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Review

ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19

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ABSTRACT

At the end of 2019, the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in China. Currently, it is breaking out globally and posing a serious threat to public health. The typically clinical characteristics of COVID-19 patients were fever and respiratory symptoms, and a proportion of patients were accompanied by extrapulmonary symptoms including cardiac injury, kidney injury, liver injury, digestive tract injury, and neurological symptoms. Angiotensin converting enzyme 2 (ACE2) has been proven to be a major receptor for SARS-CoV-2 and could mediate virus entry into cells. And transmembrane protease serine 2 (TMPRSS2) could cleave the spike (S) protein of SARS-CoV-2, which facilitates the fusion of SARS-CoV-2 and cellular membranes. The mRNA expressions of both ACE2 and TMPRSS2 were observed in the heart, digestive tract, liver, kidney, brain and other organs. SARS-CoV-2 may have a capacity to infect extrapulmonary organs due to the expressions of ACE2 and TMPRSS2 in the cells and tissues of these organs. It seems that there is a potential involvement of ACE2 and TMPRSS2 expressions in the virus infection of extrapulmonary organs and the manifestation of symptoms related to these organs in patients with COVID-19. Here, we revealed the expressions of ACE2 and TMPRSS2 in extrapulmonary organs, and we also summarized the clinical manifestation and the management of extrapulmonary complications in patients with COVID-19.

1. Introduction

Since the late 2019, a novel coronavirus, officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the pathogen to cause pneumonia [1,2]. As a member of the *Betacoronavirus* genus, SARS-CoV-2 has 82 % genomic nucleotides identity with human severe acute respiratory syndrome coronavirus (SARS-CoV), and shares 76.47 % amino acid sequence identity with SARS-CoV [3,4]. The World Health Organization (WHO) named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). Until April 20, 2020, the virus has swept through 213 countries, more than 2.2 million cases with COVID-19 have been confirmed and more than 150 000 cases died, which has been posing significant threats to public health. SARS-CoV-2 can cause respiratory diseases, and may lead to acute respiratory distress syndrome (ARDS), multiple organ failure, and even death in severe cases [1,5]. In addition to typical symptoms such as cough and fever, some patients developed the symptoms in multiple systems such as cardiovascular system, digestive system and

Abbreviations: ACE2, Angiotensin converting enzyme 2; AKI, Acute kidney injury; ALI, Acute liver injury; ALP, Alkaline phosphatase; ALS, Artificial liver system; ALT, Alanine aminotransferase; AMI, Acute myocardial infarction; ARDS, Acute respiratory distress syndrome; AST, Aspartate aminotransferase; AT2, Alveolar cells; BUN, Blood urea nitrogen; CCLE, Cancer Cell Line Encyclopedia; CNS, Central nervous system; COVID-19, Coronavirus disease 2019; GEO, Gene Expression Omnibus; GGT, Gamma-glutamyltransferase; GI, Gastrointestinal injury; GTEx, Genotype-Tissue Expression; ICU, Intensive care unit; MCS, Mechanical circulatory support; NP, Nucleoprotein; PCI, Percutaneous coronary intervention; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; Scr, Serum creatinine; ScRNA-Seq, Single-cell RNA sequencing; STEMI, ST-elevation myocardial infarction; TBIL, Total bilirubin; TEM, Transmission electronic microscope; TMPRSS2, Transmembrane protease serine 2; V-V, venous-venous; WHO, World Health Organization.

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nervous system in the early stages of COVID-19, which brings more challenges to the timely diagnosis of patients [6,7].

Angiotensin converting enzyme 2 (ACE2) as a metalloproteinase is a carboxyterminal dipeptidyl peptidase [8]. The primary physiological role of ACE2 is involved in the regulation of vasoconstriction and blood pressure [9–11]. Transmembrane protease serine type2 (TMPRSS2), belonging to the type II transmembrane serine protease family, could cleave the coronavirus spike (S) protein [10,12–16]. It was demonstrated that ACE2 and TMPRSS2 were crucial for the entry of SARS-CoV and SARS-CoV-2 into the host cells [11,17,18]. Cell entry of SARS-CoV-2 depends on binding of the S protein to the specific cellular receptor and S protein priming by host cell proteases. As shown in Fig. 1, each S protein of SARS-CoV-2 consists of two subunits: a globular S1 domain at the N-terminal region, and the membrane-proximal S2 domain. SARS-CoV-2 utilizes receptor-binding domain within the S1 domain to bind to the cellular receptor ACE2, which could trigger the effects of TMPRSS2 on the cleavage of protein S at the S1 and S2 sites, and priming cell membrane fusion for viral entry [17,19,20]. As receptors and mediators of virus entry are important for determining viral host and organ, the route of SARS-CoV-2 infection and the infected organ may depend on the expression and distribution of ACE2 and TMPRSS2 [21,22]. Studies have shown that ACE2 and TMPRSS2 are expressed not only in lung tissues, but also in extrapulmonary organs including heart, kidney, liver, colon, esophagus, brain, gallbladder and testis, suggesting that SARS-CoV-2 may also affect extrapulmonary organs [23–27].

In this review, the distributions of ACE2 and TMPRSS2 in extrapulmonary organs, and the characteristics and clinical managements of extrapulmonary organ injury caused by SARS-CoV-2 were summarized. We believe that this will be important in understanding on the infection of extrapulmonary organs in patients with COVID-19.

2. The mRNA expressions of ACE2 and TMPRSS2 in extrapulmonary organs

Studying the viral susceptibility of extrapulmonary organs is important for a deeper understanding for the pathogenesis of SARS-CoV-2 infection. Studies have shown that ACE2 and TMPRSS2 were expressed not only in the cells and tissues of lung, but also in extrapulmonary organs [25,28–33] (Fig. 2). In this section, the expression levels of ACE2 and TMPRSS2 in extrapulmonary organs including heart, kidney, liver, digestive tract, brain and other organs were reviewed.

2.1. Heart

The mRNA expressions of ACE2 in different human organs were analyzed and the results showed that ACE2 was expressed in the heart [27,34]. Furthermore, Chen et al. analyzed the feature of ACE2 expressions among cardiac cell types and found that ACE2 was specifically expressed in pericyte [35]. Moreover, RNA sequencing from 40 patients with failing hearts and 15 normal donors revealed that myocardial ACE2 expressions were significantly increased in patients with heart failure, which was further validated at the protein level by proteomics profiling from 8 heart failure and 8 normal donors [35]. Another study also showed that the expression of ACE2 in heart tissues of patients with underlying heart disease was higher than that in normal heart tissues [36]. These two studies suggested that the expression of ACE2 in heart tissue of patients with underlying heart disease was higher than that in normal heart tissue. Guo et al. analyzed the mRNA expression of TMPRSS2 from the Genotype-Tissue Expression (GTEx) database, and the results showed that TMPRSS2 is also expressed in the heart [29]. By single-cell RNA sequencing (scRNA-Seq) to profile the gene expression landscapes of 4000 cardiac cells from human embryos, Qi et al. revealed that the cardiomyocytes from the heart contain 6% ACE2-expressed cells and 0.8 % TMPRSS2-expressed cells, and the cardiovascular progenitor cells contain 12.5 % ACE2-expressed cells and 0.4 % TMPRSS2-expressed cells, respectively [27]. These data showed that both ACE2 and TMPRSS2 were expressed in the heart.

2.2. Kidney

Expression analysis from the GTEx database showed that kidney displayed the fifth high expression of ACE2 [35]. To investigate the expression of ACE2 in kidney, Lin et al. analyzed the public single-cell transcriptome dataset of normal kidneys from healthy donors, the

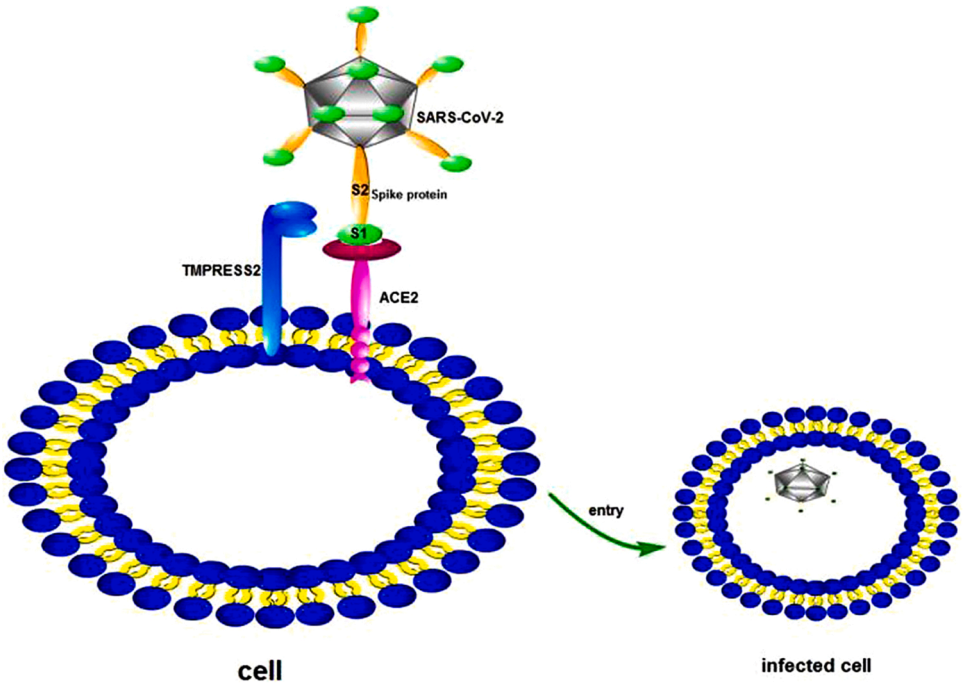

Fig. 1. Entry of SARS-CoV-2 into host cells.
SARS-CoV-2 infected the host cells by the spike protein of the virus and the functions of ACE2 and TMPRSS2 in host cells.

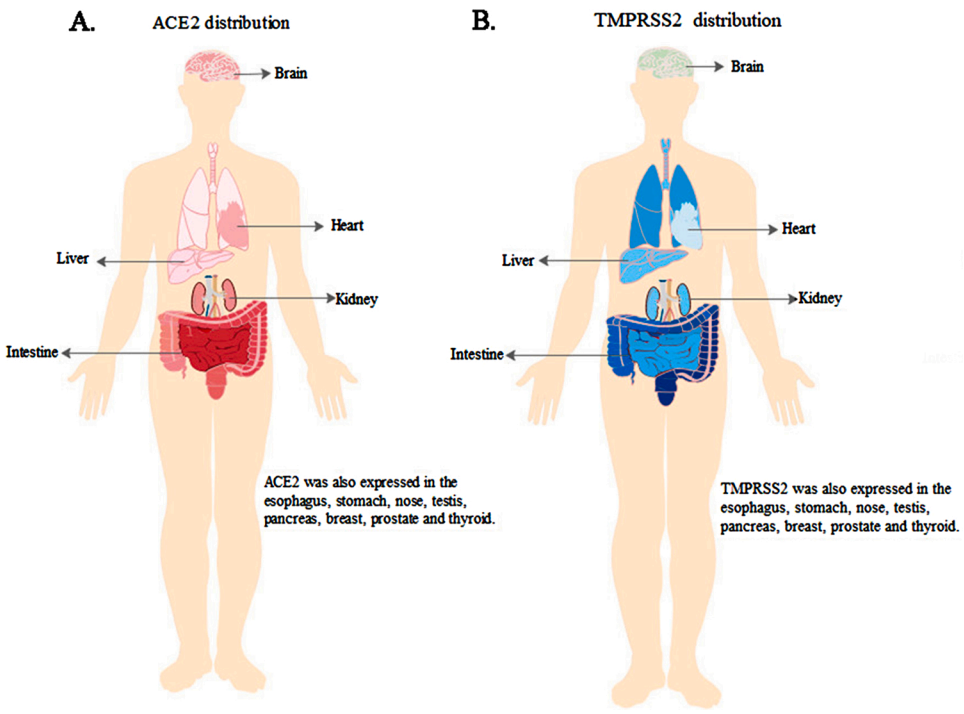

Fig. 2. Tissue distributions of ACE2 and TMPRSS2 in human.
(A–B) the schematic diagram of the expressions of ACE2 (A) and TMPRSS2 (B) in multiple human tissues. The colour strength is corresponding to the gene expression level. ACE2 and TMPRSS2 were expressed in the brain and heart; ACE2 expression is expressed at a relative low level in hepatocytes and mainly located in cholangiocytes, while TMPRSS2 is expressed in the hepatocytes and cholangiocytes; ACE2 and TMPRSS2 were highly expressed in kidney and intestinal epithelial cells. Both ACE2 and TMPRSS2 were also expressed in the esophagus, stomach, nose, testis, pancreas, breast, prostate and thyroid.

results showed that the ACE2 was distributed across multiple cell types and was mostly enriched in proximal tubule cells [32]. Fan et al. confirmed the specific ACE2 expression in tubular cells from the Gene Expression Omnibus (GEO) dataset, while it was not observed in immune cells and glomerular parietal epithelial cells. RNA and protein expression data of ACE2 in different human tissues and cancer cell lines were obtained from three online datasets including the Cancer Cell Line Encyclopedia (CCLE), GTEx database, and the Human Protein Atlas dataset, and the results indicated that both mRNA and protein expression levels of ACE2 were relatively high in kidney cells especially in renal tubular cells [37]. Meanwhile, Suryawanshi et al. analyzed the data of kidney tissues in scRNA-Seq datasets, and found that either proximal tubular cells or tubular progenitor cells in the kidney co-expressed ACE2 and TMPRSS2 [38]. The data of the scRNA-seq from GEO dataset (GSE134355) showed that ACE2 and TMPRSS2 expression levels were high in nephron epithelial cells, epithelial cells, endothelial cells, and mesangial cells of the kidney [27]. Recently, Pan et al. also found that the TMPRSS2 gene was co-expressed with ACE2 in kidney podocytes [31]. These data showed that both ACE2 and TMPRSS2 were highly expressed in tissues and cells of kidney.

2.3. Liver

Chai et al. analyzed the scRNA-seq data from GEO database (GSE124395) to evaluate ACE2 gene expression in liver, the results showed that ACE2 was highly expressed in cholangiocytes, which level was about 20 times higher than that in hepatocytes [39]. The GTEx database also showed that both ACE2 and TMPRSS2 were expressed in the liver [29]. Zhou et al. identified that TMPRSS2 is highly expressed in hepatocytes from Human Cell Atlas database [26]. Recently, Wen et al. indicated that ACE2 and TMPRSS2 are specifically co-expression in TROP2^{+} liver progenitors of human liver tissue using scRNA sequencing [40]. These data indicate that ACE2 expression is expressed at a relative low level in hepatocytes and mainly located in cholangiocytes, while TMPRSS2 is expressed in hepatocytes.

2.4. Digestive tract

A previous study showed that ACE2 could be found in the upper esophagus, and it could be detected in stratified epithelial cells and absorptive enterocytes of the ileum and colon [41]. Quantitative mRNA expression profiling of ACE2 across 72 human tissues by Harmer et al. showed that ACE2 was expressed at a high level in gastrointestinal tissues [42]. Zhang et al. analyzed 4 datasets with single-cell transcriptomes of esophagus, gastric, ileum, colon and lung, and the data showed that ACE2 was not only highly expressed in the type II alveolar cells (AT2) of lung but also in the stratified epithelial cells, ileum absorptive enterocytes cells and colon enterocytes [33]. Similarly, the immunofluorescent staining of esophagus, stomach, duodenum and rectum showed that ACE2 was stained mainly in the cytoplasm of gastrointestinal epithelial cells [43]. Besides, the scRNA-seq data showed that ACE2 was significantly elevated in the proximal and distal enterocytes [44]. Guo et al. suggested that TMPRSS2 was highly expressed in almost all organs of the digestive tract including colon, stomach, small intestine and esophagus [29]. Using published scRNA-seq data and seven in-house normal colon samples, Lee et al. reported that the co-expressions of ACE2 and TMPRSS2 transcripts were mainly observed in the small intestine and colon [45]. The highest expressions of TMPRSS2 and ACE2 were found in enterocytes among the intestinal cell types [26].These data showed that TMPRSS2 and AEC2 are highly expressed in the digestive tract.

2.5. Nervous system

Analysis using the GTEx database showed that both TMPRSS2 and ACE2 are expressed at relatively low levels in the brain cortex [29]. Chen et al. found that ACE2 was relatively highly expressed in some important brain areas such as the substantia nigra and brain ventricles using seven brain transcriptome databases [24]. ACE2 was expressed at high level in the piriform cortex of human brain, and its expression could also be detected in many neurons including both excitatory and inhibitory neurons, and some non-neuron cells including astrocytes and oligodendrocytes in human middle temporal gyrus and posterior cingulate cortex [24]. Qi et al. analyzed the scRNA-seq data of substantia nigra

and cortex of brain from GEO database, the results showed that both ACE2 and TMPRSS2 were expressed in the oligodendrocyte precursor cells and the astrocytes of the substantia nigra and cortex [27]. There are limited reports on the expressions of ACE2 and TMPRSS2 in peripheral nervous system. Brann et al. analyzed the ACE2 and TMPRSS2 expression in different cell type from human scRNA-seq dataset (GSE139522), and found that neither olfactory sensory neurons nor olfactory bulb neurons expressed these two genes, while ACE2 and TMPRSS2 were expressed in the non-neuronal cells including the sustentacular cells and olfactory bulb pericytes [46]. These data showed that ACE2 and TMPRSS2 could also be co-expressed in the nervous system.

2.6. Other organs or tissues

Moreover, ACE2 and TMPRSS2 were also reported to be co-expressed in some other organs [27,29,37,47]. It has been revealed that both ACE2 and TMPRSS2 are expressed in testis by scRNA sequencing and expression profile analysis, indicating that testicular cells might be the potential targets of SARS-CoV-2. Another report revealed that multiple kinds of cells in the nose, including nasal brushing epithelial cells, nasal turbinate epithelial cells, and nasal airway epithelial cells, contained ACE2-expressed and TMPRSS2-expressed cell clusters [27]. Moreover, ACE2 and TMPRSS2 were also expressed in pancreas, breast, prostate and thyroid [29,37,47], and these organs might also be the targets of SARS-Cov-2.

3. Infection of SARS-CoV-2 and extrapulmonary organ injury of patients with COVID-19

3.1. SARS-CoV-2 infection and cardiac injury

Recently, autopsy analysis by Fox et al. revealed that the histopathology of the heart was consistent with the typical pattern of viral myocarditis [48]. SARS-CoV-2 RNA was detected in the cardiac tissues of the patients with COVID-19 [49]. These data suggested that SARS-CoV-2 may directly infect heart.

The epidemiology of COVID-19 reported that cardiac injury was one of the most severe organ damages [5,50,51]. The clinical manifestations of cardiac injury in COVID-19 patients are complex and could present with heart failure, arrhythmias or acute myocardial infarction (AMI) [5,52,53]. Inciardi et al. reported the first case who had the symptom of heart failure at first and later the patient was positive for SARS-CoV-2 using nucleic acid test [52]. Cardiac injury is a common symptom in patients with COVID-19. Shi et al. reported that 19.7 % (82/416) patients with COVID-19 had cardiac injury [54]. Moreover, there were 5 (12 %) patients with acute cardiac injury in a cohort including 41 COVID-19 patients, and 4 (31 %) of 13 patients with acute cardiac injury in the intensive care unit (ICU) [50]. Furthermore, a study by Wang et al. showed that there were 10 (7.2 %) patients with acute cardiac injury and 23 (16.7 %) patients presented with arrhythmia of 138 COVID-19 patients, while acute cardiac injury was observed in 8 (22.2 %) of 36 patients with CIVID-19 in the ICU [5]. These cases suggested that SARS-CoV-2 may cause serious heart damage, which should be widespreadly concerned. Furthermore, acute cardiac injury is more prevalent in severe cases with COVID-19 [5,50,55–58] (Table 1). And it has been reported that COVID-19 patients with cardiac injury had higher mortality than those without cardiac injury [54].

In this review, we also summarized the possible relationship between basic heart disease and further cardiac injury [54,59–62] (Table 2). In a cohort of 416 COVID-19 patients from Renmin Hospital of Wuhan University, China, Shi et al. demonstrated that cardiac injury occurred in 82 patients during hospitalization, of which 36 (43.9 %) had basic heart disease including coronary heart disease and chronic heart failure. And only 25 (7.5 %) patients with basic heart disease of 334 COVID-19 patients without cardiac injury [54]. Similarly, Liu et al. suggested that 5 (33.3 %) patients with basic heart disease in 15 COVID-19 patients had cardiac injury compared with 10 (3.7 %) patients with basic cardiovascular diseases of 276 COVID-19 patients without cardiac injury [59]. Other studies also indicated that the patients with basic cardiovascular disease are more likely to present heat injury in COVID-19 patients [60,61]. In view of the points above, COVID-19 patients with underlying cardiac conditions seem to have higher rates of cardiac injury.

Table 1
Characteristics of acute cardiac injury after SARS−CoV-2 infection.

Study	Country	Subject	Basic heart disease	Acute cardiac injury	Clinical classification of acute cardiac injury
Wang et al [5]	China	138	20 (14.5 %)	10 (7.2 %)	Non-ICUcases 2/102 (2.0 %) ICU cases 8/36 (22.2 %)
Huang et al [50]	China	41	6 (14.6 %)	5 (12.2 %)	Non-ICUcases 1/28 (3.6 %) ICUcases 4/13 (30.8 %)
Li et al [55]	China	193	NA	24 (12.4 %)	Non-severe cases 5/128 (3.9 %) Severecases19/65 (29.2 %)
Chen et al [56]	China	274	24 (8.8 %)	89/203 (43.8 %)	Recoveredcases 18/109 (16.5 %) Died cases 72/94 (76.6 %)
Hong et al [57]	Korea	98	11 (11.2 %)	11 (11.2 %)	Non-ICUcases 2/85 (2.4 %) ICUcases 9/13 (69.2 %)
Zhou et al [58]	China	191	15 (7.9 %)	33 (17.3 %)	Survivor cases 1/137 (0.7 %) Non-survivor cases 32/54 (59.3 %)

Table 2
Comorbidity with cardiac injury in COVID-19 patients with basic heart disease.

Study	Subjects with COVID-19	Proportion of basic heart disease	Patients with Cardiacinjury	Patients with basic heart disease	
				With cardiac injury	Without cardiac injury
Shi et al [54]	416	61 (14.7 %)	82 (19.7 %)	43.9 % (36/82)	7.5 % (25/334)
Liu et al [59]	291	15 (4.8 %)	15 (5.2 %)	33.3 % (5/15)	3.6 % (10/276)
Xu et al [60]	53	6 (11.3 %)	30 (56.6 %)	16.7 % (5/30)	4.3 % (1/23)
Ma et al [61]	84	5 (6.0 %)	13 (15.5 %)	7.7 % (1/13)	5.6 % (4/71)
Guo et al [62]	187	29 (15.5 %)	52 (27.8 %)	48.1 % (25/52)	3.0 % (4/135)

3.2. SARS-CoV-2 infection and kidney injury

Recently, autopsy analysis on six COVID-19 patients showed that varying degrees of acute tubular necrosis were observed in all the renal specimens. Nucleoprotein (NP) antigens and NP positive inclusion body of SARS-CoV-2 could be seen in kidney tissues from all the samples. Moreover, virus-like particles were seen in kidney tissues by transmission electronic microscope (TEM) [63]. Su et al. analyzed kidney abnormalities in 26 autopsies of patients with COVID-19 and found that diffuse proximal tubular damage with the loss of brush border were

observed. Further investigation showed that diffuse necrosis can be seen under the light microscope and electron microscopic examination also showed the clusters of coronavirus particles with distinctive spikes in the tubular epithelium and podocytes [64]. It was reported that both NP antigens and RNA of SARS-CoV-2 were detected in urine of COVID-19 patients [65,66]. These data coincide with the finding of the SARS-CoV-2 invasion in kidney. Collectively, SARS-CoV-2 could directly infect human renal tubules and lead to kidney damage.

Recent studies have shown that the incidence of acute kidney injury (AKI) in COVID-19 patients ranged from 0.5 %–28.5 %, and higher frequency of renal function damage with elevated blood urea nitrogen (BUN) or serum creatinine (Scr) was observed in COVID-19 patients [1,5,50,51,53,55–57,67–73] (Table 3). A study of 193 patients with COVID-19 indicated that levels of BUN and Scr were increased in 27 (14.0 %) and 20 (10.4 %) patients with COVID-19, respectively. And routine urine tests were performed on 129 patients, among which 76 (58.9 %) patients were positive for urinary protein and 57 (44.2 %) patients were positive for hematuria [55]. Another study also showed that about 14 % patients with COVID-19 had abnormal renal function [67]. Moreover, COVID-19 patients with more severe disease progression have higher rates of AKI. Huang and colleagues reported that 3 (23.1 %) of 13 patients with AKI in the ICU were observed, and none of the 28 patients who did not require care in the ICU suffered AKI [50]. Xu et al. found that the fatality rate was obviously higher in COVID-19 patients with AKI than those without renal injury [53]. Furthermore, in another study investigating 193 patients with COVID-19 at hospital admission, more severe patients had higher rates of AKI, and the Cox regression analysis also suggested that COVID-19 patients who developed AKI had a significantly higher mortality risk [55]. Therefore, AKI is more prevalent in severe cases with COVID-19.

3.3. SARS-CoV-2 infection and liver injury

An autopsy report of a 50-year-old patient with COVID-19 showed moderate microvesicular steatosis and mild lobular activity in liver tissues [74]. Moreover, Zhao et al. used human liver ductal organoids as a tool to investigate the SARS-CoV-2 infection and the tissue damage induced by SARS-CoV-2 ex vivo, and the results showed that the expression of SARS-CoV-2 NP was easily detected in the patchy areas of the hepatic duct, indicating that liver ductal organoids were susceptible to SARS-CoV-2 infection [75]. In addition, SARS-CoV-2 infection could disrupt the barrier and bile acid transporting functions of cholangiocytes, which indicated that SARS-CoV-2 might directly induce cholangiocyte injury and consequently bile acid accumulation [75]. In view of the points above, liver damage in the COVID-19 patients might be directly caused by the viral infection.

Abnormal liver functions were frequently reported in COVID-19 patients [50,76,77]. Epidemiologic studies showed that almost half of the patients had differing degrees of liver damage [1,5,50,51,53,55–57,69–72] (Table 4). Chen et al. reported that 28 (28.3 %) out of 99 patients had elevated alanine aminotransferase (ALT), 35 (35.6 %) patients had elevated aspartate aminotransferase (AST) and 18 (18.2 %) had elevated total bilirubin (TBIL) in Wuhan Jinyintan Hospital, Wuhan, China [1]. Similarly, a nationwide study involving 1099 patients with COVID-19 in China showed that more than 20 % of patients had elevated ALT and AST, and 10.5 % of patients had elevated TBIL [51]. It was revealed that the levels of direct bilirubin, indirect bilirubin, ALT, alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) were significantly higher in males than that in females with COVID-19, and multivariate logistic regression analysis showed that male was an important independent risk factor for predicting acute liver injury (ALI) in COVID-19 patients [76,78]. These data indicated that male patients with COVID-19 may be more susceptible to liver injury. Furthermore,

Table 3
Characteristics of acute kidney injury after SARS−CoV-2 infection.

Study	Country	Subject	Pre-existing kidney conditions	Abnormal renal functional indices	AKI	Clinical classification of AKI
Chen et al [1]	China	99	NA	Scr 24 (24.2 %) BUN 23 (23.2 %)	3 (3.0 %)	NA
Wang et al [5]	China	138	4 (2.9 %)	NA	5 (3.6 %)	Non-ICU cases 2/102 (2.0 %) ICU cases 3/36 (8.3 %)
Huang et al [50]	China	41	NA	Scr 4 (9.8 %)	3 (7.3 %)	ICU cases 3/13 (23.1 %)
Guan et al [51]	China	1099	8 (0.7 %)	Scr 12/752 (1.6 %)	6 (0.5 %)	Non-severe cases 1/926 (0.1 %) Severe cases 5/173 (2.9 %)
Xu et al [53]	China	355	NA	Scr 111 (30.7 %)	56 (15.8 %)	Mild cases 24/244(10.7 %) Severe cases 11/60 (18.3 %) Critical ill cases 21/71 (29.2 %)
Li et al [55]	China	193	NA	Scr 20 (10.4 %) BUN 27 (14.0 %)	55 (28.5 %)	Non-severe cases 12 /128 (9.4 %) Severe cases 43/65 (66.2 %)
Chen et al [56]	China	274	4 (1.5 %)	NA	29 (10.6 %)	Recovered cases 1/161 (0.6 %) Died cases 28/113 (24.8 %)
Hong et al [57]	Korea	98	NA	Scr 29 (29.6 %) BUN 12 (12.2 %)	9 (9.2 %)	Non-ICU cases 1/85 (1.2 %) ICU cases 8/13 (61.5 %)
Cheng et al [67]	China	701	NA	Scr 101 (14.4 %)	36 (5.1 %)	NA
Xiao et al [68]	China	287	5 (2%)	NA	55 (19.2 %)	Non-severe cases 21/163(12.9 %) Severe cases 34/124 (27.4 %)
Richardson et al [69]	America	5700	454 (8.0 %)	NA	1370 (24.0 %)	Cured cases 176/2081 (8.5 %) In hospital cases 847/3066 (27.6 %) Died cases 347/553 (62.7 %)
Wan et al [70]	China	135	NA	NA	5 (3.7 %)	Mild cases 4/95 (4.2 %) Severe cases 1/40 (2.5 %)
Li et al [71]	China	548	10 (1.8 %)	Scr 146/539 (27.1 %) BUN 85/539 (15.8 %)	95 (17.3 %)	Non-severe cases 33/279 (11.8 %) Severe cases 62/269 (23.0 %)
Qian et al [72]	China	91	NA	Scr 24 (26.4 %)	NA	NA
Pei et al [73]	China	333	NA	NA	35 (10.5 %)	Moderate cases 5/144 (3.5 %) Severe cases 6/133 (4.5 %) Critically ill cases 24/56 (42.9 %)

Scr: Serum creatinine; BUN: Blood urea nitrogen; AKI: Acute kidney injury.

Table 4
Characteristics of liver injury after SARS−CoV-2 infection.

Study	Country	Subject	Patients with pre-existing liverconditions	Patients with abnormal liver functional indices	Abnormal liver functional indices in the Non-severe patients*			Abnormal liver functional indices in the severe patients#		
					ALT	AST	TBIL	ALT	AST	TBIL
Chen et al [1]	China	99	NA	ALT 28 (28.3 %) AST 35 (35.6 %) TBIL 18 (18.2 %)	NA	NA	NA	NA	NA	NA
Wang et al [5]	China	138	4 (2.9 %)	NA	NA	NA	NA	NA	NA	NA
Huang et al [50]	China	41	1 (2.4 %)	AST 15 (36.6 %)	NA	7/28 (25.0 %)	NA	NA	8/13 (61.5 %)	NA
Guan et al [51]	China	1099	23 (2.1 %)	AST 168/757 (22.2 %) ALT 158/741 (21.3 %) TBIL 76/722 (10.5 %)	120/606 (19.8 %)	112/615 (18.2 %)	59/594 (9.9 %)	38/135 (28.1 %)	56/142 (39.4 %)	17/128 (13.3 %)
Xu et al [53]	China	355	NA	ALT 91 (25.6 %) AST 102 (28.7 %)	NA	NA	NA	NA	NA	NA
Li et al [55]	China	193	NA	ALT 44 (22.7 %) AST 73 (37.8 %) TBIL 18 (9.3 %)	26/128 (20.3 %)	35/128 (27.3 %)	9/128 (7.0 %)	18/65 (27.7 %)	38/65 (58.5 %)	9/65 (13.8 %)
Chen et al [56]	China	274	11 (4.0 %)	ALT 60 (21.9 %) AST 84 (30.7 %)	30/161 (18.6 %)	25/161 (15.5 %)	NA	30/113 (26.5 %)	59/113 (52.2 %)	NA
Hong et al [57]	Korea	98	1 (1.0 %)	ALT 19 (19.4 %) AST 42 (42.9 %) TBIL 16 (16.3 %)	16/85 (18.8 %)	31/85 (36.5 %)	12/85 (14.1 %)	3/13 (23.1 %)	11/13 (84.6 %)	4/13 (30.8 %)
Richardson et al [69]	America	5700	30(0.5 %)	AST 3263 (58.4 %) ALT 2176 (39.0 %)	NA	NA	NA	NA	NA	NA
Wan et al [70]	China	135	2(1.5 %)	AST 30 (22.2 %)	NA	15/95 (15.8 %)	NA	NA	15/40 (37.5 %)	NA
Li et al [71]	China	548	5 (0.9 %)	ALT 125/541 (23.1 %) AST 179/540 (33.1 %) TBIL 24/541 (4.4 %)	61/275 (22.3 %)	64/275 (23.3 %)	7/275 (2.3 %)	64/266 (24.1 %)	115/266 (43.4 %)	17/266 (6.4 %)
Qian et al [72]	China	91	NA	ALT 13(14.3 %) AST 18 (19.8 %)	NA	NA	NA	NA	NA	NA

* Non-severe patients include patients without ICU care and recovered patients.
# Severe patients include patients with ICU care and death.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin.

multiple studies found that AST, ALT, and TBIL were significantly higher in patients treated in the ICU than that in non-ICU patients [5,50]. Li et al. suggested that among the patients with abnormal liver function, moderate and severe types of patients were more likely to have liver injury (58.8 % and 66.7 %, respectively) [79]. Fu et al. analyzed the relationship between ALI and mortality risk in 355 COVID-19 patients, and the results showed that ALI is more common in the critically ill patients and ALI at the early stage increased death risk of COVID-19 patients [78,80]. Together, abnormal liver functions might be associated with the severity of patients with COVID-19.

3.4. SARS-CoV-2 infection and digestive tract injury

Epithelial cells of the esophagus, stomach, duodenum and rectum in one COVID-19 patient tested positive for SARS-CoV-2 RNA, and the staining of viral NP was also visualized in the cytoplasm of epithelial cells in stomach, duodenum and rectum [43]. Moreover, minimally invasive autopsies were performed on three patients died of COVID-19, and the results showed that some epithelial cells of the gastrointestinal mucosa were degenerated, necrotic and detached [81]. These studies strongly supported that SARS-CoV-2 may directly infect the epithelial cells of digestive tract.

Table 5
SARS−CoV-2 detection in gastrointestinal specimens.

Study	Subject	Gastrointestinal samples	Tested positive in gastrointestinal specimens	The positive time in gastrointestinal specimens (days)	Positive time for Gastrointestinal samples after respiratory samples were negative (days)
Xiao et al [43]	73	Stool	39	1- 12	NA
Zhang et al [82]	178	Anal swabs	14	NA	NA
Tan et al [83]	1	Rectal swab	1	18	3
Xing et al [84]	3	Stool	3	6−30	8−20
Younget al [85]	8	Stool	4	1−3	NA
Holshue et al [86]	1	Stool	1	1	NA
Lescure et al [87]	5	Stool	2	5−6	NA
Tang et al [88]	1	Stool	1	9	NA
Wanget al [89]	153	Stool	44	NA	NA
Xu et al [90]	10	Rectal swabs	8	3−28	2−20

Multiple studies have identified that the SARS-CoV-2 RNA was detected in anal swabs [82], rectal swabs [83], and stool specimens [43,84] of COVID-19 patients. It has been demonstrated that SARS-CoV-2 RNA could be detected in feces from more than half of COVID-19 patients [43,85]. In another study, Xing et al. reported that SARS-CoV-2 RNA was detected in the feces of three pediatric cases with COVID-19 in Qingdao, China, and the persistence of SARS-CoV-2 in the digestive tract lasted for 6−30 days [84]. The possibility of fecal-oral transmission of SARS-CoV-2 infection needs to be taken into account. Furthermore, as shown in Table 5, long duration of SARS-CoV-2 detection in digestive tract by RT-PCR has been reported, and viral RNA remained detectable in the digestive tract for 2−20 days after nucleic acid turned negative in respiratory samples [43,82–90]. The studies suggested that SARS-CoV-2 could be detected from respiratory tract specimens during the early period to digestive tract specimens during the late period, and viral nucleic acid tests in both the respiratory and digestive tract are necessary to confirm the complete clearance of virus.

Some COVID-19 patients presented gastrointestinal symptoms such as diarrhea, nausea, vomiting and abdominal pain [91]. Holshue et al. reported the first case of COVID-19 patient in the USA, which had nausea and vomiting before admission [86]. Multiple studies found that gastrointestinal symptoms, including diarrhea (2.0 %–43.8 %), nausea and vomiting (1.0 %–20.7 %), and abdominal pain (2.2 %–19.1 %), were common at presentation in COVID-19 patients [1,5,6,43,50,51,55,56,58,70–72,77,85,92–100] (Table 6). In a cohort of 212 patients with COVID-19 in Wuhan, China, gastrointestinal symptoms were described in up to 64.5 % [93]. Moreover, Sun et al. showed that 72 (86.7 %) critically ill patients with COVID-19 had gastrointestinal injury (GI) during hospital stay, and the survival curves showed that the mortalities of patients with GI was greater than that of patients without GI [101]. Jin et al. also found that the rate of the severe type was markedly higher in COVID-19 patients with GI symptoms than that in those without GI symptoms [94]. These data suggested that GI is one of the common extrapulmonary organ injuries in COVID-19 patients and may be related to the severity of the disease. On the other hand, many studies showed that patients with COVID-19 could present initially with the typical gastrointestinal symptoms, and diarrhea may even occur earlier than pyrexia or respiratory symptom in some cases with COVID-19 [5–7]. Luo et al. reported that 183 of 1141 COVID-19 cases presented initially only with gastrointestinal symptoms [7]. The COVID-19 patients initially only with gastrointestinal symptoms are more difficult to diagnose and might be overlooked, which could lead to potentially serious consequences. Together, digestive tract symptoms (especially diarrhea) are the main complications of COVD-19 patients, which should be noticed during the outbreak of COVID-19.

3.5. SARS-CoV-2 infection and nervous system injury

Transmission electron microscopy of autopsy sections showed the presence of SARS-CoV-2 viral-like particles in frontal lobe brain and neural cell bodies [102]. Moreover, researchers confirmed the presence of SARS-CoV-2 in cerebrospinal fluid by genome sequencing [103,104]. The pathological mechanism may be the invasion of SARS-CoV-2 into the nervons system. The viral-like particles in brain capillary endothelium was also observed [102], which suggested that hematogenous route might act as the pathway for SARS-CoV-2 to the brain. In addition, study using the mouse model have shown that SARS-CoV can lead to neuroinvasion via disruption of the nasal epithelium and subsequent neuronal dissemination [105], which suggested that coronavirus may use the olfactory nerve to enter the brain.

The symptoms from nervous system of COVID-19 patients, including headache, dizziness, anosmia, and dysgeusia, have been observed in the clinic [1,5,50,51,55,70–72,100,106–108] (Table 7). Disturbance of consciousness and seizures can occur as complications in the cases with severe COVID-19 [103]. It was convincing enough that the neurological deficits of patients with COVID-19 could be ongoing if it did not get noticed [106]. It was indicated that SARS-CoV-2 can cause nervous system damage [104]. The neurological deficits, meningo-encephalitis and acute myelitis in COVID-19 patients have been reported in the USA, Switzerland and China [104,109–111]. According to a recent study, 53 out of 214 (24.8 %) COVID-19 patients had central nervous system (CNS) symptoms including dizziness, headache, impaired consciousness, ataxia, and epilepsy [106]. Up to 70.3 % of patients with COVID-19 have headache, and clinical manifestations of dizziness were found from 6.7%–16.8% of the patients with COVID-19 [5,55,71,100,106]. Olfactory and gustatory disorders are prevalent peripheral nervous system (PNS) symptoms in COVID-19 patients. In patients with mild and moderate COVID-19, a high proportion of patients presented olfactory and gustatory dysfunctions, and olfactory dysfunction appeared prior to the other symptoms in some cases [106–108,112,113]. These studies showed that the damage of neurological system may also act as a significant feature of COVID-19.

Table 6
Gastrointestinal symptoms after SARS−CoV-2 infection.

Study	Country	Subject	Diarrhoea	Nausea	Vomiting	Abdominal pain
Chen et al [1]	China	99	2 (2.0 %)	1 (1.0 %)	1 (1.0 %)	NA
Wang et al [5]	China	138	14 (10.1 %)	14 (10.1 %)	5 (3.6 %)	3 (2.2 %)
Liu et al [6]	China	137	11 (8.0 %)	NA	NA	NA
Xiao et al [43]	China	73	26 (35.6 %)	NA	NA	NA
Huang et al [50]	China	41	1/38 (2.6 %)	NA	NA	NA
Guan et al [51]	China	1099	42 (3.8 %)	55 (5.0 %)	55 (5.0 %)	NA
Li et al [55]	China	193	35 (18.1 %)	11 (5.7 %)	5 (2.6 %)	8 (4.1 %)
Chen et al [56]	China	274	77 (28.1 %)	24 (8.8 %)	16 (5.8 %)	19 (6.9 %)
Zhou et al [58]	China	191	9 (4.7 %)	7 (3.7 %)	7(3.7 %)	NA
Wan et al [70]	China	135	18 (13.3 %)	NA	NA	NA
Li et al [71]	China	548	179 (32.7 %)	NA	45 (8.2 %)	16 (2.9 %)
Qian et al [72]	China	91	21 (23.1 %)	11 (12.1 %)	6 (6.6 %)	NA
Shi et al [77]	China	81	3 (3.7 %)	NA	4 (5%)	NA
Young et al [85]	Singapore	18	3 (16.7 %)	NA	NA	NA
Yang et al [92]	China	52	NA	NA	2 (3.8 %)	NA
Zhang et al [93]	China	212	93 (43.8 %)	44 (20.7 %)	44 (20.7 %)	NA
Jin et al [94]	China	651	56 (8.1 %)	18 (2.8 %)	17 (2.6 %)	NA
Songel al [95]	China	51	5 (9.8 %)	3 (5.8 %)	3 (5.8 %)	NA
Luet al [96]	China	171	15 (8.8 %)	NA	11 (6.4 %)	NA
Xu et al [97]	China	62	3 (4.8 %)	NA	NA	NA
Zhang et al [98]	China	140	18 (12.9 %)	24 (17.3 %)	7 (5.0 %)	8 (5.8 %)
Lian et al [99]	China	465	36 (7.7 %)	22 (4.7 %)	22 (4.7 %)	NA
Lechien et al [100]	European	1420	473 (38.1 %)	272 (19.2 %)	272 (19.2 %)	270 (19.1 %)

Table 7
Neurological symptoms after SARS−CoV-2 infection.

Study	Country	Subject	Manifestation
Chen et al [1]	China	99	Headache 8 (8.1 %)
Wang et al [5]	China	138	Headache 9 (6.5 %) and dizziness 13 (9.4%)
Huang et al [50]	China	41	Headache 3/38 (7.9 %)
Guan et al [51]	China	1099	Headache 150 (13.6 %)
Li et al [55]	China	193	Headache 20 (10.4 %) and dizziness 13 (6.7 %)
Wan et al [70]	China	135	Headache 34 (32.5 %)
Li et al [71]	China	548	Headache 62 (11.3 %), dizziness 56 (10.2 %) and confusion 17 (3.1 %)
Qian et al [72]	China	91	Headache 7 (7.7 %)
Lechien et al [100]	European	1420	headache 998 (70.3 %), loss of smell 997 (70.2 %), taste dysfunction 770 (54.2 %) and loss of appetite 649 (45.7 %)
Mao et al [106]	China	214	Headache 28 (13.1 %), dizziness 36 (16.8 %), dysgeusia 11 (5.1 %) and hypogeusia 12 (5.6 %)
Lechien et al [107]	European	417	Anosmia 284 (79.6 %) and hyposmia 73 (20.4 %)
Levinson et al [108]	Israel	42	Anosmia 15 (35.7 %), dysgeusia14 (33.3 %) and both anosmia and dysgeusia 14 (33.3 %)

3.6. Indirect causes of extrapulmonary organ injury in patients with COVID-19

In addition to direct damage caused by the virus, other mechanisms have been hypothesized to be involved in the injury of the extrapulmonary organs in patients with COVID-19. Recent studies demonstrated that a rapid reduction of T lymphocytes was observed in the peripheral blood of COVID-19 patients [74,114]. Qin et al. also found that both helper T cells and suppressor T cells in COVID-19 patients were decreased [115]. The abnormal innate immune responses could promote virus infection and exacerbate extrapulmonary organ injury [116]. Moreover, drugs used in the treatment of COVID-19 may cause the damages of extrapulmonary organs. For example, most patients with COVID-19 showed signs of gastrointestinal and liver damages after being treated with lopinavir-ritonavir [85]. Chloroquine significantly prolonged the QTc interval in patients with COVID-19 [117]. Furthermore, hypoxia or microthromboses might also be the possible causes for extrapulmonary organ injuries in patients with COVID-19 [118].

4. Clinical management for extrapulmonary organ injury in COVID-19

Until now, there have not been specific treatments for COVID-19 and its management is mainly based on patient isolation and supportive medical care when it is necessary. In this review, we also focus on the clinical therapies and management for extrapulmonary organ injury of COVID-19 patients.

4.1. Clinical therapy and management for cardiac injury

Mahmud et al. provided a series of clinical recommendations for the care of patients with AMI during the COVID-19 progression [119]. Primary percutaneous coronary intervention (PCI) should remain the standard for the care of ST-elevation myocardial infarction (STEMI) patients with COVID-19, and COVID-19 patients with non-STEMI presentation should be managed medically and only be treated with urgent coronary angiography and possible PCI in the presence of high-risk clinical features or hemodynamic instability. Mechanical circulatory support (MCS) might be considered for acardiomyopathy and cardiogenic shock of patients with COVID-19. Venous-venous (V-V) extracorporeal membrane oxygenation should be considered for the COVID-19 patients with the severe pulmonary decompensation and the failure to oxygenate [119]. Kanrenone, furosemide, and bisoprolol may be effective for heart failure in COVID-19 patients [52]. In addition, Wang et al. proposed that a potential anti-oxidative therapy could alleviate cardiogenic casualties caused by COVID-19 [120]. A proper dose of Vitamin C, Vitamin E, curcumin and baicalin may ameliorate cardiac injuries of critically ill patients with COVID-19 [120]. However, some drugs used to treat COVID-19, including chloroquine, hydroxychloroquine, azithromycin and lopinavirritonavir, may increase the risk of QT prolongation and ventricular arrhythmias [117,121]. Guzik and colleagues advocate follow-up for regular assessment of cardiovascular risk in all COVID-19 patients who have survived [122].

4.2. Clinical therapy and management for kidney injury

The indicators of kidney damage were associated with high risk of in-hospital death of patients with COVID-19 [67]. For the treatment of patients with COVID-19, there should be prompt screening for risk factors of AKI and the indicators of kidney damage. The use of nephrotoxic drugs should be avoided unless it is absolutely necessary in the treatment of patients with COVID-19 [123]. Cao et al. found that lopinavir\ritonavir might reduce AKI in the treatment of COVID-19 patients [124]. Therefore, clinicians should pay attention to kidney damage and the related treatment for patients with COVID-19.

4.3. Clinical therapy and management for liver injury

The evaluation of liver function is usually mild during disease progression of COVID-19 and could be recovered without treatment [1]. However, severe liver injury had also been reported in patients with COVID-19 [1,78]. When severe liver damage occurs, liver protective drugs were usually used for the treatment of patients with COVID-19 [125]. It was reported that glycyrrhizic acid and its derivatives might play important roles in the treatment of liver disease and also have an antiviral activity against SARS-CoV-2 [126,127]. The artificial liver system (ALS) is one of the effective methods for treating liver failure, and its treatment mechanism is based on the ability of liver cell regeneration [128]. And ALS is vital to reduce the mortality for critical patients with COVID-19 and offers treatment options for COVID-19 patients with severe liver injury [129].

4.4. Clinical therapy and management for digestive tract injury

Clinicians should be alert for gastrointestinal symptoms of COVID-19 patients, especially as they may occur before the onset of pyrexia and respiratory symptoms. Moreover, there might be fecal-oral transmission for SARS−COV-2 [43,86]. Therefore, COVID-19 patients need to pay attention to hand hygiene and contact precautions, which could help minimize the risk of exposure and transmission. Diarrhea is the most common symptom of the digestive tract injury of COVID-19 patients [93,94]. Adequate fluid rehydration and potassium monitoring should be performed in the treatment of COVID-19 patients with diarrhea [130]. Hashimoto et al. suggested that ACE2 expression in the epithelial cells was required for maintaining amino acid homeostasis and the ecology of gut microbiome in intestine [131]. In addition, in a pilot study of 15 patients with COVID-19, Zuo et al. found that the fecal microbiome continued to change during hospitalization, and the change in fecal microbiome was associated with the severity of COVID-19 [132]. Therefore, we speculate that gastrointestinal tract symptoms in COVID-19 patients may have some relationship with the gut microbiota, and the gut microbiota might be a new therapeutic target. Actually the National Health Commission of China recommended that probiotics can be used to maintain the balance of intestinal microecology and prevent

secondary bacterial infection in the treatment of severe patients with COVID-19 [133]. The gastrointestinal symptoms of the patients might be relieved and even completely disappeared after starting antiviral therapy [134]. Camostat is an effective inhibitor of TMPRSS2 and can be used to treat the reflux esophagitis and chronic pancreatitis [135], and it may be effective in COVID-19 patients with digestive symptoms.

4.5. Clinical therapy and management for nervous system injury

Sudden anosmia needed to be recognized as one of the important symptoms of SARS−COV-2 infection. The median onset of acute anosmia and dysgeusia features was 3.3 days after onset of COVID-19, and most patients had a rapid recovery, which indicated that olfactory dysfunction and dysgeusia may be self-limiting [108]. Antiepileptic therapy with lacosamide, levetiracetam and phenytoin was used for seizures control in the treatment of COVID-19 patients [136]. SARS-CoV-2 could act as an infective trigger and may lead to a systemic inflammatory response syndrome, and prompt invasive treatment should be adopted to avoid hypoxic neurotoxicity and prevent CNS injuries [136]. In conclusion, clinical physical examination of the nervous system, prompt endotracheal intubation and rapid mechanical respiratory support should be proposed for the COVID-19 patients with neurological symptoms.

4.6. Clinical therapy and management for other organs

There is a potential pathogenicity of SARS−COV-2 to testis, pancreas, breast, prostate and thyroid, and functional changes in these organs should also be monitored in the management of COVID-19 patients [26,27,38]. For example, due to the potential pathogenicity of SARS−COV-2 to testicular tissues, the possible testicular damage caused by the virus may exist as a late complication [27,137]. Therefore, clinicians should take care of the possible occurrence of orchitis. Following-up and evaluation of the reproductive functions should also be done in recovered male patients with COVID-19.

5. Probable relationship between the infection of extrapulmonary organs and positive SARS-CoV-2 test in recovered patients

So far, more than 1 million patients with COVID-19 have been clinically cured and discharged. However, multiple discharged COVID-19 patients were positive for SARS-CoV-2 again [138]. In a cohort form Guangdong, China, 14.5 % (38/262) of convalescent patients from COVID-19 were re-detected to be positive for SARS-CoV-2 during their followed-up period [139]. Similarly, the data from Brunei Darussalam showed that 19.8 % (21/106) recovered patients were found to be re-positive for SARS-CoV-2 detection [140]. The re-detectable positive patients were confirmed by RT-PCR tests on anal or nasopharyngeal swabs. These studies suggest that a proportion of recovered patients still may be virus carriers.

The SARS-CoV-2 virus could be detected in respiratory specimens, stool, urine, serum, kidney tubules and gastrointestinal epithelium from COVID-19 patients [43,86,141,142]. Moreover, the viral RNA in urine and stool specimens remained positive after throat swabs turned negative, and the viral RNA can persist in feces for up to 30 days [84,143]. Yao et al. detected SARS-CoV-2 virus by digital PCR on tissue sections from the lung, liver, heart, intestine and skin of a COVID-19 patient who was ready-for-discharge but died of cardiac arrest. The patient was positive for SARS-CoV-2 in the cells and tissues of lung, and the results highlight the remaining of SARS-CoV-2 in the lung of discharged COVID-19 patient [144]. In addition, Shastri et al. demonstrated for the first time that male subjects have delayed viral clearance of SARS-CoV-2, and suggested that testicular viral reservoirs may play an important role in viral persistence in males [145]. It seemed that SARS-CoV-2 may be stored in the lung or extrapulmonary organs, which may be the reason for the virus positive again in discharged patients.

6. Discussion and conclusion

The emergence of the novel coronavirus (SARS-CoV-2) from the late 2019 has become one of the most significant public health threats worldwide [1,50,146]. In addition to respiratory symptoms, SARS-CoV-2 was also shown to cause cardiac injury, kidney injury, liver injury, digestive tract injury and other symptoms, which indicated the effects of SARS-CoV-2 on extrapulmonary organs. The patients with severe COVID-19 were more likely to have acute cardiac injury, acute kidney injury, liver injury, gastrointestinal injury or nervous system injury [5,50,79,94,103]. ACE2 and TMPRSS2 could help SARS-CoV-2 entry into the human cells, and it has been showed that ACE2 and TMPRSS2 expressions are widely distributed across human tissues including lung, liver, kidney, heart, brain and multiple digestive tract organs [28,33,147,148]. The co-expression of ACE2 and TMPRSS2 in the intestinal enterocytes may explain the disruption of intestinal absorption that leads to diarrhea [38,149]. Moreover, ACE2 and TMPRSS2 are highly expressed in renal tubular cells, implying that SARS-CoV-2 may directly bind to ACE2-positive cells in the kidney and destroy the function of renal tubules [32,38]. Furthermore, ACE2 and TMPRSS2 were co-expressed in heart, which may be related with the attack of SARS-CoV-2 in heart and lead to cardiac injury in patients with COVID-19 [29,35,38]. Besides, the expression of ACE2 in the heart tissue of patients with underlying heart disease was higher than that of normal people, which may explain that COVID-19 patients with basic cardiovascular disease are more likely to progress to heat injury [35,36]. It is noteworthy that all datasets confirm a consistently high expression of ACE2 in the testis, some datasets found that ACE2 and TMPRSS2 were also co-expressed in the testis, which indicated that testis are the potential targets of SARS-CoV-2 [26,27,148]. Pan et al. reported that 19 % (6/34) of mild to moderate COVID-19 patients had scrotal discomfort as one of the symptoms, while SARS−COV-2 was not detected in semen of these patients with COVID-19 [150]. In another study, Li et al. indicated the presence of SARS-CoV-2 in semen samples of six COVID-19 patients [151]. The direct influence of this virus on the male urogenital organs is still to be evaluated [152]. However, clinicians still should assess the reproductive function of male COVID-19 patients for prognosis. It was also found that the expression of ACE2 in adipose tissue was relatively high, which indicated that infection of SARS-CoV-2 may be related with obesity [34,35].

Recent studies of the epidemiological characteristics of COVID-19 have revealed that severe infection is more likely to occur in people with an existing chronic medical condition [1,58]. Pinto et al. analyzed over 700 lung transcriptome samples of severe COVID-19 patients with comorbidities and found that ACE2 was expressed at higher level in these patients compared to other groups, indicating that patients with comorbidities may have higher chances of developing severe COVID-19 [153]. Furthermore, the significantly higher expressions of ACE2 were detected in cardiac tissues of patients with heart failure and tumor tissues of patients with colorectal cancer, cervical squamous cell carcinoma, endocervical adenocarcinoma, pancreatic adenocarcinoma, rectum adenocarcinoma or kidney renal papillary cell carcinoma [35, 154–156]. Patients with cancer had a higher risk of COVID-19 than those without cancer [157]. Moreover, cancer history is one of the independent risk factors for mortality in hospitalized COVID-19 patients [158]. These studies may indicate that patients with existing chronic medical conditions are susceptible to the SARS-CoV-2 infection.

The understanding of the transmission routes for SARS-CoV-2 infection is crucial in controlling the outbreak. Respiratory droplets and close contact have been confirmed as the main transmission routes of SARS-CoV-2 [1,50,159]. The high expressions of ACE2 and TMPRSS2 in the digestive tract [26,149] and the detection of SARS-CoV-2 in gastrointestinal tissue samples and feces [43,89], imply a fecal-oral transmission route for SARS-CoV-2 infection. Although it has been

reported that ACE2 is expressed in human placenta, which provides a theoretical basis for the risk of vertical transmission of SARS-CoV-2, the existence of mother-to-child transmission of SARS-CoV-2 remains controversial [160].

Extrapulmonary organ injuries of patients with COVID-19 present a challenge to the clinician for the clinical diagnosis and treatment. More attention should be paid to the early clinical manifestations of extrapulmonary organs in patients with COVID-19, and clinicians should closely monitor the functions of extrapulmonary organs during the treatment of COVID-19.In conclusion, the distribution of ACE2 and TMPRSS2, which could help the entry of SARS-CoV-2 into the cells, provides us with a better understanding for the infection of extrapulmonary organs and the transmission routes of SARS-CoV-2. In addition, the understanding of ACE2 and TMPRSS2 in extrapulmonary organs could provide some theories and suggestions for the treatments of the patients with COVID-19.

Declaration of Competing Interest

All authors declare no conflicts of interest.

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