Original Article

Introducing Markers which are Involved in COVID-19 Disease Severe Condition Versus Mild State, a Network Analysis

Vahid Mansouri[1], Mostafa Rezaiee Tavirani[1*], Farshad Okhovatian[2], Hojjat Allah Abbaszadeh[3]

Abstract

Background: Coronavirus disease 2019 (COVID-19) had a pandemic spread worldwide. Most infected patients had a good prognosis, but some developed severe illnesses, which led to fatalities. It is urgent to define markers that reveal the severity of the disease. This study aimed to introduce the main plasma protein biomarkers involved in severe conditions versus mild infection states.

Materials and Methods: A total of 91 significant differentially expressed proteins (DEPs) in the sera of the patients with the severe condition versus mild states were extracted from an original article. The protein interaction is included in a network designed via STRING database and Cytoscape software to find the critical proteins which differentiate severe conditions versus mild states.

Results: A total of 6 hub nodes identified as critical target proteins were: APOB, SERPINA1, CP, ORM1, HASPA8, and VW, according to the Degree value of nodes.

Conclusion: The expression of different biomarkers in the sera of COVID-19 patients can be considered differential markers that separate severe conditions from mild states; however, a more thorough investigation is required.

Keywords: COVID-19, Protein, Plasma, Biomarker, Network analysis

1. Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Physiotherapy Research Center, School of Rehabilitation, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Laser Application in Medical Sciences Research Center, Shohada-e-Tajrish Hospital, Department of Biology and Anatomical Sciences, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author: Mostafa Rezaiee Tavirani, Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Email: Tavirany@yahoo.com

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Introduction

Coronavirus disease 2019 (COVID-19) has infected millions worldwide (1, 2). Age-related COVID-19 infections fatalities have been increased among populations (3). It is necessary to introduce markers that define disease severity (4). Due to the diversity of genomic and proteomic profiles in research, different symptoms have been reported (5-7). Another factor is the virus's genetic diversity (8-11). Each virus variant triggers its exceptional host response; however, the host immune response to SARS-COV 2 is not entirely known so far (12, 13). However, the mortality rate in the patients could be predicted using blood-borne markers with more than 90% accuracy (4). Proteomics mass spectrophotometry-based (MS) analysis is a powerful technology that could extract remarkable amounts of clinical information from the blood sera of patients in an untargeted manner. At the onset of SARS-Cov 2 infections, specific antibodies, IgM and IgG, were detected at different time points after the onset of COVID-19 disease. However, a persistent level of IgG was detected for a longer period than IgM,

and the pattern of detectability of IgG and IgM is a basis to distinguish between acute, recent, and past infections (14).

As described, different biomarkers reported by other researchers, there are some contradictions between the results, and there is no precise biomarker to detect different phases of COVID-19 disease. This study is based on differentially expressed proteins (DEPs) extracted from the original article to evaluate central proteins that differentiate between severe and mild conditions of COVID-19 infection published by Park et al. described in methods (13).

Methods

The original data of extraction methods and sampling about sera biomarkers related to a cohort study of severe and mild stages of COVID-19 patients are described in the article published by Park et al. (13). As described in the original paper, plasma data of 8 confirmed COVID-19 positive patients, including 3 milds and 5 severe cases collected. Significantly expressed high-resolution LC-MS distinguished proteins. Increased in-depth proteome provided based on BoxCar acquisition. A total of 1639 proteins were identified in the original data, and an average of 1222 were subjected to statistical analysis. Biological and signaling pathways associated with DEPs were investigated to recapitulate the functional characteristic of differentially expressed plasma proteins. Methods related to protein identification and bioinformatics analysis are explained here. Ninety-one differentially expressed proteins extracted from data of the original article considering fold change>1.5 and p-value <0.05 (13). A network included the queried proteins via "protein query" of STRING database designed by Cytoscape software 3.7.2. Score cutoff=0.4 was confidently applied to construct the interactive network. Among the 91 queried proteins, 61 proteins were recognized by STRING. The network was built by 61 proteins using Cytoscape software. The main connected component of the constructed network was analyzed using the "Network analyzer" application of Cytoscape to determine the central nodes.

Results

A total of 61 differentially expressed proteins among the 63 queried proteins were recognized and interacted to construct a network using Cytoscape software 3.7.2 via protein query of STRING database. The data was related to the proteins in sera of severe and mild COVID-19 patients, extracted from a high throughput study. Analysis of constructed scale-free network with 61 queried proteins led to the introduction of the hub nodes (Table 1). The 6 hub nods are identified based on the highest value of the degree. The two unrecognized proteins were BST1 and LSAMP.

The topological properties, including Degree, "Betweenness Centrality" (BC), and Closeness Centrality (CC) of hub nodes, are tabulated in table 1. APOB, SERPINA1, CP, ORM1, HSPA8, and VWF are the 6 hub nodes identified as critical dysregulated proteins that can separate the severe condition of infection from the mild state of disease. Interaction between the 6 introduced hubs is shown in figure 1, This figure shows that APOB is linked directly to SERPINA1, HSPA8, CP, and VWF.

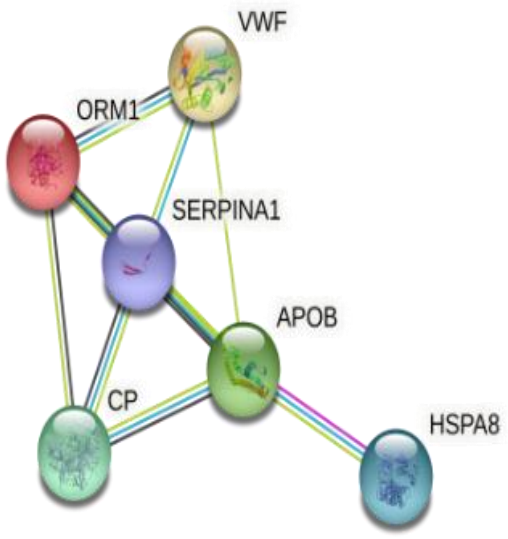

Figure 1. Sub-network including 6 hub nodes.

Table 1: The list of 6 hub proteins related to the network of COVId-19 severe condition versus mild state

Name	Degree	Betweenness Centrality	Closeness Centrality
APOB	18	0.180982599	0.491803279
SERPINA1	15	0.100977926	0.476190476
CP	15	0.125885255	0.45112782
ORM1	14	0.102720842	0.45112782
HSPA8	14	0.20168242	0.413793103
VWF	13	0.187909488	0.472440945

Discussion

Numerous studies have been conducted to find effective drugs in the treatment of COVID-19. The most indirect damage caused by this disease has been reported as a patient's lung infection. Identifying and targeting the host factors that cause secondary infections and inflammatory responses are the research priorities for treating COVID-19 disease (15). Some preliminary investigation seems to be promising as IL6, a marker of severe COVID-19 pro-inflammatory signaling condition (16), or inhibition of IL6 receptor by tocilizumab with clinical improvement (17).

Few proteomics MS-based studies applied to the COVID-19 patients, although no remarkable protein was still introduced as a promising one (18, 19). The use of high throughput clinical proteomics methods and network analysis to the function of genes and proteins related to different aspects of COVID-19 is the interest of researchers to interpret obtained data (20-22). After spreading COVID-19, analyzed the serum proteome of the Chinese cohort to classify COVID-19 patients (18). Messner et al. introduced proteins to distinguish between COVID-19 and healthy persons with a high throughput proteomic method. They reported that IL-6 is a center response to inflammatory functions of COVID-19 disease (19). Park et al. reported the in-depth plasma proteome of the COVID-19 cohort study using sera of severe and no severe cases to compare (13). They identified six differentially expressed proteins (DEPs), ITIH4, SERPINA3, ORM1, VWF, SERPING1, and LBP; these were familiar with the proteins introduced by Shen et al. and may be reliable blood proteins for COVID-19 (13). Severe COVID-19, accompanied by the role of neutrophils, is at the center of researchers' attention. Hem mat et al., in a microarray study, revealed that in COVID-19 patients' blood neutrophil markers were up-regulated and overexpressed, suggesting neutrophilia in COVID-19 patients (23). Park et al. reported essential neutrophil-related functions and blood coagulation in COVID-19 disease. They introduced up-regulated neutrophil markers involved in immune responses as PIGR, ALDOC, HSPA8, SERPINAB10, VAPA, IQGAP2, SERPINA1, and SERPINA3 (13). Messner et al. reported CRP, SERPINA10, SSA1 up-regulated proteins, and down-regulated ALB in severe COVID-19 conditions, which did not match the results of Park et al. in severe cases of COVID-19 infections (13, 24). In other studies, coagulation factors up-regulation is demonstrated as fibrinogen and SERPINA10 in severe COVID-19 disease (25). Previous studies reported elevated fibrinogen levels in COVID-19 coagulopathy, and platelet count was variable according to different studies (26, 27). Potentially, releasing intracellular angiotensin II in SARS-COV-2 infected cells leads to platelet degranulation (28). Reasonably some researchers suggested anticoagulation drugs and adjunctive therapy to reduce mortality (29). D, Alessandro et al. revealed that LIF as a pro-inflammatory cytokine is associated with the severity

of COVID-19. They identified significant dysregulation of serum coagulation factors and increased antifibrinolytic factors such as the SERPINAs family (30). Liu et al. reported in a proteomic study of COVID-19 patients' sera that complement system proteins accompanied infectious disease proteins, activated with up-regulated ICAM1/2, IgG, DBH, SHGB, TF, THBS1, and C1Rl as immune system function (31). According to signaling pathway enrichments, some research revealed platelet function and coagulation in COVID-19 disease as reported previously (26, 32). On the other hand, Shi et al. reported that inhibition of IL2 signaling might decrease CD8+ T cells in severe COVID-19 patients as lysosome-mediated signaling (33).

A common infection caused by COVID-19 disease is an acute respiratory infection that has resulted in the death of many patients. This study showed an increase in APOB and SERPINA1, CP, ORM1, and HSPA8 proteins in the serum of patients with a severe condition of COVID-19 disease. Lower cholesterol, HDL, and LDL are associated with acute cases of COVID-19 and mortality from the disease (34). Research has shown that the anti-infective effect of HDL is reduced in conditions such as influenza and HIV (35, 36). Apo-lipoproteins associated with HDL interact with lipids of cell membranes enriched in immune cell receptors such as macrophages and T cells receptors (37, 38). However, some research revolved around the inverse relationship between HDL and the risk of hospitalization from infectious disease (39). Our investigation revealed upregulation of Apolipoprotein B(APOB), which could be related to HDL effects in severe infections caused by COVID-19; other researchers reported APO family changes in sera of COVID-19 patients (40). SERPINA1 was another upregulated serum protein, according to our results, referred to alpha1 antitrypsin protein production.

Serine protease inhibitor family or SERPINs are essential proteins that play crucial roles in the homeostasis of blood coagulation (41). Dutta et al. suggested the relationship between serum level of SERPINA1, including alpha 1 antitrypsin status, and the smoking habit of COVID-19 patients (42). Serine protease is essential for SARS-COV2 host cell entry after binding to its cell membrane receptor ACE2 (43). The Major blood serine protease inhibitor is alpha-1 antitrypsin which is encoded by the *SARPINA1* gene and is produced in the liver (44). Genetic deficiency rate of alpha-1 antitrypsin in different populations correlated with COVID-19 infections (45). Alpha-1 antitrypsin is considered a host protective factor against covid19 associated with our results (46). Ceruloplasmin (CP) is another protein expressed significantly based on our investigations in selected data. Ceruloplasmin is a protein playing a role in maintaining copper and iron homeostasis in the body. Copper transportation, angiogenesis, blood coagulation, and oxidative stress are other functions of CP. Many viral infections are accompanied by downregulation of CP, such as HIV (47). Copper increased in pregnant women with Covid -19 disease (48). However, regardless of the agents such as viruses, fungi, and bacteria, there is a progressive increase in serum copper as a standard feature of infection (49-51). Increased Ceruloplasmin in our results may be according to copper and zinc insufficiency in COVID -19 patients based on other research (52). ORM1 protein increasing in serum of severe COVID-19 patients was another point of view. ORM1 is an increasing serum protein in the acute phase of COVID -19 responding to inflammation and infection (53). ORM1 may regulate immune system activity (54). ORM1 is an inflammatory factor controlled by multi cytokines such as IL-1B, TNF-α, and IL6 (55). HSPA8 is another serum upregulated protein in severe COVID-19 patients, according to our results. HSPA8 was first recognized to interact with the spike protein of infectious bronchitis virus, the first identified coronavirus (56). HSPA8 or HSC70 is a member of the molecular chaperon family, implicated in various intracellular and extracellular processes, and is essential for cellular homeostasis. On the other hand, this protein is used in viral infections to decisively bind some viruses to cell membranes. Is coronavirus cell entry depends on HSC70 participation is still unknown and needs more investigations; however, as a chaperon for stabilizing protein homeostasis in the cell, HSC70 may participate in the different life cycles of coronavirus (57).

Increased expression of different proteins in the serum of acute COVID-19 patients indicates the

activation of various defense mechanisms. For example, changes in the amount of HDL and cell membrane lipids and the reaction of immune cells to the APOB protein family are contemplative. On the other hand, we can mention the function of SERPINA1, which prevents the binding of a serine protease in the blood to the ACE2 receptors of the virus. The amount of serum copper ion, which is dependent on zinc ions and participates in the mechanisms of blood coagulation and homeostasis, is notable, also sarcoplasmic activity, as the regulator of copper in the serum of severe COVID-19 patients is prominent. Increased activity of OMR1 also intensifies the action of the immune system and the activity of cytokines in infections caused by acute COVID-19 disease. In addition to increasing the level of HSPA8 as a chaperon and its contribution to the transmission of the virus into the cell, HSAP8 is also one of the cases that need further research and proof.

Conclusion

Various research has been conducted on COVID-19 disease and its complications to find a suitable treatment. However, the expression of different biomarkers in this research compared to others has led to commonalities and differences that may have several reasons, such as different stages of the disease and genetic patients' variety. What is certain is that COVID-19 causes acute respiratory infections that lead to the activity of various cytokines in the body. More research is required to find a definitive and appropriate treatment for this disease. It can be suggested that the blood level of the introduced 6 critical proteins be investigated in the severe condition versus mild state to find a suitable biomarker panel that differentiates mild and severe infected patients.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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