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REVIEW

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Gastrointestinal and renal complications in SARS-CoV-2-infected patients: Role of immune system

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Abstract

The recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease has been accompanied by various gastrointestinal (GI) and renal manifestations in significant portion of infected patients. Beside studies on the respiratory complications of coronavirus infection, understanding the essential immunological processes underlying the different clinical manifestations of virus infection is crucial for the identification and development of effective therapies. In addition to the respiratory tract, the digestive and urinary systems are the major sources of virus transmission. Thus, knowledge about the invasion mechanisms of SARS-CoV-2 in these systems and the immune system responses is important for implementing the infection prevention strategies. This article presents an overview of the gut and renal complications in SARS-CoV-2 infection. We focus on how SARS-CoV-2 interacts with the immune system and the consequent contribution of immune system, gut, and renal dysfunctions in the development of disease.

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 is a newly discovered species of human coronavirus, similar to SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus), which can lead to severe respiratory infections and even death.[1,2] Upon attack of SARS-CoV-2, innate and adaptive immune system responses trigger inflammation and cytokine storm in various organs such as respiratory and digestive tracts as well as renal organs. The immune system response is undoubtedly one of the most important determinants of disease susceptibility and/or severity. While the risk of disease severity can be increased by weakening the immune system, an increased inflammatory response to the infection may cause organ damage that is usually seen in infected patients.[3]

The most common clinical manifestations in SARS-CoV-2-infected patients are including: leukopenia or leukocytosis, pneumonia, diarrhoea, nausea, vomiting, proteinuria, haematuria and acute kidney injury (AKI).[4-7] The reported incidence of gut complications and acute kidney injury (AKI) in COVID-19 patients ranged from 12% to 61% and 0.5% to 29%, respectively.[8,9] Patients with atypical gastrointestinal (GI) symptoms have had long-term SARS-CoV-2 infection and needed more antimicrobial treatment than patients without that. Moreover, infected patients who need ICU care are more expected to develop AKI than non-ICU patients.[10] Besides, Stool and urine of SARS-CoV-2-infected patients has been proved to be the potential routes of viral transmission.[11,12] Multi-organ disorders in SARS-CoV-2 infection infer the presence of virus receptor in these organs.[13,14] Indeed, small GI epithelial cells and colonocytes express main host cell receptor of SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2), abundantly on their apical surfaces.[15] In addition, ACE2 expression is mostly localized in proximal tubular brush border, and to a less extend in the glomerular visceral and parietal epithelial cells, endothelial, and smooth muscle cells of renal vessels.[16] It seems likely

that gut and renal manifestations of SARS-CoV-2 infection as well as the severity of inflammatory response of immune system are largely related to the expression of virus receptor in these organs. This review summarizes the gastrointestinal and renal complications in SARS-CoV-2-infected patients and role of immune system in the pathogenesis of the virus.

2 | IMMUNE SYSTEM AND SARS-COV-2 INFECTION

SARS-CoV-2 is an enveloped virus contains a positive-stranded RNA genome which encodes several structural and non-structural proteins. The structural protein S of SARS-CoV-2 is used for virus attachment to ACE2 and virus entrance into the host cells. E, M and N proteins are accessory parts of virus for replication, assembly and host immune response suppression.[17,18] Upon entrance of SARS-CoV-2, viral genomic RNA or dsRNA is recognized by endosomal and cytoplasmic receptors including toll-like receptor 3 (TLR3), TLR7 and retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5) and then pro-inflammatory cytokines such as interferon-γ (IFN-γ), inducible protein 10 kD (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP-1A) and tumour necrosis factor-α (TNFα) are expressed.[19,20] Thereinafter, neutrophils as the first inflammatory immune cells are recruited into the infected sites and their antiviral activities cause cytokine storm and more attraction of immune cells such as monocytes and T cells into the infected area (Figure 1).[21,22] Afterwards, antigen-presenting cells (APCs) such as dendritic cells (DC) and macrophages phagocyte SARS-CoV-2 and become functionally mature. Both cells increase production of MHC class II costimulatory molecules, cytokines and chemokines, like interleukin-6 (IL-6), IL-12, TNF-α, MIP-1α, RANTES, IP-10 and MCP-1; thereafter, cellular and humoral immune responses such as killing the infected cells by cytotoxic T cells and producing the anti-SARS-CoV-2 antibodies by plasma cells are occurred as a result of matured APCs activities.[23-25]

On the other hand, it has reported that secreted IFNs by neutrophils and APCs could prevent virus progression, stimulate phagocytosis of antigens by DCs and macrophages, and target infected cells by natural killer (NK) and T cells.[26,27] However, SARS-CoV-2 may cause severe viral infection through prolonging virus survival in the host by suppressing IFN production via different mechanisms, including ubiquitination and degradation of RNA sensor adaptor molecules, mitochondrial antiviral signalling protein (MAVS) and tumour necrosis factor receptor–associated factor 3/6 (TRAF3/6), prevention of interferon regulatory factor 3 (IRF3) nuclear translocation, and repression of histone modification.[28-30]

In severe infected patients, NK cells, CD4+ and CD8+ T cells are reduced, although the CD4+/CD8+ T cells ratio are un-affected; therefore, it has suggested that lymphopenia is a hallmark finding in SARS-CoV-2 infection.[31-33] Several studies have documented the significant role of T cells in the pathogenesis of SARS-CoV-2 infection. T cells, especially

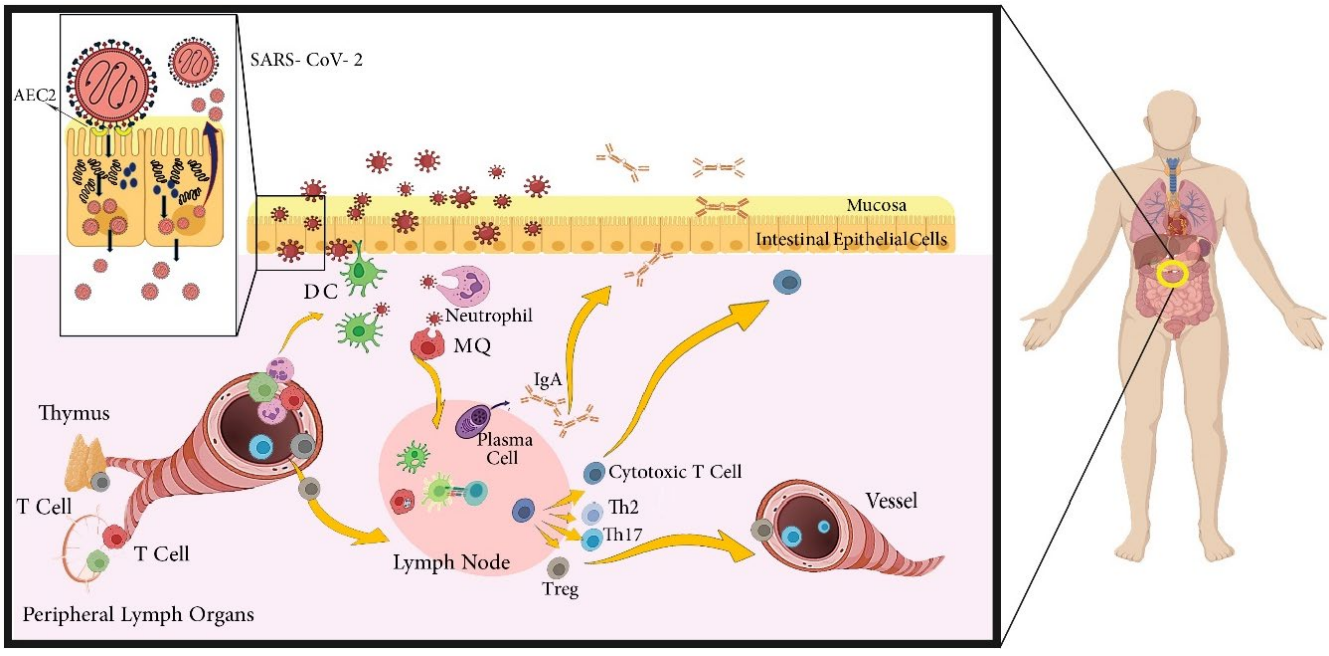

FIGURE 1 Immune system responses to SARS-CoV-2 invasion: Viral exposure, production of pro-inflammatory cytokines, recruitment of immune cells, and differentiation of B cells to plasma cells and antibody production, phagocytosis of antigens results in differentiation of T and B cells and antibody production. ACE2, angiotensin-converting enzyme 2; DC, dendritic cell; IgA, immunoglobulin A; MQ, macrophage; Th, T helper cell; Treg, T regulatory cell

virus-specific CD4+ T and CD8+ T cells, have important roles in removing virus-infected cells and balancing immune responses to pathogens.[33-35] T cells could rescue organs from severe damage by the control of excessive innate immune responses. Indeed, T helper cells promote production of antiviral antibodies by activating CD4+ T-dependent B cells and induction of pro-inflammatory cytokines through the NF-kβ signalling pathway.[31,36] Elevation of Th1 and Th17 cells along with high expression of IFNγ and IL17 were observed in SARS-CoV-2 patients. IL17 stimulates recruiting of neutrophils and monocytes into the inflamed infected regions and induces cytokine cascade. Poor outcome in viral infected patients can be attributed to increased IL-17 and reduced IFN-γ and IFNI production.[37-39] Regulatory T cells (Tregs), which identifies them as immunosuppressive cells, are moderately amplified in mild SARS-CoV-2 infection. Elevation of Treg cells is associated with the pathogenesis of COVID-19 disease.[40,41] It has reported that in severe SARS-CoV-2 infection, the naive/memory T cell ratio is higher than that in mild infection. Memory viral-specific T cells, as infection-fighting T cells, would be exist in the improved patients after clearance of SARS-CoV-2 infection and, upon re-exposure to the virus, are rapidly converted into effector T cells and provided necessary response to overcome the virus infection. These memory T cells are restricted to epitopes of structural viral proteins including the S, M, and N proteins and can induce effective responses against SARS-CoV-2.[42-44] Reduction of T cells in COVID-19 patients is might be because of a BH3-like region in the C-terminal cytosolic domain of SARS-CoV-2 protein, which could facilitate binding of virus protein to Bcl-xL in the T cells and induce T cells apoptosis.[45]

Humoral immunity is fundamental element for controlling the SARS-CoV-2 infection through neutralization of viruses and lysis of infected cells via complement activation or antibody-dependent cytotoxic cells (ADCC).[46] In severe SARS-CoV-2 infection, IgA, IgG and IgM levels are similar to that in mild infection.[32,33] Anti-SARS-CoV-2 antibodies, such as IgG, IgM and IgA, are at the highest level in the serum of infected patients within 20-30 days after onset of illness, and sustained for about 5 months thereafter. However, serum IgG can be detected early (about 4 days) after the onset of disease.[47] IgG and IgA are the most important antibodies in the serum and mucus, respectively.[48] Among them, anti-S protein antibody is a strongly neutralizing anti-SARS-CoV-2 antibody with either high or low avidity binding activity. This antibody can induce protective immunity against many variants of S protein in different SARS-CoV-2 strains.[49,50]

Despite the antiviral cellular and humoral responses, SARS-CoV-2 escapes from immune system responses via (a) induction of cytosolic constructions without any PRRs for dsRNA recognition, (b) suppression of IFNs and (c) suppression of T cells activity through downregulation of MHC classes I and II in macrophages or dendritic cells.[30,51-53]

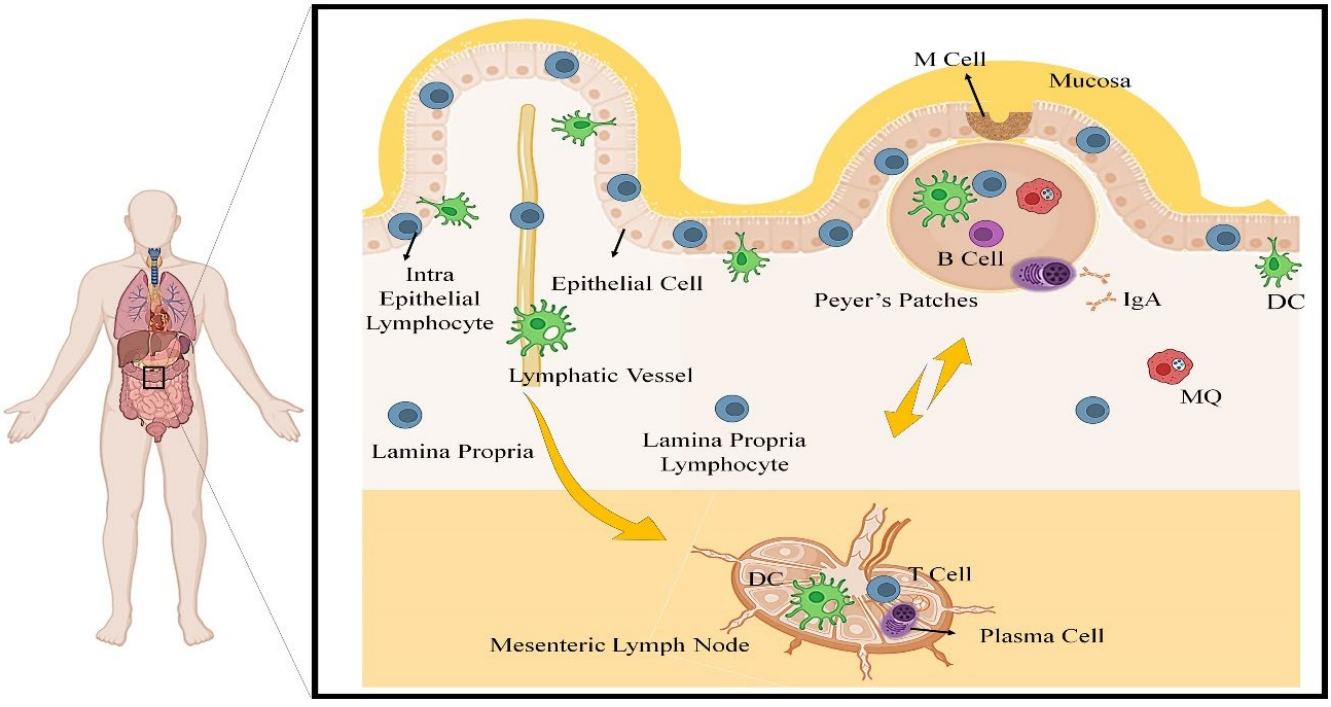

FIGURE 2 The immune system in GI tract: The GI mucosal immune system consists of epithelium, lamina propria and gut-associated lymphoid tissue. DCs uptake antigens and migrate to the LP, secondary lymphoid tissue and draining lymph nodes. M cells in the epithelium of Peyer's patches pass the antigens to DCs, macrophages and other APCs. Naive T cells become activated in secondary lymphoid tissues. DC, dendritic cell; IgA, immunoglobulin A; M cell, microfold cell; MQ, macrophage

3 | IMMUNE SYSTEM IN THE GI TRACT

The immune system in GI tract, intestinal mucosal immune system or gut-associated lymphoid tissue (GALT), constitutes the largest immune component with three different structures: epithelial and mucosal barrier, the lamina propria, and the Peyer's patches (PPs) (Figure 2).[9] The mucosal barrier, as a component of immune system, consists of the small intestinal epithelium and Paneth cells which secrete antimicrobial peptides (AMPs).[55] This barrier participates in the immune surveillance of the gut and sends signals to the mucosal immune system by producing cytokines and chemokines. Immune cells of mucosal barrier contain innate lymphoid cells, intraepithelial lymphocytes, NK cells, cytolytic and immunoregulatory αβ+ and γδ+ T cells, DCs and Tregs.[56-58] The lamina propria, the lower layer of intestinal epithelial cells, carries a large population of innate lymphoid cells (ILCs), B, NK and T cells (γδ+ T, Th17). T cells in the lamina propria quickly respond to the signals from the lumen and initiate inflammatory and anti-inflammatory responses through secreting cytokines (IL17, IL22, IFN-γ and IL26), and inducing defensins and chemokines.[54,56,59] Peyer's patches are an important source of precursor IgA-producing cells in the mucosa of the small intestine. PPs contain proliferating B cells, population of CD4 T cells, dendritic cells, follicular dendritic cells and macrophages. M cells, the specialized cells in PPs, phagocyte bacteria, viruses, proteins, and inert particles and transcytose them into the PPs to trigger the appropriate immune responses.[56,59-61]

4 | PATHOPHYSIOLOGY OF GI TRACT IN SARS-COV-2 INFECTION

The first step of SARS-CoV-2 infection is the virus entry to the cell via its target, ACE2 receptor. This receptor is abundantly expressed (100 times than that in the lung) in the epithelial cells of the stomach, duodenum, ileum, and rectum as well as cholangiocytes and hepatocytes of the liver, while less expression of ACE2 receptor has demonstrated in oesophageal mucosa.[15,62,63] The highly expression of ACE2 receptor in the absorptive enterocytes of the ileum and colon suggests a potential explanation for some digestive symptoms such as diarrhoea observed in many COVID-19 patients. In the second step, new virions will be assembled through synthesizing viral-specific RNA and proteins of positive-strand viral RNA, and released in to the GI tract.[64,65] New virions and released SARS-CoV-2 could destruct epithelial cells, induce immune responses and trigger cytokine storm. Some in vivo studies suggested that SARS-CoV-2 may affect absorption of tryptophan through ACE2, resulting in decreased antimicrobial peptide, which in turn leads to an altered gut microbial composition. Indeed, gut microbiota dysbiosis has been reported in some SARS-CoV-2-infected patients, and treatment with probiotic has also been suggested, but it has not been confirmed yet.[66,67]

Cytokine storm in COVID-19 patients is accompanied by a general inflammatory reaction, abnormal immune responses and several organ dysfunctions, such as digestive injury which may lead to more severe disease and even death.[63,68] Experimental studies suggested that lung infection can be secondary to a primary gut viral infection; nevertheless, whether intestinal injury caused by the virus could be a secondary response to primary general inflammation or as a result of primary intestinal infection, or a combination of both, needs further investigation.[63,69]

Up to 50% of patients with COVID-19 represent liver enzyme abnormalities which are related to hepatic damage. ACE2 appears to play an important role in the pathogenesis of hepatic injury in COVID-19. High expression of ACE2 on the cholangiocytes and hepatocytes of the liver may explain a direct cytotoxic effect of the virus against hepatic cells. It has suggested that SARS-CoV-2 may deteriorate hepatic injury through various pathogenic mechanisms such as direct cytopathic effect on cholangiocytes and hepatocytes, inflammatory cytokine storm, hypoxic injury of the liver and drug toxicity. However, further studies are required to determine the exact pathogenesis of the liver injury seen in COVID-19 patients.[70-72]

5 | GUT-LUNG AXIS, SARS-COV-2 AND GI DISORDERS

Intestinal microbiome dysbiosis is accompanying by bilateral deviation in the connection between the gut and vital organs such as the lungs. In addition, changes in the microbial community of the lungs can affect the gut microbiome composition. It has therefore been suggested that the 'gut-lung axis' is like a two-way communication network where several respiratory infections are accompanied by digestive symptoms and, in other way, gut microbiome dysbiosis is linked to respiratory infections. Additionally, in gut-lung axis, immune cells from the gastrointestinal tract migrate through the bloodstream to the lung and influence immune responses within the lung. Further, viral lung infections can change the composition of intestinal bacteria, where gut microbiota regulate adaptive immune responses against the lung pathogens. Similar crosstalk between the gut and lungs has been suggested in SARS-CoV-2 infection. Indeed, following infection of lung cells with SARS-CoV-2, intestinal immune disorder and diarrhoea can occur due to the effect of CD4+ T cells that reached it through the gut-lung axis.[60,69,73]

Early studies on SARS-CoV-2 infection reported that diarrhoea (2%–10.1%), nausea and vomiting (1%–3.6%) are not usual symptoms in infected patients,Table 1.[10,74] However, later studies revealed that gastrointestinal symptoms are frequent and associated with severe form of disease.[75] In fact, diarrhoea

TABLE 1 Summary of clinical features of SARS-CoV-2 patients with digestive symptoms

Country	Authors	DOI	Patients, No	Diarrhea%	Nausea%	Vomiting%	Anorexia%	Abdominal pain%
Turkey	E Avci et al[82]	10.21203/rs.3.rs-48569/v1	2152	0.05	NA	0.05	NA	NA
China	T Zheng et al[83]	10.1002/jmv.26146	1320	8.1	4.3	4.3	NA	NA
China	S Luo et al[84]	10.1016/j.cgh.2020.03.043	1141	37	73	65	98	25
China	W J Guan et al[33]	10.1056/NEJMoa2002032	1099	3.8	5	5	NA	NA
USA	S R Bauer et al[85]	10.3949/ccjm.87a.ccc046.	1059	22.1	15.9	8.6	NA	NA
USA	S N Baig et al[86]	10.21203/rs.3.rs-55080/v1	711	17.3	16.2	13.7	NA	NA
China	C Huang, et al[38]	10.1136/gutjnl-2020-320926	651	8	1.5	1.7	NA	NA
China	H Shang et al[87]	10.1080/00365521.2020.1800078	564	27.8	26.8	20.4	NA	NA
Italy	E Buscarini et al[88]	10.1136/gutjnl-2020-321434.	411	3.6	4.3	3.8	NA	NA
USA	V Gayam et al[89]	10.1002/jmv.26306.	408	27.2	27.2	27.2	NA	NA
USA	P Goyal et al[90]	10.1056/NEJMc2010419	395	23.7	19.1	19.1	NA	NA
USA	WD Redd et al[91]	10.1053/j.gastro.2020.04.045	318	33.7	26.4	15.4	NA	NA
China	Z Zhou et al[92]	10.1053/j.gastro.2020.03.020	254	18.1	8.3	5.9	NA	1.2
China	L Mao et al[93]	10.1001/jamaneurol.2020.1127	214	19.2	NA	NA	NA	4.7
USA	G Cholankeril et al[94]	10.1101/2020.04.23.20076935	207	10.8	10.8	10.8	NA	NA
China	C Han et al[95]	10.14309/ajg.0000000000000664	206	32.5	NA	11.7	15.5	NA
China	L Pan et al[10]	10.14309/ajg.0000000000000620	204	34	NA	3.88	78.6	1.94
China	J Wu et al[96]	10.1016/S0140-6736(20)30566-3	191	4.7	3.7	3.7	NA	NA
China	L Kim et al[97]	10.15585/mmwr.mm6932e3	180	26.7	24.4	24.4	NA	8.3
China	N Mehta et al[98]	10.1001/jamacardio.2020.1855	171	8.8	NA	6.4	NA	NA
China	P Ramachandra et al[99]	10.1159/000509774	150	10	4	NA	NA	NA
China	W Yang et al[100]	10.1016/j.jinf.2020.02.016	149	7.4	1.3	1.3	NA	NA
China	SY Park et al[101]	10.4168/aair.2018.10.4.387	139	12.9	17.3	NA	12.2	5.8
China	Y Bai et al[102]	10.1001/jama.2020.1585	138	10.1	10.1	3.6	39.9	2.2
China	K Liu et al[103]	10.1097/CM9.0000000000000744	137	8	NA	NA	NA	NA
China	YD Peng et al[104]	10.3760/cma.j.cn112148-20200220-00105	112	13.4	NA	NA	NA	NA
Italy	A Papa et al[105]	10.26355/eurrev_202007_21923	105	9	NA	NA	NA	NA
China	J Cao et al[106]	10.1093/cid/ciaa243	102	10.8	NA	NA	NA	NA
China	W Zhao et al[107]	10.2214/AJR.20.22976	101	3	2	2	NA	NA
China	N Parri et al[108]	10.1056/NEJMc2007617	100	9	NA	NA	NA	4
China	N Chen et al[109]	10.1016/S0140-6736(20)30211-7	99	2	1	1	NA	NA
China	L Lin, et al[75]	10.1136/gutjnl-2020-321013	95	24.2	17.9	4.2	17.9	NA

(Continues)

TABLE 1 (Continued)

Country	Authors	DOI	Patients, No	Diarrhea%	Nausea%	Vomiting%	Anorexia%	Abdominal pain%
China	Y Xu et al[110]	10.1038/s41591-020-0817-4	91	23	NA	NA	NA	NA
China	X Xu et al[111]	10.1007/s00259-020-04735-9	90	5.6	5.6	2.2	NA	NA
China	K Li et al[112]	10.1097/RLI.0000000000000672.	83	8.4	NA	NA	NA	NA
China	H Shi et al[113]	10.1016/S1473-3099(20)30086-4	81	3.7	NA	4.9	1.2	NA
China	J Wu et al[114]	10.1093/cid/ciaa199	80	1.25	1.25	1.25	NA	NA
China	J Wu et al[115]	10.1097/RLI.0000000000000670.	80	8.8	NA	NA	NA	NA
China	Z Zhao et al[116]	10.1101/2020.03.01.20029785	75	44	9	9	NA	NA
China	F Xiao et al[62]	10.1053/j.gastro.2020.02.055	73	35.6	NA	NA	NA	NA
China	Z Wang et al[117]	10.1093/cid/ciaa272	69	14.5	NA	4.3	NA	NA
China	J Liu et al[118]	10.1101/2020.03.09.20033118	64	5	NA	NA	NA	NA
China	XW Xu et al[119]	10.1136/bmj.m606	62	8	NA	NA	NA	NA
China	S Zhou et al[120]	10.2214/AJR.20.22975. Epub 2020 Mar 5.	62	14	NA	NA	NA	NA
China	MFY Mohamud et al[121]	10.2147/IDR.S263632	60	16.7	16.7	16.7	NA	NA
Hong Kong	KS Cheung et al[122]	10.1053/j.gastro.2020.03.065	59	22	NA	1.7	NA	11.9
China	X Yang et al[123]	10.1016/S2213-2600(20)30079-5	52	NA	3.8	5	NA	NA
China	YH Xu et al[124]	10.1016/j.jinf.2020.02.017.	50	NA	NA	NA	NA	NA
China	J Xu et al[125]	10.1038/s41420-020-00307-w	48	6.2	2	NA	6.2	NA
China	Y Xiong et al[126]	10.1097/RLI.0000000000000674.	42	23.8	NA	NA	NA	NA
China	C Huang et al[38]	10.1016/S0140-6736(20)30183-5	41	2.6	NA	NA	NA	NA
Austria	M Effenberger et al[127]	10.1136/gutjnl-2020-321388.	40	55	27.5	12.5	NA	NA
European	G Spiteri et al[128]	10.2807/1560-7917.ES.2020.25.9.2000178	38	2.6	2.6	NA	NA	NA
China	C Zhang et al[129]	10.1371/journal.pmed.1003130	34	12	12	12	NA	NA
China	Y Huang et al[130]	10.1016/j.tmaid.2020.101606	34	14.7	NA	NA	NA	NA
China	D Wang et al[131]	10.3760/cma.j.cn112140-20200225-00138	31	10	NA	NA	NA	NA
China	YY Li et al[132]	10.3760/cma.j.cn112147-20200214-00095	31	9.7	16.1	16.1	41.9	NA
China	M Liu et al[133]	10.3760/cma.j.issn.1001-0939.2020.0016	30	30	30	30	NA	NA
China	L Chen et al[134]	10.3760/cma.j.issn.1001-0939.2020.03.013	29	14	NA	NA	NA	NA
S. Korea	I Kong et al[135]	10.24171/j.phrp.2020.11.1.03	28	7	NA	NA	NA	NA
China	F Pan et al[136]	10.1148/radiol.2020200370	21	NA	NA	NA	42.9	NA
China	W Xia et al[137]	10.1002/ppul.24718	20	15	10	10	NA	NA
Singapore	BE Young et al[138]	10.1001/jama.2020.3204	18	16.7	NA	NA	NA	NA
China	L Zou et al[139]	10.1056/NEJMc2001737	18	5.6	5.6	5.6	5.6	NA

(Continues)

TABLE 1 (Continued)

Country	Authors	DOI	Patients, No	Diarrhea%	Nausea%	Vomiting%	Anorexia%	Abdominal pain%
China	L Wang et al[140]	10.1183/13993003.00398-2020	18	16.7	5.6	5.6	NA	NA
France	M Luong-Nguyen et al[141]	10.1016/j.jviscsurg.2020.04.016	15	6.7	NA	NA	NA	NA
China	D Chang et al[142]	10.1001/jama.2020.1623	13	7.7	NA	NA	NA	NA
China	Y Liu et al[143]	10.1007/s11427-020-1643-8	12	16.7	16.7	16.7	NA	NA
China	R Huang et al[144]	10.1016/S1473-3099(20)30147-X.	11	1	NA	NA	NA	NA
China	H Zhu et al[145]	10.21037/tp.2020.02.06	9	11.1	NA	NA	NA	NA
China	H Chen et al[146]	10.1016/S0140-6736(20)30360-3	9	11	NA	NA	NA	NA
China	MQ Zhang et al[147]	10.3760/cma.j.issn.1001-0939.2020.03.015	9	11.1	NA	NA	NA	NA
China	CD Russell et al[148]	10.1016/S0140-6736(20)30154-9	6	33.3	NA	NA	NA	NA

Abbreviation: NA, not available.

is one of the atypical gastrointestinal symptoms in COVID-19 patients.[74] Viral diarrhoea in SARS-CoV-2 infection might be occurred due to the induction of inflammation by SARS-CoV-2 in the ACE2+ epithelium. Indeed, inflammation can cause epithelial atrophy and disrupt the balance between the absorption and secretion of water and electrolytes.[76-79] Diarrhoea can also be induced by a wide variety of antiviral and antibacterial medications that patients may receive.[60] In addition, inhibited innate immune responses by SARS-CoV-2 might permit infiltration, replication and infection of opportunistic intestinal bacteria in the epithelium, resulting in bacterial diarrhoea.[80] However, in mild viral diarrhoea, upregulation of immune inhibitory cytokine TGF-β may induce apoptosis of antiviral T cells, and an anti-apoptotic response of host cells may reduce inflammation and destruction of intestinal epithelial cells (Figure 3).[45,81]

6 | SARS-COV-2 INFECTION AND INFLAMMATORY BOWEL DISEASES

An important concern in SARS-CoV-2 pandemic is patients with immune-mediated disease like IBD (inflammatory bowel diseases) and concurrent SARS-CoV-2 infection. It seemed that patients with IBD like Crohn's disease and ulcerative colitis are more susceptible to viral infections.[149,150] IBD as an inflammatory condition in the colon and small intestine is caused by an excessive immune response against luminal bacteria in the GI tract.[151] The common medications in IBD are immunosuppressive drugs, mainly anti-TNF agents.[152] Remarkable points in IBD patients are the high expression of ACE2 in the GI tract accompanied by immune system suppression, which increase the susceptibility of patients to the viral infections (Figure 4).[153,154] However, severe SARS-CoV-2 infection or high mortality rate has not been reported in treating IBD patients; therefore, an international consensus is that IBD patients are not more susceptible to SARS-CoV-2 infection than individuals without IBD. In fact, there are two forms of ACE2 in IBD patients which are distinct in structure and function: (a) membranous ACE2, consists of 2 domains, extracellular domain which is bind to S protein of SARS-CoV-2, and trans-membrane domain which is connector of extracellular domain and cell membrane and (b) soluble ACE2, which contains an extracellular domain of ACE2 without any cell membrane connector.[153,155,156] High levels of soluble ACE2 in IBD patients could bind to SARS-CoV-2, prevent virus interactions with membranous ACE2 and consequently decrease the patients' susceptibility to the virus.[156] On the other hand, it was thought that suppression of cytokine storm-driven inflammation by immunosuppressive drugs (azathioprine, methotrexate) might increase infection susceptibility, but interestingly, it has revealed that the effects of anti-inflammatory drugs on the immune system may not only be beneficial for diminishing the mucosal inflammation, but also for avoiding SARS-CoV-2 pneumonia.[152,157] Indeed,

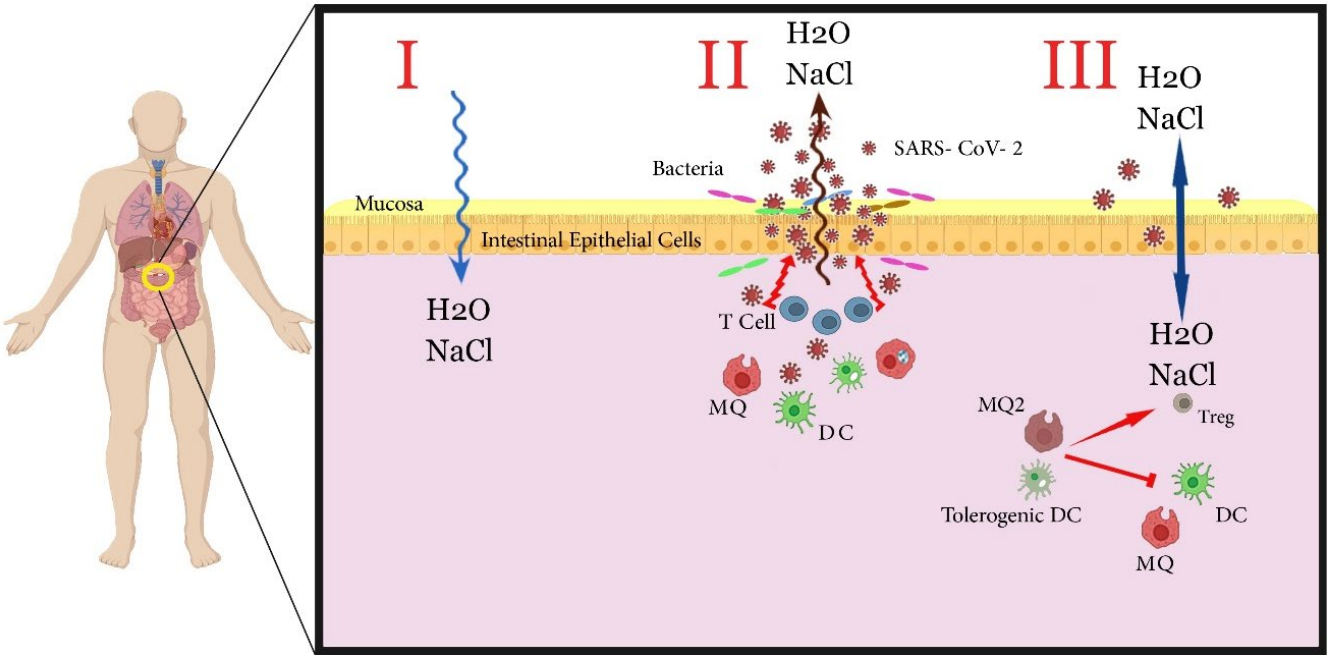

FIGURE 3 SARS-CoV-2 and diarrhoea: Water and electrolytes transport across the endothelial cells in: I, normal condition; II, severe infectious diarrhoea; III, SARS-CoV-2 infection: suppression of inflammatory cells (cytotoxic T cells and type 1 macrophages) by anti-inflammatory cells (Treg cells and type 2 macrophages) reduces distribution of intestinal water and electrolytes transport and barrier functions. DC, dendritic cell; MQ, macrophage; Treg, T regulatory cell

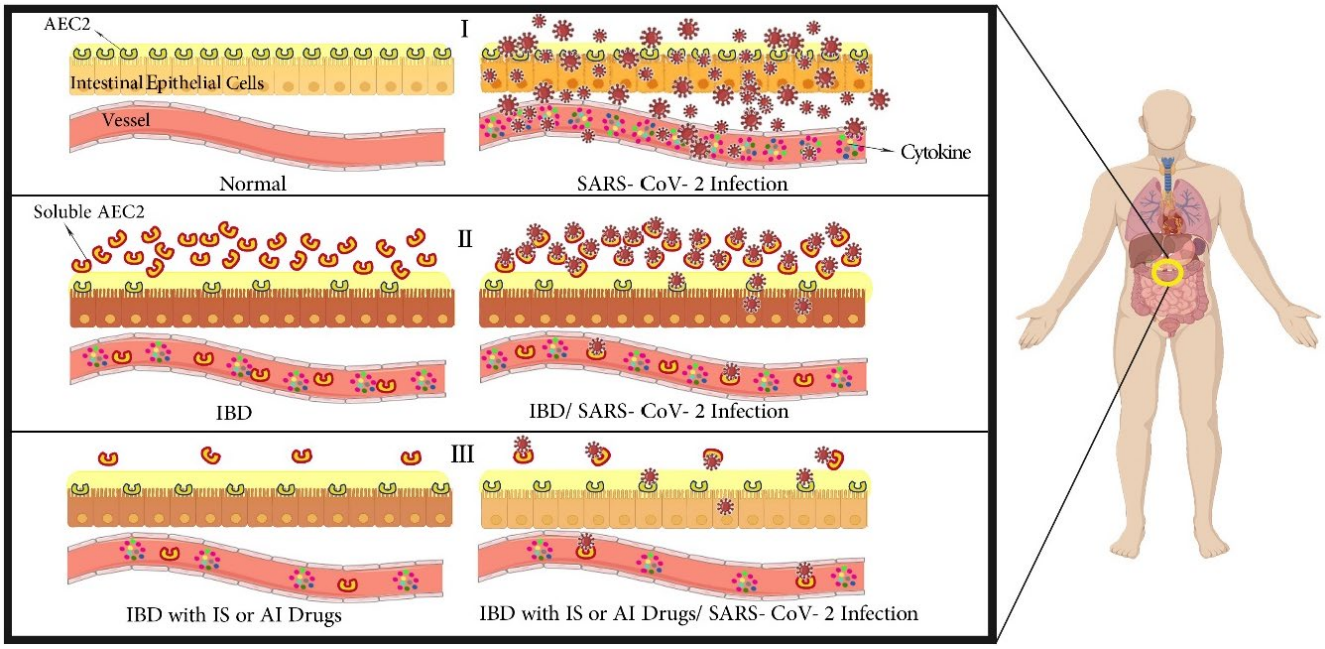

FIGURE 4 SARS-CoV-2 and IBD: I, in normal condition, high expression of ACE2 on the epithelial cells increases binding of SARS-CoV-2 to the gut epithelial cells, and induces production of inflammatory cytokines. II, In IBD patients, shedding ACE2 (soluble ACE2) from inflamed cells decreases and inhibits virus attachment to the epithelial cells, and reduces production of inflammatory cytokines. III, Medication of IBD by immunosuppressive drugs (IS) or anti-inflammatory drugs (AI) might decrease soluble ACE2 while inhibit induced inflammation in IBD patients with SARS-COV-2 infection. ACE2, angiotensin-converting enzyme 2; AI, anti-inflammatory medicine; IBD, inflammatory bowel disease; IS: immunosuppressive medicine

an increase in pro-inflammatory cytokines such as IL-1, TNF-α or IL-6 is related to the severity of gut inflammation, so cytokines modulation in immune cells may be a major therapeutic management of IBD patients.[158-160] However, usage of more than one immunosuppressive drug could increase the risk of SARS-CoV-2 infection.[157]

7 | SARS-COV-2 INFECTION AND COLORECTAL CANCER

Viral infection of gastrointestinal cancer patients such as colorectal cancer (CRC) is another area of concern during SARS-CoV-2 pandemic. (Figure 5). It has reported that about 1%-20% of SARS-CoV-2-infected patients in China and Italy had a history of active cancer and fatality rate in these patients was more than two times higher than in the general.[161-163] In fact, high expression of immunoinhibitory cytokines and proteins such as TGFβ, IL10, programmed death 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA4) inhibit anti-tumour responses of immune system and raise the possibility of viral infection.[164-166] Furthermore, anticancer treatments including chemotherapy or surgery have negative effect on the immune system and cause systemic immunosuppressive status.[161] Consequently, in CRC patients, suppressed immune system could not induce the essential antiviral responses against SARS-CoV-2, and infection of ACE2+ gastrointestinal epithelial cells with SARS-CoV-2 may cause more severe symptoms than in non-cancer patients.[161,163,167]

8 | IMMUNE SYSTEM IN THE KIDNEY

The kidneys may be affected in some bacterial/viral infections through their functional activities in clearance of metabolic waste products, toxins, drugs, circulating cytokines and blood borne proteins.[169,170] Elimination of microbial components and cytokines by renal filtration could limit immune cell activation and inflammation, while long-term exposure of immune cell to cytokines and toxins could lead to persistent stimulation of immune system and cause cytokine storm and consequently tissue damages.[168,170,171] In the kidneys, peripheral tolerance is maintained by the renal resident immune cells consisting of DCs, macrophages and lymphocytes, in the absence of immunological danger (bacterial and viral) signals.[172,173] However, during pathogenic infections, the direct and indirect immune-mediated renal damages can be created respectively via targeting the specific renal antigens and through bystander effects of immune system responses.[166-168,171]

9 | PATHOPHYSIOLOGY OF KIDNEY IN SARS-COV-2 INFECTION

In COVID-19 patients, viral RNA is detectable in kidney tissue and urine, and the presence of virus particles in the tubular epithelial cells, podocytes and glomerular capillary endothelium has been demonstrated. It has been shown that the ACE2 expression in the kidneys is higher (about 100-fold) than respiratory organs. In addition, according to histopathological findings, SARS-CoV-2 can exert direct cytopathic effect on the infected renal cells.[8] Therefore, kidney may be an essential target organ for SARS-CoV-2 infection.[74,174,175]

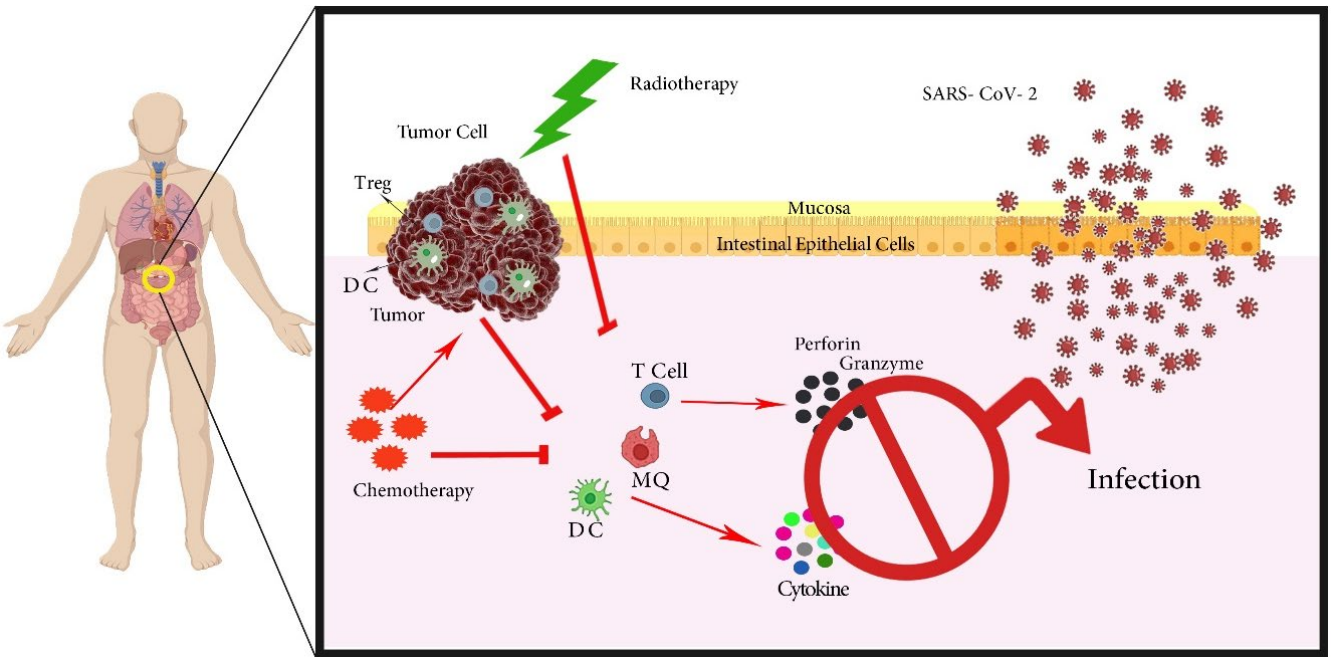

FIGURE 5 SARS-CoV-2 and cancer: Radiation therapy and chemotherapy suppress inflammatory cells production which predisposes CRC patients for SARS-CoV-2 infection. DC, dendritic cell; MQ, macrophage; Treg, T regulatory cell

10 | GUT-KIDNEY AXIS, SARS-COV-2 AND RENAL DISORDERS

The kidney and the gut share a bidirectional association of synergy during homoeostasis known as the gut-kidney axis, which can be divided into metabolism-dependent and immune pathways.[176,177] The first pathway is mainly mediated by the gut microbiome metabolites that can regulate the host physiological functions, while in the second one, the connection between the gut and the kidneys is mainly through the components of the immune system.[176,178] Crosstalk between these two pathways also plays a critical role in keeping the balance of the gut-kidney axis. Therefore, disruption of this bidirectional communication may lead to severe complications such as AKI and chronic kidney disease (CKD).[178-180]

11 | SARS-COV-2 INFECTION AND ACUTE KIDNEY INJURY

AKI has been reported to occur in 6% of SARS-CoV-2-infected patients.[181,182] AKI is characterized by rapid deterioration in renal function, which results in the build-up of toxic waste products and disruption of internal homoeostasis. Multiple aetiologies may be contributing to AKI, and medication-induced nephrotoxicity is a relatively common cause among them which mostly affects the tubulointerstitial compartment.[183,184] The pathophysiological mechanism of drug-induced nephrotoxicity is complex and often mediated by intraglomerular haemodynamic changes, inflammation, and defect in tubular secretion, uric acid deposition, and rhabdomyolysis.[185,186]

SARS-CoV-2-mediated AKI could be due to the cytotropic effect of the virus and systemic inflammatory response induced by cytokines (Figure 6).[55] Incidence of AKI might be affected by multi-factors and be associated with death in severe SARS-CoV-2 infection.[182,187] Furthermore, cytokine storm may play a main role in the immunopathology of AKI. Indeed, once SARS-CoV-2 infiltrates into the renal cells, innate immune system and inflammation responses might be trigger a cytokine storm, which induces hypoxia, shock, and rhabdomyolysis and thus causes kidney injury.[188-190] It has been proposed that in COVID-19 patients, cytokine storm is an underlying mechanism of the 'viral sepsis' and multiple-organ failure, such as AKI.[60] Additionally, the dehydration resulted from fever or diminished intake of fluids in these patients, reduces glomerular filtration rate and causes AKI.[15,191,192] On the other hand, secreted anti- SARS-CoV-2 antibodies bind to viral antigens and lead to the formation of virus-antibody immune complexes. Deposition of these immune complexes on the renal cells along with antiviral humoral and cellular immune responses (specific antibody or T lymphocyte) might destruct kidney organs.[183,193,194]

12 | SARS-COV-2 INFECTION AND IMMUNOCOMPROMISED PATIENTS

Immunocompromised hosts are another high-risk group of patients such as haemodialysis patients. Blood samples analysis of these patients with SARS-CoV-2 infection has

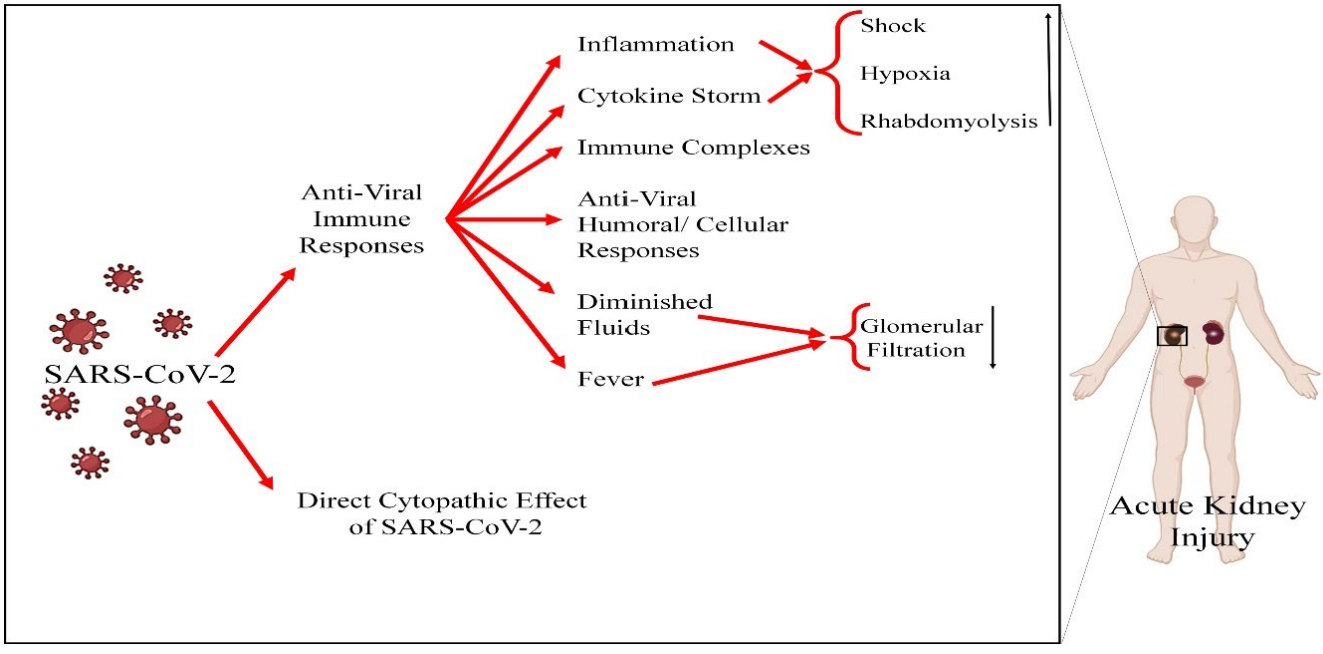

FIGURE 6 SARS-CoV-2 and acute kidney injury: Immune system responses against SARS-CoV-2 and cytopathic effect of SARS-CoV-2 may cause acute kidney injury

indicated a notable decrease in helper and cytotoxic T cells, NK cells counts, and low levels of inflammatory cytokines compared to non-haemodialysis patients with SARS-CoV-2 infection.[13,195] In fact, lymphopenia in dialysis and chronic renal failure patients is a common finding which is related to the disruption of regulatory mechanisms of apoptosis.[196,197] Decreased immune response and cytokine release in haemodialysis patients increase susceptibility of these patients to the mild SARS-CoV-2 infection without serious pneumonia. The reason of death in these patients is apparently not associated to pneumonia. However, these patients are at higher risk of SARS-CoV-2 infection and further care is essential in the management of haemodialysis patients in SARS-CoV-2 pandemic.[13,195,198]

13 | MANAGEMENT OF SARS-COV-2 PATIENTS WITH GI MANIFESTATIONS

Besides to the direct effects of SARS-CoV-2, infected people might be at risk of GI complications that should be managed. Diarrhoea is one of the most common GI manifestation in one-third to one-half of COVID-19 patients. Liver enzymes may also be elevated, but acute liver failure has not been reported so far in infected patients. Many of the treatments prescribed for COVID-19 patients may have GI and hepatic complications and should be considered in the differential diagnosis.[199] Thus, it is important to monitor the baseline liver enzyme activity both prior to starting and during treatment. Moreover, before starting treatment, the patient should be checked for the presence of chronic viral hepatitis, hepatitis B virus (HBV) and hepatitis C virus (HCV), and also for the risk factors of chronic liver disease, especially alcohol consumption. Major American gastroenterological societies have recommended postponing non-emergency endoscopies and using personal protective equipment in emergency endoscopies.[199-201] For IBD patients, it is recommended that immunosuppressive drugs be delayed until the symptoms of COVID-19 have resolved; however, the recommended management for severe GI diseases is mainly focused on prevention and supportive measures (64,[202]).

14 | MANAGEMENT OF SARS-COV-2 PATIENTS WITH RENAL MANIFESTATIONS

In COVID-19 patients with renal involvement, guidelines for supportive care in renal disease (eg regular control of urinary output and blood creatinine, avoidance of nephrotoxins, and haemodynamic monitoring) should be followed to reduce the severity of AKI in these patients. Use of lung-protective ventilation has recommended in order to minimizing both volutrauma and barotrauma, and reducing the risk of new or worsening AKI. Moreover, fluid balance should be adjusted according to fluid responsiveness and tolerance test. Because COVID-19 patients commonly have a fever and fluid resuscitation is usually not performed prior to admission, volume depletion may be common in patients at the time of admission. Thus, in order to prevent AKI, hypovolaemia should be corrected.[203,204]

15 | CONCLUSION

Expression of ACE2 receptors, which are widely expressed in various organs including the respiratory tract, GI tract and kidneys, is making them potential targets for SARS-CoV2 infection.

COVID-19 patients may develop a variety of gastrointestinal symptoms (ie nausea, vomiting and diarrhoea) which may due to the immune system responds to viral infection. For instance, induction of cytokine storm and inflammation in the infected ACE2+ epithelium and/or inhibited innate immune responses could induce severe viral diarrhoea, while upregulation of inhibitory cytokines and reduction of antiviral T cells could reduce inflammation and destruction of intestinal epithelial cells which may result in mild diarrhoea.

Severe clinical manifestations and poor prognosis might take place in COVID-19 patients with hepatic complications. Thus, the liver function should be monitored before and during treatment to diminish the liver-related complications in these patients. In IBD patients with SARS-CoV2 infection, immunosuppressive drugs can be temporarily withheld until the resolution of active infection. However, in CRC patients, high expression of immunoinhibitory factors and anticancer treatments may suppress the immune system; thereby the immune system could not induce the essential antiviral responses against SARS-CoV-2. On the other hand, cytokine storm, anti- SARS-CoV-2 antibodies, immune complexes and activated immune cells may cause severe renal damages such as AKI in COVID-19 patients. Use of lung-protective ventilation is recommended to prevent worsening of AKI, and more care has been advised for immunocompromised patients such as haemodialysis patients in the COVID-19 pandemic. Consequently, understanding the immune mechanisms underlying GI tract and kidney injury in SARS-CoV-2 infection will likely provide more effective treatment and reducing mortality and morbidity of infected patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

AUTHORS' CONTRIBUTIONS

Fatemeh Maghool, Mohammad Hassan Emami and Samane Mohammadzadeh designed the project. Fatemeh Maghool, Samane Mohammadzadeh, Ali Valiani and Tahereh Safari contributed to the implementation and writing of the manuscript. Samane Mohammadzadeh, Anasik Lalazarian and Fatemeh Maghool designed the figures.

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