The pleiotropic approach to coronavirus disease-19 pathogenesis: The impact of liver diseases associated host genetic variants

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Abstract

Coronavirus disease-2019 (COVID-19) is a novel multisystemic viral disease caused pandemic. The disease impact involves liver and associated systems. Undoubtedly, host genetic background influences the predisposition and prediction of infection. Variants among human populations might increase susceptibility or protect against severe outcomes. In this manner, rs738409 variant of patatin-like phospholipase domain-containing protein 3 gene appears to be protective in some populations in spite of its aggravating effect on non-alcoholic fatty liver diseases (NAFLDs) and steatohepatitis. DRB1*15:01 allele of human leukocyte antigen is associated with protective effect in European and Japanese populations. DRB1*03:01 contrarily increases the susceptibility of severe COVID-19 infection in European populations. rs1260326 in glucokinase regulatory protein gene, rs112875651 in tribbles homolog 1 gene, rs429358 in apolipoprotein 1, and rs58542926 in transmembrane 6 superfamily 2 alleles are found related with NAFLD and obesity; thus, hypercoagulability and severe COVID-19 outcomes. In chronic or acute liver diseases, comorbid syndromes are the key factors to explain increased severity. There might not be a direct association between the variant and severe COVID-19 infection. As it is concluded, there are genes and variants known and unknown yet to be studied to reveal the association with disease severity.

Keywords: Autoimmune; COVID-19; genetic polymorphism; hepatitis; liver; NAFLD; pathogenesis.

Introduction

The causative agent of coronavirus disease-2019 (COVID-19) pandemic is a novel virus named SARS-CoV-2.[1] Primarily affected system is respiratory system along with cardiovascular, nervous, and gastrointestinal systems involving liver, kidney, and vasculature.[2] Virus enters host cells through several modalities. Angiotensin-converting enzyme 2 and transmembrane serine protease 2 cell surface proteins play a major role on viral entry.[3] As virus enters cell, innate and adaptive immune systems get activated.[2] As well as virus itself, host immune response also has a large impact on disease prediction and pathogenesis. Immune response mainly covers all chemical and physical interactions having place in our body to fight against foreign bodies in specific and non-specific manner. This process is mediated by immune cells, hormones, cytokines, and other proteins secreted from several organs and tissues.

Liver as an Immune Mediator Organ

The liver is considered the main organ that is associated with metabolic, nutrient storage, and detoxification activities. There are also specific cell groups in liver tissue that mediates immune function.[4] Due to the fact that the liver confronts numerous different antigens while properly functioning, it should have a regulatory mechanism to differentiate and alert the immune system in case of an abnormal situation such as malignancy, infection, and tissue damage. The liver also produces immune mediators such as acute phase reactants, chemokines, cytokines, complement proteins, and several immune cells. Myeloid immune cell populations form the resident cells in hepatic tissue. Antigen-presenting cells, macrophages, natural killer cells, and T and B lymphocytes are found in the liver.[4,5] A study showed that human hepatic CD141+ dendritic cells produce cytokines and induce T-cell immunity.[5] In addition, in the liver parenchyma, non-immunologic cell populations have immunologic receptors.[6]

Despite the fact that virus might or might not injure hepatic tissues, the liver itself has immunity-controller duty. This control may be affected by hepatic or non-hepatic diseases. Remarkably, when conditions such as alcoholic or non-alcoholic fatty liver diseases (NAFLD), cirrhosis, hepatitis, and others are comorbidities to an infectious disease as COVID-19, it might change the prognosis of the main infectious disease. Having chronic liver diseases (CLDs), in particular, cirrhosis, worsen the situation of patients in terms of hospitalization and increase the mortality rates in COVID-19 infection.[7]

Immunity, inflammation processes, disease pathogenesis, viral entry through receptors, metabolism, and other pathways that are covered by our physiologic responses are maintained by inherited and acquired explicit genetic sequence. This genetic code is under risk of mutation. When these mutations are seen extensively among populations, we call them variants. Polymorphic variants might have differential prognostic contributions to the disease status. In this study, we aimed to summarize the effects of these variants related to liver and liver diseases on COVID-19 disease pathogenesis. Some of the specific diseases are more researched, and thus, we gathered and presented data disease by disease.

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Autoimmune Hepatitis (AIH)

AIH is a disease which requires long-term immunosuppressive therapy and it occurs in patients occasionally after bacterial or viral infections.[8] AIH patients have hepatic injury and increased risk for cirrhosis and portal hypertension,[8] and this might be a risk factor for poor prognosis of COVID-19. Dilemma in particular situation is using immunosuppressive drugs such as thiopurines and corticosteroids. One might think that getting an immunosuppressive therapy may increase risk of poor prognosis of COVID-19 infection. However, it also may reduce the risk of cytokine storm and improperly processing immune system. One multi-institutional cohort study indicated no statistically significant association between the use of systemic immunosuppressive therapy and increased risk of COVID-19 infection.[9] Another study about cancer patients receiving immunosuppressive treatment did not find any association with poor COVID-19 prognosis.[10] Other studies found that patients who use immunosuppressive drugs have also increased risk of mortality and longer hospitalization period.[11,12] There is one issue to mention, none of these studies include AIH disease; they mainly included rheumatoid diseases, dermatologic cases, and cancer patients. We might say that there is no consensus whether immunosuppression causes severe COVID-19 disease vice versa. According to a study,[13] AIH patients getting immunosuppressive treatment have higher risk of severe COVID-19 disease. However, this study has a small population and not very strong statistical analyses.

Genetic disposition of human leukocyte antigen (HLA) gene variants increases the risk of having AIH according to a genome-wide association study; HLA variants specifically HLA-DRB1*0301 and HLA- DRB1*0401 genotypes are found to be strongly associated with AIH.[14] DRB1*03:01 and DRB1*04:01 variants in European populations; DRB1*04:04, DRB1*04:05, and DRB1*13:0 in Latin American populations; DRB1*04:01 and DRB1*04:05 in Japanese populations (also DRB1*08:02 and DRB1*08:03 with DRB1*04:05); DRB1*04:05 in Korean populations; DRB1*01, DRB1*03, DRB1*04, DRB1*08, DRB1*13, and DRB1*14 in Iranian and Indian populations; and DRB1*13 and DRB1*14 in Pakistani populations are linked to increased susceptibility to AIH, whereas DRB1*15:01 variant in European and Japanese populations and DRB1*13:02 variant in Latin American and Japan populations have been found to be protective against AIH.[15] When compared between healthy and AIH patients, AIH patients are found to have higher hospitalization rates but not so different risk of ICU admission and mortality.[13] Cirrhosis is the most powerful predictor of severity and mortality of COVID-19 in AIH patients.[7] According to a review, patients that have AIH also were low in levels of antibodies after vaccination when compared to healthy group, and the difference was statistically significant.[7] Thus, severe AIH patients should be given immunosuppressive treatment routinely but AIH patients with mild injury might stop using until recovery from COVID-19.[7] From all the data presented here, it is concluded that the gene variants that increase risk of having AIH might also increase the severity of COVID-19 disease along with decrease of protective measures such as immunization. We must abstain saying that gene variants solely increase the risk of severe COVID-19 infection, disregarding AIH and infection relationship.

NAFLD

The definition of NAFLD is the steatosis of liver when other diseases are ruled out.[16] Organelle stress, cytokines, and innate immunity are the main factors that have a role in NAFLD pathogenesis.[17]

NAFLD itself does not give rise to severe COVID-19 complications and increased mortality.[18] Since NAFLD is extensively associated with obesity, indirectly obesity might have a role on COVID-19 sever-

ity. When related independent variants are investigated, rs1260326 in glucokinase regulatory protein gene, rs112875651 in tribbles homolog 1 gene, rs429358 in apolipoprotein 1, rs58542926 in transmembrane 6 superfamily 2, and rs738409 in patatin-like phospholipase domain-containing protein 3 (PNPLA3), all these variants were found associated with NAFLD.[18] Carriers of these variants are significantly associated with NAFLD and positively correlated with obesity.[18] Only possible way to explain severe COVID-19 outcomes of NAFLD patients that are carriers of these mutations might be comorbidities; mostly obesity. The overall effect of comorbid syndromes and COVID-19 infection state has the responsibility of increased mortality and severe COVID-19 cases.

Independent Gene Variants Related to Liver and COVID-19

Leucine zipper transcription factor-like 1 rs10490770 variant has been found to be associated with increased risk of severe respiratory failure, vein thromboembolism, and hepatic injury.[19]

It is found that GG genotype of PNPLA3 (rs738409) gene is associated with severe consequences.[20] PNPLA3 gene is one of the genes that are associated with NAFLD and lipidosis in the liver.[21] Furthermore, PNPLA3 (G-G allele) and non-compliance to lifestyle changes (Mediterranean diet and physical activity) were associated with weight gain.[22] Valenti et al.[23] found a protective effect of PNPLA3 rs738409 variant in terms of NAFLD genetic risk against COVID-19.

Innes et al.[24] moot that rs738409 G may also affect COVID-19 severity.They have 2 reasons to think so: First, this polymorphism has an association with retinoid storage levels in liver mesenchymal cells and these retinoid levels may be involved in generating immune response after viral infections. Second, this polymorphism also increases the amount of omega-3 polyunsaturated fatty acids such as alpha-linolenic acid, which can modulate levels of inflammatory processes.[24] Therefore, rs738409 G allele in PNPLA3 is thought to be associated with COVID-19 infection and its inflammatory response. However, Innes et al.[24] pointed on the fact that their study did not end with a result of a positive correlation of PNPLA3 rs738409 variant with severe COVID-19 outcome; instead, a reduced risk was concluded.

In the same manner, it is found that the same variant (PNPLA3 rs738409 variant) is associated with a reduced risk for severe COVID-19 disease and also lower C-reactive protein and albumin levels but higher alanine transaminase levels.[25] According to studies that have been conducted, there is a tendency of a specific variant (rs738409) of PNPLA3 gene to be associated with better outcomes. Despite the possibility that markers which show hepatic injury is higher in certain populations, the overall effect of having this mutation might be protective against severe COVID-19 disease. However, it appears more extensive research should be conducted to understand properly what is the mechanism and why this variant might reduce the risk of severe disease.

Severe Vitamin D deficiency is found associated with no response to treatment, disease progression to cirrhosis, and death from hepatic reasons.[26] Furthermore, severe Vitamin D deficiency is used in the prognosis of AIH.[26] Despite the fact that skin color, sun exposure, geographic features, and air pollution have an effect on Vitamin D formation by sunlight, the main mediator for the actions of Vitamin D is intranuclear receptor (VDR) which is mostly found in respiratory epithelial cells, lymphocytes, macrophages, and monocytes.[27] Vitamin D deficiency is considered one of the factors that increase predisposition, severity of COVID-19 infection, and risk of acute respiratory distress syndrome.[27,28] VDR polymorphisms found significantly related with these symptoms, respectively: ApaI (rs7975232) with dyspnea

and asthma in critical patients; BsmI (rs1544410) with chronic renal disease in mild to moderate patients; Tru9I (rs757343) with vomiting, dyspnea, and high blood pressure; FokI (rs2228570) with pyrexia and high blood pressure in critical patients; CDX2 (rs11568820) with dyspnea, high blood pressure, and diabetes in critical patients; and EcoRV (rs4516035) with diabetes.[29] Vitamin D binding protein (DBP) is known as the most polymorphic protein.[30] DBP has an effect on biological functions. Polymorphism (G allele at the rs7041 locus) of this protein gene is associated with increased susceptibility to Hepatitis C and metabolic syndrome.[31] It was found that there is a positive significant correlation between the prevalence and mortality rates and GT genotype while there was a negative significant correlation between prevalence and mortality rates and TT genotype at rs7041 locus among all populations (China, Japan, Nigeria, Kenya, Mexico, Italy, Turkiye, Finland, Germany, and Czechia) in a study.[31] As it is concluded from the studies and papers, COVID-19 and hepatic diseases are influenced by Vitamin D-related gene variants. Patients with CLDs and Vitamin D deficiency are under risk of more severe COVID-19 infection, possibly because of immunologic effects such as depressing inflammatory cytokine secretion and inducing anti-inflammatory cytokine secretion.

Liver as a Coagulation Regulator

COVID-19 pandemic caused millions of deaths. Increased mortality and morbidity are associated with thrombotic event such as deep vein thrombosis and pulmonary embolism.[32] Three components are main factors for thromboembolic event: Stasis, endothelial injury, and hypercoagulability (Virchow's triad).[33] In obesity and insulin-resistant state, increased risk of thromboembolism is related to pro-thrombotic parameters, pro-inflammatory pathways, and endothelial dysfunction.[34] Visceral lipidosis is important for cardiometabolic risk.[32] The liver is one of the organs that can be steatotic. In NAFLD patients, steatohepatitis results in higher risk for thromboembolic event.[35]

In a study,[32] BMI levels have been found to be positively associated with D-Dimer, fibrinogen, FVII, FVIII, FXI, and protein S but negatively with antithrombin levels. Liver fat content was found to be positively associated with fibrinogen, FVII, FVIII, protein C, and protein but negatively with antithrombin.[32] By this interpretation, it is possible to say that NAFLD is a hypercoagulability-associated disease. High protein S and C levels may indicate an acquired counteracting mechanism against thromboembolic event.[32]

Conclusions

In this paper, we have been discussing the effects of gene variants that are associated with liver diseases on COVID-19 infection and vice versa. Genetic mutations might predict disease progression and impose their effect through several mechanisms. COVID-19 disease has a multilayered pathogenesis, especially in case of a comorbid syndrome. Comorbidities occasionally are the cause of mortality. These include obesity, type 2 diabetes mellitus, CLDs, hypertension, hypercoagulability status, and other several diseases that shorten life expectancy and increase the risk of having severe disease. We have come to the following conclusion; the more studied and the more samples taken from a carrier of a specific genetic variant, the greater will be the evidence to support an association. Hereby, PNPLA3 (rs738409) gene variant is mostly associated with severe COVID-19 disease and related with NAFLD. In spite of the results that are indicative of a protective effect, evidence of this variant increases the level of biologic markers that show hepatic injury, thus increasing the severity of infection.

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