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Differential expression and immune correlation analysis of COVID-19 receptor ACE2 and TMPRSS2 genes in all normal and tumor tissues

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Abstract. – The outbreak of COVID-19 seriously affected people's life and safety, and it has not been effectively controlled all over the world at present. The binding of S protein of SARS-COV-2 virus to ACE2 receptor requires the assistance of Transmembrane Serine Protease 2 (TMPRSS2), which can activate the S protein on the surface of virus and promote its binding to the ACE2 receptor. With the continuous accumulation of experience in the treatment of COVID-19 patients and the experimental studies of a large number of scientific researchers, it was found that COVID-19 patients had a higher mortality rate in patients with underlying diseases. Therefore, for COVID-19 patients with tumors, the mortality rate may be significantly higher than other people. Clinical studies had found that some patients were complicated with cytokine storm in clinical treatment, which was also the direct cause of death for some patients. The infiltration of immune cells and the release of a variety of cytokines were important factors causing cytokine storm. Therefore, for COVID-19 patients with tumors, it was of great clinical significance to explore the relationship between COVID-19 virus receptor ACE2, TMPRSS2 and immune cell infiltration, which can help clinicians to make some more appropriate treatment plans.

Key Words:
COVID-19, SARS-COV-2, ACE2, TMPRSS2.

Abbreviations

COVID-19: Corona Virus Disease 2019; SARS-COV-2: Severe acute respiratory syndrome coronavirus 2; TCGA: The Cancer Genome Atlas; GTEx: Genotype-Tissue Expression; ACE2: Angiotensin converting enzyme 2; TMPRSS2: Transmembrane Serine Protease 2; ACC: Adrenocortical carcinoma; BLCA: Bladder Urothelial Carcinoma; BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: Cholangiocarcinoma; COAD: Colon adenocarcinoma; DLBC: Lymphoid Neoplasm Diffuse Large B-cell Lymphoma; ESCA: Esophageal carcinoma; GBM: Glioblastoma multiforme; HNSC: Head and Neck squamous cell carcinoma; KICH: Kidney Chromophobe; KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute Myeloid Leukemia; LGG: Brain Lower Grade Glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MESO: Mesothelioma; OV: Ovarian serous cystadenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and Paraganglioma; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcoma; SKCM: Skin Cutaneous Melanoma; STAD: Stomach adenocarcinoma; TGCT: Testicular Germ Cell Tumors; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine Corpus Endometrial Carcinoma; UCS: Uterine Carcinosarcoma; UVM: Uveal Melanoma.

Introduction

Short Report

Current studies found that the key to the invasion of SARS-COV-2 virus was the binding of S protein on the surface of virus to human angiotensin converting enzyme 2 (ACE2). ACE2 was the binding target for the virus to invade human cells. The article published by Wrapp et al[1] in the top international journal "Science" on March 13, 2020 confirmed that the binding

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ability of the S protein of SARS-COV-2 virus to ACE2 was much higher than that of SARS coronavirus, which was also one of the reasons why the transmission ability of SARS-COV-2 virus was much higher than that of SARS virus. With further development of the research Hoffmann et al[2] published in the top international journal "Cell" on April 16, 2020. It was confirmed that the binding of S protein of SARS-COV-2 virus to ACE2 requires the assistance of Transmembrane Serine Protease 2 (TMPRSS2) in human cells, which can activate the S protein on the surface of the virus and promote its binding to the ACE2 receptor. With the continuous accumulation of experience in the treatment of COVID-19 patients and the experimental studies of a large number of scientific researchers, it was found that COVID-19 patients have a higher mortality rate in patients with underlying diseases[3,4]. Therefore, for COVID-19 patients with tumors, the mortality rate may be significantly higher than other people[5]. Clinical studies[6-9] found that some patients were complicated with cytokine storm in clinical treatment, which was also the direct cause of death for some patients. The infiltration of immune cells and the release of a variety of cytokines are important factors causing cytokine storm. Therefore, for COVID-19 patients with tumor, it is of great clinical significance to explore the relationship between SARS-COV-2 virus receptor ACE2, TMPRSS2 and immune cell infiltration, which can help clinicians to make some more appropriate treatment plans.

The GTEx database[10-12] contains the whole genome sequencing information of 31 normal human tissues, so it can be used to study the expression of ACE2 and TMPRSS2 genes in normal human tissues and the correlation between them. Tissues with high expression of ACE2 and TMPRSS2 genes may be more vulnerable to SARS-COV-2 virus, especially those tissues with positive correlation between ACE2 and TMPRSS2 gene expression. The data were downloaded from UCSC Xena (https://xenabrowser.net/datapages/) website, the data were normalized. As shown in Figure 1, we found that ACE2 gene was highly expressed in adipose tissue, small intestine, esophagus, kidney, thyroid, testis, colon and other tissues. As shown in Figure 2, we found that TMPRSS2 gene was highly expressed in small intestine, pituitary, thyroid, prostate, kidney, liver, lung, testis, colon and other tissues. This is also consistent with the conclusion reported in the literature that SARS-COV-2 virus can attack testis[13,14]. Through correlation analysis (Spearman correlation analysis), as shown in Figure 3 (drawing statistically significant tumor types, $p<0.05$), we found that there was a positive correlation between ACE2 and TMPRSS2 gene expression in small intestine, thyroid, esopha-

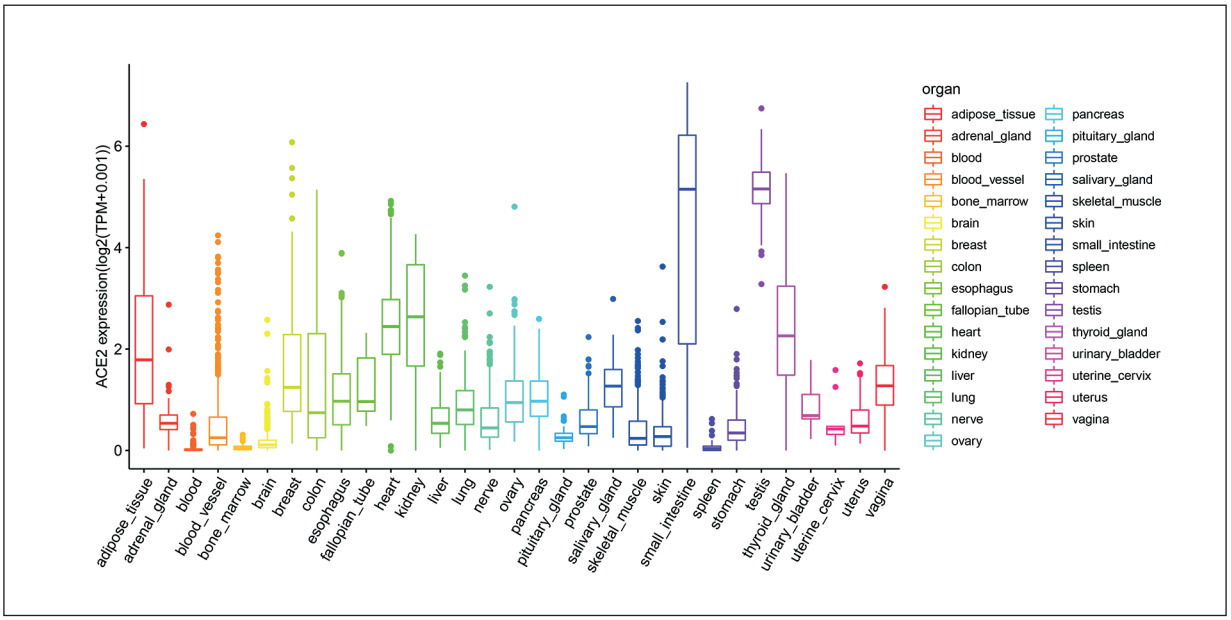

Figure 1. Expression of ACE2 gene in normal tissues.

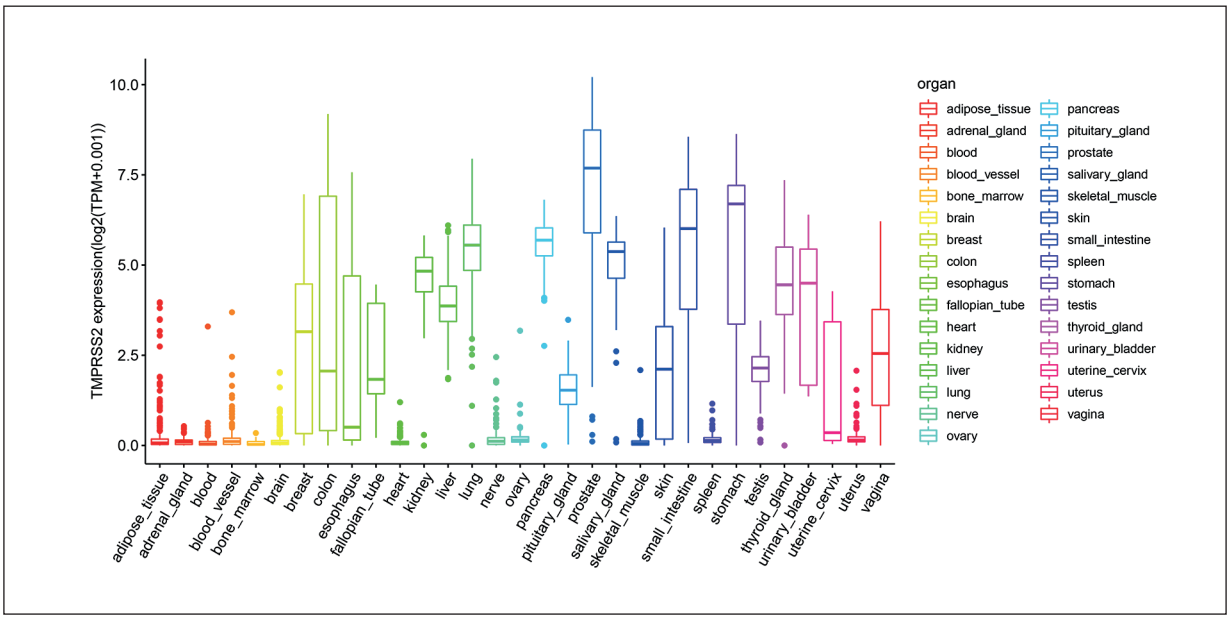

Figure 2. Expression of TMPRSS2 gene in normal tissues.

gus, kidney, lung, liver, colon and other tissues, and the correlation was statistically significant(p<0.05).

The TCGA database[15-17] contains the whole genome sequencing information of 33 kinds of tumor patients, so it can be used to study the difference of ACE2 and TMPRSS2 gene expression between normal tissue and tumor tissue. At the same time, it can also be used to explore the relationship between genes and immune cell infiltration. The data were downloaded from UCSC Xena (https://xenabrowser.net/datapages/) website, the data were normalized. As shown in Figure 4, the expression of ACE2 gene in cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), glioma (GBM), kidney renal papillary cell carcinoma (KIRP), lung adenocarcinoma (LUAD) and uterine corpus endometrial carcinoma (UCEC) were significantly higher than that in paracancerous tissues, and the difference were statistically significant(p<0.05). Therefore, patients with this kind of tumors may be more vulnerable to be attacked by SARS-COV-2 virus, which needs special attention in clinical work. As shown in Figure 5, the expression of TMPRSS2 gene in kidney chromophobe (KICH), Prostate adenocarcinoma (PRAD) and uterine corpus endometrial carcinoma (UCEC) was significantly higher than that in paracancerous tissues, and the difference is statistically significant(p<0.05). Because TMPRSS2 gene mainly promotes the binding of SARS-COV-2 virus S protein to ACE2. So, we need to pay attention not only to tumor tissues with high expression, but also to paracancerous tissues with high expression. The expression of TMPRSS2 gene were also high in paracancerous tissues such as esophageal cancer (ESCA), colon adenocarcinoma (COAD), rectum adenocarcinoma (READ), lung adenocarcinoma (LUAD), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP) and so on.

Patients infected with SARS-COV-2 virus often had cytokine storm in the treatment process, which was a strong systemic inflammatory response syndrome[6,18]. For tumor patients, immune cell infiltration was an important part of tumor microenvironment[19,20]. Therefore, it was of great clinical significance to calculate the correlation between ACE2, TMPRSS2 genes and immune cells infiltration in tumor patients with COVID-19. Through the "estimate" package of R software, the immune cells were scored by "ESTIMATE" method[21], and the correlation between immune cells and ACE2, TMPRSS2 genes expression were calculated. As shown in Figure 6 (drawing statistically significant tumor types, p<0.05), we found that ACE2 gene were positively correlated with immune

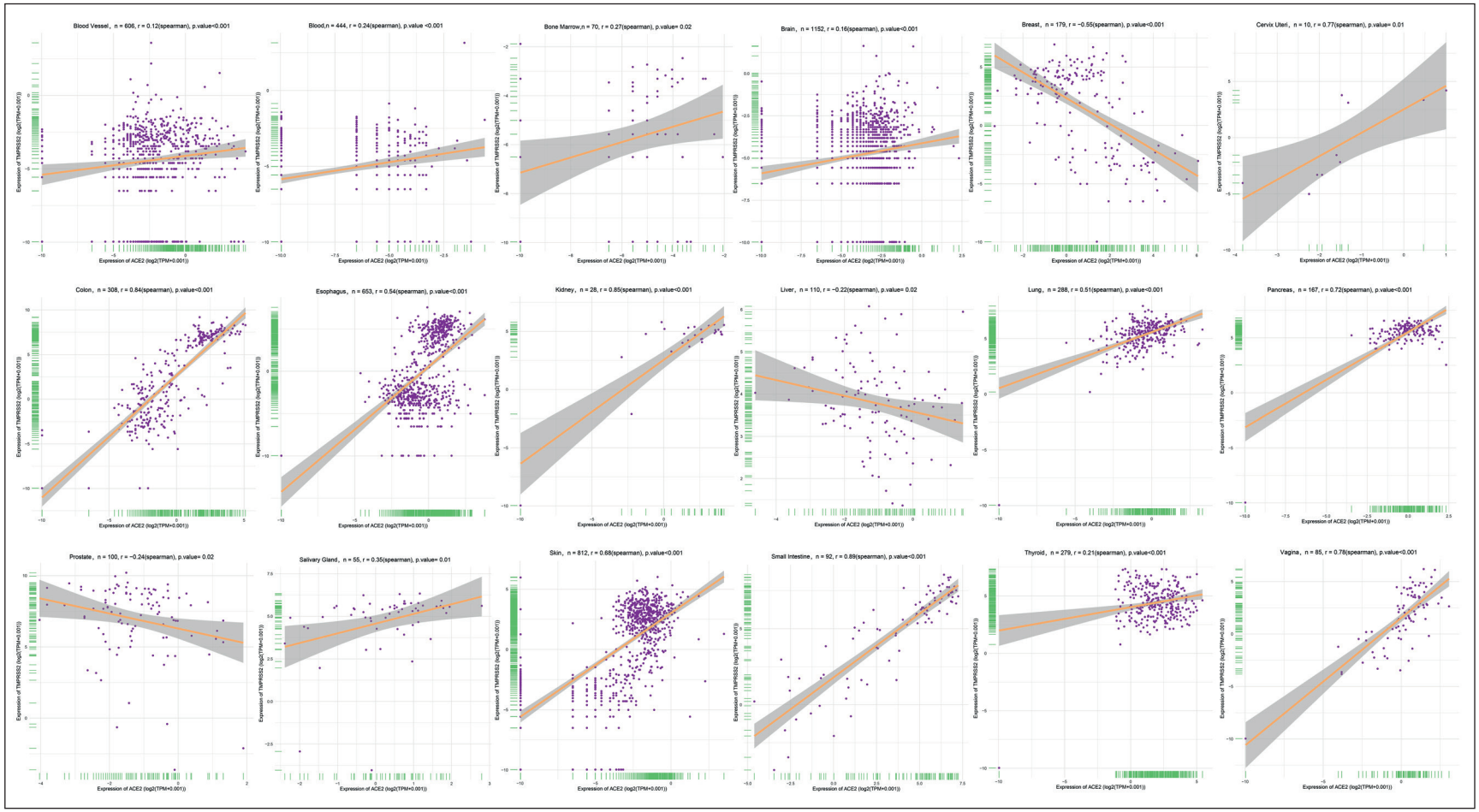

Figure 3. Correlation analysis of ACE2 and TMPRSS2 genes expression in normal tissues.

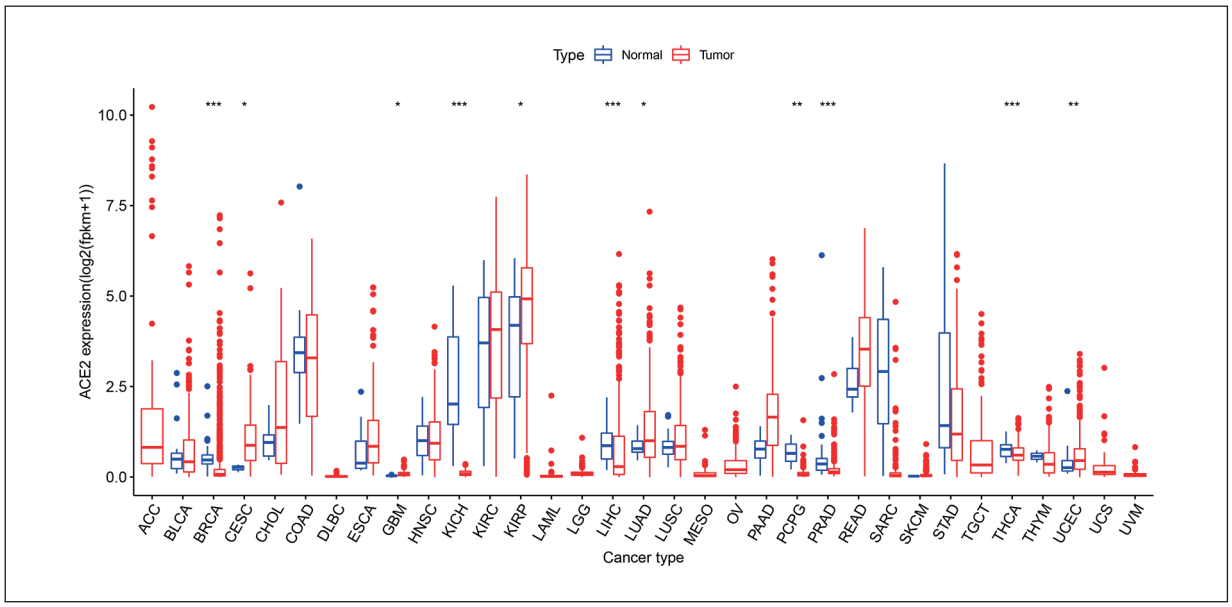

Figure 4. Differential expression of ACE2 gene in paracancerous and tumor tissues. ('***' p<0.001 '**' p < 0.01 '*p <0.05).

score in BLCA (Bladder Urothelial Carcinoma), BRCA (Breast invasive carcinoma), CESC(Cervical squamous cell carcinoma and endocervical adenocarcinoma), HNSC(Head and Neck squamous cell carcinoma), OV (Ovarian serous cystadenocarcinoma), PAAD (Pancreatic adenocarcinoma), PRAD (Prostate adenocarcinoma), STAD (Stomach adenocarcinoma), THCA(Thyroid carcinoma) and UCEC (Uterine Corpus Endometrial Carcinoma), and the correlation(-Spearman correlation analysis) were statistically significant (p<0.05). TMPRSS2 gene were positively correlated with immune score in BRCA (Breast invasive carcinoma), LGG (Brain Lower Grade Glioma), LUSC (Lung squamous cell carcinoma), THCA (Thyroid carcinoma) and UCS

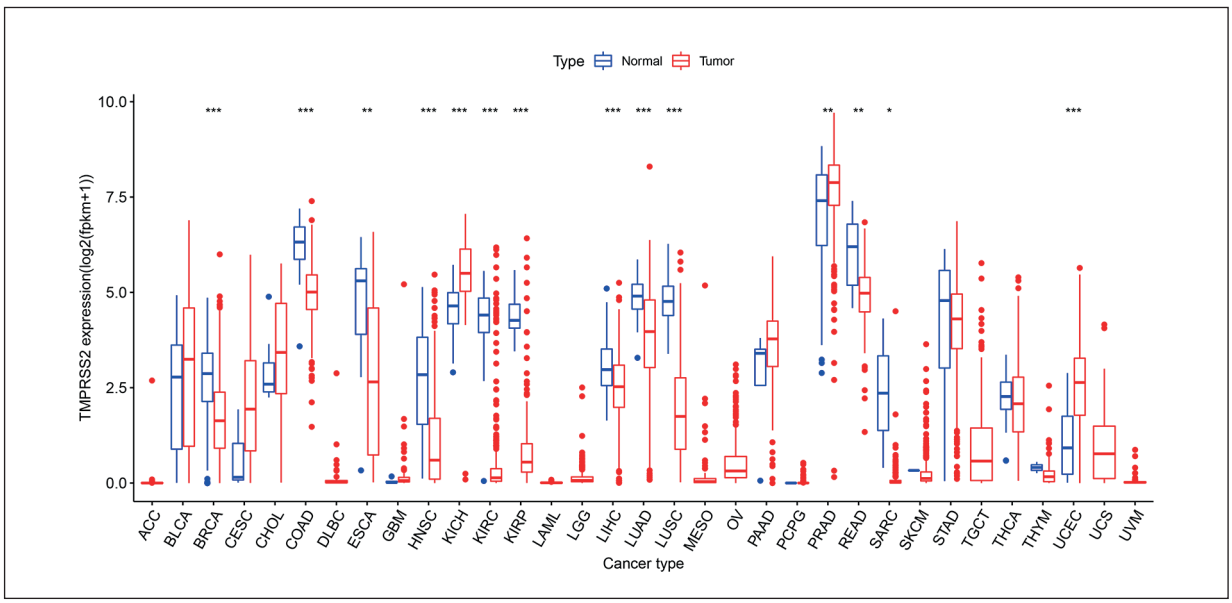

Figure 5. Differential expression of TMPRSS2 gene in paracancerous and tumor tissues. ('***' p <0.001 '**' p < 0.01 '*' p <0.05).

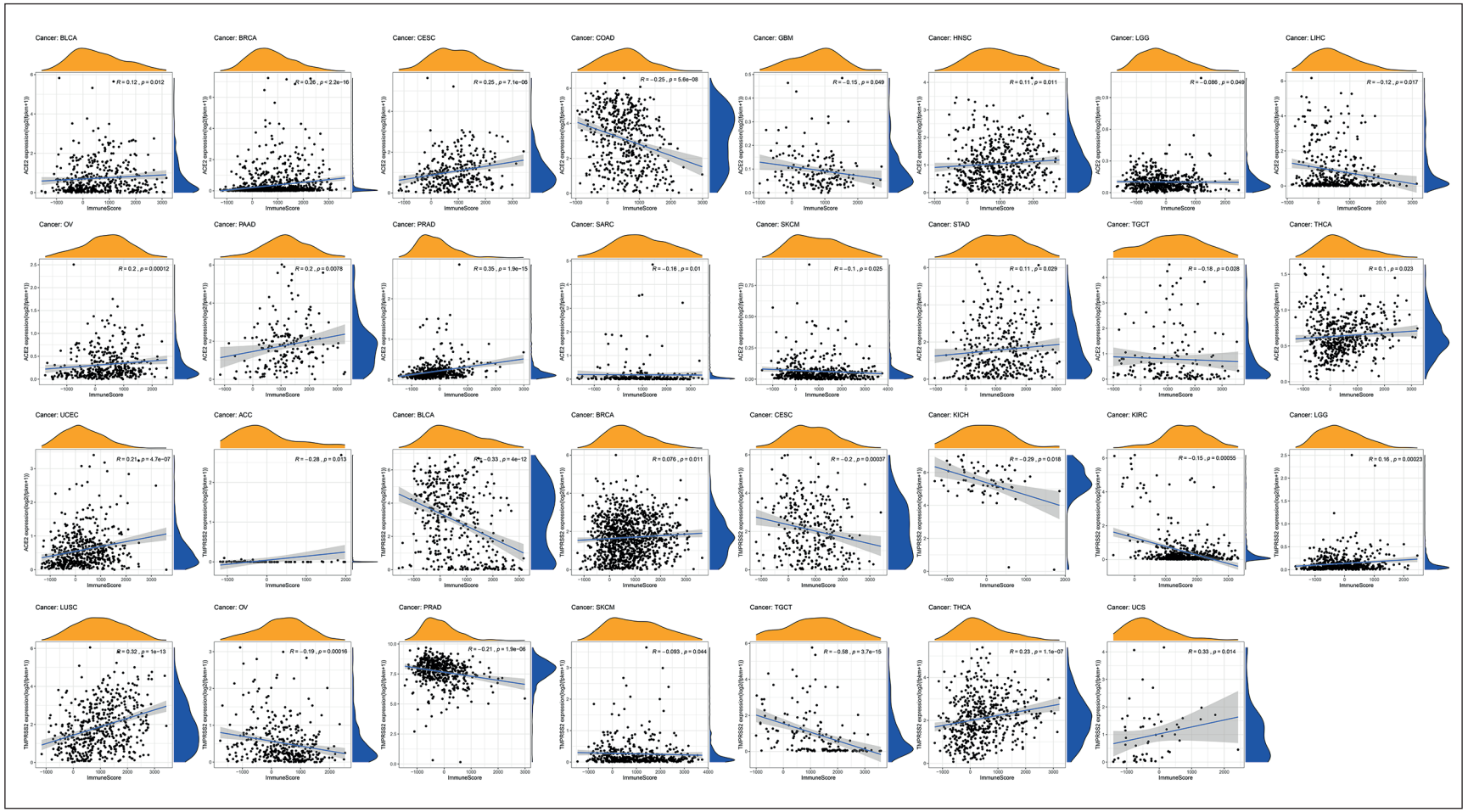

Figure 6. Correlation between ACE2, TMPRSS2 genes expression and immune score.

(Uterine Carcinosarcoma), and the correlation (Spearman correlation analysis) were statistically significant ($p<0.05$).

Through this study, we revealed the expression of ACE2 and TMPRSS2 genes in all normal and tumor tissues and their immune correlation and had a preliminary understanding of the attack ability of SARS-COV-2 virus on various organs and tissues of human body. For example, ACE2 and TMPRSS2 genes were highly expressed in small intestine, esophagus, kidney and other tissues, and the expression of these two genes were positively correlated.

Conclusions

Therefore, benign diseases associated with these tissues require our special attention because they were more vulnerable to COVID-19 virus. For patients with uterine corpus endometrial carcinoma (UCEC), the expression of ACE2 and TMPRSS2 genes were significantly higher than that in paracancerous tissues, and the difference were statistically significant, so patients with UCEC were more likely to be infected with COVID-19. There was a significant positive correlation between ACE2 gene expression and immune cell infiltration in patients with esophageal cancer (ESCA), uterine corpus endometrial carcinoma (UCEC) and other tumors, so we must pay attention to immune-related therapy for such patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

Hu, and Liu drafted the manuscript. Gong and Cao conceived the idea and recommended this magazine. All the authors participated in the revision of this manuscript. All authors read and approved the final manuscript.

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