVID-19 and comorbidities:

Deleterious impact on infected patients. J Infect Public Health. 2020/08/04. 2020 Dec;13(12):1833–9Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 20: 305-16.

16. Sastroasmoro S. Fundamentals of Clinical Research Methodology. 5th ed. Sastroasmoro S, Ismael S, editors. Jakarta: Sagung Seto; 2018; 352–86.

17. Joost WW, Rhodes A, Cheng AC, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. Netherlands. JAMA. 2020

18. Khan MS, Dogra R, Miriyala LKV, Salman FNU, Ishtiaq R, et al. Clinical characteristics and outcomes of patients with Corona Virus Disease 2019 (COVID-19) at Mercy Health Hospitals, Toledo, Ohio. PLOS One. 2021; 16(April 4): 1–11.

19. Williamson EJ, Walker AJ, Bhaskaran K et al. Factors associated with COVID-19-related death using Open SAFELY. Nature. 584 (7821): 430-6.

20. Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, et al. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. Aging Clin Exp Res [Internet]. 2020/06/16. 2020; 32(8): 1599–608.

21. Pal S, Tyler JK. Epigenetics and aging. Sci Adv. 2016 Jul 29; 2(7): e1600584.

22. Ghweil AA, Hassan MH, Khodeary A, Mohamed AO, Mohammed HM, et al. Characteristics, outcomes and indicators of severity for covid-19 among sample of esna quarantine hospital's patients, egypt: A retrospective study. Infect Drug Resistant. 2020; 13: 2375–83

23. Kheir M, Saleem F, Wang C, Mann A, Chua J. Higher albumin levels on admission predict better prognosis in patients with confirmed COVID-19. PLOS One. 2021; 16: 1–10.

24. Shah VP, Farah WH, Hill JC, Hassett LC, Binnicker MJ, et al. Association between SARS-CoV-2 Cycle Threshold Values and Clinical Outcomes in Patients with COVID-19: A Systematic Review and Meta-analysis. Open Forum Infect Dis. 2021; 8(9): 1–12.

25. Liu X, Wang H, Shi S, Xiao J. Association between IL-6 and severe disease and mortality in COVID-19 disease: A systematic review and meta-analysis. Postgrad Med J. 2021; 1–9.

26. Zhang J, Hao Y, Ou W, Ming F, Liang G, et al. Serum interleukin-6 is an indicator for severity in 901 patients with SARS-CoV-2 infection: a cohort study. J Transl Med. 2020; 18(1): 1–9.

27. Herold T, Jurinovic V, Arnreich C, Hellmuth JC, von Bergwelt-Baildon M, et al. Level of IL-6 predict respiratory failure in hospitalized symptomatic COVID-19 patients. medRxiv. 2020; 20047381.

28. Vatansever HS, Becer E. Relationship between IL-6 and COVID-19: to be considered during treatment. Future Virol [Internet]. 2020; 15(12): 817–22.

29. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet (London, England). 2020 Feb; 395(10224): 565–74.

30. Okabayashi T, Kariwa H, Yokota S, Iki S, Indoh T, et al. Cytokine regulation in SARS coronavirus infection compared to other respiratory virus infections. J Med Virol. 2006; 78(4): 417–24

31. Faes C, Abrams S, Van Beckhoven D, Meyfroidt G, Vlieghe E, et al. Time between symptom onset, hospitalization and recovery or death: Statistical analysis of Belgian COVID-19 patients. Int J Environ Res Public Health. 2020; 17(20): 1–18

32. Awasthi S, Wagner T, Venkatakrishnan AJ, Puranik A, Hurchik M, et al. Plasma IL-6 levels following corticosteroid therapy as an indicator of ICU length of stay in critically ill COVID-19 patients. Cell Death Discov. 2021; 7(1).

33. Wahid AH, Shenoy V, KR Study correlating interleukin-6 levels with demographics, symptomatology and clinical outcomes among COVID-19 patients. Int J Adv Med. 2021; 8(10): 1499

34. Liu Y, Mao B, Liang S, Yang JW, Lu HW, et al. Association between age and clinical characteristics and outcomes of COVID-19. Eur Respir J. 2020; 318(6).

35. Hippchen T, Altamura S, Muckenthaler MU, Merle U. Hypoferremia is associated with increased hospitalization and oxygen demand in COVID-19 patients. HemaSphere. 2020; 4(6): 1–9.

36. Cheng L, Li H, Li L, Liu C, Yan S, Chen H, et al. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Lab Anal. 2020;34(10):e23618

37. Gandini O, Criniti A, Ballesio L, Giglio S, Galardo G, et al. Serum Ferritin is an independent risk factor for Acute Respiratory Distress Syndrome in COVID-19. The Journal of infection. 2020; 81: 979–97

38. Kappert K, Jahić A, Tauber R. Assessment of serum ferritin as a biomarker in COVID-19: bystander or participant? Insights by comparison with other infectious and non-infectious diseases. Biomarkers Biochem Indic Expo response, susceptibility to Chem. 2020; 25(8): 616–25

39. Perricone C, Bartoloni E, Bursi R, Cafaro G, Guidelli GM, et al. COVID-19 as part of the hyperferritinemic syndromes: the role of iron depletion therapy. Immunol Res. 2020: 68(4): 213–24.

40. M Hussein A, Taha ZB, Gailan Malek A, Akram Rasul K, Hazim Kasim D, et al. D-Dimer and Serum ferritin as an Independent Risk Factor for Severity in COVID-19 Patients. Mater Today Proc. 2021.

41. Chen S, Zhang D, Zheng T, Yu Y, Jiang J. DVT incidence and risk factors in critically ill patients with COVID-19. J Thromb Thrombolysis. 2021; 51(1): 33–9.

42. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. Crit Care. 2020;24(1):255.

43. Huang J, Cheng A, Kumar R, Fang Y, Chen G, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol. 2020; 92(10): 2152–8.