

ABSTRAK

Latar Belakang. Interaksi HMGB1 dengan RNA SARS-CoV-2 menginduksi pelepasan sitokin proinflamasi pada COVID-19 lewat aktivasi TLR4, RAGE, dan TLR7. *Glycyrrhizin* dan *haptoglobin* dapat mengikat HMGB1 ekstraseluler untuk mencegah interaksinya dengan reseptor. Penelitian ini bertujuan untuk menganalisis kadar HMGB1 dan IL-18 pada COVID-19 dibandingkan non-COVID-19, mengeksplorasi mekanisme HMGB1 dan RNA SARS-CoV-2 dalam memicu produksi sitokin proinflamasi serta potensi penghambatannya dengan *glycyrrhizin* dan *haptoglobin*.

Metode. Penelitian tahap pertama secara observasional dilakukan pada sampel serum yang dikirim ke Lab COVID-19 FK-KMK UGM. Berdasarkan konfirmasi RT-PCR swab nasofaring, serum dikelompokkan menjadi kelompok COVID-19 dan non-COVID-19. Kadar HMGB1 dan IL-18 dideteksi pada kedua kelompok menggunakan metode ELISA. Penelitian tahap berikutnya secara eksperimental pada kultur sel THP1 (*monocyte cell line*) yang dipaparkan dengan rekombinan HMGB1 manusia dan RNA SARS-CoV-2 sintetik. Potensi penghambatan jalur ini diobservasi melalui penambahan *glycyrrhizin* dan *haptoglobin*. Ekspresi TLR4, RAGE, dan TLR7 dideteksi dengan qPCR. Kadar IL-6, TNF- α , dan IL-18 dideteksi pada supernatan kultur dengan metode ELISA. Data yang diperoleh dianalisis menggunakan uji t berpasangan/uji Wilcoxon.

Hasil. Kadar serum HMGB1 meningkat pada pasien non-COVID-19 ($p = 0,0199$) dan COVID-19 rawat inap ($p = 0,0316$). Kadar serum HMGB1 berkorelasi positif dengan kadar IL-18 pada pasien COVID-19 rawat inap ($r = 0,5500$; $p = 0,0337$). Ekspresi mRNA TLR4, RAGE, dan TLR7 meningkat pada paparan HMGB1 dan RNA SARS-CoV-2 ($p=0,0408$; $p=0,0083$; dan $p=0,0014$). Peningkatan kadar IL-6, IL-18 dan TNF- α terjadi pada konsentrasi tinggi HMGB1 dan RNA SARS-CoV-2 ($p=0,0078$; $p=0,0287$; dan $p=0,0350$). *Glycyrrhizin* 20 μ M menurunkan ekspresi TLR4 dan TLR7, sementara *haptoglobin* 10 μ g/ml menurunkan ekspresi TLR4, RAGE, dan TLR7 akibat paparan HMGB1 dan RNA SARS-CoV-2.

Kesimpulan. Kadar serum HMGB1 – IL-18 berkorelasi positif pada COVID-19 rawat inap. Peningkatan kadar IL-6, IL-18 dan TNF- α terjadi pada paparan HMGB1 dan RNA SARS-CoV-2 konsentrasi tinggi. *Glycyrrhizin* dan *haptoglobin* menurunkan ekspresi TLR4, RAGE, dan TLR7 pada paparan HMGB1 dan RNA SARS-CoV-2.

Kata kunci: HMGB1; RNA SARS-CoV-2; PRR, *glycyrrhizin*; *haptoglobin*

ABSTRACT

Background. HMGB1- SARS-CoV-2 RNA interaction induces the release of proinflammatory cytokines in COVID-19 via activation of TLR4, RAGE, and TLR7. Glycyrrhizin and Haptoglobin bind extracellular HMGB1 to prevent its interaction with the receptor. This study aims to analyze HMGB1 and IL-18 levels in COVID-19 compared to non-COVID-19, exploring the mechanism of HMGB1 and SARS-CoV-2 RNA in triggering the production of pro-inflammatory cytokines and their potential inhibition by glycyrrhizin and haptoglobin.

Methods. In the observational study, research was carried out on serum samples sent to the UGM FK-KMK COVID-19 Lab. Based on RT-PCR confirmation of nasopharyngeal swabs, sera were grouped into COVID-19 and non-COVID-19 groups. HMGB1 and IL-18 levels were estimated in both groups using the ELISA method. In the experimental study, THP1 (monocyte cell line) cell cultures were exposed to recombinant human HMGB1 and synthetic SARS-CoV-2 RNA. This pathway is potentially inhibited by adding glycyrrhizin and haptoglobin to the THP1 culture. Expression of TLR4, RAGE, and TLR7 was detected by qPCR. The ELISA method detected IL-6, TNF- α , and IL-18 levels in culture supernatants. The data obtained was analyzed using pair t test/Wilcoxon test.

Results. Serum HMGB1 levels were increased in inpatient non-COVID-19 ($p = 0.0199$) and inpatient COVID-19 ($p = 0.0316$). Serum levels of HMGB1 were positively correlated with IL-18 levels in COVID-19 patients inpatients ($r = 0.5500$; $p = 0.0337$). TLR4, RAGE, and TLR7 mRNA expression increased upon exposure to HMGB1 and SARS-CoV-2 RNA ($p=0.0408$; $p=0.0083$; and $p=0.0014$). Increased levels of IL-6, IL-18, and TNF- α occurred at high concentrations of HMGB1 and SARS-CoV-2 RNA ($p=0.0078$; $p=0.0287$; and ($p=0.0350$). Glycyrrhizin 20 μ M decreased TLR4 and TLR7 expression, and haptoglobin 10 μ g/ml decreased TLR4, RAGE, and TLR7 expression due to exposure of HMGB1 and SARS-CoV-2 RNA.

Conclusion. HMGB1 – IL-18 serum levels are positively correlated in COVID-19 inpatients. Increased levels of IL-6, IL-18, and TNF- α occurred upon exposure to high HMGB1 and SARS-CoV-2 RNA concentrations. Glycyrrhizin and haptoglobin decreased the expression of TLR4, RAGE, and TLR7 upon exposure to HMGB1 and SARS-CoV-2 RNA.

Keywords: HMGB1; SARS-CoV-2 RNA; PRR, Glycyrrhizin; Haptoglobin