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Relation between macrophage inflammatory protein-1 and intercellular adhesion molecule-1 and computed tomography findings in critically-ill Saudi Covid-19 patients

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A B S T R A C T

Background: Several, clinical and biochemical factors were suggested as risk factors for more severe forms of Covid-19. Macrophage inflammatory protein-1 alpha (MIP-1α, CCL3) is a chemokine mainly involved in cell adhesion and migration. Intracellular adhesion molecule 1 (ICAM-1) is an inducible cell adhesion molecule involved in multiple immune processes. The present study aimed to assess the relationship between baseline serum MIP-1α and ICAM-1 level in critically-ill Covid-19 patients and the severity of computed tomography (CT) findings.

Methods: The study included 100 consecutive critically-ill patients with Covid-19 infection. Diagnosis of infection was established on the basis of RT-PCR tests. Serum MIP-1α and ICAM-1 levels were assessed using commercially available ELISA kits. All patients were subjected to a high-resolution computed tomography assessment.

Results: According to the computed tomography severity score, patients were classified into those with moderate/severe (n=49) and mild (n = 51) pulmonary involvement. Severe involvement was associated with significantly higher MIP-1α and ICAM-1 level. Correlation analysis identified significant positive correlations between MIP-1α and age, D-dimer, IL6, in contrast, there was an inverse correlation with INF-alpha. Additionally, ICAM-1 showed significant positive correlations with age, D-Dimer, TNF-α, IL6, while an inverse correlation with INF-alpha was observed.

Conclusions: MIP-1α and ICAM-1 level are related to CT radiological severity in Covid-19 patients. Moreover, these markers are well-correlated with other inflammatory markers suggesting that they can be used as reliable prognostic markers in Covid-19 patients.

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Background

Despite the significant successes achieved in the battle against Covid-19, the pandemic is thought to continue as a predominant global health threat for years to come. The unique virological, epidemiological, and clinical characteristics of Covid-19 infection had
shaped the unprecedented worldwide combat against the pandemic with many questions remaining unanswered [1]. One of the most challenging issues in the management of Covid-19 is the early identification of patients liable for a worse prognosis; so that, resources can be focused on their follow-up and management. Several genetic, clinical, and biochemical factors were suggested as risk factors for more severe forms of Covid-19 [2].

Genetic risk factors entail variations within the angiotensin-converting enzyme 2 (ACE2) gene, genes regulating multiple Toll-like receptors, and many complement pathways and others [3–5]. Clinical risk factors include obesity diabetes poor diabetic control, and vitamin D deficiency [6–9]. In addition, there is a wide spectrum of biochemical markers that were studied as correlates of Covid-19 severity including immune parameters [10], coagulation factors [11], metabolic mediators [12], and inflammatory markers [13].

In spite of the fact that many of these risk factors proved to successfully predict bad prognostic scenarios in some studies, other studies failed to document such relations. So, the pursuit of other metabolic mediators like receptors, and many complement pathways and others converting enzyme 2 (ACE2) gene, genes regulating multiple Toll-like receptors, and many complement pathways and others.

In our work, we adopted the same steps for CT assessment of lung involvement. Thus, the lobar scores were summed up to yield the total CT score as a measure of the total lung involvement in a given patient. The total lung involvement was categorized according to the total score into groups, which for the purposes of this study we reduced to two categories only: mild (≤7) and moderate/severe (≥8).

Results

The present study included 100 Covid-19 patients. They comprised 44 males and 56 females with an age of [median (IQR): 54.5 (42.0–62.0)] year. According to the CT severity score, patients were classified into patients with moderate/severe (n = 49) and mild (n = 51) pulmonary involvement (Table 1). Comparison between the studied groups regarding the clinical and laboratory data revealed that patients with moderate/severe involvement had significantly higher D-dimer [median (IQR): 1.51 (0.99–2.51) versus 0.73 (0.4–0.93) mg/L, p < 0.001], lower INF-alpha [median (IQR): 54.1 (48.2–65.1) versus 68.8 (59.4–82.9) pg/mL, p < 0.001], higher IL-6 [median (IQR): 51.7 (32.9–124.3) versus 25.1 (14.9–45.4) pg/mL, p < 0.001] and higher TNF-α [median (IQR): 35.2 (32.1–44) versus 31.3 (23.2–35.3) pg/mL, p < 0.001] when compared with patients with mild involvement (Table 1). Moreover, moderate/severe involvement was associated with significantly higher MIP-1α [median (IQR): 8.38 (7.27–10.69) versus 6.45 (5.14–7.3) pg/mL, p < 0.001] and ICAM-1 [median (IQR): 216381 (100513–379289) versus 73033 (52595–11681) pg/mL, p < 0.001] (Table 1). Patients with moderate/severe involvement had significantly longer ICU stay [17.0 (9.0–35.5) versus 7.0 (4.0–10.0) days, p < 0.001] and higher mortality rate (18.4% versus 0%, p < 0.001) (Table 1).
Correlation analysis identified significant positive correlations between MIP-1α and age (r = 0.3), D-dimer (r = 0.592), TNF-α (r = 0.42), IL6 (r = 0.368) and inverse correlation with INF-alpha (r = -0.225) (Table 2). Also, ICAM-1 showed significant positive correlations with patients’ age (r = 0.241), D-Dimer (r = 0.746), TNF-α (r = 0.471), IL6 (r = 0.475) and inverse correlation with INF-alpha (r = -0.336) (Table 3).

Receiver operator characteristic analysis showed both markers (MIP-1α and ICAM-1) had good performance in distinguishing moderate/severe from mild lung involvement with an AUC of 0.852 and 0.829 respectively (Figs. 1 and 2). The performance of other parameters compared to MIP-1α and ICAM-1 is shown in Table 4.

### Discussion

The present study identified significant relations between MIP-1α and also ICAM-1 levels and the severity of pulmonary involvement in Covid-19 patients. Moreover, both markers were well-correlated with inflammatory and coagulation markers related to Covid-19 infection. To the best of our knowledge, no previous study documented a relation between these markers and the extent of lung involvement in similar patients. The relation between MIP-1α and pro-inflammatory markers (IL-6 and TNF-α) reflects a probable contribution of this mediator in the Covid-19-related cytokine storm.

Yang et al., [29] published their findings in China, where they examined the CT scan results of 102 people infected with COVID-19 and discovered that patients with severe COVID-19 infections had a significantly higher total CT severity score than those with moderate infections.

In support of our conclusions, Fonseca et al., [30] noted an association between elevated MIP-1α levels and ICU admission and mortality among African American Covid-19 patients. In another work, cytokine profiling including MIP-1α was performed during the early and late phases of COVID-19 onset. Results showed that MIP-1α in the early and late phases of illness could reliably distinguish mild from severe cases [31]. Moreover, the study of Pons et al., [32], reported an association between elevated MIP-1α levels and Covid-19 severity in Peruvian patients. Similar conclusions were reported by Young et al., [33], Chi et al., [34] and Patterson et al., [35], using a bioinformatics approach.

The relation between ICAM-1 level and Covid-19 severity was previously reported by many studies. The retrospective study of Tong et al., [36], found a link between ICAM-1 level and Covid-19 severity. This finding was confirmed by other studies [37]. Moreover, Kaur et al., [38] found that elevated ICAM-1 level is related to 28-day mortality. In another work, an association was detected between Covid-19 viral RNA load and ICAM-1 level [39].
The findings of our work may have therapeutic implications. The study of Bermejo-Martin et al. [40] studied the antiviral and anti-inflammatory activities of a traditional Chinese agent against Covid-19. The investigators demonstrated that the efficacy of this agent was associated with a significant decline in MIP-1α levels. Likewise, it was shown that the use of bromelain and acetyl cysteine resulted in a significant reduction of MIP-1α levels in the tracheal aspirate of Covid-19 patients [41].
Table 4: Performance of acute inflammatory proteins in identifying cases with CT determined severity of lung involvement.

|       | AUC | CI (LI-UL) | SE | Cutoff | Sensitivity | Specificity | PPV | NPV | P-value |
|-------|-----|------------|----|--------|-------------|-------------|-----|-----|---------|
| D-Dimer | 0.878 | 0.813 | 0.942 | 0.033 | > 1.01 | 0.735 | 0.882 | 0.857 | 0.776 | < 0.001 |
| MIP-1α | 0.852 | 0.779 | 0.925 | 0.037 | 7.280 | 0.755 | 0.745 | 0.740 | 0.760 | < 0.001 |
| ICAM-1 | 0.829 | 0.751 | 0.907 | 0.040 | > 126279 | 0.633 | 0.843 | 0.795 | 0.705 | < 0.001 |
| IFN-α | 0.782 | 0.693 | 0.872 | 0.046 | 59.550 | 0.745 | 0.694 | 0.723 | 0.717 | < 0.001 |
| IL6 | 0.754 | 0.660 | 0.848 | 0.048 | > 44.3 | 0.633 | 0.725 | 0.589 | 0.673 | < 0.001 |
| TNF-α | 0.760 | 0.645 | 0.835 | 0.049 | > 33.8 | 0.612 | 0.725 | 0.674 | 0.649 | < 0.001 |

AUC=Area under the curve; CI= 95% confidence interval; LL=Lower limit; UL=Upper limit; SE=Standard error; PPV= Positive predictive value; NPV=Negative predictive value

Conclusions

In conclusion, MIP-1α and ICAM-1 levels are related to CT-scored radiological severity in Covid-19 patients regardless of the severity of clinical illness. Moreover, these markers are well-correlated with other inflammatory markers suggesting that they can be used as reliable prognostic markers in Covid-19 patients. ROC curve results showed the performance of MIP-1α and ICAM-1 level in identifying cases with higher CT chest severity scores.

Ethical consideration

The study protocol was approved by the ethical committee of King Abdullah Bin Abdulaziz University Hospital with IRB registration Number (20–0073):H-01-R-059 (July,13,2020). A written informed consent was obtained from all patients.

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CRediT authorship contribution statement

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Conflict of interest

None declared.

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Consent for publication

All authors reviewed the manuscript and approved its submission.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Research involving Human Participants and/or Animals

Not applicable.

Informed consent

Informed consent was obtained from all patients.

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