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# Evaluation of Salivary sIgA Levels in Hospitalized COVID-19 Patients with COVID-19 Disease Severity: A Cross-sectional Study

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#### ABSTRACT

Since late 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has dramatically affected public health worldwide. Although systemic antibodies like Immunoglobulin G (IgG) and Immunoglobulin M (IgM)have been widely studied in Coronavirus disease 2019 (COVID-19), the role of Immunoglobulin A (IgA) in mucosal immunity remains less understood. This study evaluated whether salivary IgA levels could serve as prognostic markers for disease severity, progression, and outcomes in hospitalized patients with COVID-19.

In this cross-sectional study, 61 hospitalized patients with COVID-19 were enrolled. After obtaining informed consent, saliva samples were collected at admission to measure IgA levels using an ELISA-based assay (Dlametra kit). Comprehensive clinical and laboratory data, including chest CT results, oxygen saturation, inflammatory markers, and clinical outcomes, were also recorded. Statistical tests were used to examine the association between salivary IgA levels and disease severity, progression, and outcomes.

We enrolled 61 hospitalized patients with COVID-19 (30 females, 31 males; mean age:  $56.20 \pm 17.45$  years; mean admission oxygen saturation:  $89.98 \pm 5.77\%$ ). At admission, 39.3% of patients reported dyspnea, and 40% demonstrated severe lung involvement on chest CT scans. The mean salivary IgA level was  $1729.69 \pm 391.35$  mg/dL. No significant associations were found between salivary IgA levels and COVID-19 severity, disease progression, or clinical outcomes, including mortality.

Our findings show that salivary IgA levels did not significantly correlate with COVID-19 severity, disease progression, or clinical outcomes in hospitalized patients. Therefore, salivary IgA alone cannot be recommended as a prognostic biomarker for COVID-19. Further research is

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needed to identify more reliable immunological indicators for predicting COVID-19 severity and outcomes.

**Keywords:** COVID-19; Immunoglobulin A; Immunoglobulin A, Secretory; Immunity, Mucosal; Prognosis

#### INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the seventh coronavirus reported to infect humans, first surfaced in late 2019 and spread over the world.<sup>1,2</sup> Like SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), it can cause signs and symptoms in different ranges from flu-like to severe pneumonia in susceptible people, resulting in high rates of mortality and morbidity globally.3-5 Despite lots of research in order to find a treatment, early attempts using repurposed antivirals (such as lopinavir/ritonavir and hydroxychloroquine) had minimal success.<sup>6</sup> As evidence of the pandemic's enormous impact, the World Health Organization (WHO) recorded more than 80 million confirmed illnesses and almost 2 million deaths worldwide by the beginning of 2021.7 Clinically, Coronavirus disease 2019 (COVID-19) ranges from asymptomatic disease to severe respiratory failure and multi-organ dysfunction.8 Its incubation period is usually 2–14 days, and patients can transmit the virus before symptoms appear. 9,10 Diagnosis relies mostly on real-time reversetranscription polymerase chain reaction (RT-PCR) testing of respiratory samples, but computed tomography (CT) scans can assist when RT-PCR results are inconclusive. 4,11 Different antibody isotypes are involved in the immunological response to SARS-CoV-2. The function of secretory IgA (sIgA) in mucosal immunity has not been as well studied as that of Immunoglobulin M (IgM) and Immunoglobulin G (IgG). sIgA can neutralize pathogens and stop them from adhering to epithelial cells, as it is the predominant immunoglobulin on mucosal surfaces. 12,13 Since SARS-CoV-2 typically enters and replicates in the upper respiratory tract, this mucosal defense likely influences the severity of infection.<sup>14</sup> Salivary IgA may therefore serve as a useful, noninvasive indicator of local immune responses and disease progression. 15-17 In this study, we measured salivary IgA levels in hospitalized patients with COVID-19 and examined how they relate to clinical outcomes. Understanding sIgA dynamics could

help guide preventive and therapeutic strategies focused on the mucosal surfaces where SARS-CoV-2 initially establishes infection.

#### MATERIALS AND METHODS

### Study Design, Setting, and Population

This is a cross-sectional study conducted at a major tertiary center that served as a referral hospital for patients with COVID-19 during the pandemic to evaluate the relationship between salivary IgA levels and COVID-19 severity, disease progression, and clinical outcomes. We included adult patients (≥18 years) hospitalized with a confirmed diagnosis of COVID-19 by a positive RT-PCR test for SARS-CoV-2 from nasopharyngeal swabs or characteristic chest CT findings of COVID-19 pneumonia combined with a clinically compatible presentation. Patients with oral or salivary gland conditions that could affect saliva secretion, such as mucositis, xerostomia, or sicca with documented syndrome, those humoral immunodeficiency disorders, and pregnant or lactating individuals were excluded. A total of 61 patients eligible with the inclusion and exclusion criteria were enrolled during the study period.

#### Saliva Sampling and Data Collection Procedures

Patients provided unstimulated full saliva samples using the passive drool method during the first 24 hours of admission. They were not allowed to eat, drink (except water), smoke, or practice oral hygiene for at least 30 minutes before sample collection. Participants were instructed to sit upright with their head slightly tilted forward and allow saliva to accumulate in the mouth without swallowing or stimulation. They then gently drooled the saliva into a sterile container every 1–2 minutes for a total of 5–10 minutes. sIgA levels were determined using a commercial ELISA kit (Dlametra, Italy) per the manufacturer's instructions. The normal reference range for individuals over 18 years, according to clinical biochemistry guidelines and the kit insert, was 61–356 mg/dL. The IgA secretion rate was calculated by

multiplying the IgA concentration by the saliva flow rate (mL/min), determined from the volume of saliva collected and the collection time.

Demographic and clinical data were recorded, including age, sex, past medical history (e.g., comorbidities), presenting symptoms, and vaccination status against SARS-CoV-2. Vital signs (temperature and mean oxygen saturation (SpO2)) and initial laboratory parameters were documented. The severity of pulmonary involvement was assessed by a radiologist blinded to the study objectives in mild, moderate, and severe scale. Need for supplemental oxygen therapy by noninvasive (e.g., face mask and nasal canula) or invasive (e.g., intubation) methods, SpO2 drop below 90%, pulmonary involvement more than 50%, need to take immunomodulator drugs or corticosteroid pulse, side effects such as pulmonary (e.g., pulmonary thromboembolism (PTE)), neurological (e.g., encephalitis cerebrovascular and events), and gastrointestinal (e.g., diarrhea and vomiting), intensive care unit (ICU) admissions, and clinical outcomes (improvement, prolonged hospitalization, or mortality) were evaluated during hospitalization and over a 28-day follow-up period after discharge.

#### **Statistical Analysis**

All collected data were entered into a computerized database and analyzed using SPSS version 21 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as means and standard deviations or medians and interquartile ranges, depending on distribution normality, as determined by the Kolmogorov-Smirnov test. Categorical variables were presented as frequencies and percentages.

Group comparisons were performed using independent t-tests for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed data. For categorical variables, Chi-square or Fisher's exact tests were employed as appropriate. Correlations between salivary IgA levels and continuous clinical indices were examined using Pearson's or Spearman's correlation coefficients, depending on normality. A significance level of p < 0.05 was considered statistically significant for all analyses.

#### **RESULTS**

## Study Population, Demographic Characteristics, Clinical, and Laboratory Findings

A total of 61 eligible patients (47 with positive RT-PCR tests for SARS-CoV-2 and 14 based on clinical evaluation and characteristic radiological findings consistent with COVID-19 pneumonia) were evaluated in this study. The patients ranged in age from 20 to 91 years, with a mean age of  $56.20 \pm 17.45$  years. Of these patients, 30 were female (49.19%) and 31 were male (50.18%), resulting in a nearly balanced gender distribution. At admission, patients had a variety of SpO<sub>2</sub> levels, respiratory function, and body temperatures (Table 1). Also, key laboratory indices for the enrolled patients are summarized in Table 1.

#### **Underlying Comorbidities**

Past medical history and underlying diseases were available for 56 of the 61 patients. Among these, 38 patients (67.9%) had at least one comorbidity. The most common underlying conditions included hypertension, diabetes, and cardiac disease (Table 2).

#### Salivary IgA Levels

The mean salivary IgA level measured in this cohort was  $166.7 \pm 161.63$  mg/dL. The study aimed to determine whether higher or lower salivary IgA levels correlated with markers of disease severity or clinical outcomes.

#### **Hospitalization Data**

The mean length of hospital stay was  $6.05 \pm 2.33$ days, ranging from a minimum of 1 to 15 days. These statistics suggest moderate variability in disease severity and resource utilization. Of the 61 patients, 8 (13.1%) required endotracheal intubation and mechanical ventilation, and 9 patients (14.8%) were admitted to the ICU. These rates reflect a subset of patients with more severe disease requiring advanced supportive care. Standard therapy (e.g., dexamethasone, remdesivir) was administered to approximately 94% of patients. Additionally, 8 patients (13.1%)received corticosteroids pulse and 10 patients (16.1%) received immunomodulatory therapy with Actemra (Tocilizumab). These interventions were guided by clinical judgment, patient condition, and evolving treatment protocols.

Table 1. Demographic characteristics, clinical, and laboratory findings of the study patients

Variable			Value
Age, y		Mean (±SD)	$56.20 \pm 17.45$
		Range	20–91
Sex	Female	n (%)	30 (49.19)
	Male	n (%)	31 (50.18)
oxygen saturation (SpO2), %		Mean (±SD)	$89.98 \pm 5.77$
Respiratory status	Normal	n (%)	37 (60.7)
	Dyspnea	n (%)	24 (39.3)
Temperature, °C		Mean ±SD	$37.05 \pm 0.893$
White Blood Count (WBC), /µL		Mean ±SD	$6700.09 \pm 3142.95$
Hemoglobin (Hb), g/dL		Mean ±SD	$12.99 \pm 2.25$
Platelet Count (PLT), /μL		Mean ±SD	$198336.27 \pm 98747.88$
Erythrocyte Sedimentation Rate (ESR) , mm/h		Mean ±SD	45.48 ± 23.17
C-reactive protein (CRP), mg/L		Mean ±SD	$48.10 \pm 33.90$
Lactate dehydrogenase (LDH), U/L		Mean ±SD	$692.58 \pm 312.01$
D-Dimer, μg/L		Mean ±SD	$1395.58 \pm 1498.50$

Table 2. Frequency of underlying diseases in the study patients

Variable		Value
Underlying diseases	n (%)	
Hypertension	n (%)	15 (24.45 %)
Diabetes	n (%)	11 (17.93 %)
Cardiac disease	n (%)	10 (16.30 %)
Pulmonary disease	n (%)	3 (4.89 %)
Metabolic disorders	n (%)	5 (8.15 %)
Neurological disease	n (%)	5 (8.15 %)
Malignancy	n (%)	5 (8.15 %)
Liver disease	n (%)	2 (3.26 %)
Renal disease	n (%)	2 (3.26 %)
Infectious disease	n (%)	1 (1.63 %)

#### 28-Day Follow-up and Outcomes

At the 28-day follow-up, complete outcome data were available for 41 patients. Of these, 10 patients (16.4%) unfortunately had died and 31 patients (50.8%) had recovered or improved. These outcome data highlight the severity of COVID-19 in this hospitalized cohort and the associated mortality risk.

#### **Analytical Findings**

No significant association was found between salivary IgA levels and patients' age or gender (p=0.607), indicating that IgA secretion did not differ notably by demographic factors. Additionally, analyses of laboratory findings showed no significant correlation with salivary IgA (all p>0.05), suggesting that mucosal IgA secretion does not directly reflect systemic

inflammation or hematologic status. The presence or absence of lymphopenia (defined as a lymphocyte count $\leq$ 2500) was not related to IgA levels (p=0.813).

Radiological assessments also failed to reveal any association with salivary IgA (p=0.448), and similarly, respiratory parameters were not associated; neither oxygen saturation (p=0.463) nor the presence of dyspnea at admission (p=0.737) was associated with IgA levels. Moreover, the need for intubation or ICU admission was not influenced by IgA secretion (p=0.725 and p=0.610, respectively).

One notable exception was the relationship between salivary IgA and the necessity for immunomodulatory therapy with Actemra (Tocilizumab). Patients with higher IgA levels were less likely to require Actemra (p=0.028), suggesting a potential protective role of mucosal immunity against severe immunological dysregulation. In contrast, no significant association was observed between IgA levels and the need for highdose corticosteroids (500-1000)mg/day methylprednisolone) (p=0.685). Although higher IgA correlated with reduced immunomodulator use, it did not predict long-term outcomes or survival, and no significant association was found with length of hospitalization (p=0.077), need for readmission (p=0.488), 28-day outcomes (p=0.512), or mortality (p=0.631).

#### DISCUSSION

Clinical manifestations following SARS-CoV-2 infection range from asymptomatic or mild presentations to moderate, severe, or fulminant respiratory disease with multi-organ failure. The primary objective of this study was to examine the correlation between salivary IgA secretion levels and disease progression in patients hospitalized with COVID-19. Additionally, we explored associations between salivary IgA levels and factors such as age, sex, laboratory findings, duration of symptoms, and overall disease course.

Salivary IgA, as a key component of mucosal immunity, provides an initial barrier against respiratory pathogens by preventing viral adhesion to epithelial receptors. Despite the theoretical importance of this immunoglobulin, our findings indicate that salivary IgA alone cannot be considered a reliable predictor of COVID-19 severity or progression. Indeed, while some studies have found that IgA correlates with disease

outcomes, 18,19 others have not observed such associations. 20

In the study by Vâță et al<sup>20</sup> similar to our research, no statistically significant differences were noted between IgA secretion levels and patient characteristics (e.g., age, sex) or key clinical parameters (e.g., dyspnea, oxygen saturation, fever). Nevertheless, they did report a significant correlation between anti–SARS-CoV-2 IgA levels and overall disease severity, especially in patients with comorbidities. By contrast, Dahlke et al<sup>19</sup> also observed that an early IgA profile could influence symptom severity but noted variable patterns across patients.

Similarly, Zervou et al<sup>18</sup> found that higher IgA levels were associated with severe or critical COVID-19. This contrasts with our findings, which showed no significant associations between salivary IgA levels and severity metrics such as oxygen saturation, dyspnea, or CT-documented pulmonary involvement. In line with these discrepancies, Xue et al<sup>21</sup> and Rangel-Ramírez et al<sup>22</sup> also noted inconsistencies across different patient cohorts regarding IgA's predictive power.

Research on mucosal immunity has highlighted the potential of sIgA in defending against respiratory infections. Kostinov et al<sup>23</sup> demonstrated that localized immune interventions, such as the use of the bacteriabased immunostimulant Immunovac VP4, enhanced sIgA levels in the nasal and pharyngeal compartments. However, these improvements were not consistently linked to systemic disease outcomes, emphasizing the complexity of translating localized immune responses into broader prognostic applications. Another investigation by Kostinov et al24 further showed that combined intranasal and oral immunostimulant therapies can modulate IgA levels in mucosal compartments but noted variability in responses, complicating the utility of IgA as a standalone diagnostic or prognostic variable.

Contrary to certain studies that identified a correlation between salivary IgA levels and the extent of pulmonary involvement on CT scans, our study did not demonstrate such an association. Meta-analyses by Rangel-Ramírez et al<sup>22</sup> and Ma et al<sup>25</sup> (as well as the Barzegar-Amini et al<sup>26</sup> study) suggested that higher IgA levels might be indicative of more severe disease, but our findings do not support the utility of IgA as a diagnostic variable in hospitalized patients.

Extensive research on treating COVID-19 supports the use of corticosteroids and immunomodulatory

agents in severely ill patients. Some studies have suggested that IgA levels could predict the necessity of these therapeutic interventions.<sup>27</sup> However, our study did not yield sufficient evidence to confirm any association between salivary IgA levels and the need for immunomodulatory therapies or high-dose methylprednisolone (500–1000 mg/day). Furthermore, despite findings by Sinnberg et al<sup>28</sup> implicating IgA-mediated responses in disease progression and mortality—we observed no correlation between salivary IgA levels and in-hospital mortality rates in our study.

Although comorbidities such as diabetes, hypertension, and cardiovascular disease were prevalent among our patients, we did not perform subgroup or multivariate analyses to explore their influence on salivary sIgA levels or COVID-19 severity. Given that these conditions may affect mucosal immunity and disease prognosis, future research should incorporate stratified analyses and adjusted models to better understand these interactions.

Although treatment data (e.g., corticosteroids, tocilizumab) were collected, we did not control for differences in timing, dosage, or treatment combinations. This variability may have influenced immune responses, including salivary IgA levels, and potentially confounded clinical outcome associations.

This study has several limitations. The relatively small sample size and single-center design may limit the generalizability of the findings. Salivary IgA was measured only upon admission, precluding the assessment of dynamic changes in IgA levels over the course of the illness. Future studies incorporating serial sampling could better characterize the relationship between mucosal immunity and disease progression. Also, one limitation of the study is that we did not screen participants for selective IgA deficiency, which could have influenced baseline sIgA levels in certain individuals. Additionally, the study did not account for potential confounding factors such as variations in treatment protocols or the timing of sample collection relative to symptom onset. Some medications that may reduce IgA levels, such as corticosteroids or anticonvulsants, were not fully accounted for in preadmission history and could represent a potential source of bias. The absence of a control group (e.g., healthy individuals or asymptomatic COVID-19 cases) limits our ability to contextualize the observed salivary IgA levels. Future studies should include control cohorts to enable meaningful baseline comparisons. Larger,

multicenter, and longitudinal studies are warranted to further elucidate the role of salivary IgA in COVID-19.

In summary, while previous studies have provided varying evidence regarding the prognostic and diagnostic roles of Salivary IgA in COVID-19, our investigation does not support the use of salivary IgA levels as a standalone indicator of disease severity, progression, or outcome. Findings by Kostinov et al<sup>23,24</sup> on the modulation of IgA levels through bacterial immunostimulants reinforce the importance of mucosal immunity but also underscore its limitations as a predictive tool. Future research should incorporate additional immunological variables and longitudinal measurements to better elucidate the complex interplay between host immune defenses and SARS-CoV-2 pathogenesis.

#### STATEMENT OF ETHICS

The Imam Khomeini Hospital Complex Ethics Committee approved the study (IR.TUMS.IKHC.REC.1400.198). Enrollment was voluntary, patients were assured that refusal or withdrawal would have no effect on their normal medical care provided and signed an informed permission before to enrollment. Patients received standard clinical care and no invasive procedures beyond that were carried out. Written informed consent was obtained from all participants prior to sample collection.

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#### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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#### DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. Requests for access should be directed to Dr. Sara Ghaderkhani at sghaderkhani@gmail.com

#### AI ASSISTANCE DISCLOSURE

No artificial intelligence tools were used in the conception, analysis, or preparation of this manuscript.

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