

ABSTRACT

Background: In COVID-19 patients with severe symptoms, there is an increase in the irregular release of cytokines. This irregular release of cytokines is referred to as a cytokine storm. Cytokine storms cause excessive inflammatory and immune responses, particularly in the lungs, leading to acute respiratory distress syndrome (ARDS), pulmonary oedema and multi-organ failure. The cytokine abnormalities that occur will vary with the severity of COVID-19 disease. This is evidenced by differences in eotaxin, IL-12p40 and EGF levels, interleukin-6 (IL-6), C-reactive protein (CRP) and hypertension, as well as clinical differences in COVID-19 patients, with shortness of breath/dyspnoea being more likely to progress to critical illness or even death, whereas patients with fever do better.

Objectives: The aim of this study is to analyse the effect of COVID-19 severity on the incidence of cytokine storm based on the parameter profile of cytokine storms at the Dr Sardjito General Hospital Yogyakarta and to know treatment patterns of cytokine storm use in COVID-19.

Methods: Methods: The study was conducted using the retrospective cohort observation method by dividing the sample into 2 groups, namely 75 hospitalized COVID-19 patients with moderate symptoms and 75 hospitalized COVID-19 patients with severe/critical symptoms to determine the effect of COVID-19 severity on the incidence of cytokine storms. . The population in this study were inpatients at Dr. Sardjito General Hospital Yogyakarta who were confirmed positive for COVID-19 by RT-PCR examination from January to October 2021. inclusion criteria in this study were COVID-19 patients with positive RT-PCR examination, patients aged > 18 years, and patients with complete medical records. Exclusion criteria in this study include mild cases of COVID-19 according to physician's diagnosis, pregnant and lactating patients, patients with a history of autoimmune diseases, patients who received immunosuppressive treatment and recovered before entering the hospital. The research instrument that will be used is secondary data in the form of data collection sheets with analysis of the incidence of cytokine storms including the status of IL-6 levels (≥ 40 pg/mL), lymphocytes (< 1000 or $103/\text{mmc}$), D-dimer (> 1000 ng/mL), LDH (> 300 IU/L), ferritin (> 500 ng/mL), CRP (> 100 mg/L) along with parameters that mark the occurrence of multi-organ failure such as BUN, creatinin, albumin, SGOT and SGPT. This study also analyzed the use of therapies that can prevent or reduce cytokine storms between severe/critical COVID-19 and moderate COVID-19.

Result: In this study, there was a significant difference in the incidence of cytokine storms between severe/critical COVID-19 and moderate degrees of COVID-19 based on abnormal laboratory tests such as (1) lymphocytopenia (lymphocyte count $< 1 \times 10^3/\mu\text{L}$) with p-Value = 0.001 and RR = 1.913 (1.30-2.82); (2) high D-dimer (> 1000 ng/mL) with p-Value = 0.005 and RR = 2.000 (1.20-3.32); (3) high LDH (> 300 IU/L) with p-Value = 0.000 and RR = 1.529 (1.26-1.86); (4) high CRP (> 100 mg/L) with p-Value = 0.000 and RR = 2.514 (1.69-3.73); (5) high IL-6 (> 40 pg/mL)

with ; (6) high BUN (>20 mg/dL) with p-Value = 0.000 and RR = 12.048 (1.36-3.09); (7) High creatinine (> 1.2 mg/dL) with p-Value = 0.013 and RR = 1.875 (1.12-3.14); (8) Low albumin (< 3.5 g/dL) with p-Value = 0.000 and RR = 1.878 (1.37-2.55).

In this study, there was also a significant difference (p-Value = 0.001) related to the use of dexamethasone in severe / critical COVID-19 more 1.302 times with 95% CI 1.11-1.53 than in moderate COVID-19 patients. Meanwhile, the use of methylprednisolone was not significantly different between the two groups.

The use of dexamethasone in COVID-19 significantly reduced the mean IL-6 and BUN laboratory values compared to patients who did not use dexamethasone.

Conclusion: Some abnormal laboratory values that can be used as a marker for the The percentage of cytokine storm events that occur in severe/critical COVID-19 compared to moderate COVID-19, based on the biomarkers of cytokine storm such as (1) lymphocyte abnormalities ($<1 \times 10^3/\mu\text{L}$) in the severe/critical degree is 59%, while the moderate degree is 31%, (2) D-dimer abnormalities (>1000 ng/mL) in the severe/critical degree is 43%, while the moderate degree is 21%, (3) LDH abnormalities (>300 IU/L) in the severe/critical degree is 96%, while the moderate degree is 63%, (4) CRP abnormalities (>100 mg/L) in the severe/critical degree is 77%, while the moderate degree is 31%, (5) IL6 abnormalities (> 40 pg/mL) in the severe/critical degree is 68%, while moderate degree is 35%. The pattern of treatment used in COVID-19 patients to prevent or reduce the incidence of cytokine storms at Dr Sardjito General Hospital Yogyakarta are dexamethasone and methylprednisolone. The use of dexamethasone in COVID-19 significantly reduced the mean IL-6 and BUN laboratory values compared to patients who did not use dexamethasone

Keywords: *COVID-19, Cytokine storm, Hospitalised patients*