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EXPRESSION PROFILE OF SARS-COV-2 ENTRY RECEPTOR ACE2 IN THE HEPATOCELLULAR CARCINOMA AND ITS IMPACT ON COVID-19 PATIENTS

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ABSTRACT

The SARS-CoV-2 infection leads to liver injury and promotes other viral infections such as hepatitis B virus (HBV) in COVID-19 patients. Obesity is involved with an increased risk of mortality in hepatocellular carcinoma (HCC) patients. In the current study, we analyzed the SARS-CoV-2 entry receptor ACE2 expression patterns in various HCC patients using different public databases on cancer. We found that the ACE2 and TMPRSS2 mRNA expressions are significantly downregulated in HCC tissues compared with the healthy population. Interestingly, high ACE2 expression is positively associated with HCC patient's obesity and age of 61 to 80 years old. A significantly lower survivability rate is revealed in extremely obese and obese HCC patients with high expression of ACE2. In addition, the expression of important innate immune-related genes such as IKBKB, MAVS, IRF3, and RELA are found to be significantly increased in HCC patients. Therefore, it might be suggested that obesity and age of the HCC patient along with the involvement of innate immune genes, might be the important triggers for COVID-19 pathogenesis.

Keywords: SARS CoV-2/COVID-19, ACE2, HCC, Obesity

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a current pandemic threat and public health emergency of international concern caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (**Lai, Shih, Ko, Tang, & Hsueh, 2020**). Comorbid conditions such as chronic lungs, kidney, and liver diseases, including hepatocellular carcinoma (HCC), may lead to the case fatality of COVID-19 patients (**Choudhary, Dhampalwar, Saraf, & Soin, 2021; Zaim, Chong, Sankaranarayanan, & Harky, 2020**). SARS-CoV-2 uses the receptor-binding domain (RBD) of its spike protein for cellular entry through binding with the host cell receptor angiotensin-converting enzyme 2 (ACE2) (**Shang *et al.*, 2020**). In addition, the SARS-CoV-2 enters into the cells by priming its spike protein using cellular transmembrane protease, serine 2 (TMPRSS2), followed by RNA genome replication in the cytoplasm, and progeny viruses have been released to infect the new cells (**Hoffmann *et al.*, 2020**). However, the ACE2 protein expresses in numerous human organs and tissues such as lungs, lymph nodes, thymus, stomach, small intestine, colon, skin, bone marrow, spleen, liver, kidney, and brain (**Ji *et al.*, 2020**). Therefore, SARS-CoV-2 is not limited to only lungs but also targets other systems of the body, which confirmed it as a kind of systemic virus (**Ji *et al.*, 2020**). Hepatocytes might be significantly infected by the SARS-CoV-2 reported by an in vitro study (**Chu *et al.*, 2020**). The SARS-CoV-2 has also been found in the hepatocytes of the COVID-19 patients (**Wang *et al.*, 2020**). A liver injury might be occurred by SARS-CoV-2 infection, and HBV may be reactivated in COVID-19 patients (**Wang *et al.*, 2020; H. Xu *et al.*, 2020**). Researchers suggested taking special care of COVID-19 patients with hepatocellular carcinoma (HCC) (**Aldhaleei, Alnuaimi, & Bhagavathula, 2020; Kudo *et al.*, 2020**). On the other hand, obesity might be a risk factor for HCC, and there is a correlation of HCC with obesity in the progression of non-alcoholic fatty liver disease to cirrhosis (**Caldwell, Crespo, Kang, & Al-Osaimi, 2004**). However, so far, there are no clinical reports on the correlations of ACE2 expression of the liver tissues of HCC patients to predict the vulnerability of hepatocytes for SARS-CoV-2. Therefore, in this piece of study, we analyzed the ACE2 expression profile of HCC patient's liver tissues from various cancer databases. The analysis of the relationship of ACE2 expression with patient's conditions such as cancer stages, race, gender, age, weight, tumor grade, and nodal metastasis status followed by the survivability rate was performed. The involvement of the expressions of important innate immune-related genes in the HCC patients was also analyzed.

MATERIAL AND METHODS

Publicly accessible online database Gene Expression Profiling Interactive Analysis 2 (GEPIA2) server (http://gepia2.cancer-pku.cn/#index) using the TCGA (The Cancer Genome Atlas) datasets were used to analyze the expression of ACE2 and TMPRSS2 in liver hepatocellular carcinoma (LIHC) (**Z. Tang, Kang, Li, Chen, & Zhang, 2019**). The mRNA expression profiles of ACE2, IKBKB, MAVS, IRF3, RELA in LIHC are analyzed by the UALCAN website (http://ualcan.path.uab.edu/index.html) using the TCGA dataset (**Chandrashekar *et al.*, 2017**). The survivability rate depending on the ACE2 expressions in the LIHC based on various factors was also analyzed using UALCAN website (http://ualcan.path.uab.edu/index.html) using the TCGA dataset (**Chandrashekar *et al.*, 2017**).

RESULTS AND DISCUSSION

The ACE2 receptor of SARS-CoV-2 expresses in numerous types of cells and/or tissue of different organs of the human body (**Ji *et al.*, 2020; Xu, Liu, Lu, Yang, & Zheng, 2020**). The cells of these organs expressing a high level of ACE2 might be a potential risk for SARS-CoV-2 infection (**L. Xu *et al.*, 2020; Zou *et al.*, 2020**). The ACE2 has also been reported to express significantly high levels in several cancer cells, such as lung adenocarcinoma (LUAD) and lung squamous carcinoma (LUSC), which might be associated with COVID-19 pathogenesis and case fatality (**Samad, Jafar, & Rafi, 2020**). SARS-CoV-2 is also found to infect hepatocytes (**Marjot *et al.*, 2021; Wang *et al.*, 2020**). In this study, we analyzed the ACE2 and important innate immune-related genes such as IKBKB, MAVS, and IRF3 expression profiles of HCC patient's liver tissues concerning the various clinical parameters and interlinked with the immune regulation and host signaling pathways.

We found significantly lower expression of ACE2 and TMPRSS2 in the HCC tissue compared with the healthy population (Figure 1). Also, ACE2 expression is found to be significantly downregulated with the advancing of HCC from stage 1

to 3 of individual cancer, tumor grade, N1 metastatic condition, and female patients HCC tissue (Figure 2ABCD). Importantly, high expression of ACE2 was detected in the HCC patient with extreme obesity and during 61 to 80 years old of ages (Figure 2EF). Increased expression of ACE2 in extremely obese HCC patients showed significantly lower survivability than the normal body weight-containing patients (Figure 3). Similarly, patient survivability is found to be lower in extremely obese and obese HCC patients with even with low expression of ACE2 levels (Figure 3). Moreover, the expression of the innate immune-related genes IKBKB, MAVS, IRF3, and RELA increased significantly in the HCC patients (Figure 4).

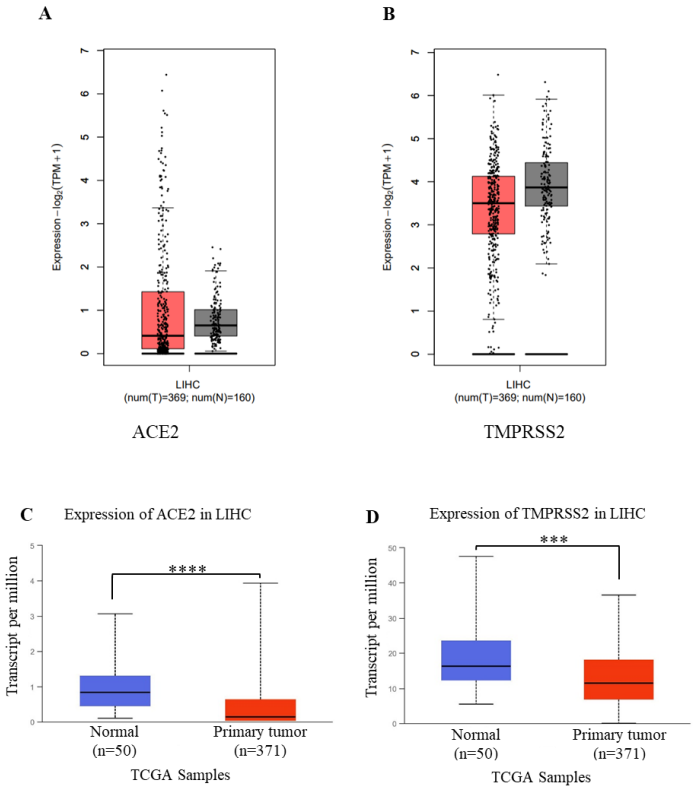

Figure 1 Expression profiles of SARS-CoV-2 entry factors in hepatocellular carcinoma (HCC). (A and B) The transcriptional expression pattern of ACE2 in liver hepatocellular carcinoma (LIHC) patients. Expression of ACE2 and TMPRSS2 in LIHC was analyzed using a box plot from the data set obtained from the GEPIA2 server. The analysis was performed under default parameter with $|Log_2FC|$ Cutoff value 1. (C and D) The mRNA expression analysis of ACE2 and TMPRSS2 in LIHC using UALCAN sever. The threshold p-value: * <0.05, ** <0.01, *** <0.001, and ****<0.0001. LIHC and TCGA stand for hepatocellular carcinoma and the cancer genome atlas, respectively.

HCC is a primary liver cancer mostly caused by chronic inflammation, and death may occur due to cirrhosis (**Forner, Llovet, & Bruix, 2012**). HCC could be induced mostly by viral hepatitis such as hepatitis B virus, hepatitis C virus, and non-infectious causes such as alcohol abuse, non-alcoholic steatohepatitis, type 2 diabetes, etc. **(Axley, Ahmed, Ravi, & Singal, 2018; Hossain, Akter, Ohsaki, & Ueda, 2020; X. Li, Wang, & Gao, 2017; Singh, Kumar, & Pandey, 2018**). However, there are no studies on the effect of COVID-19 in patients so far, though several reports showed that SARS-CoV-2 was found to infect hepatocytes and cause direct liver injury with an incidence of 14-52 % (**Aldhaleei *et al.*, 2020; Chu *et al.*, 2020; Wang *et al.*, 2020; H. Xu *et al.*, 2020**).

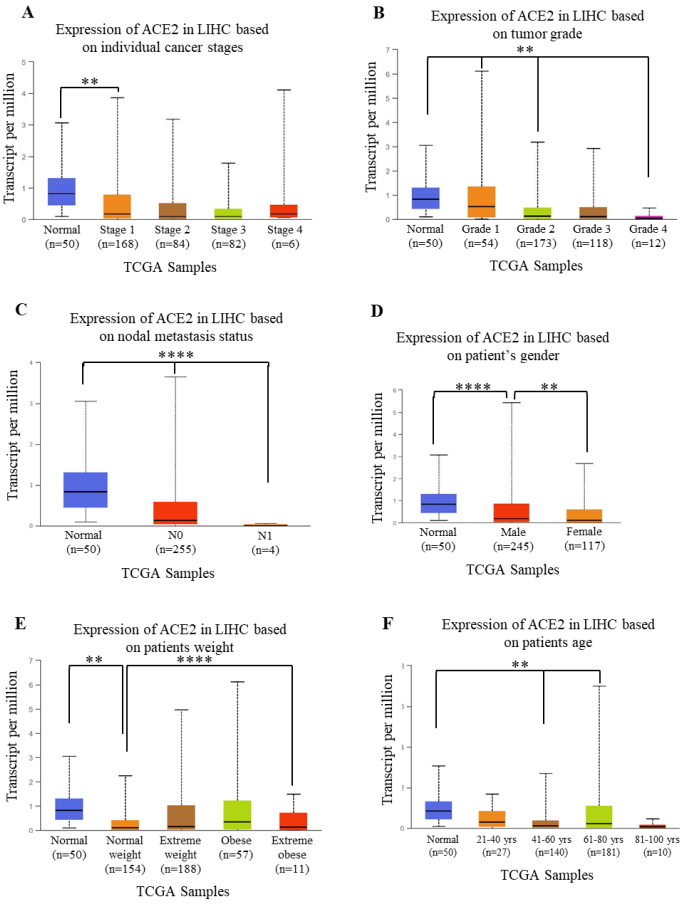

Figure 2 SARS-CoV-2 entry factor ACE2 mRNA expression profile in various conditions of HCC and with their clinical features. Expression of ACE2 in LIHC based on cancer stages (A), tumor grade (B), nodal metastasis status (C), patients' gender (D), patients' weight (E), and patients age (F). ACE2 mRNA expression in LIHC retracted from the UALCAN web and analyzed. The threshold p-value: * <0.05, ** <0.01, *** <0.001, and ****<0.0001. LIHC and TCGA stand for hepatocellular carcinoma and the cancer genome atlas, respectively.

Liver dysfunction is very common in COVID-19 patients, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were found to be increased in the patients with the severe condition compared with the mild cases **(Liang *et al.*, 2020)**. SARS-CoV-2 is prevalent (2 to 11%) in pre-existing liver diseases **(Sarin *et al.*, 2020; Zhang, Shi, & Wang, 2020)**. A nationwide analysis in China showed that patients with various pre-existing cancers might be associated with an increased risk for SARS-CoV-2 as well as a poor outcome **(Liang *et al.*, 2020)**. The ACE2 is expressed in hepatocytes. Therefore, liver damage may directly occur by the SARS-CoV-2 infection **(L. Xu *et al.*, 2020)**. However, in our study, ACE2 expression is significantly lower in HCC tissue, reduced in advancing the cancer stage and in a female patient. The results of the ACE2 expression profile in this study correlated with these findings (**L. Xu *et al.*, 2020**). The COVID-19 associated death rate is lower in female and aged patients (**Biswas, Rahaman, Biswas, Haque, & Ibrahim, 2020; Jin *et al.*, 2020**). Therefore, it might be predicted that the possibility of direct liver damage in this group of HCC patients is lower.

Low expression of ACE2 might be better for immune function, which protects the children from severe COVID-19 **(Lingappan, Karmouty-Quintana, Davies, Akkanti, & Harting, 2020**). ACE2 and TMPRSS2 expression are very low in infants and young children than adults and increase with age which protects them from severe COVID-19 conditions **(Asselta, Paraboschi, Mantovani, & Duga, 2020; Saheb Sharif-Askari *et al.*, 2020**). Moreover, the production of increased immunomodulatory cytokines and decreased proinflammatory cytokines in children further support the mechanism of mild infection in children (**Dulek *et al.*, 2020; Lingappan *et al.*, 2020**). In our analysis, extremely low ACE2 expression was reported in the HCC tissue and even decreased with the advancing of the cancer stage.

On the other hand, obesity might be a risk factor for HCC, and there is a correlation of HCC with obesity in the progression of non-alcoholic fatty liver disease to cirrhosis (**Caldwell *et al.*, 2004**). Also, obesity is independently associated with the increased risk of SARS-CoV-2, and older COVID-19 patients are more prone to death (**Zheng *et al.*, 2020**). Importantly, our results demonstrated that ACE2 is highly expressed in HCC tissue of obese patients compared with the normal weight

and older aged people suggesting the importance of taking special care to those groups of HCC patients. These results were further correlated with the low survivability rate and ACE2 expression level in HCC tissue of the patient with obesity.

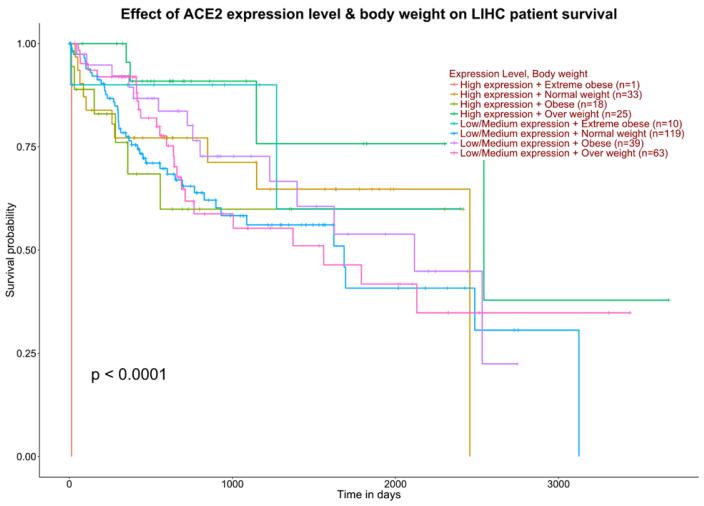

Figure 3 HCC patient survivability in relation to ACE2 expression. The data were extracted from the UALCAN web and analyzed. The threshold p-value: * <0.05, ** <0.01, *** <0.001, and ****<0.0001. LIHC and TCGA stand for hepatocellular carcinoma and the cancer genome atlas, respectively.

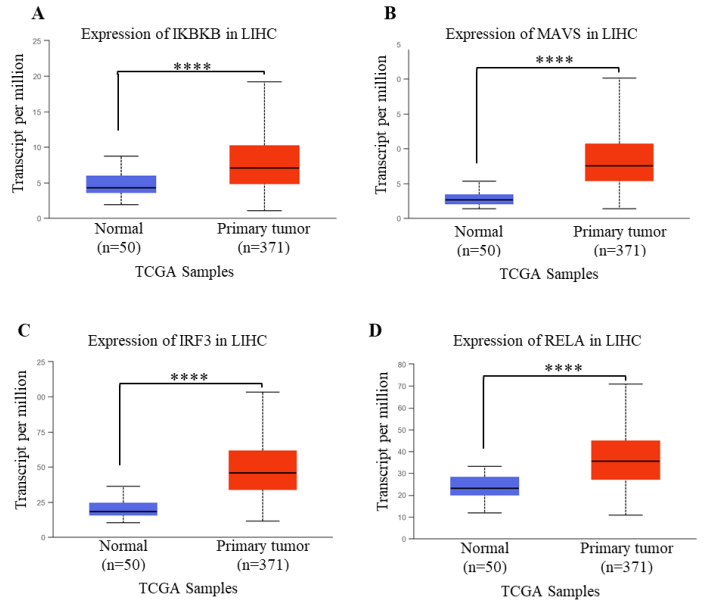

Figure 4 The mRNA expression analysis of innate immune-related genes (IKBKB, MAVS, IRF3, and RELA) in LIHC using UALCAN sever. The threshold p-value: * <0.05, ** <0.01, *** <0.001, and ****<0.0001. LIHC and TCGA stand for hepatocellular carcinoma and the cancer genome atlas, respectively.

The SARS-COV-2 infection and its pathogenesis are severely affected by innate immune-related factors (**Sallenave & Guillot, 2020**). Previously, it has also been reported that hepatocyte tumorigenicity might be decreased by the suppression of IKBKB through the NF-κB signaling pathway, suggesting an adverse effect on the patients due to the upregulation of nuclear factor-kappa B kinase subunit B (IKBKB) in HCC (**H. P. Li *et al.*, 2013**). The cytokine storm during SARS-CoV-2 infection may lead to the critical illness of the patients suffering from cancer, including multi-organ failure (**Bhaskar *et al.*, 2020; Y. Tang *et al.*, 2020**). However, the cytokine storm could be inhibited by the downregulation of NF-κB pathway (**Kircheis *et al.*, 2020**). Accordingly, in this analysis, an inhibitor of IKBKB, a key factor of NF-κB pathway, has been significantly increased in the HCC patients compared to normal healthy patients, which is consistent with our and previous findings. However, the mitochondrial antiviral signaling protein (MAVS) and interferon regulatory factor 3 (IRF3) might be inhibited by the ORF6 of SARS-CoV-2, suggesting the involvement of these innate immune genes in the HCC and COVID-19 pathogenesis (**Lei *et al.*, 2020**).

CONCLUSION

Though the ACE2 expression is significantly downregulated in HCC tissues compared with the healthy population, both high and low expressions of ACE2 in extremely obese and obese HCC patients showed a significantly lower survivability rate compared with the normal body weight. Hence, the ACE2 expression in the HCC is positively associated with HCC patient's obesity and age of 61 to 80 years old, and the obesity of the HCC patient is an important trigger for COVID-19 pathogenesis. On the other hand, innate immune-related genes (IKBKB, MAVS, IRF3, and RELA) involved in the COVID-19 pathogenesis are also upregulated in the HCC. Therefore, it might be suggested that the possibility of direct liver injury of the HCC patient by SARS-CoV-2 might be rare due to low expression of ACE2 whereas HCC patients with obesity are more prone to COVID-19 related severe pathogenesis and poor prognosis.

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