

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

Md. Golzar Hossain^{*1}, Sharmin Akter² and Md Jamal Uddin^{3,4}

Address(es):

¹Department of Microbiology and Hygiene, Bangladesh Agricultural University, Mymensingh-2202, Bangladesh.

²Department of Physiology, Bangladesh Agricultural University, Mymensingh-2202, Bangladesh.

³Graduate School of Pharmaceutical Sciences, College of Pharmacy, Ewha Womans University, Seoul 03760, Korea.

⁴ABEx Bio-Research Center, East Azampur, Dhaka-1230, Bangladesh.

*Corresponding author: mghossain@bau.edu.bd

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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) (Aldhalei, 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).

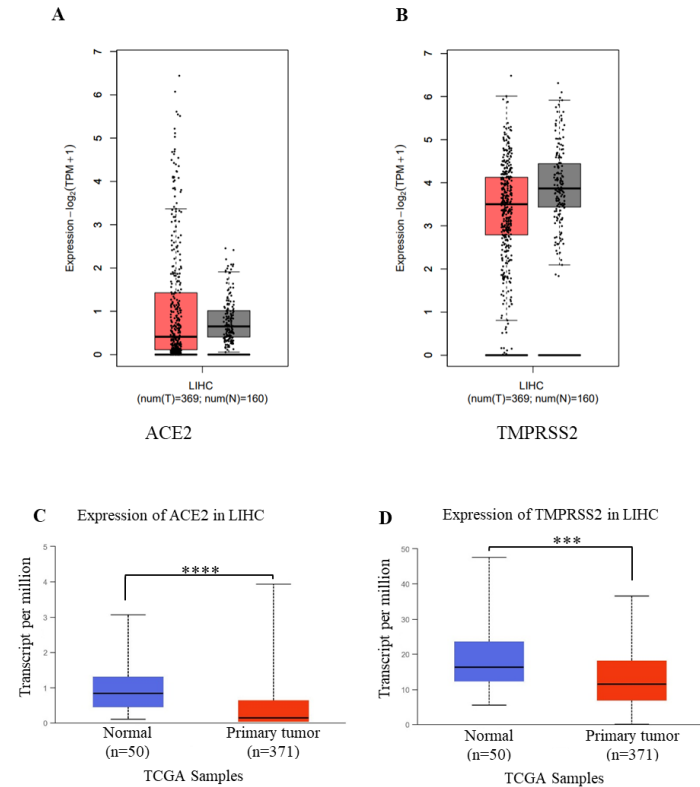


Figure 1 Expression profiles of SARS-CoV-2 entry factors in hepatocellular carcinoma (HCC). (A and B) The transcriptional expression pattern of ACE2 in liver hepatocellular carcinoma (LIHC) patients. Expression of ACE2 and TMPRSS2 in LIHC was analyzed using a box plot from the data set obtained from 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).

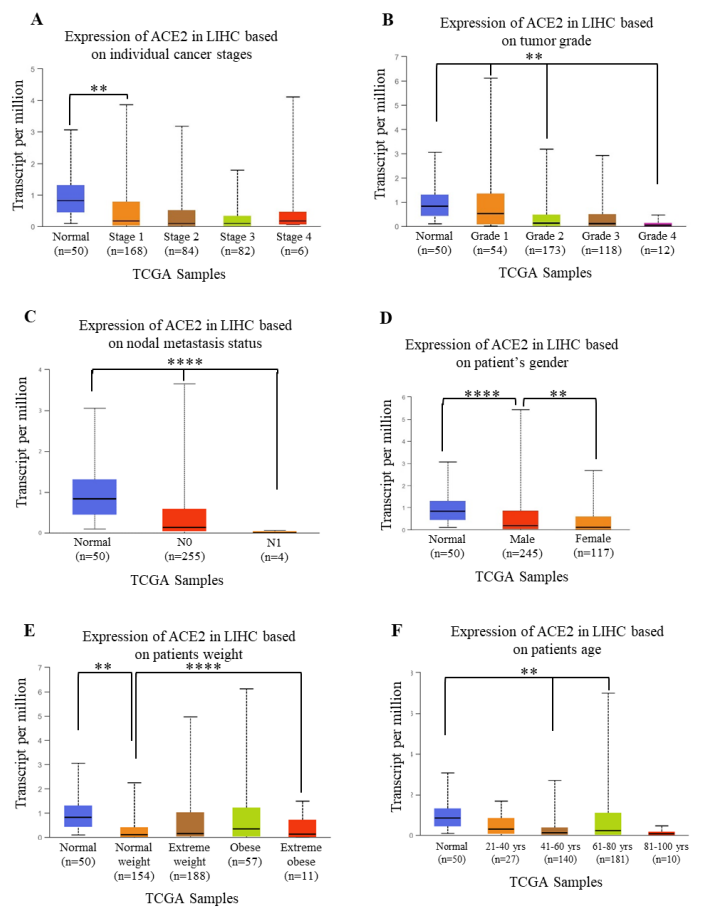


Figure 2 SARS-CoV-2 entry factor ACE2 mRNA expression profile in various conditions of HCC and with their clinical features. Expression of ACE2 in LIHC based on cancer stages (A), tumor grade (B), nodal metastasis status (C), patients' gender (D), patients' weight (E), and patients age (F). ACE2 mRNA 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.

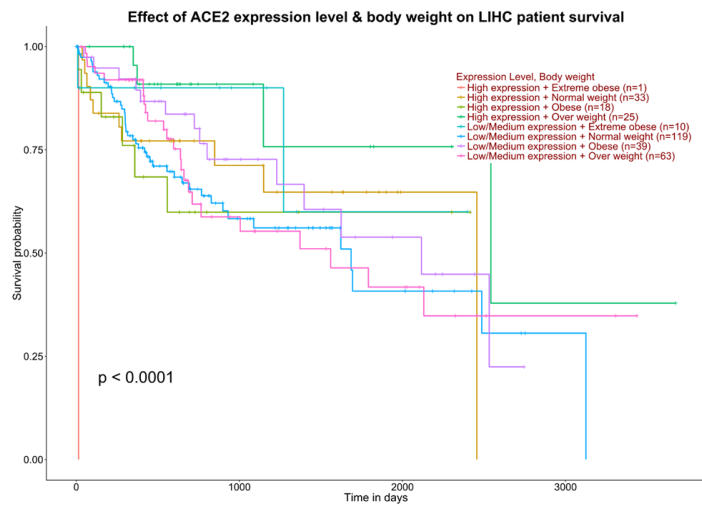


Figure 3 HCC patient survivability in relation to ACE2 expression. The data were extracted from the UALCAN web and analyzed. The threshold p-value: * <math>< 0.05</math>, ** <math>< 0.01</math>, *** <math>< 0.001</math>, and **** <math>< 0.0001</math>. LIHC and TCGA stand for hepatocellular carcinoma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

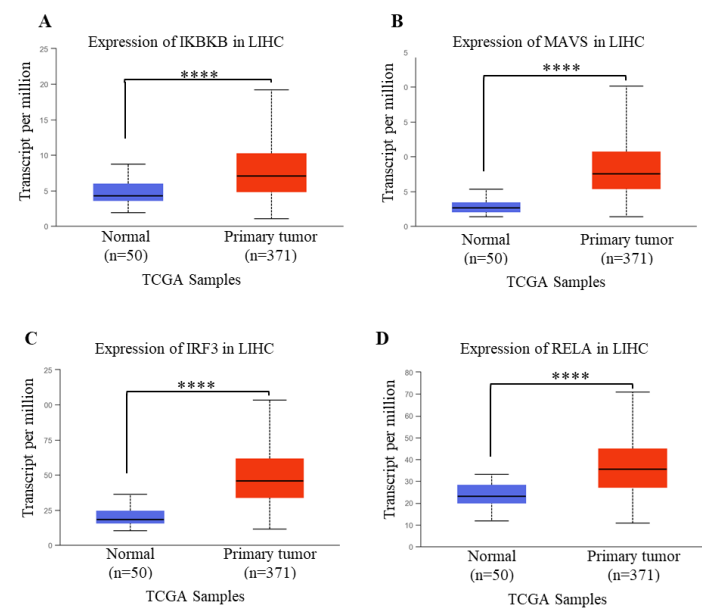


Figure 4 The mRNA expression analysis of innate immune-related genes (IKBK, MAVS, IRF3, and RELA) in LIHC using UALCAN sever. The threshold p-value: * <math>< 0.05</math>, ** <math>< 0.01</math>, *** <math>< 0.001</math>, and **** <math>< 0.0001</math>. LIHC and TCGA stand for hepatocellular carcinoma 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- κ B signaling pathway, suggesting an adverse effect on the patients due to the upregulation of nuclear factor-kappa B kinase subunit B (IKBK) 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- κ B pathway (Kircheis et al., 2020). Accordingly, in this analysis, an inhibitor of IKBKB, a key factor of NF- κ B 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 (IKBK, 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.

REFERENCES

Aldhalei, W. A., Alnuaimi, A., & Bhagavathula, A. S. (2020). COVID-19 Induced Hepatitis B Virus Reactivation: A Novel Case From the United Arab Emirates. *Cureus*, 12(6), e8645-e8645. <https://doi.org/10.7759/cureus.8645>

Asselta, R., Paraboschi, E. M., Mantovani, A., & Duga, S. (2020). ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. *Aging (Albany NY)*, 12(11), 10087-10098. <https://doi.org/10.18632/aging.103415>

Axley, P., Ahmed, Z., Ravi, S., & Singal, A. K. (2018). Hepatitis C Virus and Hepatocellular Carcinoma: A Narrative Review. *Journal of clinical and translational hepatology*, 6(1), 79-84. <https://doi.org/10.14218/JCTH.2017.00067>

Bhaskar, S., Sinha, A., Banach, M., Mittoo, S., Weissert, R., Kass, J. S., . . . Kutty, S. (2020). Cytokine Storm in COVID-19-Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper. *Frontiers in immunology*, 11, 1648. <https://doi.org/10.3389/fimmu.2020.01648>

Biswas, M., Rahaman, S., Biswas, T. K., Haque, Z., & Ibrahim, B. (2020). Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. *Intervirology*, 1-12. <https://doi.org/10.1159/000512592>

Caldwell, S. H., Crespo, D. M., Kang, H. S., & Al-Osaimi, A. M. (2004). Obesity and hepatocellular carcinoma. *Gastroenterology*, 127(5 Suppl 1), S97-103. <https://doi.org/10.1053/j.gastro.2004.09.021>

Chandrashekar, D. S., Bashel, B., Balasubramanya, S. A. H., Creighton, C. J., Ponce-Rodriguez, I., Chakravarthi, B. V. S. K., & Varambally, S. (2017). UALCAN: A Portal for Facilitating Tumor Subgroup Gene Expression and Survival Analyses. *Neoplasia*, 19(8), 649-658. <https://doi.org/10.1016/j.neo.2017.05.002>

Choudhary, N. S., Dhampalwar, S., Saraf, N., & Soin, A. S. (2021). Outcomes of COVID-19 in Patients with Cirrhosis or Liver Transplantation. *Journal of clinical and experimental hepatology*. <https://doi.org/10.1016/j.jceh.2021.05.003>

Chu, H., Chan, J. F.-W., Yuen, T. T.-T., Shuai, H., Yuan, S., Wang, Y., . . . Yuen, K.-Y. (2020). Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: an observational study. *The Lancet Microbe*, 1(1), e14-e23. [https://doi.org/10.1016/S2666-5247\(20\)30004-5](https://doi.org/10.1016/S2666-5247(20)30004-5)

Dulek, D. E., Fuhlbrigge, R. C., Tribble, A. C., Connelly, J. A., Loi, M. M., El Chebib, H., . . . Bassiri, H. (2020). Multidisciplinary Guidance Regarding the Use of Immunomodulatory Therapies for Acute Coronavirus Disease 2019 in Pediatric Patients. *Journal of Pediatric Infectious Diseases Society*, 9(6), 716-737. <https://doi.org/10.1093/jpids/piaa098>

Forner, A., Llovet, J. M., & Bruix, J. (2012). Hepatocellular carcinoma. *The Lancet*, 379(9822), 1245-1255. [https://doi.org/10.1016/S0140-6736\(11\)61347-0](https://doi.org/10.1016/S0140-6736(11)61347-0)

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., . . . Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, 181(2), 271-280.e278. <https://doi.org/10.1016/j.cell.2020.02.052>

Hossain, M. G., Akter, S., Ohsaki, E., & Ueda, K. (2020). Impact of the Interaction of Hepatitis B Virus with Mitochondria and Associated Proteins. *Viruses*, 12(2), 175. <https://doi.org/10.3390/v12020175>

Ji, D., Qin, E., Xu, J., Zhang, D., Cheng, G., Wang, Y., & Lau, G. (2020). Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *Journal of hepatology*, 73(2), 451-453. <https://doi.org/10.1016/j.jhep.2020.03.044>

Jin, J.-M., Bai, P., He, W., Wu, F., Liu, X.-F., Han, D.-M., . . . Yang, J.-K. (2020). Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Frontiers in public health*, 8, 152-152. <https://doi.org/10.3389/fpubh.2020.00152>

Kircheis, R., Haasbach, E., Lueftenegger, D., Heyken, W. T., Ocker, M., & Planz, O. (2020). NF- κ B Pathway as a Potential Target for Treatment of Critical Stage COVID-19 Patients. *Frontiers in immunology*, 11, 598444. <https://doi.org/10.3389/fimmu.2020.598444>

Kudo, M., Kurosaki, M., Ikeda, M., Aikata, H., Hiraoka, A., Torimura, T., & Sakamoto, N. (2020). Treatment of hepatocellular carcinoma during the COVID-19 outbreak: The Working Group report of JAMTT-HCC. *Hepatology Research*, 50(9), 1004-1014. <https://doi.org/10.1111/hepr.13541>

- Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J., & Hsueh, P. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *International Journal of Antimicrobial Agents*, 55(3), 105924. <https://doi.org/10.1016/j.ijantimicag.2020.105924>
- Lei, X., Dong, X., Ma, R., Wang, W., Xiao, X., Tian, Z., . . . Wang, J. (2020). Activation and evasion of type I interferon responses by SARS-CoV-2. *Nature Communication*, 11(1), 3810. <https://doi.org/10.1038/s41467-020-17665-9>
- Li, H. P., Zeng, X. C., Zhang, B., Long, J. T., Zhou, B., Tan, G. S., . . . Yang, J. Y. (2013). miR-451 inhibits cell proliferation in human hepatocellular carcinoma through direct suppression of IKK- β . *Carcinogenesis*, 34(11), 2443-2451. <https://doi.org/10.1093/carcin/bgt206>
- Li, X., Wang, X., & Gao, P. (2017). Diabetes Mellitus and Risk of Hepatocellular Carcinoma. *BioMed Research International*, 2017, 5202684-5202684. <https://doi.org/10.1155/2017/5202684>
- Liang, W., Guan, W., Chen, R., Wang, W., Li, J., Xu, K., . . . He, J. (2020). Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *The Lancet Oncology*, 21(3), 335-337. [https://doi.org/10.1016/S1470-2045\(20\)30096-6](https://doi.org/10.1016/S1470-2045(20)30096-6)
- Lingappan, K., Karmouty-Quintana, H., Davies, J., Akkanti, B., & Harting, M. T. (2020). Understanding the age divide in COVID-19: why are children overwhelmingly spared? *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 319(1), L39-L44. <https://doi.org/10.1152/ajplung.00183.2020>
- Marjot, T., Webb, G. J., Barritt, A. S. t., Moon, A. M., Stamatakis, Z., Wong, V. W., & Barnes, E. (2021). COVID-19 and liver disease: mechanistic and clinical perspectives. *Nature Reviews Gastroenterology & Hepatology*, 18(5), 348-364. <https://doi.org/10.1038/s41575-021-00426-4>
- Saheb Sharif-Askari, N., Saheb Sharif-Askari, F., Alabed, M., Temsah, M.-H., Al Heialy, S., Hamid, Q., & Halwani, R. (2020). Airways Expression of SARS-CoV-2 Receptor, ACE2, and TMPRSS2 Is Lower in Children Than Adults and Increases with Smoking and COPD. *Molecular Therapy - Methods & Clinical Development*, 18, 1-6. <https://doi.org/10.1016/j.omtm.2020.05.013>
- Sallenave, J.-M., & Guillot, L. (2020). Innate Immune Signaling and Proteolytic Pathways in the Resolution or Exacerbation of SARS-CoV-2 in Covid-19: Key Therapeutic Targets? *Frontiers in Immunology*, 11, 1229-1229. <https://doi.org/10.3389/fimmu.2020.01229>
- Samad, A., Jafar, T., & Rafi, J. H. (2020). Identification of angiotensin-converting enzyme 2 (ACE2) protein as the potential biomarker in SARS-CoV-2 infection-related lung cancer using computational analyses. *Genomics*, 112(6), 4912-4923. <https://doi.org/10.1016/j.ygeno.2020.09.002>
- Sarin, S. K., Choudhury, A., Lau, G. K., Zheng, M. H., Ji, D., Abd-Elsalam, S., . . . Omata, M. (2020). Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). *Hepatology International*, 14(5), 690-700. <https://doi.org/10.1007/s12072-020-10072-8>
- Shang, J., Ye, G., Shi, K., Wan, Y., Luo, C., Aihara, H., . . . Li, F. (2020). Structural basis of receptor recognition by SARS-CoV-2. *Nature*, 581(7807), 221-224. <https://doi.org/10.1038/s41586-020-2179-y>
- Singh, A. K., Kumar, R., & Pandey, A. K. (2018). Hepatocellular Carcinoma: Causes, Mechanism of Progression and Biomarkers. *Current Chemical Genomics and Translational Medicine*, 12, 9-26. <https://doi.org/10.2174/2213988501812010009>
- Tang, Y., Liu, J., Zhang, D., Xu, Z., Ji, J., & Wen, C. (2020). Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Frontiers in Immunology*, 11, 1708-1708. <https://doi.org/10.3389/fimmu.2020.01708>
- Tang, Z., Kang, B., Li, C., Chen, T., & Zhang, Z. (2019). GEPIA2: an enhanced web server for large-scale expression profiling and interactive analysis. *Nucleic Acids Research*, 47(W1), W556-W560. <https://doi.org/10.1093/nar/gkz430>
- Wang, Y., Liu, S., Liu, H., Li, W., Lin, F., Jiang, L., . . . Zhao, J. (2020). SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *Journal of hepatology*, 73(4), 807-816. <https://doi.org/10.1016/j.jhep.2020.05.002>
- Xu, H., Zhong, L., Deng, J., Peng, J., Dan, H., Zeng, X., . . . Chen, Q. (2020). High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *International Journal of Oral Science*, 12(1), 8. <https://doi.org/10.1038/s41368-020-0074-x>
- Xu, L., Liu, J., Lu, M., Yang, D., & Zheng, X. (2020). Liver injury during highly pathogenic human coronavirus infections. *Liver International*, 40(5), 998-1004. <https://doi.org/10.1111/liv.14435>
- Zaim, S., Chong, J. H., Sankaranarayanan, V., & Harky, A. (2020). COVID-19 and Multiorgan Response. *Current Problems in Cardiology*, 45(8), 100618. <https://doi.org/10.1016/j.cpcardiol.2020.100618>
- Zhang, C., Shi, L., & Wang, F.-S. (2020). Liver injury in COVID-19: management and challenges. *The Lancet Gastroenterology & Hepatology*, 5(5), 428-430. [https://doi.org/10.1016/S2468-1253\(20\)30057-1](https://doi.org/10.1016/S2468-1253(20)30057-1)
- Zheng, K. I., Gao, F., Wang, X.-B., Sun, Q.-F., Pan, K.-H., Wang, T.-Y., . . . Zheng, M.-H. (2020). Letter to the Editor: Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. *Metabolism - Clinical and Experimental*, 108. <https://doi.org/10.1016/j.metabol.2020.154244>
- Zou, X., Chen, K., Zou, J., Han, P., Hao, J., & Han, Z. (2020). Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Frontiers of Medicine*, 14(2), 185-192. <https://doi.org/10.1007/s11684-020-0754-0>