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Article

Assessing the Vulnerability of Cancer Patients for COVID-19

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Cite This: *ACS Omega* 2022, 7, 35735−35742

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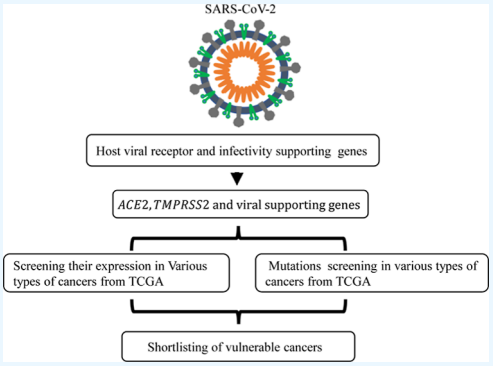
ABSTRACT: Severe acute respiratory syndrome involving corona virus-2 (SARS-CoV-2) has been implied to cause COVID-19 disease, leading to an unprecedented health emergency across the globe with a staggering figure of mortality rate. Measures to control the pandemic are pushing the economy into a tailspin, putting burden not only on the individuals but also on the nations. Despite the widespread infection rates, young people have shown better recovery rate while COVID-19 symptoms are more pronounced in elderly and people with comorbid conditions such as diabetes, cardiac and respiratory diseases. Cancer is a highly prevalent disease affecting millions of individuals. In this study, we analyzed the expression status of genes that are required for SARS-CoV-2 infectivity and its propagation to assess the susceptibility of certain cancer patients to infection and subsequent complications. Our data indicate that patients with colon, rectum, cholangiocarcinoma, lung adenoma, kidney renal papillary cell carcinoma and kidney renal clear cell carcinoma are more at risk for COVID-19. Genes that are responsible for severe COVID-19 are also highly expressed in many cancer types. We also carried out the association rule mining analysis which is helpful in predicting the expression of proviral genes in various cancers.



INTRODUCTION

Severe acute respiratory syndrome novel corona virus-2 (SARS-CoV-2), presently assigned as COVID-19, has caused a pandemic affecting human population worldwide with devastating effects on health[1] resulting in economic burden on individuals as well as on nations. Although it causes less-severe symptoms and significant recovery rates in younger populations, it is fatal in elderly and individuals with comorbidities such as diabetes, hypertension, and respiratory diseases (chronic obstructive pulmonary disease, asthma, etc.).[2] There are no specific drugs or combination of drugs that are available to manage COVID-19, except the recently approved drug remdesivir[3] sold under the brand name Veklury that is shown to have effect on patients with better prognosis and is approved by the FDA on a fast-track basis. Remdesivir in combination with other drugs is used to dampen inflammation, which leads to acute pneumonia.[3] Despite several vaccines that are approved and due to their lack of availability to the masses, the second wave of COVID-19 virus infections caused much higher mortality in many countries, including Brazil, India, United Sates, and Europe.[4] Most of the recombinant viral, RNA-based and attenuated virus vaccines are shown to be effective against most of the variants of COVID-19 virus. Due to the aggressive and subsidized vaccination drive, much of the population had at least one dose of vaccination worldwide.[5] However, due to non-availability, non-affordability or ignorance, a significant population is yet to be vaccinated[6] in many developing/poor countries. Despite the vaccination success rate and treatments, recent research shows that COVID-19 may have long-term lingering health implications in some of the COVID-19 survivors.[7]

It is estimated that SARS-CoV-2 has infected nearly half a billion population of the world so far. Some of the studies[8] indicate that infection of SARS-CoV-2 may pose serious health effects on people with comorbidities. Severe effects of viral infection are well documented in people with diabetes, heart diseases, asthma and other diseases leading to critical illness.[2] Cancer is a widespread disease with a significant number of patients suffering globally.[9] Cancer is characterized by the uncontrolled rapid cell division of the associated organ, leading to metastasis.[10]

SARS-CoV-2 uses host proteins such as angiotensin converting enzyme 2 (*ACE2*), a surface receptor in association with transmembrane serine protease 2 (*TMPRSS2*) for releasing the viral RNA genome into the cytoplasm of host cells to be translated into structural and polyproteins, resulting

Received: June 16, 2022
Accepted: September 8, 2022
Published: September 30, 2022

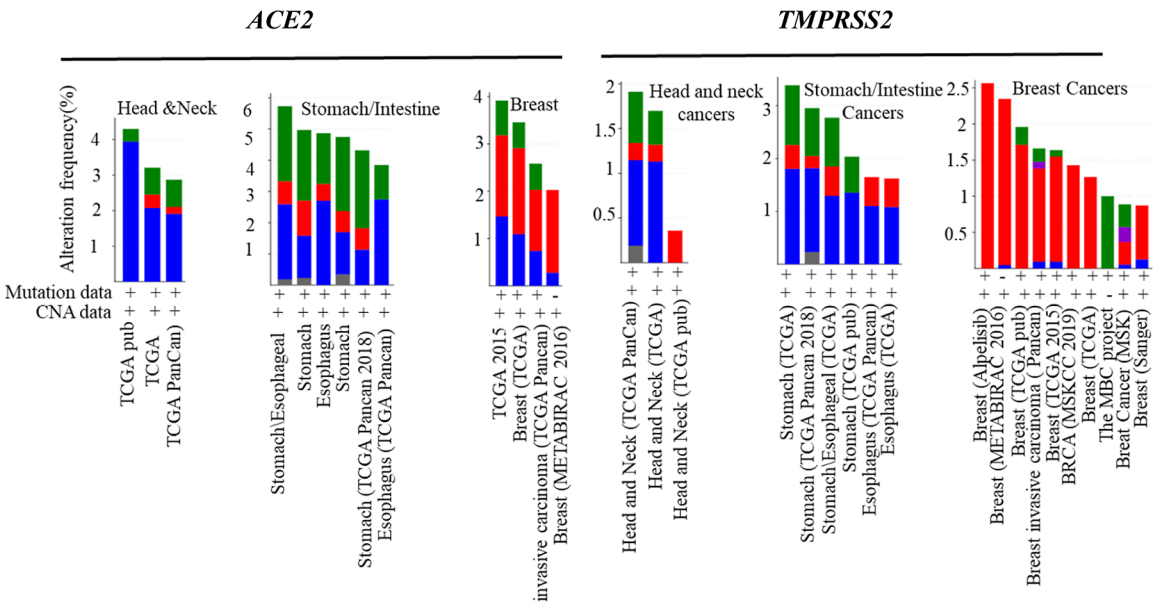


Figure 1. Mutations, amplifications, and deletions of *ACE2* and *TMPRSS2* in various cancers. Red indicates amplification, blue indicates deletion, and green indicates mutation.

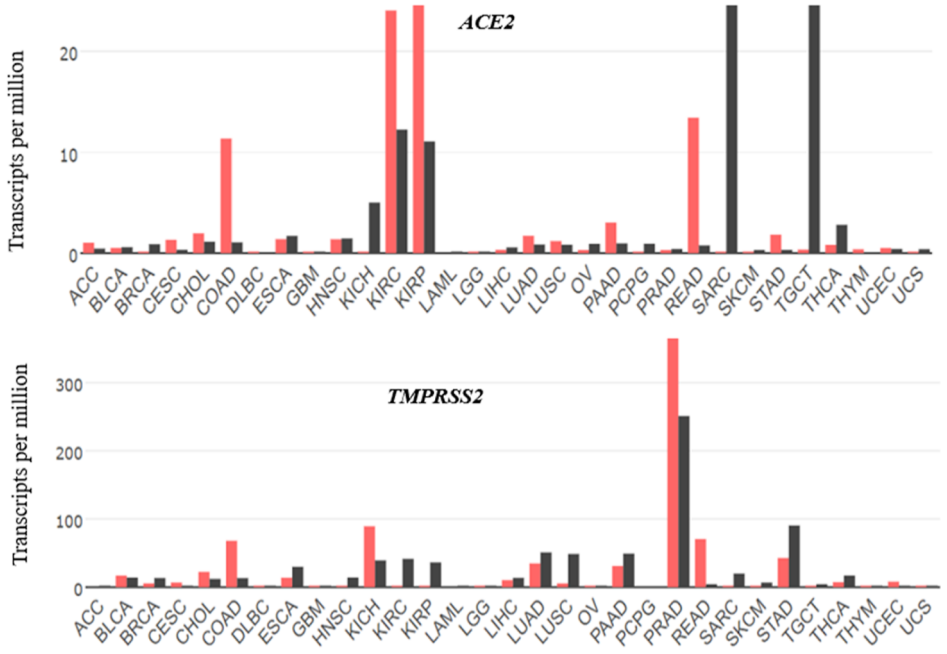


Figure 2. mRNA expression of *ACE2 and TMPRSS2* in different cancers (varied among different types of cancers shown on the *x*-axis). BLCA, BRCA, CESC, CHOL, ESCA, GBM, HNSC, KICH, KIRC, KIRP, LIHC, LUAD, LUSC, PAAD, PRAD, PCPG, READ, SARC, SKCM, THCA, THYM, STAD, and UCEC. Samples were taken from TCGA. Red color denotes tumor samples and blue, normal samples.

in viral replication.[11] *ACE2* and *TMPRSS2* are shown to be expressed on many cells in multiple vital organs.[12] However, it is not confirmed that the mere expression of *ACE2* and *TMPRSS2* always leads to viral infection and associated symptoms. After viral entry, many host genes that are responsible for viral genome integration and propagation play a crucial role for viral replication.[13] As the widespread infection of SARS-CoV-2 causing COVID-19 pandemic is soaring across the globe, it is generating severe strain on health resources and management of the infected patients. Under these circumstances, treating and managing patients with dreadful diseases such as cancer is becoming a daunting task. Recently, several efforts have been made to understand the impact and management of COVID-19 on cancer patients. Also, some reports are available to understand the implications of COVID-19 on cancer patients.[14] To understand whether cancer patients are particularly vulnerable for SARS-CoV-2 infection, analysis of the expression status of viral receptors and proviral genes in various cancer types would give better information for clinicians to manage treatment options for cancer patients. Therefore, in the present study, we sought to analyze the expression of *ACE2*, *TMPRSS2* and proviral genes in various human cancers, which allows prediction of the degree of susceptibility of cancer patients to SARS-CoV-2

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ACS Omega 2022, 7, 35735−35742

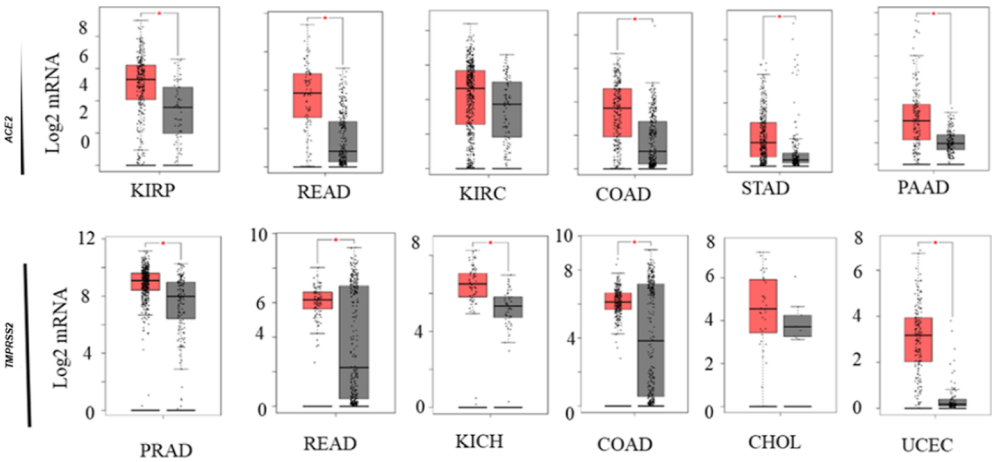

Figure 3. Overexpression of *ACE2* and *TMPRSS2* across different cancers as compared to normal expression. Red and gray boxes indicate the diseased and normal samples, respectively. (T = tumor samples and N = normal samples). * represents p value < 0.05. The x-axis of the plot will follow the order of KIRP, KIRC, COAD, READ, PAAD and STAD, PRAD, READ, KICH, COAD, UCEC, and CHOL data sets.

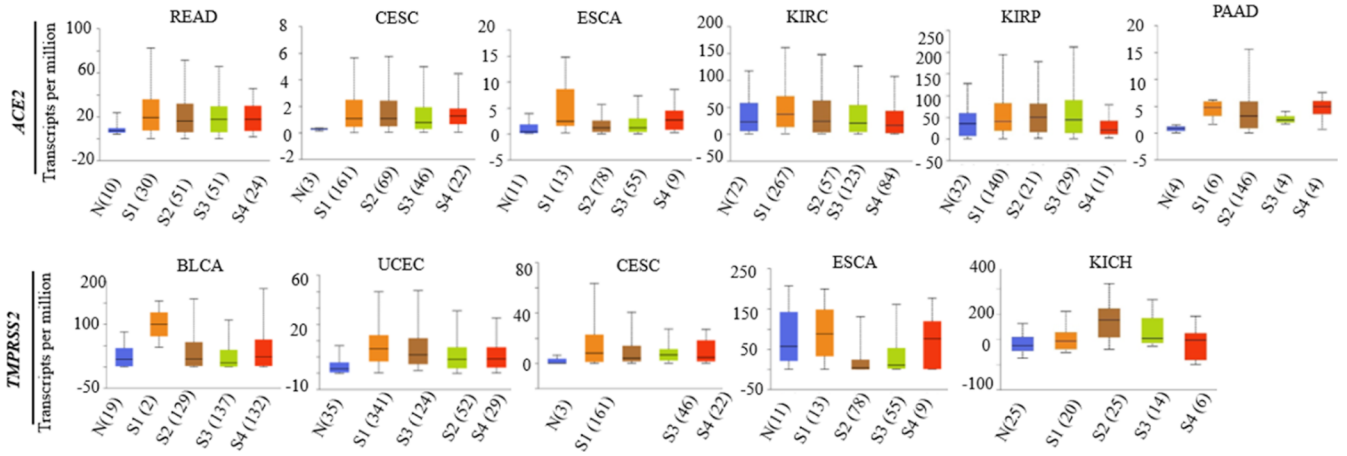

Figure 4. mRNA stage-wise expression of *ACE2 and TMPRSS2* in different cancers. mRNA expression of *ACE2* across different cancers: READ, CESC, ESCA, KIRC, KIRP and PAAD and mRNA expression of *TMPRSS2* in BLCA, UCEC, CESC ESCA and KICH. Individual cancer stages of the mRNA expression pattern of *ACE2* are shown. N stands for normal stage, followed by stage 1, stage 2, stage 3, and stage 4 depicted as S1, S2, S3, and S4, respectively, on the x-axis. Expression with p value less than 0.01 satisfies the criteria. The median is the center black line in the graph. Y-axis shows the RNA in transcripts per million. Samples were taken from TCGA.

infection. We also carried out association rule mining analysis to predict the expression of a gene(s) in other cancers, having known the expression of a gene(s) in a set of cancer types. Interaction of viral proteins with host proteins and in particular proteins that operate in cancer is also explored in this study.

RESULTS

Status of *ACE2* and *TMPRSS2* across Different Cancers. *ACE2* and *TMPRSS2* receptors have been clearly shown as the two most important proteins involving in SARS-CoV-2 entry and propagation inside the host cell. Knowing their expression status and whether they have undergone any mutations in the context of various cancers may give an idea of vulnerability of cancer patients to SARS-CoV-2 infection. It is well known that certain cancer-related genes such as *MYC* and *P53* undergo mutations, amplifications, and deletions.[15,16] Using The Cancer Genome Atlas (TCGA), RNA sequence data from the respective cancer patient samples, occurrence of amplifications and mutations or deletions was analyzed for both *ACE2* and *TMPRSS2*. Results indicate that *ACE2* and *TMPRSS2* show deletions and mutations in head and neck and stomach cancers (Figure 1). In breast cancer, amplification is observed for both *ACE2* and *TMPRSS2* (Figure 1).

As the presence of these two receptors is essential for viral entry, we explored their expression in various cancers. Data show that *ACE2* is expressed more in cervical squamous cell carcinoma (CESC), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), lung adenocarcinoma (LUAD), lung squamous carcinoma (LUSC), pancreatic adenocarcinoma (PAAD), rectum adenocarcinoma (READ), and stomach adenocarcinoma (STAD) (Figure 2). The expression of *ACE2* in many other cancers is either low or similar to the corresponding normal tissue (Figure 2). The expression levels of *TMPRSS2* is higher in CESC, CHOL, COAD, kidney chromophobe (KICH), PAAD, prostate adenocarcinoma (PRAD), READ, and UCEC (Figure 2). Further analysis revealed that higher expression of *ACE2* is statistically significant in KIRP, READ, KIRC, COAD, STAD, and PAAD (Figure 3). A statistically significant higher expression of *TMPRSS2* is observed in PRAD, READ,

https://doi.org/10.1021/acsomega.2c03764
ACS Omega 2022, 7, 35735−35742

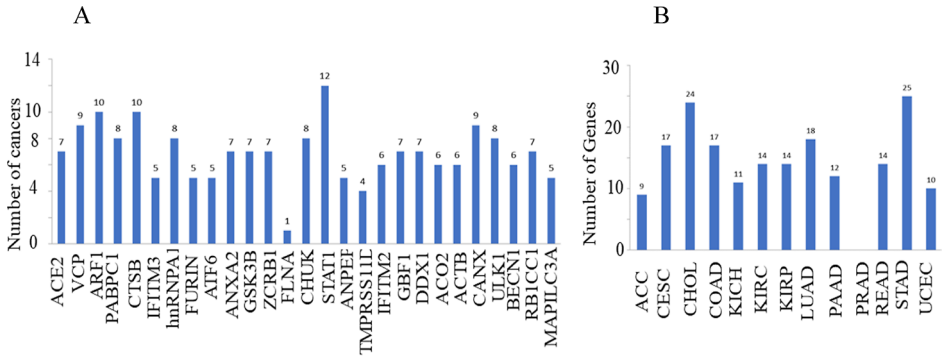

Figure 5. Graphical representation of genes showing higher expression in different cancers. (a) Represents the genes that show higher expression in how many number of cancers. (b) Represents the cancers that show the number of highly expressed genes.

KICH, COAD, CHOL, and uterine corpus endometrial carcinoma (UCEC) (Figure 3).

Note that in READ and COAD, both *ACE2* and *TMPRSS2* show higher expression, which is statistically significant. Further, we explored stage-wise expression of these two genes in various cancers. *ACE2* shows higher expression in different stages of the various cancers such as READ, CESC, ESCA, KIRC, KIRP, and PAAD. For *TMPRSS2*, higher expression is observed in many stages of various cancers such as bladder urothelial carcinoma (BLCA), UCEC, CESC, ESCA and KICH (Figure 4). It is interesting to note that higher expression of these two genes is statistically significant between normal and stage-1 of various cancers as shown in Figure 4.

Expression Status of Proviral Genes in Various Cancers. There are many genes from the host that are supportive of viral infection and propagation in infected cells. We compiled a list of such genes[17] and analyzed their expression in various cancers. Many of these genes show higher expression in some of the cancers that were analyzed. For example, genes such as *ACE2*, *ANXA2*, *GSK3B*, *ZCRB1*, *GBF1*, *RB1CC1*, and *DDX1* showed higher expression in seven different cancers (Figure 5A). Interestingly, genes such as *PABPC1*, *HNRNPA1*, *CANX*, and *ULK1* showed higher expression in 8 types of cancers; *VCP* and *CHUK* in 9 kinds of cancers; *ARF1* and *CTSB* in 10 types of cancers; and *STAT1* in 12 types of cancers. We also explored which cancer type shows higher expression of a large number of proviral genes. CHOL and STAD showed higher expression of almost all proviral genes (Figure 5B). A higher expression of the proviral genes, ranging between 14 and 18, was detected in CESC, COAD, LUAD, READ, KIRC, and KIRP. Adenoid cystic carcinoma (ACC), KICH, PAAD, and UCEC exhibited higher expression of 9−12 proviral genes, whereas PRAD did not have data for gene expression of proviral genes (Figure 5B). We analyzed the frequency of particular gene expression in various cancers and association rules[18] of cancers with respect to gene expression. A set of 16 genes were found to be expressed always in CHOL, COAD, and STAD (Table 1). Similarly, a set of 16 genes were also found to be expressed in CHOL, LUAD, and STAD as shown in Table 1. Also, 22 genes were seen to be expressed by CHOL and STAD (Table1). Other useful association rules derived from frequent cancer patterns are shown in Table 2. The association rules are helpful in predicting the expression of a proviral gene in other cancers, given a set of cancers being expressed.

Table 1. Frequency of Gene Expression in Various Types of Cancers

sl. no.	frequently co-occurring cancer patterns	number of genes being expressed
1	CHOL, COAD, STAD	16
2	CHOL, LUAD, STAD	16
3	CHOL, STAD	22
4	LUAD, STAD	18
5	CESC, STAD	17
6	COAD, STAD	17

Expression of Critical Genes Responsible for Severe Form of COVID-19. Recently, genes such as *IFNAR2*, *TYK2*, *OAS1*, *OAS3*, *DPP9*, and *CCR2* have been identified to be critical for the occurrence of severe form of COVID-19.[19] Our data show that many of these genes exhibited higher expression in cancers such as CESC, CHOL, COAD, KICH, KIRC, KIRP, LUAD, READ, and STAD (Table 3).

Viral and Host Protein Interactions. For the virus to enter and integrate into the host genome, several interactions between the viral and host proteins are essential. We chose SARS viral proteins (as they are very similar to SARS-CoV-2 viral proteins) for interaction studies with human proteins. Except for a few, most of the viral proteins do not show interaction with host proteins (Figure 6). Further, some of the human cancer-related proteins were used to understand whether they interact with viral proteins. Some of the viral proteins such as 3a interact with cancer-related protein STAT3 (Figure S3). It would be interesting if this interaction could influence any outcome in the context of cancer as STAT3 is a well-known promoter of cancer spread and metastasis.[20]

DISCUSSION

Rapid infection rates of SARS-CoV-2 causing COVID-19 and ensuing pandemic of unprecedented levels are forcing intensive research efforts to better understand COVID-19 and its effective management. As cancer is one of the most prevailing conditions affecting millions of people worldwide, treating these patients is arduous as most of the health resources are steered for managing COVID-19 patients. In this context, it is important to assess whether cancer patients are more vulnerable for COVID-19 infection. There are several research reports available for managing the cancer patients during the pandemic.[21] However, there are very few studies to understand whether a particular type of cancer patients are more predisposed to COVID-19 after viral infection. *ACE2* and *TMPRSS2* are two prominent genes that are vital for viral

https://doi.org/10.1021/acsomega.2c03764
ACS Omega 2022, 7, 35735−35742

Table 2. Gene Expression and Association Rules among Various Types of Cancers

sl. no.	association rules between cancers	interpretation
1	CESC (17) ⇒ STAD (17)	if CESC cancer shows the expression of a gene, the same gene is also expressed in STAD
2	CHOL, COAD (16) ⇒ STAD (16)	if CHOL and COAD cancers show the expression of a gene, the same gene is also expressed in STAD
3	CHOL, LUAD (16) ⇒ STAD (16)	if CHOL and LUAD cancers show the expression of a gene, the same gene is also expressed in STAD
4	COAD, STAD (17) ⇒ CHOL (16)	If COAD and STAD show the expression of a gene, the same gene is also expressed in CHOL by 94% of the time
5	COAD (17) ⇒ CHOL, STAD (16)	if COAD cancer shows the expression of a gene, the same gene is also expressed in STAD by 94% of the time
6	CHOL (24) ⇒ STAD (22)	if CHOL cancer is expressed by a gene, the same gene is also expressed in STAD by 94% of the time

Table 3. Critical Genes for COVID TYK1, DPP9, CCR2, and OAS3 Showing High Expression across Different Cancers[a]

	ACC				CESC				CHOL				COAD				KICH				KIRC			
gene	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
TYK2			H	H		H	H	H	H	H		H	H	H	H	H		H		H	H	H	H	H
0AS1					H	H	H	H		H			H	H		H	H		H		H	H	H	H
DPP9		H	H	H	H	H	H	H	H	H		H	H	H	H	H		H	H		H	H	H	H
CCR2									H				H	H	H	H	H	H	H	H	H	H	H	H
0AS3				H	H	H	H	H	H	H			H	H	H	H	H	H	H		H	H	H	H

	KIRP				LUAD				READ				STAD				UCEC			
gene	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
TYK2	H	H	H		H	H	H		H	H	H	H	H	H	H	H	H	H	H	H
0AS1	H	H	H	H	H	H	H	H		H				H	H		H		H	
DPP9		H	H		H	H	H		H	H	H	H	H	H	H	H				
CCR2						H	H		H	H	H	H	H					H	H	H
0AS3	H	H	H		H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H

[a]H indicates higher expression in different stages of cancer indicated by 1, 2, 3 and 4 for each cancer type.

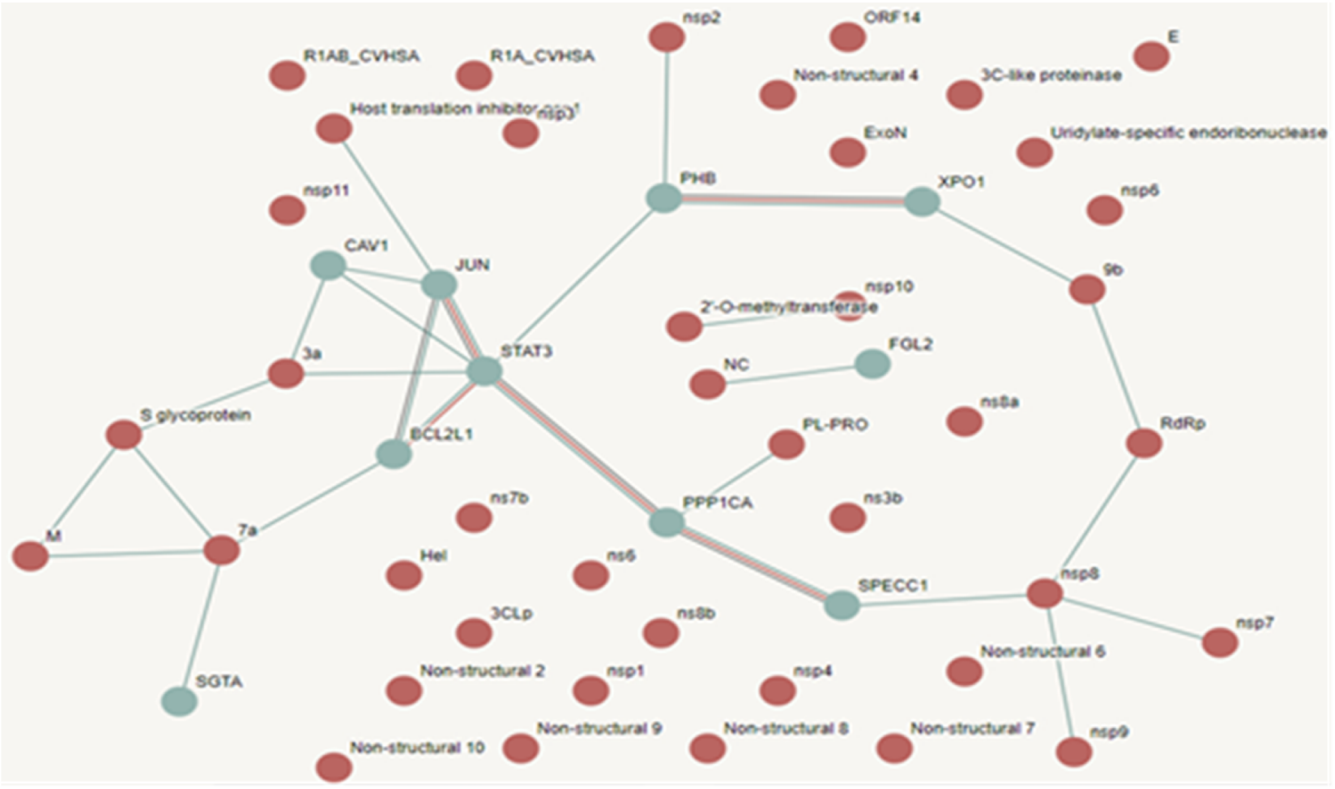

Figure 6. Network of 41 proteins of SARS-CoV2 (in red) interacting with human proteins (gray).

entry into the host cell. There are also a set of host genes that support the virus propagation and growth in host cells, called proviral genes. Our analysis revealed that both *ACE2* and *TMPRSS2* show higher expression in READ and COAD cancers. It is remarkable that the higher expression in colon (COAD) and rectal (READ) cancer types is closely related as they affect the portions of large intestine. Moreover, some studies indicate greater vulnerability of Chinese patients suffering from COAD and READ for COVID-19 viral infections.[22−24] This supports our results that higher

https://doi.org/10.1021/acsomega.2c03764
ACS Omega 2022, 7, 35735−35742

expression of *ACE2* and *TMPRSS2* seen either alone or in combination is associated with READ and COAD cancers.[23] Some cancers which are predominant in their occurrence such as BRCA, HNSC, LICH, LUAD, and LUSC do not show higher expression of these two genes. Further analysis is required to show that patients of these cancer types are not at a higher risk for COVID-19 viral infection and subsequent severity of the symptoms. Many of the proviral genes that support viral propagation are highly expressed in many cancers. Among all the cancers, CHOL and STAD show higher expression of almost all of the proviral genes, thereby increasing the susceptibility of the patients infected with COVID-19. Our results also show that CESC, CHOL, READ, KICH, KIRP, KIRC, COAD, STAD, and LUAD cancers exhibit higher expression of five critical genes that are shown to be responsible for severe COVID-19 infection.

In many cancers, the immune system is so weak not only because of the cancer but also due to the treatment regimens that patients undergo. As immune response plays a major role in the context of COVID-19 viral infections, cancer patients in general are at higher risk of developing severe form of COVID-19. Our results clearly indicate that patients of certain cancers are more susceptible to SARS-CoV-2 infections essentially because of higher expressions of viral receptors and proviral genes.

CONCLUSIONS

In this study, we analyzed the expression of host genes that support the entry and propagation of SARS-CoV-2 across many cancer types. Cancers such as KIRP, READ, KIRC, COAD, STAD, PAAD, PRAD, READ, KICH, COAD, CHOL, and UCEC show higher expression of either *ACE2* or *TMPRSS2* genes, indicating that patients of these cancers may be more vulnerable to the infection. Most of the proviral genes of the host are also expressed in some of the cancers such as CHOL, STAD, and COAD. In general, majority of the cancers that were investigated in our study show higher expression of proviral genes. Further, association rule analysis was carried out to aid clinicians to suspect certain cancers in patients having known the presence of other types of cancers.

MATERIALS AND METHODS

Gene Expression Analysis. For the analysis of gene expression of receptors *ACE2* and *TMPRSS2*, "cBioPortal" (http://www.cbioportal.org/) exploratory analysis tool was used.[14] The gene expression data was found in different cancer data sets. An OncoPrint gives the gene expression a for each sample. A red bar indicates amplification and a blue bar indicates deeply deleted expression. The mRNA expression data is obtained from cBioPortal as a result of computing the relative expression of an individual gene to the distribution of that gene's expression in a reference population. The number of individuals deviating from the mean expression of the gene (z-score) gives a measure of gene expression in terms of either amplification or deletion in tumor samples compared to normal samples. Similar data of expression of *ACE2* and *TMPRSS2* in different cancer types was analyzed using an online web tool UALCAN.[26] It analyses the TCGA data and uses transcripts per million as a measure of gene expression generating box plots by comparing the stage-wise gene expression in tumor versus corresponding normal samples in that data set. Further, differential expression of *ACE2* and *TMPRSS2* was studied across different cancer types using the tool "gene expression profiling interactive analysis" (GEPIA) by comparing the differential expression of the genes in diseased and healthy individuals.[25] The data was plotted as box plots using sex, age, ethnicity, and disease state (tumor vs normal) as variables to get the difference between median of tumor and median of normal sample for obtaining the differential expression data defined by log2FC.

Cancer Stage-Wise Expression. The web tool UALCAN was used to obtain the levels of gene expression in different stages of various cancer types.[26]

Frequent Cancer Pattern and Association Rule Mining. In this study, we used frequent pattern analysis to find frequent cancer patterns that co-express a set of genes. Here, the expression levels of a gene against different types of cancers are considered as a transaction. From the frequent patterns, association rules are generated. An association rule reveals a relationship among the various types of cancers that express a particular gene. For instance, an association rule could be of the form "C1, C2 (10) ⇒ C4 (9)", where C1, C2, and C4 are different types of cancers. In other words, if C1 and C2 express a gene (in this case, they express 10 genes together), then C4 also expresses the gene by 90% (9 among 10 genes are expressed, also known confidence) of the time. We use Apriori algorithm[27] for obtaining frequent items (patterns) and association rules, which is implemented in Waikato Environment for Knowledge Analysis (WEKA).[18]

Frequent pattern (item set) is a set of items (e.g., {C1, C2, C4}) that appears in atleast t number of transactions (t, the threshold) as decided by the user. The Apriori algorithm[15] finds frequent item sets iteratively in increasing order of item size. It starts with finding singleton frequent item sets (e.g., {C1}, {C2}, and {C3}); next, it finds two-item frequent sets by combining the singleton frequent item sets (e.g., {C1, C2} and {C1, C3}). In general, it finds k-item frequent sets based on (k-1)-item frequent item sets. For instance, let {C1, C2}, {C1, C3}, {C2, C3}, and {C2, C4} are two-item frequent sets. From these, first, it generates three-item candidate sets (e.g., {C1, C2, C3} and {C2, C3, C4}). Subsequently, transaction count is computed by reading the database to verify if they are frequent.

Protein Network. String database (https://string-db.org) was used for the construction of the network diagram between human proteins and viral proteins.[28] Cancer (oncogenic) proteins from Catalogue of Somatic Mutations in Cancer (COSMIC, https://cancer.sanger. ac.uk/cosmic/download) were loaded into Cytoscape (https://cytoscape.org/) to plot a network between the human cancer genes and their interactions with viral proteins.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c03764.

mRNA expression of *ACE2* across different cancers; mRNA expression of *TMPRSS2* across different cancers; and PPI network of human proteins (PDF)

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https://doi.org/10.1021/acsomega.2c03764
ACS Omega 2022, 7, 35735−35742

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a grant from the Department of Science and Technology, Government of India [ECR/2016/001685], to Dr. D.N.R.S. T.K. was supported by the fellowship from this grant.

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https://doi.org/10.1021/acsomega.2c03764
ACS Omega 2022, 7, 35735−35742