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Is the value of anti-SARS-CoV-2 IgA antibody detection underappreciated in our current COVID-19 pandemic response?

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Despite the nature of COVID-19 as a disease of mucosal tissue sites, current serological tests are primarily focused on IgM and IgG antibody detection. The significance of testing for IgA antibody response to SARS-CoV-2 infection and their potential role in COVID-19 disease progression is not yet well explored. Intriguingly, several studies revealed that heightened IgA antibody response to SARS-CoV-2 correlated with COVID-19 disease severity. We hypothesize that the assessment of serum IgA levels can aid in the prognostication of severe COVID-19 progressors. Our hypothesis posits that an IgA antibody response to SARS-COV-2 that is skewed towards Fc binding to CD89 (FcαRI) to form immune complexes (IgA-IC) rather than inhibiting viral entry to host epithelial cells, results in IgA-IC-mediated hyperinflammatory response. The propensity for an elevated non-neutralizing IgA antibody response in sera of COVID-19 patients may lead to the unregulated crosstalk between PRR-induced priming of inflammation and IgA-IC-induced NLRP3 inflammasome formation. Therefore, we believe that looking into the dynamics of the SARS-CoV-2-specific IgA response and their threshold values associated with the clinical severity of COVID-19 warrants further investigations. If our hypothesis is correct, serum IgA may supplement, if not precede, traditional serum diagnostic markers of end-organ damage that are currently used for COVID-19. Investigating the feasibility of using IgA as a biomarker for severe COVID-19 progressors in future studies may reveal its underappreciated value in improving current clinical management and treatment of SARS-CoV-2 positive patients.

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Date received: July 2, 2020
Date revised: July 28, 2020
Date accepted: July 28, 2020

KEYWORDS

IgA, COVID-19, prognostics, hyperinflammation, IgA-IC, inflammasomes

INTRODUCTION

The Coronavirus Disease-2019 (COVID-19) is an ongoing health crisis in 216 countries and is thus considered a current pandemic (WHO, 2020b). In the Philippines, more than 80,000 cases have been reported by the Department of Health (DOH, 2020). Health authorities have resorted to different strategies in addressing the disease, as a vaccine and treatment protocols are yet to be optimized.

Central to combatting the COVID-19 pandemic is a reliable and early diagnosis for screening, as well as effective isolation of infected patients (Zhai et al., 2020). The current gold standard for diagnosing COVID-19 is reverse transcription-polymerase chain reaction (RT-PCR)-based detection of the etiologic virus, Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), using nasopharyngeal swab samples (Azzi et al., 2020). However, the number of RT-PCR tests that are performed per day is limited by the availability of resources and facilities to conduct RT-PCR in the Philippines (Galvez, 2020). As such, symptomatic patients are prioritized for screening, leaving possible asymptomatic transmission among the population largely unchecked (Gandhi et al., 2020). Given the concern on

the availability and adaptability of the current gold standard for diagnosis in mass testing, public interest for COVID-19 rapid antibody tests increased.

COVID-19 rapid antibody tests are principally used for detecting previous SARS-CoV-2 infection as they are indicative of antibody seroconversion and are not as reliable for diagnosing an ongoing infection (WHO, 2020a). Health professionals do not recommend the use of COVID-19 rapid antibody tests for issuing return for work certificates, and government health agencies emphasize caution for interpreting antibody test results. The recommended uses of rapid antibody-based diagnostic tests are primarily for identifying seropositive individuals to screen for potential convalescent plasma donors and epidemiological studies. (PSMID, 2020). In addition to these recommended uses, we also recognize the value of using validated SARS-Cov-2-specific antibody tests in determining the demographic and geographical seroprevalence in our communities.

Interestingly, despite the nature of COVID-19 as a disease of mucosal tissue sites, unlike IgM and IgG, IgA has not gotten much attention as a serology marker. Of the 62 Rapid Antibody Tests approved by the Philippine Food and Drug Administration on June 16, 2020, not one test is designed to detect IgA. Intriguingly, several studies revealed that heightened IgA antibody response to SARS-CoV-2 correlated with disease severity (Dahlke et al., 2020; Ma et al., 2020; Yu et al., 2020). Consistent with this, elevated serum IgA was indicated in chronic inflammatory diseases. Therefore, we hypothesize that assessment of serum IgA levels can aid in the prognostication of severe COVID-19 progressors. Here, we discuss the potential mechanism on how high IgA serum level may induce the development hyperinflammatory response in SARS-CoV-2 infected individuals and the potential use of IgA in COVID-19 prognostics. We believe that biomarkers that may help optimize patient care and reduce the overall case fatality ratio (CFR) of COVID-19 warrants further investigations.

COVID-19 Disease Presentation

As a pandemic, COVID-19 is considered highly infectious but less fatal than its predecessor, Severe Acute Respiratory Syndrome (SARS) (Kakodkar et al., 2020; Yu et al., 2020). It is reported that most patients have mild to moderate symptoms and can recover through supportive therapy alone (WHO, 2020c). Non-specific symptoms include fever, cough, sore throat, nasal congestion, muscle aches, chills, headache, nausea, vomiting, and diarrhea (Kakodkar et al., 2020). In one study involving 138 COVID-19 patients, the reported median hospital stay for discharged patients was ten (10) days (Wang et al., 2020).

However, elderlies and patients with pre-existing medical conditions appear to be more vulnerable to manifest severe presentations of COVID-19 (WHO, 2020c). It has been suggested that increased expression of angiotensin-converting-enzyme-2 (ACE2), the receptor for SARS-CoV-2 internalization in lung tissue, may explain the increased prevalence of COVID-19 in elderlies with co-morbidities (South et al., 2020; Hoffmann et al., 2020). ACE2 is a key enzymatic component that antagonizes the renin-angiotensin-aldosterone system (RAAS), which can control the systemic blood pressure (Kuba et al., 2013). Currently approved medications for hypertension and dyslipidemia such as ACE-inhibitors, mineralocorticoid blockers and even statins, benefit from the action of ACE2. In turn, these therapeutic strategies increase the expression of ACE2 (South et al., 2020). With the increased number of elderlies taking medications for their pre-existing conditions, it has been a clinical concern whether RAAS and statin therapy be discontinued in the context of COVID-19 management (South et al., 2020).

Severe presentations of COVID-19 usually include acute lung injury that leads to acute respiratory distress syndrome (ARDS) within 8-12 days of disease onset, before proceeding to septic shock (Kakodkar et al., 2020). These severe cases can eventually lead to patient mortalities. ARDS and septic shock are reported to be the major contributors to intensive care unit (ICU) admission and mortality in COVID-19 patients older than 60-years, with smoking history and co-morbidities (Kakodkar et al., 2020). Not surprisingly, common co-morbidities include hypertension, cardiovascular and cerebrovascular disease, and diabetes (Kakodkar et al., 2020). It is noteworthy that ARDS, septic shock, as well as all aforementioned common co-morbidities in severe COVID-19 presentation are well-established to be mediated by inflammation and immunologic processes (Baudouin, 2006; Bosmann & Ward, 2013; Zhong & Shi, 2019).

With the different disease presentations of COVID-19, tests that can predict the disease's clinical progression may prove to be of value in managing patients. As such, a robust COVID-19 prognosticator can significantly aid in better clinical management and care of SARS-Cov-2 positive patients. Potential treatment strategies, such as anti-inflammatory therapy for severe COVID-19 presentation (Soy et al., 2020), can be anticipated before the onset of severe symptoms.

Immunoglobulin-A Isotype

IgA is the most abundant antibody isotype found in mucosal surfaces (Breedveld & Van Egmond, 2019). They are the primary antibodies secreted in dimeric form into the external environment through mucus, saliva, tears, and breast milk. Protection against potential pathogens through neutralization, immune exclusion, and antigen excretion are well-established functions of IgA in the nasal, bronchial, gastric, and intestinal mucosa (Hansen et al., 2019).

IgA is also found in its monomeric form in the systemic circulation. However, serum IgA functions are considered to be relatively underexplored compared to that of mucosal IgA (Breedveld & Van Egmond, 2019; Yu et al., 2020). Nevertheless, it has been recently reported that monomeric IgA, when found as an immune complex (IC), actively contribute to the initiation of inflammation while unbound monomeric IgA induces an anti-inflammatory phenotype (Breedveld & Van Egmond, 2019; Hansen et al., 2019; Yu et al., 2020; Heineke & van Egmond, 2017). IgA-IC's trigger Fc-alpha-receptor I (FcαRI) that strongly promotes pro-inflammatory cytokine secretion of various myeloid cells, including dendritic cells, monocytes, and macrophages (Breedveld & Van Egmond, 2019; Hansen et al., 2019). As such, the increased formation of IgA-IC's can result to excessive inflammation, leading to severe tissue damage in multiple inflammatory or auto-immune conditions (Breedveld & Van Egmond, 2019).

Moreover, high serum levels of serum IgA have been reported in several metabolic disorders (Gonzalez-Quintela et al., 2008; Rodriguez-Segade et al., 1996). Increased circulating IgA levels have been reported as a generalized phenomenon in diabetic patients (Rodriguez-Segade et al., 1996). In the same study, the presence of diabetic complications was associated with a significant IgA increase. In addition to diabetes, obesity, and metabolic syndrome have also been associated with the increased levels of serum IgA (Gonzalez-Quintela et al., 2008). Among the components of the metabolic syndrome, abdominal obesity, and increased levels of serum triglycerides were associated the most with serum IgA (Gonzalez-Quintela et al., 2008). Interestingly, both diabetes and metabolic syndrome are associated with chronic inflammation (Zhong & Shi, 2019).

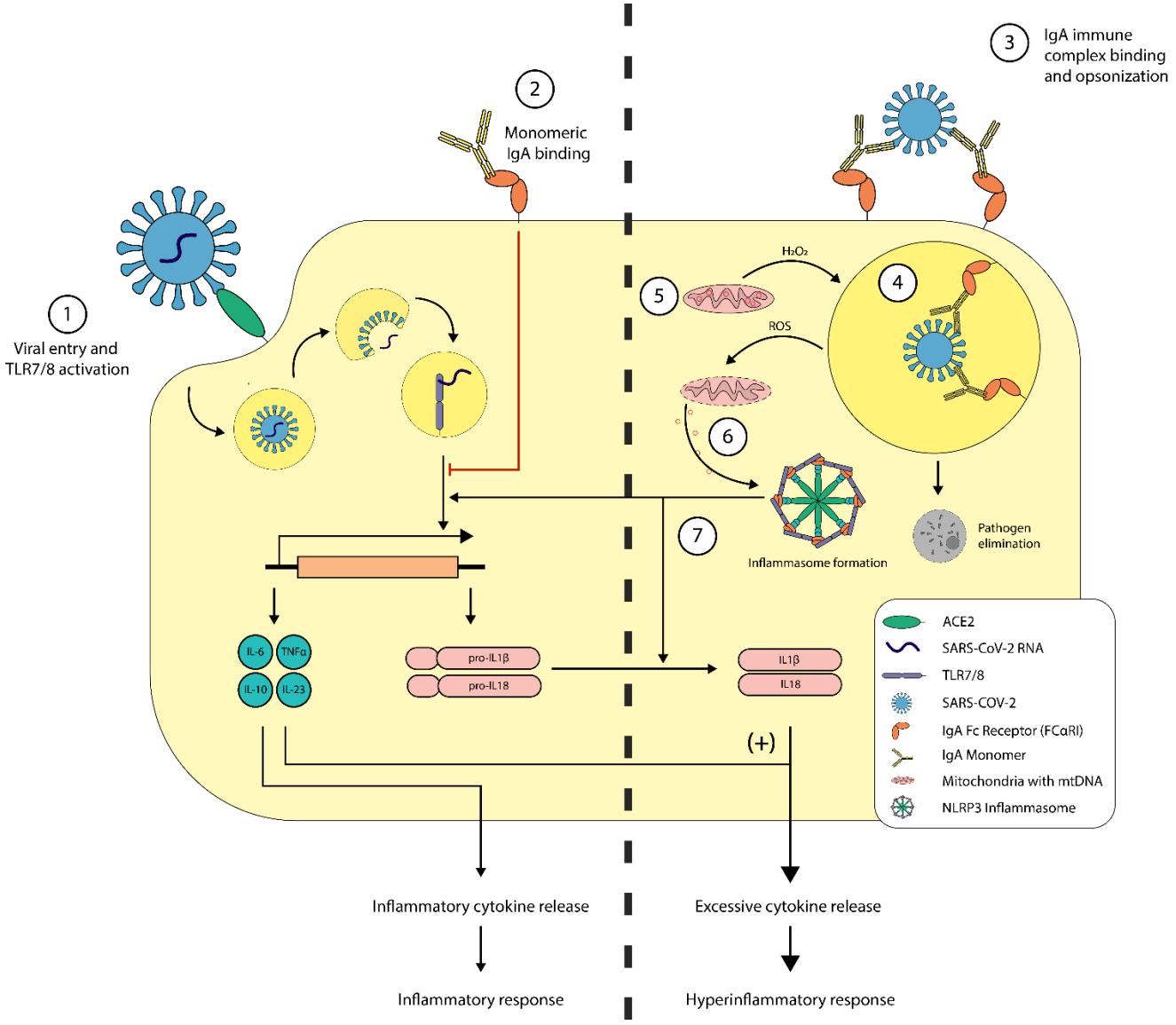

Figure 1: Proposed mechanism of IgA-mediated enhancement of inflammatory response in SARS-CoV-2 infection. (1) The entry of SARS-CoV-2 through the ACE2 receptor leads to the detection of the viral RNA by PRRs, specifically, TLR7/8. The activated TLR7/8 induces the expression of pro-inflammatory genes, along with the cytosolic accumulation of inactive IL-1β and IL-18. This cytokine milieu induces a robust and controlled inflammatory response. (2) However, when monomeric IgAs are bound by macrophage FcαRI through the IgA Fc, it is unable to cause cross-linking. This induces an anti-inflammatory signal through the inhibitory ITAM signaling, thereby potently counteracting the TLR7/8 activation necessary for the translation of inflammatory proteins. (3) On the other hand, IgA-ICs are capable of cross-linking ITAMs through Srckinases resulting in cell activation. (4) The SARS-CoV-2 pathogen is then opsonized and phagocytosed by the macrophage with the help of the antigen-bound IgA-FcαRI interaction. (5) The pathogen is destroyed through the respiratory burst, where H2O2 from mitochondria is used as a substrate for the formation of toxic oxygen metabolites to destroy the phagocytosed material. (6) ROS formed from the respiratory burst promotes mitochondrial permeability and release of mtDNA into the cytosol. The presence of mtDNA in the cytosol is a potent signal for the formation of the NLRP3 inflammasome complex. (7) The formation of the NLRP3 inflammasome leads to activation of the inactive precursors of IL-1β and IL-18, along with the enhanced expression of other pro-inflammatory cytokines that are upregulated in CoViD-19 patients. Expression of active IL-6, TNFα, IL-10, IL-23, IL-1β, and IL-18 induce further inflammatory cytokine release and recruitment of immune cells such as macrophages and neutrophils, thereby promoting a positive feedback loop and exacerbation of the inflammatory state.

IgA in COVID-19 patients

In contrast to IgM and IgG, SARS-CoV-2-specific IgA secretion is not widely investigated *per se* (Ma et al., 2020). Even so, increasing IgA levels have been observed in the clinical course of severe COVID-19 cases (Dahlke et al., 2020; Padoan et al., 2020). In a study of 87 COVID-19 patients, average IgA seroconversion was reported within 4-6 days of disease onset while demonstrating significantly increased IgA levels in severe cases when compared to that of mild and moderate cases (Ma et al., 2020).

Given the ability to promote immune hyper-activation through myeloid cell activity and pro-inflammatory cytokine release, we hypothesize that increased levels of IgA can induce severe COVID-19 disease presentation by promoting cytokine storm. This is consistent with the reported association of organ injuries to severe cases of COVID-19, such as acute pulmonary embolism and acute kidney injury to increased IgA production (Yu et al., 2020).

It has been suggested that macrophage activation syndrome leads to cytokine storm and ARDS in COVID-19 patients (Soy et al., 2020). With IgA's ability to directly interact with macrophages through FcαRI, IgA immune complexes can

activate NLRP3 inflammasomes in macrophages, as reported in IgA nephropathy (Tsai et al., 2017). In congruence, anti-inflammatory therapy and anti-rheumatic drugs that interfere with macrophage activation syndrome have been reported to have significant roles in managing severe cases of COVID-19 (Soy et al., 2020).

Proposed mechanism of IgA-mediated enhancement of inflammatory response to SARS-CoV-2 infection

Our hypothesis posits that the generation of anti-SARS-CoV-2 IgA antibody response that is skewed towards Fc binding to CD89 (FcαRI) in myeloid cells rather than inhibiting of viral entry to host epithelial cells results in IgA-IC-mediated immunopathology.

Although monomeric IgA, that is, IgA unbound to an immune complex, has anti-inflammatory effects, serum IgA-ICs are known to induce the formation of the NLRP3 inflammasome synergistically with the activation of PRRs (Hansen et al., 2017; Heineke & van Egmond, 2017). The propensity for an IgA-skewed antibody response in the sera of COVID patients may lead to the enhanced inflammatory response through the unregulated crosstalk between PRR-induced priming of inflammation and NLRP3 inflammasome formation (Hansen et al., 2017; Dahlke et al., 2020; Padoan et al., 2020).

The complete inflammatory response requires two phases: a priming phase driven by various pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), and C-type lectin receptors (CTLRs), and a second stimulus which generates the formation of the inflammasome (Hansen et al., 2017; Heineke & van Egmond, 2017). For the case of the RNA virus, SARS-CoV-2, we hypothesize that the most relevant PRRs for priming would be TLR7/8, which are capable of detecting viral RNA in endosomal membranes upon viral entry into the host cell (Moreno-Eutimio et al., 2020).

Initially, the viral entry into the host cell through the ACE2 protein leads to the formation of the viral endosome where SARS-CoV-2 RNAs may be detected by TLR7/8 (Moreno-Eutimio et al., 2020). This leads to the expression of various inflammatory-related genes such as IL-6, TGFα, IL-10, and IL-23 (Hansen et al., 2017; Moreno-Eutimio et al., 2020). This may result in a controlled inflammatory response, which allows for a protective environment for the infected and neighboring cells (Moreno-Eutimio et al., 2020).

The FcαRI is present in myeloid cells, including macrophages, and is capable of binding to the Fc domain of monomeric and dimeric IgA but not to secretory IgA (Maliszewski et al., 1990; Heineke & van Egmond, 2017). FcαRI binding of IgA IC's leads to opsonization (Heineke & van Egmond, 2017). Phagocytosis and clearance of the pathogen via the respiratory burst leads to reactive oxygen species (ROS) release, neutrophil recruitment, and lymphokine release by the macrophages (Heineke & van Egmond, 2017). The increase in ROS leads to mitochondrial permeability and subsequent leakage of mitochondrial DNA (mtDNA) into the cytosol (Tsai et al., 2017). Thus, mitochondrial integrity is important in controlling the activation of macrophages (Coll et al., 2018; Tsai et al., 2017).

The presence of mtDNA in the cytosol signals the formation of the NLRP3 inflammasome and enhanced expression of several pro-inflammatory cytokines such as IL-6, TGFα, IL-10, and IL-23, along with the excessive processing and secretion of IL-1β and IL-18 (Coll et al., 2018; Hansen et al., 2017; Tsai et al., 2017). The synergistic activities of the initial PRR-mediated priming and NLRP3-mediated production induce a potent pro-inflammatory signal, which causes the recruitment of more phagocytes such as neutrophils and macrophages to further exacerbate the inflammatory response (Martin et al., 1984; Tsai et al., 2017).

A summary of our hypothesis on how anti-SARS-CoV-2 antibody response may contribute to hyperinflammatory response is shown in Figure 1.

CONCLUSION

We hypothesize that serum anti-SARS-Cov-2 IgA level is a potential COVID-19 prognostic biomarker. Given the highly inflammatory nature of associated co-morbidities and disease presentation of severe COVID-19 cases, we believe that current trends in antibody tests against SARS-Cov-2 reflect an underappreciation of testing for IgA. Reported IgA seroconversion (4-6 days from onset of disease) precede the reported onset of ARDS in severe CoVID-19 cases (8-12 days from onset of disease). Therefore, we emphasize the need for investigating the dynamics of COVID-19-specific IgA response further to determine potential threshold values in predicting the clinical severity of COVID-19. Serum IgA may supplement, if not precede, traditional serum diagnostic markers of end-organ damage that are currently used for COVID-19. Investigating the feasibility of using IgA as a biomarker for severe COVID-19 progressors in future studies may reveal its value in improving current clinical management and treatment of SARS-CoV-2 positive patients.

ACKNOWLEDGMENT

JAI and GKD were supported by the University of the Philippines Office of the Vice President for Academic Affairs EIDR program (EIDR-C-04-003).

CONTRIBUTIONS OF INDIVIDUAL AUTHORS

GKD reviewed the literature on IgA and inflammation, prepared the illustration, and helped conceptualize and write the manuscript; ICVJI reviewed the literature on the clinical aspect of COVID-19 and helped conceptualize and write the manuscript; GKD and ICVJI contributed equally in preparing the manuscript; JAI ideated the hypothesis, conceptualized the potential role of IgA on inflammation and COVID-19 disease severity, conceptualized the potential mechanism of IgA-mediated inflammation in the context of SARS-CoV-2 infections, helped write and edited the final manuscript.

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