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Mini review article

SIGNIFICANCE OF SERUM AMYLOID A FOR THE COURSE AND OUTCOME OF SARS-COV-2 INFECTION

ZNAČAJ SERUMSKOG AMILOIDA A ZA TOK I ISHOD SARS-COV-2 INFEKCIJE

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Abstract

The occurrence of a new coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), quickly became a global threat after it had spread across the continents in just a few months. Over the next three years, it caused infections in over 646.6 million people and resulted in over 6.6 million deaths. As a novel disease, Coronavirus Disease 19 (COVID-19) became the subject of intensive research. Due to various clinical manifestations of the infection with possible fatal outcomes, it became evident that a finer understanding of COVID-19 pathogenesis, clinical manifestations, and complications is necessary. Investigation of acute-phase reaction as a component of the immune system response to infection can be very helpful. Serum amyloid A (SAA) was investigated for this purpose as one of the acute-phase reactants primarily synthesized by the hepatocytes in response to pro-inflammatory cytokines. It has been found that elevated SAA levels were independent factors for gastrointestinal manifestations and liver injury during COVID-19 but also one of the factors in COVID-19-associated coagulopathy. Studies showed that SAA levels positively correlate with disease severity and prognosis. Patients with severe infection demonstrated significantly higher levels of SAA. Higher SAA levels were observed in COVID-19 patients with chronic diseases such as diabetes mellitus, hypertension, cerebrovascular diseases, and obesity, all recognized as independent risk factors for critical disease and poor prognosis. Patients with COVID-19 who died had higher levels of SAA than survivors. This short review will summarize current studies and knowledge about SSA in COVID-19, its role in the pathogenesis of SARS-CoV-2 infection, and its clinical usefulness in COVID-19 patients.

Keywords:
serum amyloid A,
SARS-CoV-2,
COVID-19,
fatal outcomes

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Sažetak

Ozbiljni akutni respiratorni sindrom izazvan novim, koronavirusom 2 (engl. *Severe Acute Respiratory Syndrome Coronavirus 2* - SARS-CoV-2) veoma brzo je postao globalna pretnja nakon što se ovaj virus proširio na sve kontinente unutar samo nekoliko meseci. Tokom sledeće tri godine inificirano je preko 646,6 miliona ljudi, od čega je preko 6,6 miliona umrlo. Prethodno nepoznata bolest, COVID-19 (engl. *Coronavirus Disease 19*) postao je subjekat intenzivnog istraživanja. S obzirom na različite kliničke manifestacije COVID-19, uz mogućnost razvoja teških oblika bolesti sa smrtnim ishodom, postalo je jasno da je neophodno bolje razumevanje patogeneze, manifestacija i komplikacija ove bolesti. Istraživanje reakcije akutne faze, kao dela imunskog odgovora na prisustvo infekcije, pokazalo se kao veoma korisno. U ovu svrhu je ispitivan serumski amiloid A (SAA), kao jedan od reaktanata akutne faze koje primarno sintetišu hepatociti kao odgovor na prisustvo proinflamatornih citokina. Pronađeno je da su povišeni nivoi SAA nezavisni faktori ne samo za težinu pneumonije nego i za pojavu gastrointestinalnih manifestacija i oštećenje jetre tokom COVID-19, ali i jedan od faktora odgovornih za koagulopatiju povezanu sa COVID-19. Takođe je pokazano da su nivoi SAA u direktnoj proporciji sa težinom kliničke slike i lošijom prognozom, tj. da su značajno viši kod pacijenata sa teškim oblikom infekcije. Vrednosti SAA su bile značajno više kod obolelih od COVID-19 sa pridruženim hroničnim bolestima kao što su dijabetes melitus, hipertenzija, cerebrovaskularne bolesti i gojaznost, pri čemu su ovi komorbiditeti prethodno već prepoznati kao nezavisni faktori rizika za teški oblik bolesti i lošiju prognozu. Pacijenti umrli od COVID-19 su imali više prosečne vrednosti SAA u odnosu na one koji su preživeli. Na osnovu do sada objavljenih studija o vezi između SSA i lošijih ishoda COVID-19 bolesti, neophodna su dalja istraživanja koja će pomoći u boljem sagledavanju njegove uloge u patogenezi SARS-CoV-2 infekcije i mogućnosti njegove upotrebe za predikciju lošijih ishoda kod osoba sa COVID-19 bolešću.

Ključne reči:
serumski amiloid A,
SARS-CoV-2,
COVID-19,
smrtni ishodi

Introduction

In the city of Wuhan, located in China's province of Hubei, in December 2019, unusual instances of severe pneumonia of unidentified etiology were recognized (1). All patents from that cluster had some connection with the seafood market in the city. Eventually, as the causative agent of this new disease, a new coronavirus was recognized (2). The International Committee on Taxonomy of Viruses designated the virus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (3), and the World Health Organization (WHO) named the resulting disease COVID-19 (4). Due to its rapid transmission rate, the infection soon spread across all continents, and on March 11, 2020, the WHO declared a pandemic (5). Over 646.6 million cases of SARS-CoV-2 infection were diagnosed worldwide in the subsequent three years, resulting in over 6.6 million deaths (6). For the past two years, five epidemiological waves with different SARS-CoV-2 variants had distinct clinical presentations, transmissibility, and mortality (7). Owing to the relatively rapid mutability of SARS-CoV-2 with the constant appearance of new virus variants, COVID-19 remains a considerable threat to people even though numerous effective vaccines are available (8). Infection with SARS-CoV-2 can present in various forms, and its clinical presentation can range from asymptomatic infection in up to 30% of people (9) to fatal pneumonia with septic shock and multiorgan failure (10). Older individuals and people with chronic diseases have the highest risk for severe disease (11). As with any other infectious disease, to understand COVID-19 pathogenesis, its clinical course, and complications, the immune response to SARS-CoV-2 needs to be elucidated. One part of immune system activation that can be studied with relative ease is the acute-phase reaction (12). Acute-phase reactants (APRs), produced during the acute-phase reaction, have various biological roles and are useful biomarkers in everyday clinical practice (13). These molecules are ordinarily present in small concentrations in the serum of healthy people. During tissue injury, for example, due to trauma, infection, or autoimmune disease, these molecules are synthesized in higher or lower quantities, and there is a proportional rise (positive APRs) or fall (negative APRs) in their serum levels (14). Positive APRs are more commonly used to assess the degree of tissue injury. Until now, some of the positive APRs studied in SARS-CoV-2 infection have been C-reactive protein (CRP) (15), ferritin (16), interleukins 1 (IL-1) (17) and 6 (IL-6) (18) and procalcitonin (PCT) (19). One of the inflammatory markers that showed usefulness in COVID-19 is serum amyloid A (SAA), even though this parameter is not routinely determined in clinical laboratories. Assessment of APRs during the early stages of the infection can help determine which patients would need more frequent follow-up and if more aggressive drug interventions should be used (20). Serum amyloid A (SAA) is a group of chemically very similar proteins produced by the liver and naturally present in the serum of healthy individuals in low concentrations (20 - 50 mg/L). However, after the onset of inflammation, their levels can increase 1000 times in the first 1 to 2 days

(21). Since the SSA levels can rise rapidly after the onset of an inflammatory stimulus and fall more quickly with the reduction of inflammation and recovery, the determination of SAA levels during COVID-19 can have potential prognostic and therapeutic implications. This short review will present the current understanding of the SSA determination benefit in COVID-19 disease.

Serum amyloid A biology

The essential role in the innate immune system of SAA is supported by the fact that it is one of the most conserved proteins in the mammalian world. There are three different SAA types in humans based on protein sequence – SAA1 (**figure 1**), SAA2, and SAA4 (21), and two types of SAA based on physiologic behavior – constitutive SAA and acute-phase SAA (22). Constitutive SAA (SAA4) is expressed at a constant rate, mainly in the liver, and it is part of the high and very low-density lipoproteins (HDL and VLDL, respectively). The acute-phase reaction does not affect its synthesis. Acute-phase SAA, which includes SAA1 and SAA2, is normally expressed at very low levels in the liver and other tissues (22, 23). In acute-phase reactions due to infection, tissue trauma, non-infectious inflammation, or another type of tissue damage, there is a proportional increase in SAA1 and SAA2 synthesis (22, 24). This is stimulated by cytokines such as interleukins (e.g., 1α, 1β, and 6), tumor necrosis factor α (TNF-α), transforming growth factor β (TGF-β), and interferon γ (INF-γ) (21), and its concentration peaks 36 hours after onset of inflammation. As inflammation starts to subside, SAA levels will quickly drop because of the short half-life (25). If inflammation persists for a long time, there is a possibility of SAA precipitation in tissues and the development of amyloidosis of AA type (26).

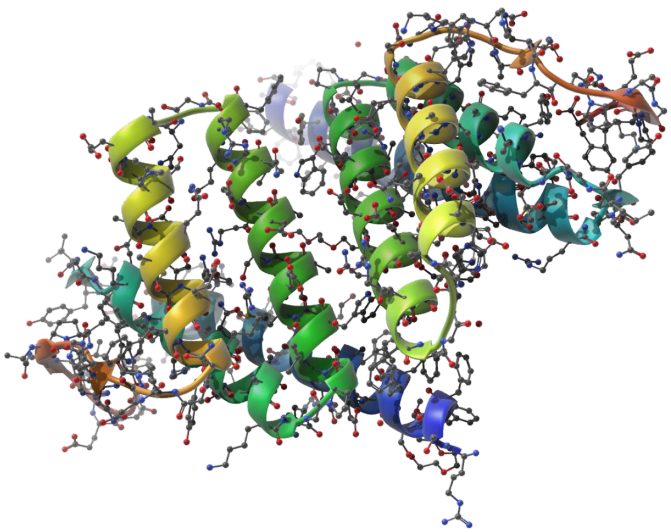

Figure 1. Tertiary protein structure of human serum amyloid A1 (SAA1) – protein amino acid sequence was downloaded from RCSB PDB database (https://www.rcsb.org/structure/4ip9) and visualized by SAMSON software.

Serum amyloid A and COVID-19 clinical manifestations

The natural course of SARS-CoV-2 infection is characterized by a few days of incubation period when there are no apparent signs and symptoms of disease, yet with ongoing viral replication (27). It is hard to predict which patients will have symptomatic and which asymptomatic infections. In this regard, it is demonstrated that there is an elevation of SAA levels in pre-symptomatic patients and that average levels of SAA in those patients were higher than in those who were asymptomatic (28).

Patients with COVID-19 can have various symptoms besides classical respiratory ones. Some of those symptoms were gastrointestinal disturbances such as nausea, vomiting, and diarrhea (29). The development of non-respiratory symptoms can be a marker of more extensive disease and inflammation (30), reinforced by the fact that patients who have gastrointestinal symptoms as a manifestation of COVID-19 had significantly higher levels of SAA than patients without them (31). Liver injury can be part of the COVID-19 clinical presentation, and measuring SAA levels could be helpful in these cases. In COVID-19 patients, elevated SAA levels were one of the significant independent factors related to liver injury (32), which can correlate with more extensive inflammation.

It is well-established that coagulation abnormalities and a pro-coagulative state can be an important part of SARS-CoV-2 infection (33). Even in patients with non-severe COVID-19, there is a risk of thrombotic complications such as deep vein thrombosis, pulmonary thromboembolism, or stroke (34). The pathogenesis of this procoagulant state is intricate and still not entirely understood. It has been found that SAA can bind fibrinogen and create the amyloid type of fibrin (35); the same study showed that SAA could mediate red blood cell agglutination. Based on those findings, elevated concentration of SAA during inflammation can activate coagulation in this unusual way and contribute to the prothrombotic state of COVID-19. Another contributing mechanism can be the ability of SAA to activate platelets and consequently lead to their aggregation and clot formation (35, 36).

Serum amyloid A and COVID-19 severity

Several studies have demonstrated a strong association between elevated levels of SAA and the more serious clinical manifestation of SARS-CoV-2 infection in adults (37–39) and children (40). The findings of these studies suggested that the severity of inflammation in individuals diagnosed with SARS-CoV-2 infection is linked to the levels of SAA. Potentially, when SAA is combined with other inflammatory markers, it could add to sensitivity for predicting more severe disease, but further research is needed. When combined with CRP, SAA can also correlate with viral load, which correlates with disease severity (41). A higher viral load indicates a lack of control over viral

replication and infection. It further implies that CRP and SAA can potentially be used as indirect and simple parameters for predicting viral load.

Serum amyloid A and prognosis of COVID-19

In addition to disease severity, it has been demonstrated that non-survivors of SARS-CoV-2 infection had considerably higher average SAA levels compared to survivors (42). One study revealed that SAA levels were significantly higher throughout COVID-19 in all patients who died compared to survivors, which is indicative of persistent inflammation and the absence of anticipated recovery (43). Utilizing SAA as a predictor for COVID-19 progression can aid in identifying patients at risk for unfavorable and severe presentation of the illness (44).

It has been shown that SAA levels are an excellent independent factor for predicting recovery from COVID-19. These levels ≤ 27.7 mg/L were associated with adequate recovery and reassurance that the patient could be safely discharged from the hospital (45). In the same study, a widely used positive APR in COVID-19 patients – the CRP – did not help predict adequate recovery.

Serum amyloid A and other clinical markers of disease severity

The imaging of the lungs is an essential diagnostic modality for assessing the seriousness of SARS-CoV-2 infection (46). Computerized tomography of the chest (chest CT scan) is one of the imaging methods for assessing lung involvement during COVID-19. The extent and seriousness of lung inflammation can be evaluated using a CT severity score of 25 points, where a higher score indicates a more severe disease (47). Patients with higher SAA values will have more extensive radiographic changes on chest CT scans (38). This finding can be used as an indirect test for the involvement of lung parenchyma in areas where a chest CT scan is unavailable or is not feasible.

Patients with chronic illnesses (e.g., hypertension, diabetes mellitus) are already at risk for severe COVID-19 (48). Studies have shown that SAA levels could correlate with disease severity in those patients. In the cohort of patients with type 2 diabetes (T2D) and COVID-19, SAA levels were significantly higher in those with severe illness than in non-severe illness. Moreover, a higher SAA level was a significant predictor for illness progression in those patients (49, 50). Patients with T2D exhibited considerably higher average SAA levels than those without T2D (34, 35). In patients with hypertension who get COVID-19, SAA levels were more elevated compared to non-hypertensive patients, which may explain why hypertension is a risk factor for severe disease (51). Patients with COVID-19 with cerebrovascular and cardiovascular diseases also had significantly higher levels of SAA than those without those chronic diseases (52). These findings suggest that more severe inflammation occurs in hypertensive COVID-19 patients. As SAA physiology is tightly connected to lipoproteins, higher baseline SAA levels have been observed in healthy obese patients than in healthy people with normal body mass index (BMI) (53). It is now known that obesity is a risk for severe COVID-19, and it has been shown that COVID-19 patients who are obese have higher SAA levels compared to COVID-19 patients with normal BMI (54). As with hypertensive patients, these findings suggest that a higher risk for severe disease in obese patients can be explained by the tendency to have higher levels of SAA and, consequently, more pronounced tissue inflammation and injury.

Serum amyloid A and amyloidosis in COVID-19

It is well known that SAA lies at the center of AA amyloidosis pathogenesis, so it could be expected that any elevation of serum SAA can accelerate the progression of amyloidosis in patients with this disease. Such an assumption was valid during the COVID-19 infection, where the rise in SAA levels worsened the existing AA amyloidosis (55). In patients without amyloidosis, there are some indications that SARS-CoV-2 envelope protein can speed up the formation of SAA amyloid. It is assumed that the mechanism involved results in an exaggerated production of SAA monomers which then can accumulate and create amyloid formations (56). This could lead to long-term detrimental effects of COVID-19 infection.

Following the resolution of acute illness, a subset of COVID-19 patients may encounter long-term symptoms, including fatigue, malaise, forgetfulness, palpitations, dyspnea during physical activity, low-grade fever, and other symptoms, collectively known as "long COVID" (57). Those patients still have low-grade inflammation and immune dysfunction (58). One research has demonstrated that patients experiencing prolonged COVID-19 symptoms for two months or more had substantially higher SAA levels after resolution of acute COVID-19 infection compared to healthy controls (59). Those findings can be significant since, as previously stated, if SAA is elevated for prolonged periods, it could lead to amyloidosis.

Conclusion

Measurement of serum amyloid A (SAA) levels during COVID-19 can provide valuable insights into the pathogenesis, clinical presentations, and complications of the disease. Additionally, it can be useful in predicting the progression of COVID-19, the course of infection, and the eventual prognosis. Based on current evidence, SAA should be included in daily practice to assess COVID-19 since it can help better management. There are numerous studies on SAA in hospitalized patients, but only a small number of those in outpatients, so there is a need for further investigation of the significance of SAA in this population. Additionally, more studies on the contribution

of SAA in different manifestations and complications of SARS-CoV-2 infection are warranted. Finally, available data suggest that clarifying the part that SAA plays in the pathogenesis of COVID-19 could potentially be used to invent new therapeutic modalities.

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