

# ABSTRACT

## ANALYSIS OF RISK FACTORS LEVELS OF TUMOR NECROSIS FACTOR- $\alpha$ (TNF- $\alpha$ ) AND INTERFERON GAMMA (IFN- $\gamma$ ) WITH MORTALITY OF COVID - 19 PATIENTS

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### Background

COVID-19 is characterized by excessive production of pro-inflammatory cytokines and acute lung damage associated with patient mortality. Several inflammatory cytokines produced by innate immune cells during SARS-CoV-2 infection can be seen in patients with COVID - 19 who are treated in intensive care units. There was a lot of increase in blood concentrations of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, TNF- $\alpha$ , and IFN- $\gamma$ . It was suspected that the synergism between TNF- $\alpha$  and IFN- $\gamma$  could trigger inflammatory cell death, tissue damage and death in SARS-CoV-2 infection.

### Methods

Prospective Cohort study in COVID-19 patients which is a part of the COVID-19 joint research. The research was conducted from August 2020 to January 2021 involving 72 subjects with positive RT PCR positive COVID-19 infection who met the inclusion criteria.

### Results

From the 72 research samples, 13 subjects died and 59 subjects survived. This research shows that there was no significant difference between the high levels of TNF- $\alpha$  ( $p=0,895$ ) and IFN- $\gamma$  ( $p=0.786$ ) with the mortality of COVID-19 patients, nor is it proven that the levels of TNF- $\alpha$  and IFN- $\gamma$  have a synergistic effect on COVID-19 death. TNF- $\alpha$  levels were highest in moderate degrees of COVID-19 (median 8.10 pg/mL), while IFN- $\gamma$  levels were highest in severe degrees of COVID-19 (median 184.25 pg/mL). TNF- $\alpha$  and IFN- $\gamma$  also had a positive relationship, indicating that an increase in TNF- $\alpha$  levels was followed by increased of IFN- $\gamma$  levels. The PaO<sub>2</sub>/FiO<sub>2</sub> ratio ( $p=0,034$ ) and creatinine ( $p=0,032$ ) were proven to be strong confounders that influenced mortality in this study.

### Conclusion

High levels of TNF- $\alpha$  and IFN- $\gamma$  are not risk factors for COVID-19 mortality. TNF- $\alpha$  and IFN- $\gamma$  levels according to the multivariate test were not shown to synergistically influence COVID-19 mortality.

### Key words

COVID-19, TNF- $\alpha$ , IFN- $\gamma$ , Synergist, Mortality

**ANALISIS FAKTOR RISIKO KADAR *TUMOR NECROSIS FACTOR- $\alpha$*  (TNF- $\alpha$ ) DAN *INTERFERON GAMMA* (IFN- $\gamma$ ) DENGAN KEMATIAN PASIEN COVID - 19**

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**Latar Belakang**

COVID-19 ditandai dengan produksi sitokin pro-inflamasi yang berlebihan dan kerusakan paru-paru akut berhubungan dengan kematian pasien. Beberapa sitokin inflamasi diproduksi oleh sel imun bawaan selama infeksi SARS-CoV-2 dapat dilihat pada pasien dengan COVID - 19 yang di rawat di unit perawatan intensif mengalami banyak peningkatan konsentrasi sitokin proinflamasi dalam darah seperti interleukin (IL)-1, IL-6, TNF- $\alpha$ , dan IFN- $\gamma$ . Diduga kuat bahwa sinergitas antara TNF- $\alpha$  dan IFN- $\gamma$  dapat memicu kematian sel inflamasi, kerusakan jaringan, dan kematian pada infeksi SARS-CoV-2.

**Metode**

Penelitian *Prospective Cohort* pada pasien COVID-19 yang merupakan bagian dari penelitian payung COVID-19. Penelitian dilaksanakan pada bulan Agustus 2020 hingga Januari 2021 melibatkan 72 subjek yang terinfeksi COVID-19 dengan RT PCR positif yang memenuhi kriteria inklusi.

**Hasil**

Dari 72 sampel penelitian didapatkan 13 subjek meninggal dunia dan 59 subjek bertahan hidup. Penelitian menunjukkan tidak didapatkan perbedaan signifikan tingginya kadar TNF- $\alpha$  ( $p=0,895$ ) dan IFN- $\gamma$  ( $p=0,786$ ) dengan kematian pasien COVID-19, juga tidak terbukti bahwa kadar TNF- $\alpha$  dan IFN-secara sinergis menunjukkan pengaruh terhadap kematian COVID-19. Kadar TNF- $\alpha$  paling tinggi pada derajat sedang COVID-19 (median 8,10 pg/mL), sedangkan kadar IFN- $\gamma$  paling tinggi didapatkan pada derajat berat COVID-19 (median 184,25 pg/mL). TNF- $\alpha$  dan IFN- $\gamma$  juga memiliki hubungan yang positif, yang menunjukkan bahwa peningkatan kadar TNF- $\alpha$  diikuti oleh peningkatan kadar IFN- $\gamma$ . Rasio PaO<sub>2</sub>/FiO<sub>2</sub> ( $p=0,034$ ) dan Kreatinin ( $p=0,032$ ) terbukti kuat sebagai perancu yang mempengaruhi kematian pada penelitian ini.

**Kesimpulan**

Kadar TNF- $\alpha$  dan IFN- $\gamma$  yang tinggi bukan sebagai faktor risiko kematian COVID-19. Kadar TNF- $\alpha$  dan IFN- $\gamma$  menurut uji multivariat secara sinergis tidak terbukti menunjukkan pengaruh terhadap kematian COVID-19.

**Kata Kunci** : COVID-19, TNF- $\alpha$ , IFN- $\gamma$ , Sinergis, Kematian