Prognostic Value of Serum MICA Levels as a Marker of Severity in COVID-19 Patients

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\textbf{ABSTRACT}

The COVID-19 global pandemic and high mortality rates necessitate the development of diagnostic and prognostic tools, as well as expanding testing capacity. Existing methods for detecting and characterizing SARS-CoV-2 infection are typically based on viral genome detection or measuring COVID-19-specific antibody levels. Despite their value, these methods are unable to predict disease outcomes in patients. Given the critical role of innate immune cells, particularly natural killer (NK) cells, in antiviral defense, this study sought to determine the prognostic value of serum secretory MHC class I polypeptide-related sequence A (sMICA) levels as an essential ligand for the NKG2D receptor, the master regulator of NK cell development and responsiveness. Serum MICA levels were measured by ELISA assay. Sera (\(n = 60\)) from SARS-CoV-2 positive patients were collected, and disease severity was determined using clinical criteria. The patient group included 30 patients with mild disease and 30 severely ill patients, as well as 30 healthy controls. Our findings revealed that serum MICA levels were significantly higher in patients than in controls, especially in cases with severe complications (\(P < .0001\)). Higher serum MICA levels may be associated with respiratory failure in COVID-19 and may serve as a marker of clinical severity in patients infected with SARS-CoV-2, particularly when clinical manifestations are insufficient to make a confident prediction.

\textbf{HIGHLIGHTS}

- Higher MICA levels may be associated with respiratory failure in COVID-19 infection.
- SMICA levels change with age, particularly for patients with severe COVID-19 disease.
- NKG2D ligands may have prognostic and therapeutic value for COVID-19 patients.

\textbf{Introduction}

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen of COVID-19 disease, continues to spread and imposes significant burdens on the public health system (Baud et al. 2020). To date, numerous studies have been

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conducted to incorporate novel COVID-19 biomarker testing into clinical practices to aid the global fight against COVID-19 infection’s life-threatening complications (Aceti et al. 2020; Ren et al. 2020; Shen et al. 2020). A vast majority of investigations into prognostic markers for COVID-19 progression have focussed on the pathogenesis of SARS-CoV-2 infection. However, many aspects of viral pathogenicity remain unknown (Zheng et al. 2021). In general, the molecular mechanisms of COVID-19 disease include suppressed antiviral immune responses, oxidative stress, and inflammatory processes caused by excessive cytokine secretion, leading to acute lung disease, tissue fibrosis, coagulopathy, and pneumonia (Mrityunjaya et al. 2020). Given the nature of the aforementioned pathologic events, immune dysregulation may play a significant role in the progression of COVID-19 and subsequent poor disease outcomes (Fathi et al. 2020). The close connection between the immune system and the various clinical manifestations of COVID-19 also demonstrates that COVID-19 may be an immune-related disease with viral origin and pathogenicity (Paces et al. 2020).

Under normal conditions, innate immune cells are the first defenders against the virus-infected cells. Indeed, early intervention of natural immunity by type I interferon (IFN-1) and natural killer (NK) cells ensures a rapid but nonspecific response to cytopathic viruses (Maggi et al. 2020). In response to tissue damage and pathogen invasion, the innate immune cells produce several pro-inflammatory cytokines, including IL-1, IL-6, TNF-α, IL-2, GM-CSF, and IFN-γ (Hosseini et al. 2020). These cytokines can promote the migration of the immune cells from the blood circulation to the infected tissues, where they trigger damage and cellular death (Hosseini et al. 2020). Similarly, the transition between innate and adaptive immune responses is critical for predicting the severity of SARS-CoV-2 infections; early CD4+ and CD8+ T cell responses serve as protective mechanisms in combination with sufficient T cell activation. In contrast, dysregulated and exacerbated responses may fail to clear viruses (Toor et al. 2021). Immune responses developed by B cells and cytotoxic T lymphocytes (CTL) contribute to antiviral responses by generating neutralizing antibodies, cytokines, and effector molecules to destroy virus-infected cells (Toor et al. 2021). Therefore, maintaining the balance between protective and destructive immune reactions may affect the outcome of the viral infection (van Eeden et al. 2020). To this end, NK cells have attracted researchers’ attention as modulators of immune responses. (van Eeden et al. 2020)

NK cells may function as regulators of adaptive immune responses regardless of serving as the first-line defense against infections (van Eeden et al. 2020). Their function is contingent upon a cooperative effort between activating receptors like natural killer group 2 member D (NKG2D), CD244, Nkp30, Nkp46 and inhibitory receptors, such as killer cell immunoglobulin-like receptors (KIRs), and the lectin-like CD94-NKG2A heterodimers (van Eeden et al. 2020). Upon cellular stress, infection, or cancer, the activatory receptors outnumber the inhibitory ones, resulting in NK cell activation and target cell killing via various mechanisms, including direct lysis, antibody-dependent cell-mediated cytotoxicity (ADCC), interaction with Toll-like receptor (TLR) ligands, and generating IFN-γ (van Eeden et al. 2020). NKG2D (killer cell lectin-like receptor K1 or KLRK1, CD314) is one of the most contentious activatory and co-stimulatory receptors that viruses typically try to evade (Burgess et al. 2008). This molecular sensor of cellular stress is expressed on several immune cells, such as NK, γδT cells and several subsets of CD4+
and CD8+ T cells (Burgess et al. 2008). These effector cells recruit NKG2D receptors in inflammation surveillance (Liu et al. 2018) by binding to several stress-induced molecules, including the MHC class I-related chains A/B (MICA/MICB) and the UL-16 binding proteins 1–6 (Babic et al. 2020).

MICA/B were the first ligands for NKG2D identified, with their genes mapping to the MHC class I region adjacent to the HLA-B locus (Burgess et al. 2008). These highly glycosylated proteins are present in membrane-bound and soluble isoforms and bear complete polymorphism with more than 100 alleles (Burgess et al. 2008; Groh et al. 2002; Luo et al. 2017). Previous research has established that prolonged interactions between NKG2D and MIC ligands could impair NK and CD8+ T-cell immune responses by down-regulation of NKG2D (Zdrenghea et al. 2012). Moreover, virus-infected cells have developed a variety of mechanisms to inhibit NKG2D/NKG2D ligand engagement, including intracellular storage of molecules, shedding them in soluble forms, and modulating MICA expression in respiratory epithelial cells (Zdrenghea et al. 2012). Given NK cells’ unique role in acute viral infections, their high prevalence in lung tissues, and the regulatory role of NKG2D receptors in NK cell development and activation, this study sought to determine serum MICA levels and their possible correlation with COVID-19 exacerbation.

Materials and methods

Study design and participants

This research project was a cross-sectional comparative study carried out in one of the centers dedicated to COVID-19 patients in Mashhad, Northeastern Iran (Mashhad University of Medical Sciences). The study population consisted of 60 patients diagnosed with COVID-19 and 30 control subjects without respiratory viral infections. The Diagnosis and Treatment Protocol for COVID-19 Patients (Trial Version 8) was used to categorize patients into mild and severe groups. China’s recent clinical experience with COVID-19 infection and treatment guidelines introduced by the World Health Organization (WHO) and others have been incorporated into the protocol. Mild patients were defined in this protocol as 30 outpatients who had a low fever, mild fatigue, olfactory and gustatory complications, and no evidence of pneumonia on imaging tests. Similarly, 30 severely ill patients were ICU-hospitalized patients developing symptoms of respiratory distress syndrome such as dyspnea, hypoxemia (oxygen saturation ≤93% at rest), shortness of breath (RR ≥ 30 times/min), and evidence of lung injury. Further characteristic features of critically ill patients comprised moderate fever, progressive lung lesions, and multiple-organ failure.

The exclusion criteria for all groups comprised the following items: possessing a comorbid condition such as chronic heart, liver, or kidney dysfunction, autoimmunity, immunodeficiency, or cancer, and being treated with antiviral, immunosuppressive, or immune-boosting therapy. All patients’ clinical characteristics and laboratory test results were obtained from their electronic medical records. A poor outcome was defined as one that met at least one of the following criteria: admission to an intensive care unit (ICU), the requirement for mechanical ventilation, or death for any reason. The study was reviewed and approved by the research ethics committee of Mashhad University of Medical Sciences (reference number: IR.MUMS.MEDICAL.REC.1399.771). All participants in this study signed a written consent form.
**Laboratory tests**

SARS-CoV-2 viral nucleic acid was detected using a real-time PCR test in all positive cases’ nose swabs. Blood samples were obtained from all patients upon admission to determine the white blood cell count (WBC), C-reactive protein (CRP), lactate dehydrogenase (LDH) activity and serum MICA concentration.

**Assays to measure serum MICA levels**

Commercial ELISA kits from Invitrogen (Thermo Fisher Scientific, USA) were used to analyze serum MICA levels. All samples were examined according to the manufacturers’ instructions. In brief, wells of the supplied microplate were coated with a MICA-specific antibody. The wells were then filled with pre-diluted samples, standards, and controls and bound to the immobilized antibody. A sandwich ELISA was formed by adding the second antibody (biotin conjugate). A one-hour incubation at room temperature with gentle shaking was required during the next stage. Subsequently, the mixture was incubated for 45 minutes with a prepared streptavidin-HRP solution. Finally, the substrate solution was mixed with the enzyme-antibody-MICA complex, resulting in a blue color that changed to yellow when the stop solution was added. The color intensity was proportional to the MICA concentration in serum samples.

**Data analysis and statistics**

The whole data set was analyzed employing Statistical Package for the Social Sciences (SPSS) version 16.0 and Graph Pad Prism 6. Variables across different groups were compared with ANOVA and Chi-Square Tests. Pearson/Spearman correlation tests were utilized to examine possible associations between variables. Logistic regression analysis was performed to determine MICA predictive value for a worse prognosis. Receiver operating characteristic (ROC) curve analysis was also conducted to evaluate the prognostic value of serum MICA in COVID-19 patients. A p-value of <.05 was considered statistically significant.

**Ethical considerations**

The research was conducted per the institutional and national research committees’ ethical standards and codes, as well as the Helsinki Declaration on human research. The study was reviewed and approved by the research ethics committee of Mashhad University of Medical Sciences (reference number: IR.MUMS.MEDICAL.REC.1399.771).

**Results**

This study enrolled 90 participants: 30 healthy controls and 60 patients with COVID-19 disease, including 30 severely ill patients and 30 outpatients with mild infection symptoms. The baseline characteristics of the participants are shown in Table 1. As indicated, the study population consisted of 52 males (58%) and 38 females (42%) aged from 25 to 68 years. Five out of 30 severe cases died during the study process. As per the data, more than half of the infected patients were middle-aged men over 30. The patients’ clinical symptoms showed
Table 1. Comparison of laboratory parameters in the study population using ANOVA and Chi-square tests, note: WBC, white blood cells; NLR, neutrophil lymphocyte ratio; CRP, C – reactive protein; LDH, lactate dehydrogenase; MICA, MHC class-I-related chain A.

| Variables       | Mild disease (mean ± SD) | Severe disease (mean ± SD) | Healthy controls (mean ± SD) | P-value |
|-----------------|--------------------------|---------------------------|-----------------------------|---------|
| Age (years)     | 38.7 ± 6.9               | 47.3 ± 10.3               | 39.5 ± 8.8                  | <.0001  |
| Male            | 18 (60%)                 | 17 (57%)                  | 17                          | ——      |
| Female          | 12 (40%)                 | 13 (43%)                  | 13                          | ——      |
| Fever           | 8 (26%)                  | 25 (83%)                  | 0                           | 0.01    |
| Cough           | 8 (26%)                  | 24 (80%)                  | 0                           | 0.006   |
| Fatigue         | 14 (46%)                 | 18 (60%)                  | 0                           | 0.006   |
| Dyspnea         | 4 (13.3%)                | 16 (53%)                  | 0                           | 0.002   |
| ARDS            | 0                        | 0                         | 0                           | ——      |
| Death           | 0                        | 0                         | 0                           | ——      |
| WBC (/µl)       | 8350 ± 960               | 12,303 ± 2090             | 7213 ± 645                  | 0.006   |
| Neutrophils(/µl)| 6939 ± 942               | 11,476 ± 2092             | 4071 ± 511                  | 0.001   |
| Lymphocytes (/µl)| 1406 ± 124            | 827 ± 71                  | 3124 ± 523                  | 0.001   |
| NLR (%)         | 4.5 ± .75                | 13.9 ± 2.9                | 1.3 ± .32                   | 0.003   |
| CRP (mg/l)      | 33.7 ± 7.8               | 259 ± 80                  | 3.26 ± 1.35                 | 0.001   |
| LDH (u/l)       | 235 ± 22                 | 639 ± 173                 | 217 ± 22                    | 0.01    |
| MICA (pg/ml)    | 1072 ± 187.2             | 1874 ± 427.8              | 434.6 ± 188.9               | <.0001  |

statistically significant changes between mild and severe groups, including fever, cough, fatigue, dyspnea, and ARDS. In addition to the clinical manifestations, laboratory tests, such as WBC, neutrophil, and lymphocyte counts, NLR, CRP, LDH, and sMICA were assessed and analyzed in each study group. As illustrated in Table 1, our data revealed significant differences between the participant groups in all parameters mentioned above.

Assessing serum MICA levels across the study groups

Our data revealed a significant increase in sMICA levels in patients with severe COVID-19 symptoms when compared to patients with mild symptoms (mean ± SD sMICA: 1874 ± 427.8 and 1072 ± 187.2 pg/ml for severe and mild cases of COVID-19, respectively) (P-value <.0001). Moreover, a statistically significant increase in sMICA levels was observed in patients with both mild and severe forms of the disease compared to controls (mean ± SD sMICA for healthy controls: 434.6 ± 188.9 pg/ml) (P-value <.0001) (Figure 1). The optimal cut-off value of sMICA level for COVID-19 diagnosis was 747 pg/ml with 98% sensitivity and 84% specificity (AUC: .92 [95% CI: .85–.99]).

A comparative analysis of the demographical, clinical and laboratory characteristics of the three studied groups is presented in Table 1. In this respect, severe cases of COVID-19 exhibited higher sMICA, WBC, neutrophil, NLR, CRP, and LDH levels and lower lymphocyte counts than mild and healthy subjects (p < .05).

Intriguingly, a significant positive correlation between MICA serum concentrations and age was observed (r: .34, p-value: .001). This relationship was especially significant in the case of participants aged 40–50 years, who were the most at-risk group of patients. However, no statistically significant correlation was observed between sMICA levels and gender (p-value: .43).
Association between serum MICA and clinical characteristics

The Spearman/Pearson correlation analysis revealed that the level of serum MICA was positively correlated with WBC and PMN counts, NLR, CRP, and LDH. Conversely, negative associations were found between serum MICA and lymphocyte levels (Table 2). Interestingly, increased sMICA levels were found to be significantly associated with the development of dyspnea in patients (P < .05) (Table 2).

Table 2. Correlation between serum MICA and other indicators.

| Variable  | Spearman/Pearson value | P-value |
|-----------|------------------------|---------|
| Age       | 0.34                   | 0.001   |
| Gender    | −.07                   | 0.43    |
| WBC       | 0.77                   | 0.002   |
| PMN       | 0.84                   | 0.04    |
| Lymphocyte| −.79                   | 0.001   |
| NLR       | 0.88                   | 0.003   |
| CRP       | 0.86                   | 0.001   |
| LDH       | 0.81                   | 0.05    |
| Fever     | 0.72                   | 0.09    |
| Cough     | 0.73                   | 0.07    |
| Dyspnea   | 0.67                   | 0.04    |
| ARDS      | 0.62                   | 0.08    |
| Death     | 0.38                   | 0.06    |
Prognostic value of serum MICA for COVID-19 patients

Prognostic performance of sMICA, WBC, neutrophils, NLR, CRP and LDH were analyzed as markers of the severity and outcome of COVID-19 disease. A ROC curve was generated, and the AUCs were calculated (Figure 2). As a result, the AUC values of sMICA, WBC, neutrophils, NLR, CRP, and LDH were as follows: 92 (95% CI: .85–.99), 89 (95% CI: .81–.97), 90 (95% CI: .83–.97), 91 (95% CI: .83–.99), 87 (95% CI: .79–.94), 97 (95% CI: .94–.99). The optimal cut-off values for these markers for differential diagnosis between severe and mild COVID-19 patients, as well as the corresponding sensitivity/specificity values, are listed in Table 3. As shown, sMICA with a cut-off value of 1070 pg/ml and LDH with a cut-off value of 487 u/l were more promising factors for discriminating between severe and mild cases. Additionally, data from this study revealed that patients with poor outcomes had significantly higher serum MICA levels than other patients; 1838 (1238.30–3689.40 pg/ml) vs. 1042 (764.6–1454 pg/ml) (p = .0001).

![ROC Curve](image)

**Figure 2.** ROC curve analysis of sMICA, WBC, neutrophil, NLR, CRP, and LDH.

**Table 3.** The prognostic values of sMICA, WBC, neutrophil, NLR, CRP, and LDH to prediction of severe COVID-19 cases.

| Variable | sMICA | WBC  | Neutrophil | NLR  | CRP  | LDH  |
|----------|-------|------|------------|------|------|------|
| AUC      | 0.92  | 0.89 | 0.90       | 0.91 | 0.87 | 0.97 |
| 95% CI   | (.85–.99) | (.81–.97) | (.83–.97) | (.83–.99) | (.79–.94) | (.94–.99) |
| Cut-off  value | 1070  | 8450 | 7600       | 5    | 44   | 487  |
| Sensitivity (%) | 90    | 87   | 90         | 93   | 90   | 80   |
| Specificity (%)   | 70    | 72   | 80         | 75   | 73   | 97   |
Discussion

The COVID-19 pandemic has caught the world by surprise and fiercely condemned many infected individuals to death. Clinical manifestations of COVID-19 patients are highly diverse and range from exhaustion and slight fever to acute respiratory distress syndrome (ARDS), septic shock, and multi-organ failure (Zhang et al. 2020). This broad range of symptoms is primarily caused by host factors, such as age, gender, genetic background, and, most notably, regulated or dysregulated immunologic responses (Zhang et al. 2020). However, detecting severe cases of COVID-19 is critical for providing effective treatment to the most vulnerable patients and reducing mortality rates (Perlman 2020). Thus, it is necessary to define easily quantifiable biomarkers that can be used to represent abnormality and predict disease outcomes in patients infected with COVID-19. In light of this concern, the purpose of this study was to determine if there is a link between sMICA levels as effective molecules in natural immunity and COVID-19 exacerbation. The most significant finding of this study is that increased sMICA levels may contribute to the progression of COVID-19 infection. In our study, serum MICA levels increased nearly threefold in COVID-19 patients compared to healthy controls, and it can be used with a cut-off value of 747 pg/ml for the early detection of COVID-19.

Recent studies have shown that the development of COVID-19 severity is strongly linked to the immunologic disturbances, including CD4+ T cell and NK cell cytopenia, decreased expression of the activatory receptor NKG2D and IFN-γ, suppressing the cytotoxic activity of NK cells, and CD8+ T lymphocytes, secreting excessive amounts of pro-inflammatory cytokines by monocytes, and deficiency in B cell function (Bozzano et al. 2021; Giamarellos-Bourboulis et al. 2020; Varchetta et al. 2021; Yao et al. 2021). Thus, several lines of research have already focussed on the markers with the ability to reflect immune activation/inhibition to identify patients with severe COVID-19 disease (Kimura et al. 2021; Ozger et al. 2021; Patterson et al. 2021). IFN-γ mediated effector molecules (Robertson et al. 2020) coagulation parameters (Szkłanna et al. 2021) and metabolomics of patients with COVID-19 (Torres-Ruiz et al., 2021) are prominent examples of immune-based markers for COVID-19 progression and exacerbation. Due to its high sensitivity and specificity in discriminating between severe and mild cases at a 1070 pg/ml cut-off value, sMICA may also be a promising biomarker for predicting COVID-19 severity on hospital admission.

Serum MICA levels or its gene expression pattern have also been evaluated as a prognostic factor in viral infections, such as hepatitis C (Huang et al. 2017) Epstein–Barr virus (Viet et al. 2021) and respiratory syncytial virus (RSV) (Luo et al. 2017). Numerous studies have established that RNA viruses can induce the expression of various NKG2D ligands that contribute to NK cell proliferation and IFN-γ production (Ebihara et al. 2007). For example, RSV infection of lung epithelial cells increased the production of IL-15, expression of MICA, and sMICA serum levels (Zdreghnea et al. 2012). On the contrary, the human metapneumovirus (HMPV), a causative pathogen of influenza-like illness in children, has proved to downregulate MICA/B through viral protein M2.2 (Diab et al, 2020). To our knowledge, this is the first study that examines sMICA in COVID-19 patients. The increased level of sMICA in these patients could result from the body’s protective responses to immune evasion via viral proteins. Another possible explanation may be the altered trafficking of MHC-I molecules on the infected cell surface during viral infection that helps the virus deceive immune cells (Fink et al. 2019). Moreover, increased
sMICA levels may affect suppressive signaling networks related to immunologic tolerance due to the virus presence (Goodnow 2021); however, additional research is necessary to determine the exact interaction mechanisms.

Unfortunately, the study did not collect additional patient data to assess sMICA levels, such as nutrition status or medication use. We excluded patients with unmet inclusion criteria, such as comorbidities, autoimmunity, and cancer to limit the confounder factors. Despite the small sample size, this study provides valuable insight into diagnostics for COVID-19 exacerbation, which may aid in the management of patients with SARS-CoV-2 infection. The significant increase in sMICA levels in patients compared with uninfected controls may help explain the pathogenesis of the infection to some extent and may have the propensity to be used for diagnostic, prognostic, and therapeutic purposes.

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