

Possible Causes of Gender Differences in COVID-19 Infection Rate and Mortality

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Research Article

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Abstract

Purpose To study the causes of gender differences in infection rate and mortality of COVID-19.

Methods According to the confirmed results so far, it was found that the expression of ACE2, TMPRSS2, NRP1 and FURIN genes were related to SARS-COV-2 virus infected cells; CD4, CD8 and NLRP3 genes were related to human immunological response; NSP1 gene was related to immunosuppression; IL6 (IL-6), IFNG (IFN- γ) and TNF (TNF- α) genes were related to the occurrence of cytokine storm. The differential expression of these genes between male and female were analyzed in normal and tumor patients, and further analyzed in different locations of normal and tumor tissues to find out risk factors affecting the infection rate and mortality.

Results In our study, we identified that in the lung tissue, the expression level of ACE2, TMPRSS2, NRP1 and FURIN genes in male patients were higher than those in female patients. In all normal tissues of patients: NRP1, FURIN and NSP1 genes were significantly higher expressed in female. In all tumor tissues of patients: ACE2, FURIN and IL-6 genes were significantly higher expressed in male, while TMPRSS2, CD4, CD8, NLRP3, NSP1 and TNF genes were significantly higher expressed in female.

Conclusions The significant differential expression of SARS-COV-2 receptor related genes and immune response related genes between male and female patients may be the reason for the difference in COVID-19 infection rate and mortality. The expression of COVID-19-related genes in normal and tumor patients were also significantly different, so clinical treatment should be treated differently.

Introduction

The outbreak of COVID-19 had seriously affected the lives and health of people all over the world. At present, many literatures had confirmed that COVID-19 infection rate and mortality of male and female patients were significantly different, but the specific reasons were not clear. As shown in Fig. 1, the SARS-COV-2 virus enters the host cells by binding of the viral surface spike glycoprotein (S-protein) to the cellular angiotensin converting enzyme 2 (ACE2) receptor^[1, 2]. TMPRSS2 and FURIN proteins^[3-5] can cooperatively activate S-protein and help virus bind to ACE2 receptor^[6]. NRP1 (neuropilin-1) can bind to the substrate cleaved by furin protein and significantly enhance the infectivity of SARS-CoV-2^[7, 8]. Therefore, from the current research, SARS-COV-2 virus infection cells mainly rely on the assistance of ACE2, TMPRSS2, NRP1 and FURIN. SARS-COV-2 virus can induce human immune response after infecting host cells and tissues. CD4⁺T and CD8⁺T cells produced by CD4 and CD8 genes were mainly involved in human immune response^[9-11]. NLRP3 (Nod-like receptor family, pyrin domain-containing 3) inflammasome triggers the release of various cytokines and also participate in human immune response^[12, 13]. NSP1 (nonstructural protein 1) was the major virulence^[14] factor of SARS-COV-2 virus, which suppresses host gene expression by ribosome association. Therefore, it can block normal immune response of the human body, so as to avoid virus being cleared by human immune cells. A growing body of clinical data show that cytokine storm was associated with the severity of COVID-19, and it was also a

crucial cause of death from COVID-19. Cytokine storm was an over-activation of the immune system caused by SARS-COV-2 virus infection, which rapidly produces a variety of cytokines such as IL-6, IFN- γ (IFNG) and TNF- α (TNF), resulting in acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS)^[15-18]. Therefore, we studied the differential expression of these genes between male and female patients in normal and tumor tissues, which may play a guiding role in finding the causes of gender differences in COVID-19 infection rate and mortality.

Data And Methods

Gene expression data of normal patients

GTEX (Genotype-Tissue Expression) database^[19] contains whole-genome sequencing information of normal human tissues. By downloading the whole-genome sequencing information of normal patients in GTEX database (<https://xenabrowser.net/datapages/>). The data were normalized to compare the differential expression of ACE2, TMPRSS2, NRP1, FURIN, CD4, CD8, NLRP3, NSP1, IL6, IFNG and TNF genes in normal patients of different genders.

Gene expression data of tumor patients

TCGA (The Cancer Genome Atlas) database^[20] contains whole-genome sequencing information of 33 types of tumors. By downloading the whole-genome sequencing information of tumor patients in TCGA database (<https://xenabrowser.net/datapages/>). The data were normalized to compare the differential expression of ACE2, TMPRSS2, NRP1, FURIN, CD4, CD8, NLRP3, NSP1, IL6, IFNG and TNF genes in tumor patients of different genders.

Statistical methods

The difference of genes expression between male and female patients were compared by “wilcox” test, and it was considered that when $P < 0.05$, the difference was statistically significant. All statistical analyses were performed by R software (version: 3.6.0).

Results

Differential expression of genes related to SARS-COV-2 infection pathways in normal and tumor patients with different genders

As shown in Fig. 2a-b: ACE2 higher expression in breast, esophagus and skeletal muscle tissues of normal male patients ($P < 0.05$). In blood, brain and heart tissues, the expression of normal female patients was higher ($P < 0.05$). ACE2 higher expression in female with BLCA, BRCA, HNSC and KIRC tumor types ($P < 0.05$). As shown in Fig. 2c-d: TMPRSS2 higher expression in breast and heart tissues of normal female patients ($P < 0.05$). TMPRSS2 higher expression in female with LIHC, LUAD and LUSC tumor types ($P < 0.05$). As shown in Fig. 2e-f: The expression of NRP1 was higher in adrenal gland tissues of normal female patients, and higher in breast and skeletal muscle tissues of normal male patients ($P < 0.05$).

NRP1 higher expression in female patients with GBM ($P < 0.05$). As shown in Fig. 2g-h: The expression of FURIN was higher in adipose and heart tissues of normal female patients, and higher in breast and nerve tissues of normal male patients ($P < 0.05$). The expression of FURIN was higher in female patients with HNSC, KIRC, KIRP, LGG, LIHC and LUSC tumors, and higher in male patients with PCPG ($P < 0.05$).

Differential expression of immune response-related genes in normal and tumor patients with different genders

As shown in Fig. 3a-b: CD4 higher expression in brain and thyroid gland tissues of normal male patients ($P < 0.05$). The expression of CD4 was higher in female patients with BLCA, BRCA, HNSC, LUAD and LUSC tumors, and higher in male patients with ACC, KIRC and SARC tumor types ($P < 0.05$). As shown in Fig. 3c-d: CD8 higher expression in breast tissues of normal female patients ($P < 0.05$). In blood vessel, the expression of normal male patients was higher ($P < 0.05$). CD8 higher expression in female with BRCA, HNSC and LUSC tumor types ($P < 0.05$). As shown in Fig. 3e-f: NLRP3 higher expression in adipose and thyroid gland tissues of normal female patients ($P < 0.05$). NLRP3 higher expression in female with BLCA, BRCA, COAD, HNSC, LUAD, LUSC, PAAD and THCA tumor types ($P < 0.05$).

Differential expression of immunosuppression-related genes in normal and tumor patients with different genders

As shown in Fig. 4a-b: NSP1 higher expression in brain and breast tissues of normal female patients ($P < 0.05$). The expression of NSP1 was higher in female patients with LIHC, and higher in male patients with KIRP and PAAD tumor types ($P < 0.05$).

Differential expression of cytokine storm-related genes in normal and tumor patients with different genders

As shown in Fig. 5a-b: IL-6 higher expression in blood vessel and esophagus tissues of normal male patients ($P < 0.05$). In brain and spleen tissues, the expression of normal female patients was higher ($P < 0.05$). The expression of IL-6 was higher in female patients with BRCA, KIRP and PAAD tumors, and higher in male patients with PCPG ($P < 0.05$). As shown in Fig. 5c-d: IFNG higher expression in adrenal gland and colon tissues of normal male patients ($P < 0.05$). In skeletal muscle, the expression of normal female patients was higher ($P < 0.05$). IFNG higher expression in female with BRCA and LUSC tumor types ($P < 0.05$). As shown in Fig. 5e-f: TNF higher expression in brain and breast tissues of normal female patients ($P < 0.05$). The expression of TNF was higher in female patients with BRCA, LUAD, PAAD and SKCM tumors, and higher in male patients with GBM ($P < 0.05$).

Differential expression of these genes in all normal and tumor tissues with different genders

As shown in Fig. 6a: In all normal patients, the expression of NRP1, FURIN and NSP1 genes in female patients were significantly higher ($P < 0.05$). As shown in Fig. 6b: In all tumor patients, The expression of ACE2, FURIN and IL-6 genes were higher in male patients, and the expression of TMPRSS2, CD4, CD8, NLRP3, NSP1 and TNF genes were higher in female patients($P < 0.05$).

Discussion

The infection rate^[21] and mortality^[22, 23] of male patients with COVID-19 were significantly higher than that of female patients, which had been recognized by many scholars, but the specific reasons were not clear^[24, 25]. SARS-COV-2 virus infection host cells mainly rely on the assistance of ACE2, TMPRSS2, NRP1 and FURIN. Human immune response induced by virus mainly depends on cytokines produced by CD4, CD8 and NLRP3 genes. NSP1 was the major virulence factor of SARS-COV-2 virus. It inhibits the expression of host gene by ribosome association and can block the normal immune response of human body, thus preventing virus from being cleared by immune cells in early stage. The expression of IL6, IFNG and TNF genes were related to the occurrence of cytokine storm. Cytokine storm was a crucial cause of death in patients with the later stage of COVID-19^[26, 27]. At present, it was generally believed that COVID-19 patients with underlying diseases had a higher mortality^[28]. Tumor patients were a special type of underlying diseases^[29, 30], because the basic immunity of tumor patients was significantly lower than that of normal patients, which required our special attention. Therefore, the study of differential expression of these genes in normal and tumor patients with different genders can help us to preliminarily understand the reasons for the differences in COVID-19 infection rate and mortality.

The study of differential expression of ACE2, TMPRSS2, NRP1 and FURIN genes between male and female patients in normal and tumor tissues, which can help us to preliminary understand the infection ability of SARS-COV-2 in patients with different genders. The study of differential expression of CD4, CD8 and NLRP3 genes between male and female patients in normal and tumor tissues, which can help us to preliminary understand the differences of immune response in patients with different genders. The study of differential expression of NSP1 gene between male and female patients in normal and tumor tissues, which can help us to preliminary understand the immunosuppressive ability of SARS-COV-2 in patients with different genders. The study of differential expression of IL-6, IFNG and TNF genes between male and female patients in normal and tumor tissues, which can help us to preliminary explain the reasons for the differences in mortality of COVID-19 patients with different genders.

This study was also the first time to study SARS-COV-2 virus-related genes of normal and tumor patients respectively, so as to make the results more reliable. Through this study, we found that the expression of ACE2, TMPRSS2, NRP1 and FURIN genes were higher in normal lung tissues of male patients. These genes were the key factors of SARS-COV-2 infected host cells, although the differential expression was not statistically significant, but this may be a reason for the higher infection rate in male patients. However, in all tumor patients, ACE2 and FURIN genes were significantly overexpressed in male patients, and the difference was statistically significant, so the infection rate of COVID-19 in male tumor patients

may be higher. For the reason that mortality of male patients was significantly higher than that of female patients, through this study, we found that the expression of NSP1 was significantly higher in normal female patients. Cytokine storm plays an important role in severe cases of COVID-19, and have been reported as a main cause of death. In the later stage of COVID-19 patients, NSP1 could appropriately inhibit the accumulation and release of cytokines, so it was possible that female patients have a lower probability of cytokine storm, resulting in a lower mortality. In all tumor patients, the expression of CD4, CD8 and NLRP3 genes were significantly overexpressed in female patients. These genes were mainly involved in the early immune response, killing infected SARS-COV-2 virus in cells and tissues. Therefore, it was possible that female patients have a faster immune response^[31] and stronger ability to kill the virus in early stage, resulting in a significantly lower mortality than male. Of course, immune response was a very complex process, and there were still many immune mechanisms which could not be explained. While, in different stages of disease, the same cytokine may play the opposite immune function^[32]. The conclusions of this paper also need to be confirmed by more studies in the future. At the same time, we also studied the differential expression of these genes between male and female patients in different locations of normal and tumor tissues, which can help us to carry out individualized treatment for different types of diseases, increase the cure rate of COVID-19 patients and reduce the mortality.

Conclusion

In summary, SARS-COV-2 virus receptor-related genes (ACE2, TMPRSS2, NRP1 and FURIN) and immune response-related genes (CD4, CD8, NLRP3) have significant expression differences in male and female patients, which may be the reasons that lead to different COVID-19 infection rates and fatality rates among patients of different genders. At the same time, because the expression levels of COVID-19-related genes in normal people and cancer patients are significantly different, clinical treatment should be treated differently.

Abbreviations

SARS-COV-2

Severe acute respiratory syndrome coronavirus 2; COVID-19: Corona Virus Disease 2019; GTEX: Genotype-Tissue Expression; TCGA: The Cancer Genome Atlas; SIRS: Systemic Inflammatory Response Syndrome; ARDS: Acute Respiratory Distress Syndrome; MODS: Multiple Organ Dysfunction Syndrome; ACE2: Angiotensin converting enzyme 2; TMPRSS2: Transmembrane Serine Protease 2; NRP1: Neuropilin-1; NLRP3: Nod-like receptor family, pyrin domain-containing 3; NSP1: Nonstructural Protein-1, IL6: Interleukin-6; IFNG: Interferon Gamma; TNF: Tumor Necrosis Factor; LGG: Brain Lower Grade Glioma; LUSC: Lung squamous cell carcinoma; ESCA: Esophageal carcinoma; CHOL: Cholangiocarcinoma; ACC: Adrenocortical carcinoma; HNSC: Head and Neck squamous cell carcinoma; LAML: Acute Myeloid Leukemia; MESO: Mesothelioma; LIHC: Liver hepatocellular carcinoma; KICH: Kidney Chromophobe; KIRC: Kidney renal clear cell carcinoma; OV: Ovarian serous cystadenocarcinoma; LUAD: Lung adenocarcinoma; PCPG: Pheochromocytoma and Paraganglioma; PRAD: Prostate adenocarcinoma; THCA: Thyroid

carcinoma; THYM:Thymoma; TGCT:Testicular Germ Cell Tumors; GBM:Glioblastoma multiforme; KIRP:Kidney renal papillary cell carcinoma; UCEC:Uterine Corpus Endometrial Carcinoma; SKCM:Skin Cutaneous Melanoma; CESC:Cervical squamous cell carcinoma and endocervical adenocarcinoma; DLBC:Lymphoid Neoplasm Diffuse Large B-cell Lymphoma; COAD:Colon adenocarcinoma; READ:Rectum adenocarcinoma; UCS:Uterine Carcinosarcoma; BLCA:Bladder Urothelial Carcinoma; PAAD:Pancreatic adenocarcinoma; STAD:Stomach adenocarcinoma; SARC:Sarcoma; UVM:Uveal Melanoma; BRCA:Breast invasive carcinoma.

Declarations

Contributorship Statement

Can Liu and Renwang Hu drafted the manuscript. Yongqing Yu 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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Competing with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This study does not contain any human or animal investigation

Informed consent

No animal or human was involved

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Figures

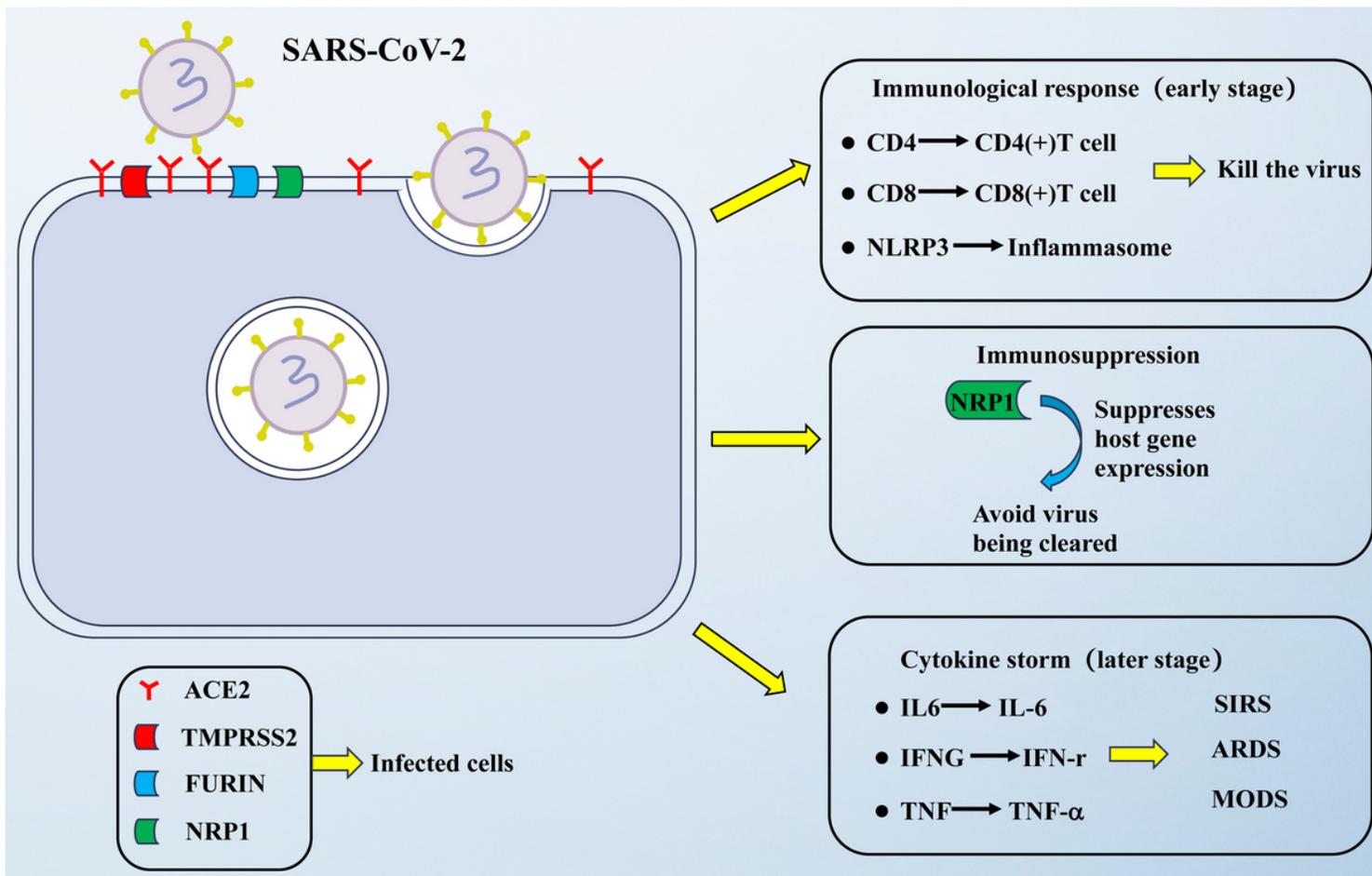


Figure 1

The interaction between SARS-COV-2 virus-related genes and host cells

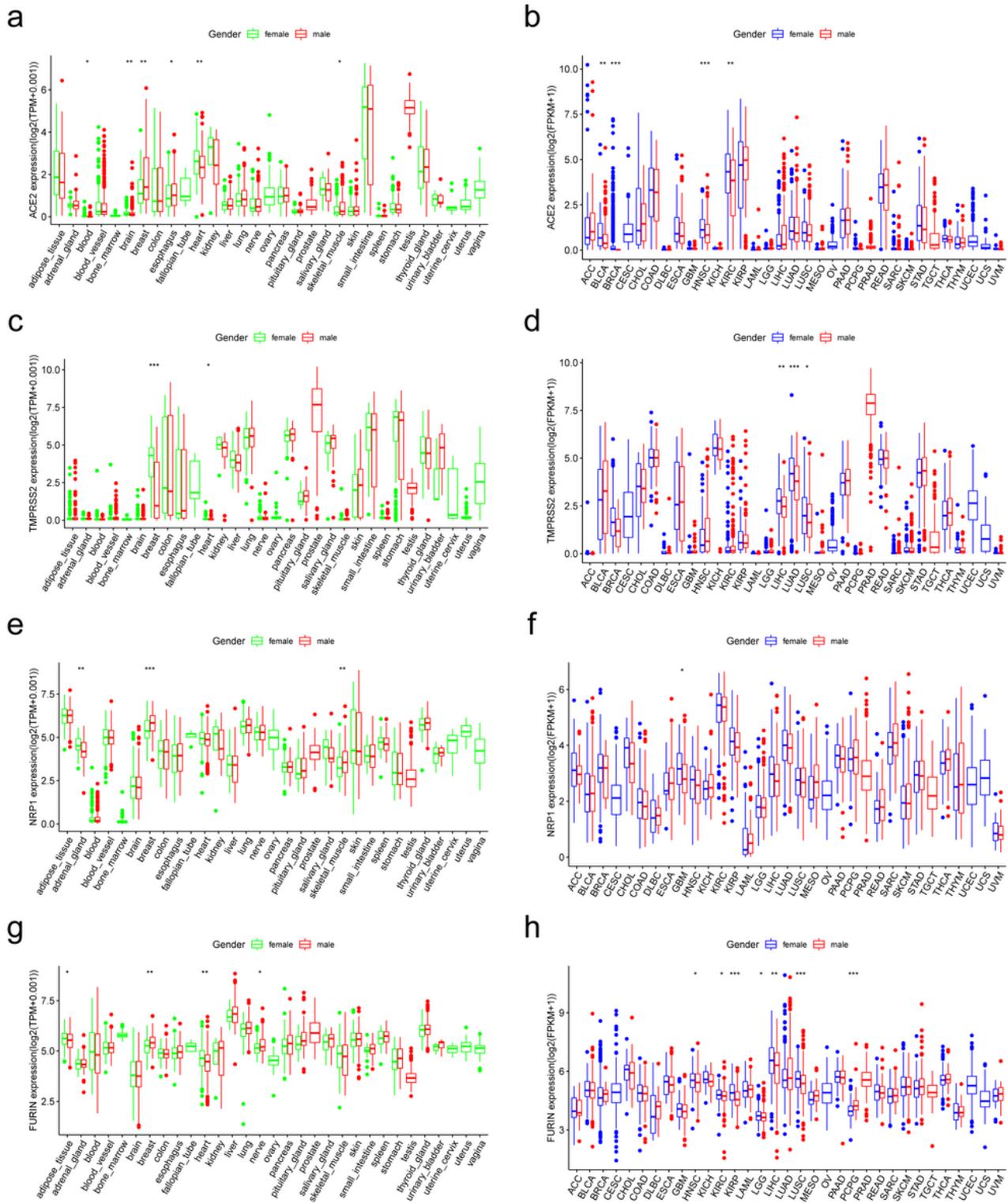


Figure 3

Differential expression of ACE2, TMPRSS2, NRP1 and FURIN genes between male and female patients in normal and tumor tissues. (‘***’ $p < 0.001$ ‘**’ $p < 0.01$ ‘*’ $p < 0.05$)

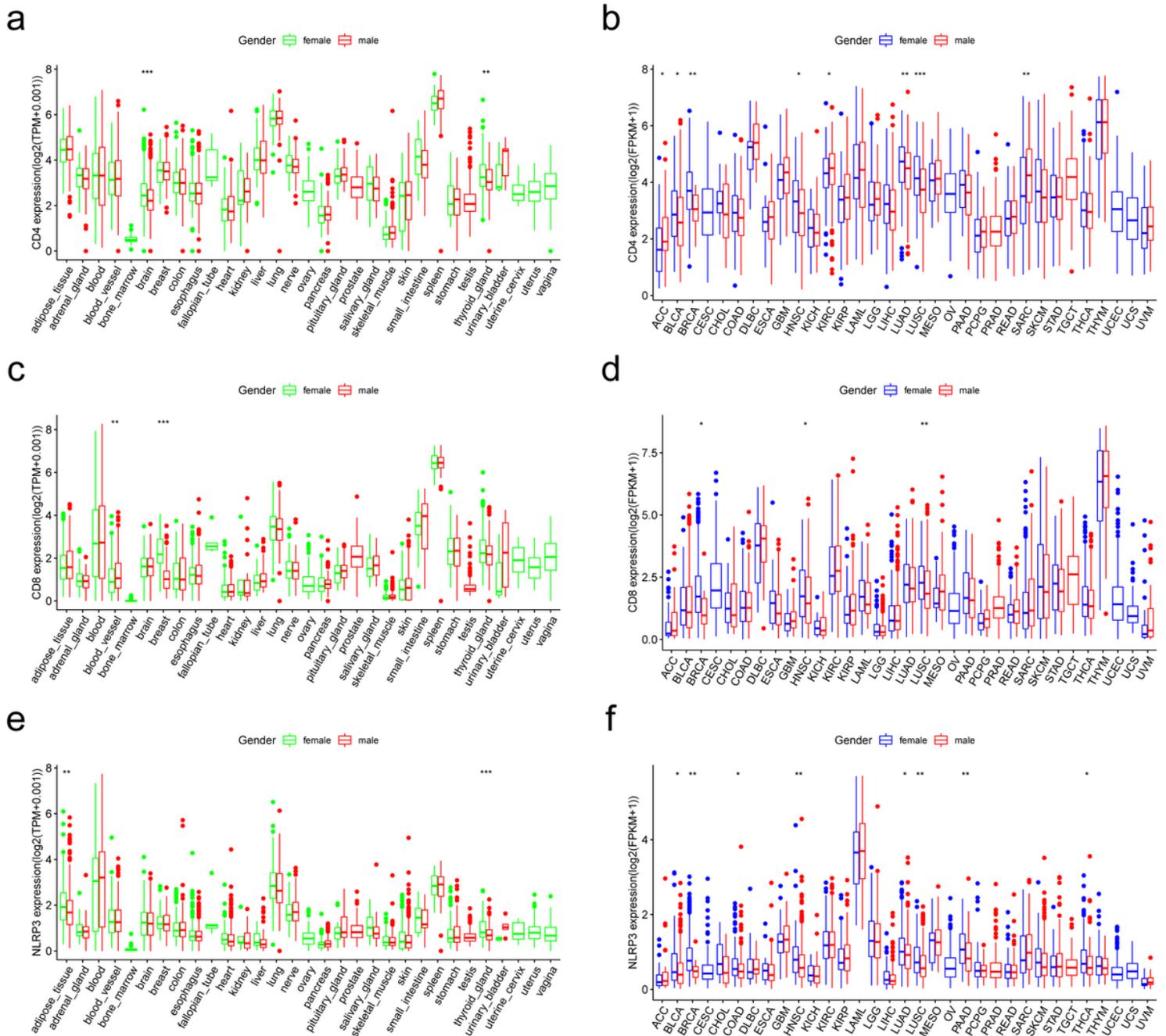


Figure 4

Differential expression of CD4, CD8 and NLRP3 genes between male and female patients in normal and tumor tissues. (*** p<0.001 ** p<0.01 * p<0.05)

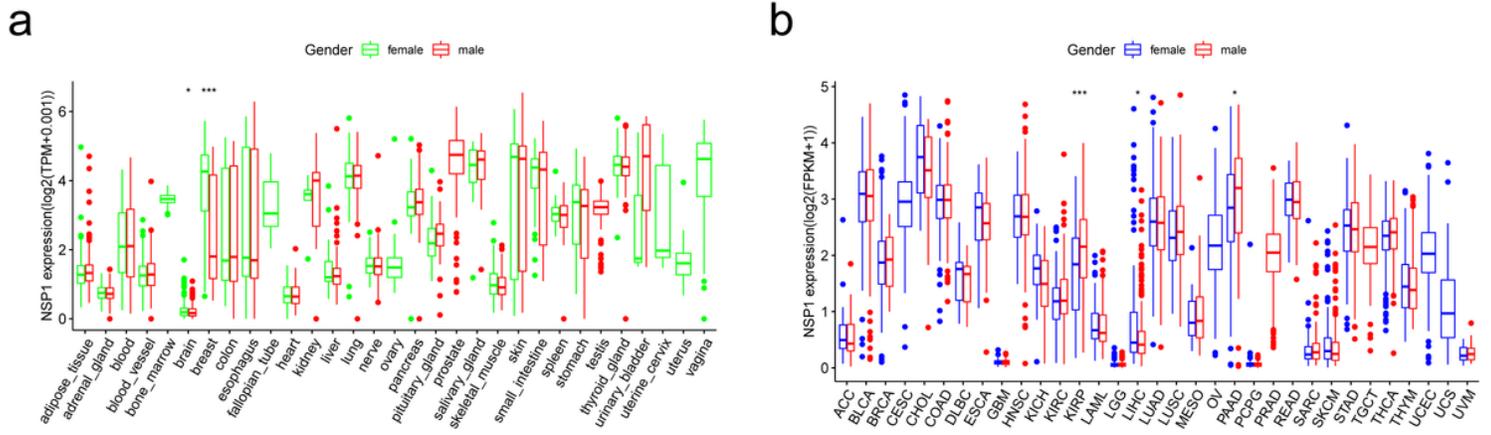


Figure 5

Differential expression of NSP1 gene between male and female patients in normal and tumor tissues.
 ('***' $p < 0.001$ '**' $p < 0.01$ '*' $p < 0.05$)

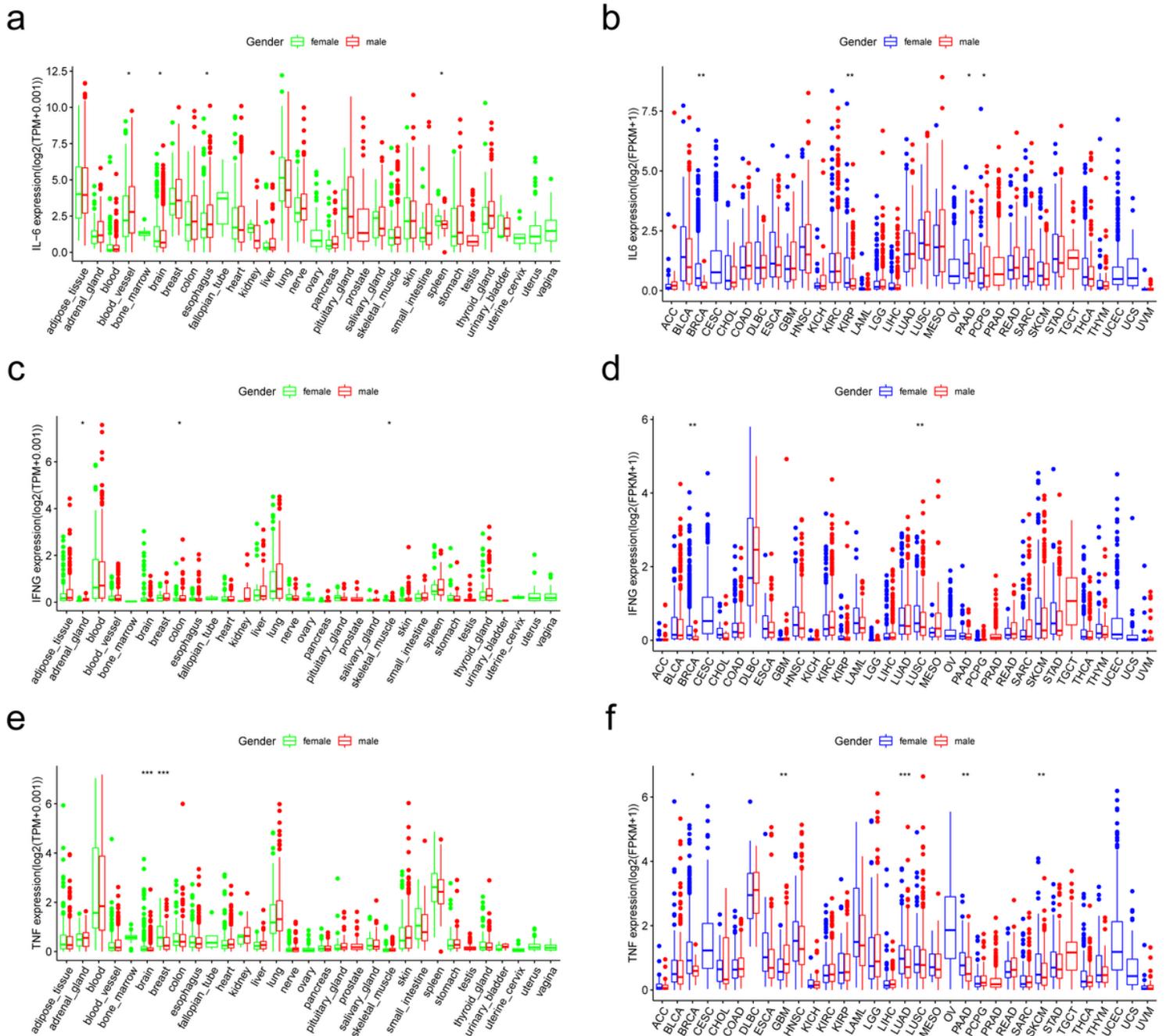


Figure 6

Differential expression of IL-6, IFNG and TNF genes between male and female patients in normal and tumor tissues. (**** p<0.001 ** p<0.01 * p<0.05)

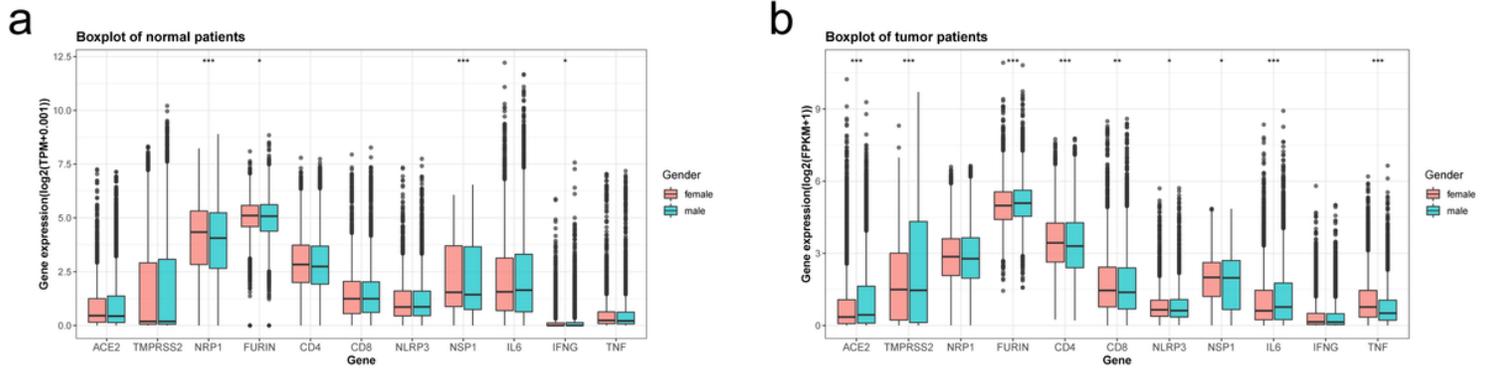


Figure 7

Differential expression of SARS-COV-2 virus-related genes in all normal and tumor tissues with different genders. ('***' $p < 0.001$ '**' $p < 0.01$ '*' $p < 0.05$)