On the whereabouts of SARS-CoV-2 in the human body: A systematic review

Wim Trypsteen*, Jolien Van Cleemput♣, Willem van Snippenberg, Sarah Gerlo♣, Linos Vandekerckhove♣

HIV Cure Research Center, Department of Internal Medicine and Pediatrics, Ghent University & Ghent University Hospital, Ghent, Belgium

These authors contributed equally to this work.

*linos.vandekerckhove@ugent.be

Abstract

Since SARS-CoV-2 appeared in the human population, the scientific community has scrambled to gather as much information as possible to find good strategies for the containment and treatment of this pandemic virus. Here, we performed a systematic review of the current (pre)published SARS-CoV-2 literature with a focus on the evidence concerning SARS-CoV-2 distribution in human tissues and viral shedding in body fluids. In addition, this evidence is aligned with published ACE2 entry-receptor (single cell) expression data across the human body to construct a viral distribution and ACE2 receptor body map. We highlight the broad organotropism of SARS-CoV-2, as many studies identified viral components (RNA, proteins) in multiple organs, including the pharynx, trachea, lungs, blood, heart, vessels, intestines, brain, male genitals and kidneys. This also implicates the presence of viral components in various body fluids such as mucus, saliva, urine, cerebrospinal fluid, semen and breast milk. The main SARS-CoV-2 entry receptor, ACE2, is expressed at different levels in multiple tissues throughout the human body, but its expression levels do not always correspond with SARS-CoV-2 detection, indicating that there is a complex interplay between virus and host. Together, these data shed new light on the current view of SARS-CoV-2 pathogenesis and lay the foundation for better diagnosis and treatment of COVID-19 patients.

Author summary

Since the beginning of 2020, SARS-CoV-2 quickly spread throughout the human population and caused a pandemic with devastating consequences at a global scale. The scientific community is challenged to find good strategies for the containment and treatment of this virus. In this context, an important step is charting the viral presence in the human body to improve diagnostics, prevention or treatment.

Here, we bring together the current scientific knowledge on SARS-CoV-2 detection in the human body and body fluids. We observe that SARS-CoV-2 impacts the human body well beyond the lungs and shows a complex interplay with the human host that is not always correlated with its entry receptor (ACE2) expression levels. Many studies identified
viral components (RNA, proteins) of SARS-CoV-2 in multiple organs (pharynx, trachea, lungs, blood, heart, vessels, intestines, brain, male genitals and kidneys) and body fluids (mucus, saliva, urine, cerebrospinal fluid, semen and breast milk). However, besides the lungs, researchers were only able to detect infectious virus in stool and urine in a limited set of SARS-CoV-2 patients.

By combining these studies, our study provides an eagle’s view on the current status of SARS-CoV-2 pathogenesis and lays the foundation for better diagnosis and treatment of COVID-19 patients.

Introduction

Coronavirus disease (COVID-19) is considered one of the largest fast expanding pandemics since the 1918 Spanish flu with serious consequences for global health and economy. As of July 1st 2020, the coronavirus causing COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected more than 10 million people and caused over half a million deaths (WHO Coronavirus Disease Dashboard, https://covid19.who.int). These numbers overshadow the impact of the related SARS coronavirus (SARS-CoV), which caused about 8,000 infections and 800 deaths [1]. As for SARS-CoV, SARS-CoV-2 is believed to be a derivative of an animal coronavirus that adopted the ability of human-to-human transmission [2]. However, in contrast to SARS-CoV, the more contagious SARS-CoV-2 rapidly spread around the world after it took off from a few human pilot infections in Wuhan, China.

SARS-CoV-2 spreads from one person to another through direct contact or over short distances in the air, either impacted in aerosol droplets or carried on fomites. Upon inhalation, SARS-CoV-2 enters host respiratory cells via interaction with its entry receptor, angiotensin-converting enzyme 2 (ACE2) and an activating receptor, a protease such as TMPRSS2 or cathepsin [3]. Viral replication in these cells elicits direct adverse effects on cells, but also induces local immune cells to quickly and abundantly secrete cytokines and chemokines. In turn, an excessive amount of immune cells are attracted to the site of infection causing a cascade of inflammatory reactions with detrimental effects on the lungs. The current view on SARS-CoV-2 pathogenesis focuses on these respiratory pathologies, causing symptoms such as coughing, fever, general malaise, dyspnea and respiratory distress, that might eventually lead to death [4]. However, increasing evidence shows that SARS-CoV-2 is not always confined to the respiratory tract, but may also spread to other organs. Indeed, the majority of COVID-19 patients show various other symptoms besides respiratory disorders including neurological, cardiovascular, intestinal and kidney malfunctions [5–11]. The pathophysiological mechanisms behind the latter symptoms are not yet fully understood. Researchers proposed viral-induced endothelial disturbances (e.g. thrombosis, hemorrhages and edema) and defective immune responses (e.g. cytokine storm or auto-immune reactions) as underlying reasons for multi-organ failure [5, 6]. In addition, direct viral replication in these organs may also account for multi-organ pathologies. In this context, the host cell entry receptor of SARS-CoV-2, ACE2, has been detected in cells from multiple tissues, including the respiratory tree, cornea, esophagus, ileum, colon, gallbladder and common bile duct tissues [12–14]. This raises the possibility for SARS-CoV-2 to engage with its receptor at multiple organ sites upon viremia, swallowing or axonal transport and cause organ-specific malfunctions. This replication in specific organs would enable the virus to be shed in multiple body fluids and would augment the chances for viral transmission to new hosts.

In order to get better insight into the different organs involved in SARS-CoV-2 infection, we performed a systematic narrative review on (pre-)published literature to determine which
human organs and cell types are targeted by SARS-CoV-2. In addition, we sought to correlate the presence of SARS-CoV-2 with organ-specific expression of ACE2, the main entry receptor of SARS-CoV-2.

**Methods**

**Systematic literature screening**

We performed a systematic literature search on SARS-CoV-2 detection studies using the online databases PubMed (www.ncbi.nlm.nih.gov/pubmed), Web of Science (WoS, www.webofknowledge.com) and bioRxiv/medRxiv for the time period January 1\(^{st}\) 2020 until June 23\(^{rd}\) 2020 (Fig 1).

The following search terms were used in Pubmed and Web of Science to construct the initial dataset of articles: ((SARS-COV2[All Fields] OR "COVID-19"[Supplementary Concept] OR "COVID-19"[All Fields] OR "covid19"[All Fields])) AND ('2020/01/01'[PDAT]: '2020/12/31'[PDAT]) NOT ('review'[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]) AND (brain OR cerebrum OR cerebellum OR "nervous system" OR neuron* OR spinal OR brainstem OR olfactory OR nasal OR pharyn* OR trachea OR lung OR airway OR bronch* OR heart OR vascular OR arterial OR vena OR "blood vessel" OR "lymph node" OR "lymph vessel" OR lymmpath OR thymus OR spleen OR "bone marrow" OR tonsils OR blood OR oral OR mouth OR? esophagus OR stomach OR pancreas OR liver OR "gall bladder" OR gut OR intestine* OR salivary OR saliva OR stool OR faeces OR kidney OR urethra OR ureter OR bladder OR kidney OR urine OR testis OR epididym* OR prostate OR penis OR sperm OR semen OR ovari* OR uterus OR vagina* OR placenta* OR testes OR skin OR muscle* OR bone OR joint OR hypothalamus OR pituitary OR thyroid OR adrenal OR reservoir OR autopsy OR cardiovascular OR immunological OR endocrinal OR genital OR urinary OR digestive OR respiratory). In addition, all preprint articles on SARS-CoV-2 were included in the screening strategy.

The total set of 11700 identified articles were pooled in EndNote (version X9.3.3), duplicates removed and a first filtering was performed based on following exclusion criteria: review or editorial articles, non-English manuscripts, non-human studies and no full text available. The remaining set of articles was manually evaluated based on their title, abstract or full text for relevance concerning anatomical compartments, SARS-CoV-2 detection and ACE2 receptor expression. During this process, the snowball method was also used to identify additional papers that were missed by the systematic literature screening approach.

**Results and discussion**

**Systematic literature screening**

The screening resulted in 182 articles that were included in this systematic review of which 113 were retrieved from the PubMed/WoS database and 69 from Bio/MedRxiv (Fig 1)[15–196]. In the examined time period January 1\(^{st}\) to June 23\(^{rd}\) 2020, a full range of SARS-CoV-2 studies were identified which investigated viral presence in a vast array of human tissues and body fluids spread across the human body (Fig 2). Therefore, information on the presence of SARS-CoV-2 viral fragments or particles and ACE2 receptor expression is organized by organ system in a body map (Figs 3 and 4) and this review will further systematically address major clinical symptoms, detection of SARS-CoV-2 and ACE2 expression levels in each organ system.

Across 182 articles, the detection of SARS-CoV-2 was performed with different methods, with RT-qPCR-based detection of viral RNA and microscopy-based detection (electron and...
fluorescence microscopy) of viral RNA/protein being the most popular techniques. It is important to note that these techniques do not offer definite proof for the presence of infectious virus, therefore we summarized the level of evidence of viral presence for each organ system (Table 1).

Fig 1. Overview of the systematic literature screening pipeline. Pubmed, Web of Science, BioRxiv and MedRxiv were used as database sources for the time period January 1st—June 23rd 2020 and for the retrieval of SARS-CoV-2 reservoir studies.

https://doi.org/10.1371/journal.ppat.1009037.g001
Respiratory system

The first brief reports describing pneumonia due to infection with the new coronavirus were published in the NEJM on January 24th 2020 [15] and Nature on February 3rd 2020 [16]. In these reports, initial identification of SARS-CoV-2 was done via sequencing and phylogenetic analysis on lower respiratory tract and broncho-alveolar lavage (BAL) fluids collected from patients in Wuhan from December 21st 2019 onwards. These patients had been present at the Huanan Seafood market close to the time of symptom onset. They presented with pneumonia of unknown etiology and showed symptoms ranging from common cold, fever, dry cough to dyspnea. In some cases, but mostly in elderly patients, these symptoms progressed to the development of severe acute respiratory syndrome (SARS), similar to the well-known acute respiratory distress syndrome (ARDS) [7]. The pathologies underlying these symptoms usually start with alveolar damage including alveolar edema, vascular decongestion and mild inflammatory infiltration. Later in infection, a diffuse alveolar damage in the organizing phase with reactive type II pneumocyte hyperplasia is observed. Whether or not this will lead to lung fibrosis is not clear yet [17]. In rare cases, excessive hypercoagulation with pulmonary embolisms can lead to sudden death [18].

Presence of SARS-CoV-2 particles has been described in different parts of the respiratory tract, including the nose, pharynx, trachea and lungs. SARS-CoV-2 viral RNA and/or antigens were mainly observed in ciliated respiratory epithelial cells and type I and II pneumocytes, but also in alveolar macrophages [19–21]. In addition, single cell RNA sequencing (scRNA-seq) studies recovered SARS-CoV-2 viral reads from secretory and ciliated epithelial cells in BAL [22] and bronchiolar protected specimen brushes (PSB) [23] from COVID-19 patients. SARS-CoV-2 viral transcripts were also detected in macrophages and neutrophils obtained from BAL, albeit at low levels [22, 23]. Whether this results from direct infection or phagocytosis of infected cells or viral particles remains to be elucidated.

To gain a better understanding of the epithelial subtypes targeted by the virus, Ravindra et al. [24] performed scRNA-seq analysis on in vitro infected human bronchial epithelial cells. This study pointed to the ciliated epithelial cells as the major initial target of infection and this
was confirmed by EM analysis. At later stages of infection, virus was also detected in other epidermal subsets, including basal, club and BC/club cells. Surprisingly, this study pointed out that ACE2 expression poorly correlated with SARS-CoV-2 detection on a per cell basis. ACE2 was mainly expressed in ciliated cells, club cells and to a lesser extent type II pneumocytes [24, 25]. In this context, ACE2 expression is seemingly higher in the upper airways than in lower airways, while the latter are more affected by SARS-CoV-2 replication [26].

Viral replication in the respiratory tract results in viral shedding in mucus, as evidenced by multiple studies showing viral RNA in nasal and throat swabs. These swabs remain positive for up to 15 days post infection, indicating that viral particles or fragments of viral RNA are still present [27]. Some researchers even demonstrate viral shedding up to 60 days after onset of symptoms [28–30]. Such prolonged viral RNA shedding was mainly observed in elderly patients [31]. Still, relapse involving aggravation of pulmonary dysfunction has only rarely been reported [32]. Moreover, in immunocompromised patients persistent viral shedding and positive PCR with threshold Ct’s of 30 have been reported [33].

Although viral RNA is routinely detected by RT-qPCR from both upper and lower respiratory tract samples and in particular cases can remain detectable up to 2 months after the onset
of symptoms, this does not prove that replication is ongoing in the sample sites and that patients are still infectious. Several studies have isolated infectious virus, that can be propagated in vitro, both from upper and lower respiratory tract samples [34–40]. Longitudinal studies indicate that successful viral culture is mostly established from samples obtained within 9 days of onset of symptoms [34, 36, 37]. Interestingly, several studies observed a clear correlation between the viral load as assessed by RT-qPCR and the infectivity of the sample, although the reported threshold C\textsubscript{T} values that would permit infectivity range from \(< 24\) to \(< 33\) [34, 35, 38], which hampers the use of RT-qPCR as a surrogate diagnostic to predict patient infectivity.

Also, viral loads detected in asymptomatic or minimal symptomatic patients were similar to those of symptomatic patients, hinting towards the transmission potential of asymptomatic patients. This is confirmed in a prevalence study conducted in a nursing home, showing that viral loads were not different between symptomatic, asymptomatic and presymptomatic residents and that viable virus could be isolated from 6 days prior to 9 days past the onset of symptoms [37]. In conclusion, the respiratory tract is the major site of infection, and although virus can be detected for up to 2 months post infection, most studies indicate infectivity is highest in the two weeks post-infection.
Table 1. Overview of SARS-CoV-2 detection in the human body, organized per organ system. Organ systems are shown on the left, followed by type of virus detection and amount of positive samples.

| Organ systems                        | RT-qPCR (viral RNA)                                      | Electron/Fluorescence Microscopy/Immunohistochemistry (viral RNA or protein) | Culturing virus out of (liquid) biopsies (infectious particles) |
|--------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------|
| **Respiratory system**               |                                                          |                                                                                |                                                                  |
| Naso- and/or oropharyngeal swabs     | used as diagnostic COVID-19 test*                        | N.D.                                                                           | Virus can be isolated out of 17–100% of qRT-PCR-positive samples [34–40] |
| Sputum                               | used as diagnostic COVID-19 test*                        | N.D.                                                                           | Virus can be isolated out of 30–100% of qRT-PCR-positive samples [35, 36, 38–40] |
| BAL                                  | used as diagnostic COVID-19 test*                        | N.D.                                                                           |                                                                  |
| Sputum                               |                                                          |                                                                                |                                                                  |
| **Cardiovascular system**            |                                                          |                                                                                |                                                                  |
| Heart biopsies                       | 12/15 [19, 42]                                          | interstitial cells of the myocardium [43]                                       | N.D.                                                            |
| Blood vessels                        | N.D.                                                    | blood vessel organoids (FM) [44]                                               | blood vessel organoids can productively be infected [44]        |
| **Immune system**                    |                                                          |                                                                                |                                                                  |
| Immune cells                         | RNA seq: rare reads [50, 52]                             | macrophages [16], virus like particles in CD4+ T cells [53]                     | N.D.                                                            |
| Blood and plasma                     | 52/384 [52–55]                                          |                                                                                |                                                                  |
| Immune system-related biopsies       | spleen and lymph node [23, 42]                           | N.D.                                                                           |                                                                  |
| **Digestive system**                 |                                                          |                                                                                |                                                                  |
| Stool                                | 504/874 [9, 30, 55, 60–90]                              | N.D.                                                                           | two reports isolated infectious virus [77, 79]                    |
| Rectal swabs                         | 22/77 [55, 72, 86, 91, 92]                              | N.D.                                                                           |                                                                  |
| Saliva                               | 683/758 [89, 94–106]                                    | N.D.                                                                           |                                                                  |
| Gut biopsies                         | 2 severe patients: esophagus, stomach, duodenum and rectum [9] | gastric, duodenal and rectal epithelia (FM) [79]                               | N.D.                                                            |
|                                      | large intestines [19]                                   | large intestines lumen (EM) [19]                                               |                                                                  |
| **Urinary system**                   |                                                          |                                                                                |                                                                  |
| Urine                                | 23/467 [36, 39, 68, 72, 77, 87–89, 92, 132–134, 142]    | N.D.                                                                           | one report isolated infectious virus [135]                       |
| Kidney biopsies                      | 3/3 severe patients [19]                                | tubular epithelium, podocytes and endothelium (EM, IHC) [19, 125–127]          | kidney organoid (FM) [44]                                       |
|                                      | kidney organoid (FM) [44]                              | kidney organoid (FM) [44]                                                      | kidney organoids can productively be infected [44]              |
| **Reproductive system**              |                                                          |                                                                                |                                                                  |
| Semen                                | 6/85 [136, 137, 141, 142]                               | N.D.                                                                           |                                                                  |
| Prostate secretions                  | 0/23 [143]                                             | N.D.                                                                           |                                                                  |
| Testis biopsies                      | 0/1 [137]                                              | spermatogenic cells, Sertoli cells and Leydig cells (IHC) [20]                  |                                                                  |
| Vaginal swabs                        | 0/35 [144]                                             | N.D.                                                                           |                                                                  |
| Placental swabs, cord swabs and/or amniotic fluid | 0/12 [148–150]                                      | N.D.                                                                           |                                                                  |
| Breast milk                          | 5/42 [156–159]                                         | N.D.                                                                           | 0/9 [159]                                                       |
| **Nervous system**                   |                                                          |                                                                                |                                                                  |
| Cerebrospinal fluid                  | 4/18 [160, 161, 167–172, 174]                           | N.D.                                                                           |                                                                  |
| Brain biopsies                       | 8/34 [19, 173, 174]                                    | N.D.                                                                           |                                                                  |

(Continued)
Cardiovascular system

The majority of humans that test positive for SARS-CoV-2 infection do not develop fulminant cardiovascular disease during the acute infection. However, about 20% of the patients admitted to intensive care units develop acute cardiac injury during the course of infection [7, 8]. Whether SARS-CoV-2 facilitates the reported cardiac injuries via direct infection or by triggering inappropriate immune activation is not known. The study of Remmelink et al. [41] reports quantification of viral RNA in the heart in post-mortem patient samples, but did not observe specific viral organ injuries [41]. Two other studies used electron microscopy to detect virus, and of these studies one was able to detect viral RNA, but not viral particles, in the heart [19]. The other study found virus particles in cytopathic, structurally damaged interstitial cells, but not in cardiac myocytes [42]. It is therefore more likely that cardiac injury in patients occurs by inflammation rather than direct infection. Interestingly, one autopsy series of three COVID-19 patients demonstrated endothelitis in vascular beds of different organs and detected viral inclusions via EM in kidney endothelial cells of one patient [43]. Susceptibility of endothelial cells to SARS-CoV-2 infection is furthermore supported by in vitro infection studies with blood vessel organoids [44] and pluripotent stem cell-derived cardiomyocytes. In line with this, relatively high expression of ACE2 in heart tissue supports the potential of direct infection [25, 45]. Furthermore, increased expression of ACE2 in patients with heart failure was observed, indicating a potential risk group [46–49]. Although in vitro infection studies and expression of ACE2 are suggestive for active infection of the heart, it remains unclear whether this results into cardiac injury as post-mortem studies are inconclusive on the matter. Therefore further research on post-mortem samples or biopsies taken during infection are required to verify if the heart and vasculature could potentially serve as a site of prolonged virus persistence.

Immune system

Even though immune responses during infection with SARS-CoV-2 can lead to severe complications, no viral replication is observed in immune cells from patients. Interestingly, there are rare reports of viral RNA detection in RNA-seq data from peripheral blood mononuclear cells (PBMCs) [50–52]. In addition, post-mortem studies showed presence of SARS-CoV-2 RNA and antigens in draining lymph nodes and spleen, predominantly in macrophages [19, 20]. One in vitro study used virus isolated from patients to test replication kinetics in PBMCs but could not find evidence of SARS-CoV-2 propagation in this heterogeneous population of cells.
despite the observation of viral-like particles in primary CD4+ T cells by electron microscopy [53]. Detection of viral RNA has been observed in plasma of severe patients, but it remains questionable whether this RNA originates from actual virus particles or merely represents the potentially infectious viral genome [54, 55]. Therefore, detecting RNA in plasma does not directly translate into the presence of infectious particles. In any case, detection of SARS-CoV-2 in multiple organs indicates that infectious virus/RNA is circulating in at least part of the COVID-19 patients. Furthermore, using RNA sequencing data it was found that immune cells barely express the ACE2 receptor required for viral entry nor any other of the major entry proteins [50, 56, 57]. These studies provide the ground for the hypothesis that virus detected in immune cells results from cellular entry by phagocytosis. Since no viral replication was observed thus far in immune cells, it seems that immune cells do not function as a functional reservoir for SARS-CoV-2.

**Digestive system**

Gastro-intestinal (GI) tract symptoms are reported in approximately 10–15% of COVID-19 cases and typically include diarrhea and to a lesser extent nausea, vomiting or abdominal pain [9, 58, 59]. Patients with only GI symptoms were more likely to be diagnosed later than patients with additional respiratory complaints and are more likely to be positive for SARS-CoV-2 RNA in fecal samples [60].

Stool samples from 874 patients across 34 studies were examined of which 504 (57.67%) resulted in a positive RT-qPCR for COVID-19 irrespective of disease severity [9, 30, 55, 60–90]. Five studies also included rectal swabs of 77 patients of which 22 tested positive (28.5%) [55, 72, 86, 91, 92]. Stool samples remained positive well after NP swabs returned negative with a range of 1–47 days, indicating longer and extended viral shedding via this route. Also, infectious virus could be isolated from stool samples in at least two reports, indicating the possibility of feco-oral transmission but no reports have shown direct evidence of this occurring [77, 79]. Indeed, stability of SARS-CoV-2 was tested in faeces *in vitro* and was shown to be stable and infectious for several hours [93].

Saliva samples from 758 confirmed COVID-19 patients across fourteen studies yielded high positive SARS-CoV-2 detection results which are often in concordance with matched NP swabs (657/758 patients, 86.7%) [89, 94–106]; however, in a limited set of cases (26 patients) saliva samples were reported positive with a negative NP swab [95, 98, 99, 106]. SARS-CoV-2 could be detected in saliva 10–37 days after onset of symptoms [97, 100, 102] and in two-out-of-three studies was shown to yield higher viral load titers than NP swabs [103, 104, 107]. In addition, SARS-CoV-2 viral particles were shown to be stable in artificial saliva up to 90 minutes [108, 109], further confirming this as a major viral shedding route.

From immunofluorescence and scRNA-seq studies it became apparent that ACE2 expression is high in epithelial cells across the entire gastro-intestinal tract including the oral mucosa of the tongue and enterocytes from the ileum and colon [110–113]. As described above, SARS-CoV-2 has already extensively been recovered from saliva samples and oral swabs. However, whether this results from actual viral replication in the oral (tongue) mucosa and/or salivary glands or is merely a spill-over from the pharynx remains unclear. Nonetheless, the apparent loss of taste in certain COVID-19 patients additionally suggests that SARS-CoV-2 replicates in cells aligning the tongue [114, 115]. Likewise, there is a limited number of studies performed which actually examine viral presence in GI tissues. One study by Lin et al. performed endoscopic sampling in 6 patients of which 2 severe patients tested positive for viral RNA measured by RT-qPCR from the esophagus, stomach, duodenum and rectum [9]. Only 1 out of 4 non-severe cases tested positive in the duodenum. Xiao et al. confirmed these findings by
visualizing SARS-CoV-2 viral capsid via intracellular staining of gastric, duodenal, and rectal epithelia in GI tissues [79]. One post-mortem study by Bradley et al. visualized viral particles in the lumen of the large intestines via electron microscopy and found borderline positive RT-qPCR results from tissue biopsies in the large intestines (Ct value between 37–40), but not in the small intestine [19]. Finally, Lamers et al. demonstrated that enterocytes of ex vivo organoids are infectable with SARS-CoV-2 and that the virus can replicate, indicating that these cells are permissive for SARS-CoV-2 infection [116].

Overall, these findings indicate the broad presence of SARS-CoV-2 RNA or viral fragments in the GI tract with a preference for saliva and stool. Indeed, live virus could be isolated from stool, although from a limited set of patients. Therefore, further studies are needed to map the actual viral presence, especially in gut tissues.

Recurring clinical features of the other solid organs of the digestive tract (liver, gallbladder, pancreas) mainly include liver injury with abnormal liver tests in 35–56% of the COVID-19 patients for aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin which is probably due to the immune cascade in the body [117, 118]. In addition, there is a single case report indicating a rare onset of SARS-CoV-2-induced pancreatitis in two patients and one cohort study describing pancreatic injury in 10% of COVID-19 patients, indicated by elevated amylase (13/121 patients) or lipase levels (12/121 patients), of which three developed pancreatitis. The limited number of reports indicate that pancreatic injury is often overlooked, hence there is in sufficient data on the widespread presence of this illness [119, 120]. To date, there are no reports on the possible presence of SARS-CoV-2 in these organs, although ACE2 expression can be high and is found in liver cholangiocytes, TROP2+ liver progenitor cells, gall bladder epithelium, pancreatic exocrine glands and islets [49, 121, 122]. Therefore, tissue biopsies with immunohistochemical viral staining or RT-qPCR for viral RNA (i.e. from post-mortem studies) could deliver necessary information, but so far robust data is lacking to conclude that solid organs of the digestive tract play a major role in SARS-CoV-2 infection.

**Urinary system**

Routine urinalysis of COVID-19 patients shows abnormalities such as proteinuria, hematuria and leukocyturia in up to 75% of the cases [123, 124]. Further, up to 27% of hospitalized COVID-19 patients even develops acute renal failure, especially elderly with comorbidities such as hypertension and heart failure [10, 125]. Tubule degeneration, necrosis and to a lesser extent renal thrombotic micro-angiopathy typically account for acute renal failure. These observations indicate that the human kidney may be a target for SARS-CoV-2. Indeed, viral RNA, proteins and particles have been found in kidney tubular epithelium, podocytes and to a lesser extent in kidney endothelium of deceased COVID-19 patients [19, 44, 125–127]. This pattern is consistent with ACE2 distribution, as ACE2 is highly expressed onto proximal tubule cells [128–131]. Of note, SARS-CoV-2 was also able to infect human kidney organoids in vitro [44]. Despite reports of SARS-CoV-2 presence in the kidney, viral shedding in urine is rather rare, as viral RNA could only be detected in urine samples of 3–4% of COVID-19 patients [36, 39, 68, 72, 77, 87–89, 92, 132–134]. However, one study was able to isolate infectious virus particles out of positive urine samples [135]. Further, viral shedding in urine may continue even after respiratory shedding has ceased, indicating that the human urinary tract may act as a long-term source of SARS-CoV-2 detection[68].

**Reproductive system**

Except for few reports on testicular pain, fertility problems or other genital tract-related disorders due to COVID-19 have not been described to date [136]. Nonetheless, SARS-CoV-2
proteins have been found inside spermatogenic cells, supporting Sertoli cells and testosterone-producing Leydig cells of a COVID-19 patient [20]. These virus-positive testes did not show any additional histological abnormalities. In contrast, the testes of another COVID-19 patient did not show any presence of SARS-CoV-2 RNA [137]. Interestingly, the spermatocytes, Sertoli and Leydig cells express a high level of ACE2, compared to other cells in the human body [138–140]. In line with SARS-CoV-2 protein detection in testes, one study detected SARS-CoV-2 RNA in 6 out of 38 semen samples from COVID-19 patients. From the positive samples 4 were collected at the acute stage of infection, whereas 2 were obtained from recovering patients [141]. Still, in four other studies all semen and prostate secretions of 47 and 23, respectively, COVID-19 patients tested negative for SARS-CoV-2 RNA [136, 137, 142, 143]. Presence of SARS-CoV-2 in the female reproductive tract has not been described so far. A number of vaginal swabs of COVID-19 patients also tested negative for viral RNA [144]. Unlike male gonads, female reproductive organs do not express ACE2 at the bulk level [25, 140]. These data indicate the male, rather than the female, genital tract may be susceptible and permissive for SARS-CoV-2 infection. Still, further studies are necessary to confirm this assumption. Although only one out of five studies detected viral RNA in semen, possible sexual transmission of SARS-CoV-2 and the role of the male genital tract in SARS-CoV-2 infection needs further study.

Regarding SARS-CoV-2-positive mothers, despite vascular abnormalities observed in up to 50% of examined placentas, there is no clear evidence of vertical virus transmission to infants [145, 146]. In line with the absence of virus in placenta, amniotic fluid or cord blood, the human placenta does not express high levels of ACE2 [147–151]. In some cases, neonates can still become infected by SARS-CoV-2 after birth through horizontal transmission [152–155]. In addition to respiratory droplets, breastfeeding has been suggested as a mechanism of SARS-CoV-2 transmission, as this has been reported for other RNA viruses, such as HIV. Data are limited, but viral RNA has been identified in breast milk of 5 out of 42 COVID-19-positive breastfeeding mothers so far [156–159]. Although still anecdotal, the most convincing evidence for the possible occurrence of SARS-CoV-2 in milk is provided by a study of milk samples from two SARS-CoV-2-positive breastfeeding mothers, demonstrating SARS-CoV-2 RNA in milk samples from one mother for four consecutive days [157]. Still, it was impossible to recover infectious virus from RNA-positive milk samples, suggesting that breastmilk itself is unlikely to pass on SARS-CoV-2 to infants [159]. However, more evidence is needed to conclude on the definite role of breastfeeding in SARS-CoV-2 transmission.

Nervous system

The majority of COVID-19 patients (up to 78%) show neurological symptoms ranging from headache, loss of smell (anosmia) and taste (ageusia), imbalance, impaired consciousness, delirium and paresthesia to extremity paralysis and convulsions [11, 114, 115, 160–163]. Severe neurological symptoms can mostly be accounted to abnormalities located in the brain (stem) and spine such as edema, hemorrhages and thrombotic events with or without stroke, demyelination and encephalomyelitis [163–166]. This has urged many researchers to look closer into the nervous system of COVID-19 patients. In COVID-19 cases with severe neurological symptoms, viral RNA has been identified in 4 out of 8 cerebrospinal fluid (CSF) samples [160, 161, 167–172]. Moreover, one autopsy study found traces of viral RNA via RT-qPCR in the brain of 8 out of 22 deceased COVID-19 patients [173]. Yet, two other studies failed to identify virus particles or RNA in brain autopsies and CSF analysis of 12 and 10, respectively, deceased COVID-19 patients [19, 174]. Therefore, it remains unclear whether severe neurological manifestations are triggered by direct viral-induced damage or virus-induced endothelial and/or
cytokine disturbances. Nonetheless, ACE2 is expressed in both neuronal and non-neuronal cell types in the human central nervous system, especially in the spinal cord, dorsal root ganglia, brainstem substantia nigra, choroid plexus, hypothalamus, hippocampus, middle temporal gyrus and posterior cingulate cortex [175, 176]. This hints towards the possibility of SARS-CoV-2 invasion of the central nervous system. In contrast to severe neurological symptoms, ageusia and anosmia are often devoid of any obvious lesions [114, 115]. Direct viral damage to the olfactory and gustatory receptors or neurons has been proposed as mechanism of sensorineural olfactory loss, but the absence or presence of SARS-CoV-2 inside olfactory epithelial or neuronal cells has not been described so far. This is probably related to technical difficulties during COVID-19 patient autopsy, such as inaccessibility of the olfactory bulb and epithelium without the use of electric saws to cut into the skull. This generates potentially virus-loaded aerosols, necessitating the use of additional, sometimes difficult to take, precautions. Interestingly, non-neuronal cells rather than neuronal cells residing in the olfactory epithelium and bulb express ACE2 and TMPRSS2 [175, 177–179]. This indicates that SARS-CoV-2 replication in the olfactory epithelium might induce anosmia through perturbation of supporting cells, rather than direct neuronal infection. Together, these findings indicate that SARS-CoV-2 is able to reach the nervous system.

**Sensory system: Eye**

Ocular symptoms remain rare in COVID-19 patients but reported symptoms in hospitalized patients include: dry eyes, blurred vision, foreign body sensation and conjunctivitis with conjunctival congestion. However, there remains a debate whether this is directly caused by the virus [180, 181]. As SARS-CoV was readily detectable in tears, Xia et al. investigated the viral presence of SARS-CoV-2 RNA in tears and conjunctival swabs from 30 COVID-19 patients who were sampled twice longitudinally [182]. Only one patient showed a positive PCR test on tears and ocular surface swabs with onset of conjunctivitis and conjunctival congestion. However, the virus could not be isolated or cultured in vitro. This was also reported by Xie et al., Kumar et al., Wu et al., and Zhou et al. who detected SARS-CoV-2 RNA in ocular surface swabs or conjunctival secretions of 2/33, 1/45, 2/28 and 1/63 patients, respectively [183–186]. One case report performed longitudinal sampling in a single patient and confirmed a positive signal of conjunctival swabs up to 17 days after onset of disease [187]. In contrast, Seah et al. and Xu et al. could not replicate these findings and did not detect SARS-CoV-2 in 64 tear samples from 34 patients [188] or in ocular surface swabs from 22 patients [189]. Reports on ACE2 expression find a limited expression at the retina and specifically in the retinal epithelium [180]. Moreover, ACE2 and TMPRSS2 are co-expressed in corneal and conjunctival epithelial cells according to scRNA-seq and immunohistochemical analyses, identifying the ocular surface as a potential viral entry site [190, 191]. Therefore, infection could occur via droplets entering the eye and travel via the nasolacrimal canal to the respiratory tract.

In total across eight studies examining ocular presence of SARS-CoV-2 RNA, 1/94 patients tested positive for tear or conjunctival secretion samples and 8/222 ocular surface swabs. These low numbers can be influenced by the time of sampling and by the onset of conjunctivitis but show that ocular fluids can contain SARS-CoV-2 viral fragments RNA. However, no reports state that SARS-CoV-2 virus could be isolated from ocular fluids at present.

**Skin and adipose tissue**

The documentation and available papers surrounding SARS-CoV-2 in relation to adipose and skin tissue is very limited. About 20% of patients present or develop cutaneous manifestations at or during the onset of COVID-19, but not related to severity of infection. These patients
presented themselves with erythema, and a positive diagnostic test for SARS-CoV-2 [192–194]. No tests on skin tissue have thus far been performed, however, and therefore it cannot be excluded as an underlying illness or as a manifestation of the immune response. Remarkably, ACE2 receptor is expressed in skin biopsies, and patients with rash and skin lesions have increased expression of TMPRSS2 (a co-receptor of SARS-CoV-2) [57]. Therefore, rash could also be the symptom of infection leading to lesions, but this needs to be confirmed and further investigated. In adipose tissue thus far no virus has been detected. However, the paper of van der Poort et al. (2020) found that patients that have an increased Body Mass Index (BMI) also have increased leptin levels in serum, which they hypothesize could correlate with severity of the infection [195, 196]. Interestingly, increased expression of the ACE2 receptor in the lung epithelia are positively correlated with obesity, indicating that obese individuals might be at higher risk for SARS-CoV-2 infection [195, 196]. In conclusion, there is no robust evidence to either demonstrate or exclude that skin and adipose tissue harbor SARS-CoV-2 viral particles.

Conclusion

SARS-CoV-2 affects many organs throughout the human body

The first studies on SARS-CoV-2 tropism and pathogenesis focused on the lungs, as these were “the viral ground zero”. However, it quickly became clear that SARS-CoV-2 also attacks other organ systems, either by direct viral infection or through indirect effects of the immune response. Our systematic review showed that traces of the virus have been found in multiple organs throughout the body, including the pharynx, trachea, lungs, blood, heart, vessels, intestines, male genitals, brain and kidneys. In line with this, SARS-CoV-2 components were also detected in a variety of body fluids such as mucus, saliva, urine, semen, faeces, cerebrospinal fluid and breast milk. Of note, although SARS-CoV-2 RNA has been detected in plasma of patients with severe disease [54, 55, 197], no study has as yet demonstrated the presence of infectious virus in blood. It therefore remains to be demonstrated that SARS-CoV-2 might infect organ systems by gaining access to the bloodstream. Although highly speculative at the moment, SARS-CoV-2 might cause a persistent chronic infection in certain individuals. In these patients, certain sites might act as a “viral reservoir”, in which the virus can persist for prolonged periods accompanied by recurrent viral shedding. This phenomenon is not new for RNA viruses, as this has already been described in Ebola virus survivors [198]. SARS-CoV-2 persistence and recurrent shedding has already been demonstrated in the respiratory tract [33], but also sites of attenuated immunity such as the testis, eye and brain might potentially preserve the virus for longer times. Nonetheless, this hypothesis should be treated with caution, as the number of studies showing actual infectious virus particles in different organs remains limited so far.

ACE2 expression and SARS-CoV-2 infectivity: not a perfect match

Given the role of ACE2 as the main cellular entry receptor for SARS-CoV-2 in vivo, ample studies have attempted to map ACE2 expression to obtain insight into tissues or cell types that are in theory susceptible to SARS-CoV-2 infection. Interestingly, presence of SARS-CoV-2 components in different tissues does not always correlate with steady-state ACE2 expression levels. For instance, high viral loads are retrieved from the lungs, which generally show rather low ACE2 expression levels. In the gastrointestinal tract, viral loads peak in the colon, while ACE2 expression is higher in the small intestine. Thus, it seems that there is not always a perfect match between ACE2 expression and SARS-CoV-2 detection. A plausible explanation for this apparent mismatch might be the fact that few ACE2 molecules might suffice to cause a productive SARS-CoV-2 infection. Alternatively, cell type heterogeneity in ACE2 expression within a given tissue can also contribute as well as a discordance between ACE2 mRNA
expression and cell-surface ACE2 expression. Further in depth analysis of cell-surface ACE2 protein expression is however required to confirm these hypotheses. Of note, most evidence on ACE2 expression in different tissues is based on a steady-state situation in healthy individuals. In diseased individuals, expression levels of ACE2 might differ. Indeed, several comorbidities associated with severity of COVID-19 disease such as smoking, diabetes, COPD, obesity and hypertension are characterized by elevated levels of ACE2 expression in the respiratory tract [199–201]. However, whether severe progression of COVID-19 in these patients is a direct consequence of abundant ACE2 expression and thus increased susceptibility to SARS-CoV-2, or is merely the result from underlying health issues in these individuals (e.g. immunosuppression) is unclear. Counterintuitively, ACE2 receptor abundance in plasma is high in children, who often show minor symptoms upon SARS-CoV-2 infection, while it goes down in the elderly, who are at greater risk of severe illness [202, 203]. This apparent paradox might be explained by the discrepancy between membrane-bound and soluble ACE2 molecules. While the membrane-bound form acts as host cell receptor for SARS-CoV-2, soluble ACE2 may neutralize free virions by shielding the viral binding protein spike (S) [204]. In this way, elevated soluble ACE2 levels in children may help them to contain the virus. Thus, it is clear that researchers only discovered the “tip of the iceberg” in SARS-CoV-2 pathogenesis so far.

Limitations

As described in this review, only a limited set of studies succeeded in isolating and culturing SARS-CoV-2 viral particles out of a biopsy that were also capable of reinfecting target cells in vitro, providing definite proof of replication-competent viral presence of SARS-CoV-2. Importantly, this “golden standard” evidence is currently only available for respiratory and gastrointestinal tract samples and it remains to be established whether the “viral signal” detected in other organ systems via RT-qPCR or microscopy derives from genuine infective viral particles [205]. For instance, in electron microscopy, viral particles might be mistakenly identified over other endogenous vesicles or endocytic bodies [206] and a (borderline) positive signal in RT-qPCR could be due to leftover viral RNA fragments rather than replication-competent virus. Indeed, as virus is phagocytosed by immune cells and these cells can travel throughout the body and invade different tissues, weak signals detected via RT-qPCR might derive from immune cells that phagocytosed virus at distant locations.

An important limitation of this study is that information on viral load/ACE2 expression in patient samples is biased towards sample types that are easily accessible such as body fluids or blood cells. For instance, although scRNAseq studies could yield interesting information on SARS-CoV-2-targeted cell types, the epithelial cells, which constitute the major target of SARS-CoV-2 according to the available evidence, are underrepresented in respiratory samples obtained from patients. Most information on less accessible tissues/cell types therefore derives from autopsy studies, which are biased towards analyses of the subset of patients with critical COVID-19 disease and also represents an endpoint analysis. These limitations could be addressed with an appropriate animal model, replicating the pathogenesis of human COVID-19 [207]. However, although the mild COVID-19 phenotype and viral replication in the respiratory tract can be mimicked in non-human primates, hamsters, ferrets and cats, none of these animals features the cytokine storm and coagulopathy that characterizes severe COVID-19 in humans [208]. Therefore, this review primarily focused on SARS-CoV-2 studies in the context of humans.

Finally, difficulties inherent to the heterogeneous SARS-CoV-2 research are the variability in study design, patient numbers and characteristics, sampling timing and testing procedures. Furthermore, the included preprint articles should be treated with caution because no strict
A peer review process was performed. This systematic review focused on research articles available in English and on studies reporting human data.

These limitations should be considered while interpreting these data.

Acknowledgments
The authors also acknowledge pathologist dr. Amélie Dendooven (Department of Pathology, Ghent University Hospital) for reading and correcting the manuscript.

Author Contributions

Conceptualization: Wim Trypsteen, Linos Vandekerckhove.

Data curation: Willem van Snippenberg, Sarah Gerlo, Linos Vandekerckhove.

Methodology: Wim Trypsteen, Jolien Van Cleemput.

Project administration: Wim Trypsteen.

Supervision: Wim Trypsteen, Jolien Van Cleemput, Linos Vandekerckhove.

Visualization: Wim Trypsteen, Jolien Van Cleemput.

Writing – original draft: Wim Trypsteen, Jolien Van Cleemput, Willem van Snippenberg, Sarah Gerlo, Linos Vandekerckhove.

Writing – review & editing: Wim Trypsteen, Jolien Van Cleemput, Willem van Snippenberg, Sarah Gerlo, Linos Vandekerckhove.

References

1. Bolles M, Donaldson E, Baric R. SARS-CoV and emergent coronaviruses: viral determinants of interspecies transmission. Current Opinion in Virology. 2011; 1(6):624–34. https://doi.org/10.1016/j.coviro.2011.10.012 PMID: 22180768

2. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nature Medicine. 2020; 26[4]:450–2. https://doi.org/10.1038/s41591-020-0820-9 PMID: 32284615

3. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herltier T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020; 181[2]:271–80.e8. https://doi.org/10.1016/j.cell.2020.02.052 PMID: 32142651

4. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection—a review of immune changes in patients with viral pneumonia. Emerging Microbes & Infections. 2020; 9[1]:727–32. https://doi.org/10.1080/22221751.2020.1746199 PMID: 32196410

5. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020; 135[23]:2033–40. https://doi.org/10.1182/blood.2020006600 PMID: 32392221

6. Giarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglu K, Antoniadou A, Antonakos N, et al. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. Cell Host & Microbe. 2020; 27[6]:992–1000.e3. https://doi.org/10.1016/j.chom.2020.04.009 PMID: 32320677

7. Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barr RG, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. Bmj-British Medical Journal. 2020; 369.

8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395[10223]:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5 PMID: 31986264

9. Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020; 69[6]:997–1001. https://doi.org/10.1136/gutjnl-2020-321013 PMID: 32241899

10. Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int. 2005; 67[2]:698–705. https://doi.org/10.1111/j.1529-1755.2005.00710.x PMID: 15673319
11. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA neurology. 2020:e201127.

12. Sungnak W, Huang N, Becavin C, Berg M, Queen R, Litvinukova M, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nature Medicine. 2020. https://doi.org/10.1038/s41591-020-0868-6 PMID: 32327758

13. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochemical and biophysical research communications. 2020; 526[1]:135–40. https://doi.org/10.1016/j.bbrc.2020.03.044 PMID: 32199615

14. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020; 14[2]:185–92. https://doi.org/10.1007/s11684-020-0754-0 PMID: 32170560

15. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020; 382[8]:727–33. https://doi.org/10.1056/NEJMoa2001017 PMID: 31978945

16. WU F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020; 579[7798]:265–9. https://doi.org/10.1038/s41586-020-2008-3 PMID: 32015508

17. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrenelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. The Lancet Infectious Diseases. 2020.

18. Polat V, Bostancı G. Sudden death due to acute pulmonary embolism in a young woman with COVID-19. J Thromb Thrombolysis. 2020; 50[1]:239–41. https://doi.org/10.1007/s11239-020-02132-5 PMID: 32394237

19. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, et al. Histopathology and Ultrastructural Findings of Fatal COVID-19 Infections. medRxiv. 2020:2020.04.17.20058545. https://doi.org/10.1016/S0140-6736(20)31305-2 PMID: 32682491

20. Hou YJ, Okuda K, Edwards CE, Martinez DR, Asakura T, Dinnon KH, et al. SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract. Cell. 2020. https://doi.org/10.1016/j.cell.2020.05.042 PMID: 32526206

21. Bost P, Giladi A, Liu Y, Bendjelal Y, Xu G, David E, et al. Host-Viral Infection Maps Reveal Signatures of Severe COVID-19 Patients. Cell. 2020. https://doi.org/10.1016/j.cell.2020.05.006 PMID: 32479746

22. Chua RL, Lukassen S, Trump S, Hennig BP, Wendisch D, Pott F, et al. Cross-talk between the airway epithelium and activated immune cells defines severity in COVID-19. medRxiv. 2020:2020.04.29.20084327.

23. Ravindra NG, Alfajaro MM, Gasque V, Wei J, Filler RB, Huston NC, et al. Single-cell longitudinal analysis of SARS-CoV-2 infection in human bronchial epithelial cells. bioRxiv. 2020.2020.03.24.005702. https://doi.org/10.7554/eLife.58040 PMID: 32463365

24. Venkatakrisnan AJ, Puranik A, Anand A, Zemmour D, Yao X, Wu X, et al. Knowledge synthesis from 100 million biomedical documents augments the deep expression profiling of coronavirus receptors. bioRxiv. 2020.2020.05.06.081695. https://doi.org/10.1101/2020.05.06.081695 PMID: 32511382

25. Saheb Sharifi-Askari N, Saheb Sharifi-Askari F, Alabed M, Temsah M-H, Al Heialy S, Hamid Q, et al. Airways Expression of SARS-CoV-2 Receptor, ACE2, and TMPRSS2 Is Lower in Children Than Adults and Increases with Smoking and COPD. Molecular Therapy—Methods & Clinical Development. 2020; 18:1–6.

26. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med. 2020; 382[12]:1177–9. https://doi.org/10.1056/NEJMc2001737 PMID: 32074444

27. Li J, Zhang L, Liu B, Song D. Case Report: Viral Shedding for 60 Days in a Woman with COVID-19. Am J Trop Med Hyg. 2020; 102[6]:1210–3. https://doi.org/10.4269/ajtmh.20-0275 PMID: 32342849

28. QU Y-M, Kang E-M, Cong H-Y. Positive result of Sars-Cov-2 in sputum from a cured patient with COVID-19. Travel Med Infect Dis. 2020; 34:101619–. https://doi.org/10.1016/j.tmaid.2020.101619 PMID: 32160971

29. Huang J, Mao T, Li S, Wu L, Xu X, Li H, et al. Long period dynamics of viral load and antibodies for SARS-CoV-2 infection: an observational cohort study. medRxiv. 2020;2020.04.22.20071258.
31. Hartman WR, Hess AS, Connor J. Prolonged viral RNA shedding after COVID-19 symptom resolution in older convalescent plasma donors. medRxiv. 2020:2020.05.07.20090621.

32. Li XJ, Zhang ZW, Zong ZY. A case of a readmitted patient who recovered from COVID-19 in Chengdu, China. Crit Care. 2020; 24[1]:152. https://doi.org/10.1186/s13054-020-02877-8 PMID: 32299477

33. Helleberg M, Niemann CU, Moestrup KS, Kirk O, Lebech A-M, Lane C, et al. Persistent COVID-19 in an Immunocompromised Patient Temporarily Responsive to Two Courses of Remdesivir Therapy. The Journal of Infectious Diseases. 2020.

34. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, et al. Predicting infectious SARS-CoV-2 from diagnostic samples. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020:ciaa638. https://doi.org/10.1093/cid/ciaa638 PMID: 3242256

35. Huang C-G, Lee K-M, Hsiao M-J, Yang S-L, Huang P-N, Gong Y-N, et al. Culture-Based Virus Isolation To Evaluate Potential Infectivity of Clinical Specimens Tested for COVID-19. Journal of Clinical Microbiology. 2020; 58[8]:e01068–20. https://doi.org/10.1128/JCM.01068-20 PMID: 32518072

36. Wolfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Muller MA, et al. Virological assessment of hospitalized patients with COVID-19. Nature. https://doi.org/10.1038/s41586-020-2196-x PMID: 3235945

37. Arons MM, Hatfield KM, Reddy SC, Kimball A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. New England Journal of Medicine. 2020; 382[22]:2081–90. https://doi.org/10.1056/NEJMoa2008457 PMID: 32329971

38. La Scola B, Le Bideau M, Andreani J, Hoang VT, Grimaldi C, Colson P, et al. Unspecific post-mortem findings despite multorgan 1 viral spread in COVID-19 patients. medRxiv. 2020:2020.05.27.20114363. https://doi.org/10.1101/s13054-020-03218-5 PMID: 32787909

39. Kujawski SA, Wong KK, Collins JP, Epstein L, Killerby ME, Midgley CM, et al. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. Nature Medicine. 2020; 26[6]:861–8. https://doi.org/10.1038/s41591-020-0877-5 PMID: 32327757

40. Yao H, Lu X, Chen Q, Xu K, Chen Y, Cheng L, et al. Patient-derived mutations impact pathogenicity of SARS-CoV-2. medRxiv. 2020:2020.04.14.2006160.

41. Remmelink M, De Mendoca R, Haene N, De Clercq S, Verocq C, Lebrun L, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail. 2020; 22[5]:911–5. https://doi.org/10.1002/ejhf.1828 PMID: 32275347

42. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, et al. Myocardial localization of SARS-CoV-2. medRxiv. 2020:2020.04.30.20081257. https://doi.org/10.1101/2020.04.30.20081257 PMID: 32511460

43. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endothelitis in COVID-19. Lancet. 2020; 395[10234]:1417–8. https://doi.org/10.1016/S0140-6736(20)30937-5 PMID: 32325026

44. Monteil V, Kwon H, Prado P, Hagelkruys A, Wimmer RA, Stahl M, et al. Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2. Cell. 2020; 181[4]:905–13 e7. https://doi.org/10.1016/j.cell.2020.04.004 PMID: 3233836

45. Xu X, Xu D, Li H, Ma M, Xu Y, Su Y, et al. Single-cell Transcriptome Analysis Indicates New Potential Regulation Mechanism of ACE2 and NPs signaling among heart failure patients infected with SARS-CoV-2. medRxiv. 2020:2020.04.30.20081257. https://doi.org/10.1101/2020.04.30.20081257 PMID: 32511460

46. Guo J, Wei X, Li Q, Li L, Yang Z, Shi Y, et al. Single-cell RNA Analysis on ACE2 Expression Provides Insight into SARS-CoV-2 Blood Entry and Heart Injury. medRxiv. 2020:2020.03.31.20047621.

47. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res. 2020; 116[6]:1097–100. https://doi.org/10.1093/cvr/cva078 PMID: 3227090

48. Ghazizadeh Z, Majd H, Richter M, Samuel R, Zekavat SM, Asgharian H, et al. Androgen Regulates ACE2 in human tissues. bioRxiv. 2020:2020.03.31.016048. https://doi.org/10.15252/msb.20209610 PMID: 32751618

49. Xiong Y, Liu Y, Cao L, Wang D, Guo M, Jiang A, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerging microbes & infections. 2020; 9[1]:761–70. https://doi.org/10.1080/22221751.2020.1747363 PMID: 32228226
51. Johri S, Jain D, Gupta I. Integrated analysis of bulk multi-omic and single-cell sequencing data confirms the molecular origin of hemodynamic changes in Covid-19 infection explaining coagulopathy and higher geriatric mortality. medRxiv. 2020;2020.04.26.20081182.

52. Moustafa A, Aziz RK. Traces of SARS-CoV-2 RNA in the Blood of COVID-19 Patients. medRxiv. 2020;2020.05.10.20097055.

53. Banerjee A, Nasir JA, Budylowski P, Yip L, Aftanas P, Christie N, et al. Isolation, sequence, infectivity and replication kinetics of SARS-CoV-2. bioRxiv. 2020;2020.04.11.037382.

54. Hogan CA, Stevens B, Sahoo MK, Huang C, Garamani N, Gombar S, et al. High frequency of SARS-CoV-2 RNAemia and association with severe disease. medRxiv. 2020;2020.06.24.20080101. https://doi.org/10.1093/cid/ciaa1054 PMID: 32965474

55. Chen W, Lan Y, Yuan X, Deng X, Li Y, Cai X, et al. Detectable 2019-nCoV viral RNA in blood is a strong indicator for the further clinical severity. Emerg Microbes Infect. 2020; 9[1]:469–73. https://doi.org/10.1080/22221751.2020.1732837 PMID: 32102625

56. Duijf PHG. Baseline pulmonary levels of CD8+ T cells and NK cells inversely correlate with expression of the SARS-CoV-2 entry receptor ACE2. bioRxiv. 2020;2020.05.04.075291. https://doi.org/10.1101/2020.05.04.075291 PMID: 32511391

57. Radzikowska U, Ding M, Tan G, Zhakparov D, Peng Y, Wawrzyniak P, et al. Distribution of ACE2, CD147, cyclophilins, CD26 and other SARS-CoV-2 associated molecules in human tissues and immune cells in health and disease. bioRxiv. 2020;2020.05.14.090332.

58. Gupta S, Parker J, Smits S, Underwood J, Dolwani S. Persistent viral shedding of SARS-CoV-2 in faeces—a rapid review. medRxiv. 2020;2020.04.17.20069526. https://doi.org/10.1111/codi.15138 PMID: 32418307

59. Parasa S, Desai M, Thogulva Chandra sekar V, Patel HK, Kennedy KF, Roesch T, et al. Prevalence of Gastrointestinal Symptoms and Fecal Viral Shedding in Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020; 3[6]:e2011335. https://doi.org/10.1001/jamanetworkopen.2020.11335 PMID: 32525549

60. Han C, Duan C, Zhang S, Spiegel B, Shi H, Wang W, et al. Digestive Symptoms in COVID-19 Patients With Mild Disease Severity: Clinical Presentation, Stool Viral RNA Testing, and Outcomes. Am J Gastroenterol. 2020; 115[5]:790. https://doi.org/10.14309/ajg.0000000000000664 PMID: 32301761

61. Cai J, Xu J, Lin D, Yang Z, Xu L, Qu Z, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clin Infect Dis. 2020.

62. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020; 395[10223]:514–23. https://doi.org/10.1016/S0140-6736(20)30154-9 PMID: 31986261

63. Chen L, Lou J, Bai Y, Wang M. COVID-19 Disease With Positive Fecal and Negative Pharyngeal and Sputum Viral Tests. Am J Gastroenterol. 2020; 115[5]:790. https://doi.org/10.14309/ajg.0000000000000610 PMID: 32205644

64. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020; 382[10]:929–36. https://doi.org/10.1056/NEJMc2001191 PMID: 32004427

65. Hosoda T, Sakamoto M, Shimizu H, Okabe N. SARS-CoV-2 enterocolitis with persisting to excrete the virus for approximately two weeks after recovering from diarrhea: A case report. Infect Control Hosp Epidemiol. 2020; 41[6]:753–4. https://doi.org/10.1017/ice.2020.87 PMID: 32188528

66. Kim JY, Ko JH, Kim YJ, Kim JM, Chung YS, et al. Viral Load Kinetics of SARS-CoV-2 Infection With Mild Disease Severity: Clinical Presentation, Stool Viral RNA Testing, and Outcomes. Am J Gastroenterol. 2020; 115[5]:790. https://doi.org/10.14309/ajg.0000000000000664 PMID: 32102625

67. Nicastri E, D’Abramo A, Faggioni G, De Santis R, Mariano A, Lepore L, et al. Coronavirus disease (COVID-19) in a paucisymptomatic patient: epidemiological and clinical challenge in settings with limited community transmission, Italy, February 2020. Euro Surveill. 2020; 25[11].
71. Pan Y, Zhang D, Yang P, Poon LLM, Wang Q. Viral load of SARS-CoV-2 in clinical samples. Lancet Infect Dis. 2020; 20[4]:411–2. https://doi.org/10.1016/S1473-3099(20)30113-4 PMID: 32105638

72. Peng L, Liu J, Xu W, Luo Q, Deng K, Lin B, et al. 2019 Novel Coronavirus can be detected in urine, blood, anal swabs and oropharyngeal swabs samples. medRxiv. 2020:2020.02.21.20026179.

73. Song L, Xiao G, Zhang X, Gao Z, Sun S, Zhang L, et al. A case of SARS-CoV-2 carrier for 32 days with several times false negative nucleic acid tests. medRxiv. 2020:2020.03.31.20045401.

74. Tan LV, Ngoc NM, That BTT, Uyen LTT, Hong NTT, Dung NTP, et al. Duration of viral detection in throat and rectum of a patient with COVID-19. medRxiv. 2020:2020.03.07.20032052.

75. Tang A, Tong ZD, Wang HL, Dai YX, Li KF, Liu JN, et al. Detection of Novel Coronavirus by RT-PCR in stool Specimen from Asymptomatic Child, China. Emerg Infect Dis. 2020; 26[6]:1337–9. https://doi.org/10.3201/eid2606.200301 PMID: 32150527

76. Wang S, Tu J, Sheng Y. Clinical characteristics and fecal-oral transmission potential of patients with COVID-19. medRxiv. 2020:2020.05.02.20089094.

77. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA. 2020; 323[18]:1843–4. https://doi.org/10.1001/jama.2020.3786 PMID: 32159775

78. Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet Gastroenterol Hepatol. 2020; 5[5]:434–5. https://doi.org/10.1016/S2468-1253(20)30083-2 PMID: 32199469

79. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology. 2020; 158[6]:1831–3 e3. https://doi.org/10.1053/j.gastro.2020.02.055 PMID: 32142773

80. Xing Y, Ni W, Wu Q, Li W, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimen s. JAMA. 2020; 323[18]:1843–4. https://doi.org/10.1001/jama.2020.3786 PMID: 32159775

81. Xu M, Liu X, Su C, Zeng Y, Zhang J, Li X, et al. A Research on the Results of Viral Nucleic Acid Tests and CT Imaging Variation of Patients with COVID-19. medRxiv. 2020:2020.03.11.20033159.

82. Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med. 2020; 26[4]:502–5. https://doi.org/10.1038/s41591-020-0817-4 PMID: 32284613

83. Zhang J, Wang S, Xue Y. Fecal specimen diagnosis 2019 novel coronavirus-infected pneumonia. Journal of Medical Virology. 2020; 92[6]:680–2. https://doi.org/10.1002/jmv.25745 PMID: 32124995

84. Zhang N, Gong Y, Meng F, Bi Y, Yang P, Wang F. Virus shedding patterns in nasopharyngeal and fecal specimens of COVID-19 patients. medRxiv. 2020:2020.03.28.20043059. https://doi.org/10.1007/s11427-020-1783-9 PMID: 32778998

85. Zhang T, Cui X, Zhao X, Wang J, Zheng J, Zheng G, et al. Detectable SARS-CoV-2 viral RNA in feces of three children during recovery period of COVID-19 pneumonia. Journal of Medical Virology. 2020.

86. Zhang W, Du RH, Li B, Zheng XS, Yang XL, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microbes Infect. 2020; 9[1]:386–9. https://doi.org/10.1080/22221751.2020.1729071 PMID: 32065057

87. Tan W, Lu Y, Zhang J, Wang J, Dan Y, Tan Z, et al. Viral Kinetics and Antibody Responses in Patients with COVID-19. medRxiv. 2020:2020.03.24.20042382.

88. Xie C, Jiang L, Huang G, Pu H, Gong B, Lin H, et al. Comparison of different samples for 2019 novel coronavirus detection by nucleic acid amplification tests. Int J Infect Dis. 2020; 93:264–7.

89. Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. Bmj. 2020; 369:m1443. https://doi.org/10.1136/bmj.m1443 PMID: 32317267

90. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. Nature Medicine. 2020.

91. Peng Z, Wang J, Mo Y, Duan W, Xiang G, Yi M, et al. Unlikely SARS-CoV-2 vertical transmission from mother to child: A case report. J Infect Public Health. 2020; 13[5]:818–20. https://doi.org/10.1016/j.jiph.2020.04.004 PMID: 32305459

92. To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infectious Diseases. 2020; 20[5]:565–74. https://doi.org/10.1016/S1473-3099(20)30196-1 PMID: 32213337

93. Liu Y, Li T, Deng Y, Liu S, Zhang D, Li H, et al. Stability of SARS-CoV-2 on environmental surfaces and in human excreta. medRxiv. 2020:2020.05.07.20094805.
94. Azzi L, Carcano G, Dalla Gasperina D, Sessa F, Maurino V, Baj A. Two cases of COVID-19 with positive salivary and negative pharyngeal or respiratory swabs at hospital discharge: A rising concern. Oral diseases. 2020.

95. Azzi L, Carcano G, Gianfagna F, Grossi P, Gasperina DD, Genoni A, et al. Saliva is a reliable tool to detect SARS-CoV-2. The Journal of infection. 2020; 81[1]:e45–e50. https://doi.org/10.1016/j.jinf.2020.04.005 PMID: 32298676

96. Chen LaZ, Jiajia and Peng, Jinfeng and Li, Xiaoshuang and Deng, Xuliang and Geng, Zhi and Shen, Zhenyu and Guo, Fengyuan and Zhang, Qianwen and Jin, Yang and Wang, Lin and Wang, Songlin. Detection of 2019-nCoV in Saliva and Characterization of Oral Symptoms in COVID-19 Patients. SSRN. 2020.

97. Han MS, Seong MW, Heo EY, Park JH, Kim N, Shin S, et al. Sequential analysis of viral load in a neonate and her mother infected with SARS-CoV-2. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020.

98. Iwasaki S, Fujisawa S, Nakakubo S, Kamada K, Yamashita Y, Fukumoto T, et al. Comparison of SARS-CoV-2 detection in nasopharyngeal swab and saliva. medRxiv. 2020:2020.05.13.20100206. https://doi.org/10.1016/j.jinf.2020.05.071 PMID: 32504740

99. Jamal AJ, Mohammad M, Coomes E, Powis J, Li A, Paterson A, et al. Sensitivity of nasopharyngeal swabs and saliva for the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). medRxiv. 2020:2020.05.01.20081026. https://doi.org/10.1016/j.jinf.2020.05.071 PMID: 32584972

100. Tajima Y, Suda Y, Yano K. A case report of SARS-CoV-2 confirmed in saliva specimens up to 37 days after onset: Proposal of saliva specimens for COVID-19 diagnosis and virus monitoring. Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy. 2020.

101. To KK, Tsang OT, Chik-Yan Yip C, Chan KH, Wu TC, Chan JMC, et al. Consistent detection of 2019 novel coronavirus in saliva. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020. https://doi.org/10.1093/cid/ciaa149 PMID: 32047895

102. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. The Lancet Infectious diseases. 2020; 20[5]:565–74. https://doi.org/10.1016/S1473-3099(20)30196-1 PMID: 32213337

103. Williams E, Bond K, Zhang B, Pullard M, Williamson DA. Saliva as a non-invasive specimen for detection of SARS-CoV-2. Journal of clinical microbiology. 2020.

104. Wyllie AL, Fournier J, Casanovas-Massana A, Campbell M, Tokuyama M, Vijayakumar P, et al. Saliva is more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs. medRxiv. 2020:2020.04.16.20067835.

105. Yoon JG, Yoon J, Song JY, Yoon SY, Lim CS, Seong H, et al. Clinical Significance of a High SARS-CoV-2 Viral Load in the Saliva. Journal of Korean Medical Science. 2020; 35[20]. https://doi.org/10.3346/jkms.2020.e195 PMID: 32449329

106. Zhu J, Guo J, Xu Y, Chen X. Viral dynamics of SARS-CoV-2 in saliva from infected patients. The Journal of infection. 2020. https://doi.org/10.1016/j.jinf.2020.06.059 PMID: 32593658

107. Cheng VCC, Wong SC, Chen JHK, Yip CCY, Chuang VWM, Tsang OTY, et al. Escalating infection control response to the rapidly evolving epidemiology of the coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 in Hong Kong. Infection control and hospital epidemiology. 2020; 41[5]:493–8. https://doi.org/10.1017/ice.2020.58 PMID: 32131908

108. Anfinrud P, Bax CE, Stadnitskiy V, Bax A. Could SARS-CoV-2 be transmitted via speech droplets? medRxiv. 2020:2020.04.02.20051177. https://doi.org/10.1101/2020.04.02.20051177 PMID: 32511430

109. Smither SJ, Eastaugh LS, Findlay JS, Lever MS. Experimental aerosol survival of SARS-CoV-2 in artificial saliva and tissue culture media at medium and high humidity. Emerging microbes & infections. 2020; 9[1]:1415–7.

110. Song J, Li Y, Huang X, Chen Z, Li Y, Liu C, et al. Systematic analysis of ACE2 and TMPRSS2 expression in salivary glands reveals underlying transmission mechanism caused by SARS-CoV-2. Journal of medical virology. 2020. https://doi.org/10.1002/jmv.26045 PMID: 32441816

111. Wang J, Zhao S, Liu M, Zhao Z, Xu Y, Wang P, et al. ACE2 expression by colonic epithelial cells is associated with viral infection, immunity and energy metabolism. medRxiv. 2020:2020.02.05.2000545.

112. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020; 12[1]:8. https://doi.org/10.1038/s41368-020-0074-x PMID: 32094336
113. Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. bioRxiv. 2020;2020.01.30.927806.

114. Dawson P, Rabold EM, Laws RL, Conners EE, Gharpure R, Yin S, et al. Loss of Taste and Smell as Distinguishing Symptoms of COVID-19. medRxiv. 2020;2020.05.13.20101006.

115. Vaira LA, Deiana G, Fois AG, Pirina P, Maddeddu G, De Vito A, et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck. 2020. https://doi.org/10.1002/hed.26204 PMID: 32342566

116. Lamers MM, Beumer J, van der Vaart J, Knoops K, Puschhof J, Breugem TI, et al. SARS-CoV-2 Productively Infects Human Gut Enterocytes. bioRxiv. 2020;2020.04.25.060350. https://doi.org/10.1126/science.abc1669 PMID: 32358202

117. Wang Q, Zhao H, Liu LG, Wang YB, Zhang T, Li MH, et al. Pattern of liver injury in adult patients with COVID-19: a retrospective analysis of 105 patients. Mil Med Res. 2020; 7[1]:28. https://doi.org/10.1186/s40779-020-00256-6 PMID: 32507110

118. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical Features of COVID-19-Related Liver Functional Abnormality. Clin Gastroenterol Hepatol. 2020; 18[7]:1561–6. https://doi.org/10.1016/j.cgh.2020.04.002 PMID: 32283325

119. Hadi A, Werge M, Kristiansen KT, Pedersen UG, Karstensen JG, Novovic S, et al. Coronavirus Disease-19 (COVID-19] associated with severe acute pancreatitis: Case report on three family members. Pancreatology. 2020; 20[4]:665–7. https://doi.org/10.1016/j.pan.2020.04.021 PMID: 32387082

120. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 2020. https://doi.org/10.1016/j.cgh.2020.04.040 PMID: 32334082

121. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. bioRxiv. 2020;2020.02.03.931766.

122. Wen Seow JJ, Pai R, Mishra A, Shepherdson E, Hon Lim TK, Goh BKP, et al. scRNA-seq reveals ACE2 and TMPRSS2 expression in TROP2&sup;+&lt;/sup&gt; Liver Progenitor Cells: Implications in COVID-19 associated Liver Dysfunction. bioRxiv. 2020;2020.03.23.002832.

123. Zhou H, Zhang Z, Fan H, Li J, Li M, Dong Y, et al. Urinalysis, but not blood biochemistry, detects the early renal-impairment in patients with COVID-19. medRxiv. 2020;2020.04.03.20051722.

124. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. J Am Soc Nephrol. 2020; 31[6]:1157–65. https://doi.org/10.1681/ASN.2020030276 PMID: 32345702

125. Diao B, Wang C, Wang R, Feng Z, Tan Y, Wang H, et al. Human Kidney is a Target for Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2] Infection. medRxiv. 2020;2020.03.04.20031120.

126. Su H, Yang M, Wan C, Yi L-X, Tang F, Zhu H-Y, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney International.

127. Pesaresi M, Pirani F, Tagliabracki A, Valsecchi M, Procopio AD, Busardo FP, et al. SARS-CoV-2 identification in lungs, heart and kidney specimens by transmission and scanning electron microscopy. European Review for Medical and Pharmacological Sciences. 2020; 24[9]:5186–8. https://doi.org/10.26355/eurr ev_202005_21217 PMID: 32432787

128. Fan C, Li K, Ding Y, Lu WL, Wang J. ACE2 Expression in Kidney and Testis May Cause Kidney and Testis Damage After 2019-nCoV Infection. medRxiv. 2020;2020.02.12.20022418.

129. Lin W, Hu L, Zhang Y, Ooi JD, Meng T, Jin P, et al. Single-cell Analysis of ACE2 Expression in Human Kidneys and Bladders Reveals a Potential Route of 2019-nCoV Infection. bioRxiv. 2020;2020.02.08.939892.

130. Hikmet F, Méar L, Uhlen M, Lindskog C. The protein expression profile of ACE2 in human tissues. bioRxiv. 2020;2020.03.31.016048. https://doi.org/10.15252/msb.20209610 PMID: 32715618

131. Ren X, Wei X, Li G, Ren S, Chen X, Zhang T, et al. Multiple expression assessments of ACE2 and TMPRSS2 SARS-CoV-2 entry molecules in the urinary tract and their associations with clinical manifestations of COVID-19. bioRxiv. 2020;2020.05.08.083618.

132. Stower H. Virological assessment of SARS-CoV-2. Nature medicine. 2020; 26[4]:465.

133. Chan JF, Yip CC, To KK, Tang TH, Wong SC, Leung KH, et al. Improved Molecular Diagnosis of COVID-19 by the Novel, Highly Sensitive and Specific COVID-19-RdRp/Hel Real-Time Reverse Transcription-PCR Assay Validated In Vitro and with Clinical Specimens. J Clin Microbiol. 2020; 58[5]. https://doi.org/10.1128/JCM.00310-20 PMID: 32132196
134. Wang L, Li X, Chen H, Yan S, Li D, Li Y, et al. Coronavirus Disease 19 Infection Does Not Result in Acute Kidney Injury: An Analysis of 116 Hospitalized Patients from Wuhan, China. Am J Nephrol. 2020; 51[5]:343–8. https://doi.org/10.1159/000507471 PMID: 32293732

135. Sun J, Zhu A, Li H, Zheng K, Zhuang Z, Chen Z, et al. Isolation of infectious SARS-CoV-2 from urine of a COVID-19 patient. Emerg Microbes Infect. 2020; 9[1]:991–9. https://doi.org/10.1080/22221751.2020.1760144 PMID: 3242249

136. Pan F, Xiao X, Guo J, Song Y, Li H, Patel DP, et al. No evidence of severe acute respiratory syndrome–coronavirus 2 in semen of males recovering from coronavirus disease 2019. Fertility and Sterility. 2020; 113[6]:1135–9. https://doi.org/10.1016/j.fertnstert.2020.04.024 PMID: 32482249

137. Song C, Wang Y, Li W, Hu B, Chen G, Xia P, et al. Absence of 2019 Novel Coronavirus in Semen and Testes of COVID-19 Patients. Biol Reprod. 2020.

138. Liu X, Chen Y, Tang W, Zhang L, Chen W, Yan Z, et al. Single-cell transcriptome analysis of the novel coronavirus (SARS-CoV-2)-associated gene ACE2 expression in normal and non-obstructive azoospermia (NOA) human male testes. Science-China Life Sciences. 2020. https://doi.org/10.1007/s11427-020-1705-0 PMID: 32361911

139. Wang Z, Xu X. scRNA-seq Profiling of Human Testes Reveals the Presence of the ACE2 Receptor, A Target for SARS-CoV-2 Infection in Spermatogonia, Leydig and Sertoli Cells. Cells. 2020; 9[4]. https://doi.org/10.3390/cells9040920 PMID: 32283711

140. Shastri A, Wheat J, Agrawal S, Chatterjee N, Pradhan K, Goldfinger M, et al. Delayed clearance of SARS-CoV2 in male compared to female patients: High ACE2 expression in testes suggests possible existence of gender-specific viral reservoirs. medRxiv. 2020;2020.04.16.20060566.

141. Li D, Jin M, Bao P, Zhao W, Zhang S. Clinical Characteristics and Results of Semen Tests Among Men With Coronavirus Disease 2019. JAMA network open. 2020; 3[5]:e208292. https://doi.org/10.1001/jamanetworkopen.2020.8292 PMID: 32379329

142. Paoli D, Pallotti F, Colangelo S, Basilico F, Mazzuti L, Turriziani O, et al. Study of SARS-CoV-2 in semen and urine samples of a volunteer with positive naso-pharyngeal swab. Journal of Endocrinological Investigation. 2020.

143. quan w, zheng q, tian j, chen j, liu z, chen x, et al. No SARS-CoV-2 in expressed prostatic secretion of patients with coronavirus disease 2019: a descriptive multicentre study in China. medRxiv. 2020:2020.03.26.20044198.

144. Cui P, Chen Z, Wang T, Dai J, Zhang J, Ding T, et al. Clinical features and sexual transmission potential of SARS-CoV-2 infected female patients: a descriptive study in Wuhan, China. medRxiv. 2020:2020.02.26.20028225.

145. Baergen RN, Heller DS. Placental Pathology in Covid-19 Positive Mothers: Preliminary Findings. Pediatr Dev Pathol. 2020; 23[3]:177–80. https://doi.org/10.1177/1093526620925569 PMID: 32397896

146. Chen Y, Peng H, Wang L, Zhao Y, Zeng L, Gao H, et al. Infants Born to Mothers With a New Coronavirus (COVID-19). Frontiers in Pediatrics. 2020; 8.

147. Pique-Regi R, Romero R, Tarca AL, Luca F, Xu Y, Leng Y, et al. Does the human placenta express the canonical cell entry mediators for SARS-CoV-2? bioRxiv. 2020:2020.05.18.101485.

148. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. The Lancet. 2020; 395[10226]:809–15. https://doi.org/10.1016/S0140-6736(20)30360-3 PMID: 32151335

149. Kalafat E, Yaprap E, Cinar G, Vardi B, Oziiski S, Uzun C, et al. Lung ultrasound and computed tomographic findings in pregnant woman with COVID-19. Ultrasound in Obstetrics & Gynecology. 2020; 55 [6]:835–7.

150. Li Y, Zhao R, Zheng S, Chen X, Wang J, Sheng X, et al. Lack of Vertical Transmission of Severe Acute Respiratory Syndrome Coronavirus 2. Emerging infectious diseases. 2020; 26[6]:1335–6. https://doi.org/10.3201/eid2606.200287 PMID: 32134381

151. Goad J, Rudolph J, Rajkovic A. Female reproductive tract has low concentration of SARS-CoV2 receptors. bioRxiv. 2020:2020.06.20.163097. https://doi.org/10.1101/2020.06.20.163097 PMID: 32607512

152. Han MS, Seong MW, Heo EY, Park JH, Kim N, Shin S, et al. Sequential analysis of viral load in a neonate and her mother infected with SARS-CoV-2. Clin Infect Dis. 2020.

153. Coronado Munoz A, Nawaratne U, McMann D, Ellsworth M, Meliones J, Boukas K. Late-Onset Neonatal Sepsis in a Patient with Covid-19. N Engl J Med. 2020; 382[19]:e49.

154. Nathan N, Prevost B, Corvol H. Atypical presentation of COVID-19 in young infants. Lancet. 2020; 395 [10235]:1481.
155. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ. 2020; 369:m2107. https://doi.org/10.1136/bmj.m2107 PMID: 32513659

156. Rodrigues C, Baia I, Domingues R, Barros H. Pregnancy and breastfeeding during COVID-19 pandemic: A systematic review of published pregnancy cases. medRxiv. 2020.2020.04.25.20079509.

157. Groß R, Conzelmann C, Müller JA, Stenger S, Steinhart K, Kirchhoff F, et al. Detection of SARS-CoV-2 in human breastmilk. The Lancet. 2020; 395(10239):1757–8. https://doi.org/10.1016/S0140-6736(20)31181-8 PMID: 32446324

158. Wu Yanting LC, Dong Lan, Zhang Chenjie, Chen Yang, Liu Jun, Zhang Chen, Duan Chenchi, Zhang Hanqiu, Mol Ben Willem, Dennis Cindy-Lee, Yin Tailang, Yang Jing, Huang He-Feng. Viral Shedding of COVID-19 in Pregnant Women. 2020.

159. Chambers CD, Krogstad P, Bertrand K, Contreras D, Bode L, Tobin N, et al. Evaluation of SARS-CoV-2 in Breastmilk from 18 Infected Women. medRxiv. 2020:2020.06.12.20127944. https://doi.org/10.1101/2020.06.12.20127944 PMID: 32587991

160. Bernard-Valnet R, Pizzarotti B, Anichini A, Demars Y, Russo E, Schmidhauser M, et al. Two patients with acute meningo-encephalitis concomitant to SARS-CoV-2 infection. medRxiv. 2020:2020.04.17.20060251.

161. Alberti P, Beretta S, Piatti M, Karantzaouis A, Piatti ML, Santoro P, et al. Guillain-Barré syndrome related to COVID-19 infection. Neurol Neuroimmunol Neuroinflamm. 2020; 7[4].

162. Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, et al. Clinical characteristics and outcomes of inpatients with neurological disease and COVID-19. medRxiv. 2020:2020.04.28.20082735.

163. Yin R, Yang Z, Wei Y, Li Y, Chen H, Liu Z, et al. Clinical characteristics of 106 patients with neurological diseases and co-morbid coronavirus disease 2019: a retrospective study. medRxiv. 2020:2020.04.29.20085415.

164. Coolen T, Lolli V, Sadeghi N, Rovai A, Trotta N, Taccone FS, et al. Early postmortem brain MRI findings in COVID-19 non-survivors. medRxiv. 2020:2020.05.04.20090316.

165. Hess DC, Eldahshan W, Rutkowsky E. COVID-19-Related Stroke. Translational Stroke Research. 2020.

166. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. Radiology. 2020;201187– .

167. Zanin L, Saraceno G, Panciani PP, Renisi G, Signorini L, Migliorati K, et al. SARS-CoV-2 can induce brain and spine demyelinating lesions. Acta Neurochirurgica. 2020.

168. Zhang T, Rodricks MB, Hirsh E. COVID-19-Associated Acute Disseminated Encephalomyelitis: A Case Report. medRxiv. 2020:2020.04.16.20068148.

169. Moriguchi T, Hari N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. International Journal of Infectious Diseases. 2020; 94:55–8.

170. Zhou L, Zhang M, Wang J, Gao J. Sars-Cov-2: Underestimated damage to nervous system. Travel Med Infect Dis. 2020:201642. https://doi.org/10.1016/j.tmaid.2020.101642 PMID: 32220634

171. Schaller T, Hirschbühl K, Burkhardt K, Braun G, Trepel M, Märkl B, et al. Postmortem Examination of Patients With COVID-19. JAMA. 2020.

172. Chen R, Yu J, Wang K, Howard D, French L, Chen Z, et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain. bioRxiv. 2020:2020.04.07.030650.

173. Shiers S, Ray PR, Wangzhou A, Tatsui CE, Rhines L, Li Y, et al. ACE2 expression in human dorsal root ganglion sensory neurons: implications for SARS-CoV-2 virus-induced neurological effects. bioRxiv. 2020:2020.05.28.123374.

174. Fodoulian L, Tuberosa J, Rossier D, Landis BN, Carleton A, Rodriguez I. SARS-CoV-2 receptor and entry genes are expressed by sustentacular cells in the human olfactory neuroepithelium. bioRxiv. 2020:2020.03.31.013268.
178. Butowt R, Bilinska K. SARS-CoV-2: Olfaction, Brain Infection, and the Urgent Need for Clinical Samples Allowing Earlier Virus Detection. ACS Chem Neurosci. 2020; 11[9]:1200–3. https://doi.org/10.1021/acscchemneuro.0c00172 PMID: 32283006

179. Brann D, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. bioRxiv. 2020:2020.03.25.009084.

180. Bozkurt B, Eğrilmez S, Şengör T, Yıldırım Ö, İrkeç M. The COVID-19 Pandemic: Clinical Information for Ophthalmologists. Turk J Ophthalmol. 2020; 50[2]:59–63.

181. Chen L, Deng C, Chen X, Zhang X, Chen B, Yu H, et al. Ocular manifestations and clinical characteristics of 534 cases of COVID-19 in China: A cross-sectional study. medRxiv. 2020:2020.03.12.20034678.

182. Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. Journal of medical virology. 2020.

183. Kumar K, Prakash AA, Gangasagara S, Rathod SBL, Ravi K, Rangaiah A, et al. Presence of viral RNA of SARS-CoV-2 in conjunctival swab specimens of COVID-19 patients. Indian J Ophthalmol. 2020; 68[6]:1015–7. https://doi.org/10.4103/ijo.IJO_1287_20 PMID: 32461418

184. Wu P, Duan F, Luo CH, Liu Q, Qu XG, Liang L, et al. Characteristics of Ocular Findings of Patients With Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. Jama Ophthalmology. 2020; 138[5]:575–8. https://doi.org/10.1001/jamaophthalmol.2020.1291 PMID: 32232433

185. Zhou Y, Zeng Y, Tong Y, Chen C. Ophthalmologic evidence against the interpersonal transmission of 2019 novel coronavirus through conjunctiva. medRxiv. 2020:2020.02.11.20021956.

186. Chen L, Liu MZ, Zhang Z, Qiao K, Huang T, Chen MH, et al. Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. British Journal of Ophthalmology. 2020; 104[6]:748–51. https://doi.org/10.1136/bjophthalmol-2020-316304 PMID: 32265202

187. Seah IYJ, Anderson DE, Kang AEZ, Wang L, Rao P, Young BE, et al. Assessing Viral Shedding and Infectivity of Tears in Coronavirus Disease 2019 (COVID-19) Patients. Ophthalmology. 2020.

188. Xu L, Zhang X, Song W, Sun B, Mu J, Dong X, et al. Conjunctival polymerase chain reaction-tests of 2019 novel coronavirus in patients in Shenyang,China. medRxiv. 2020:2020.02.23.20024935.

189. Hamashima K, Gautam P, Lau KA, Khiong CW, Blenkinsop TA, Li H, et al. Potential modes of COVID-19 transmission from human eye revealed by single-cell atlas. bioRxiv. 2020:2020.05.09.085613.

190. Zhou L, Xu Z, Castiglia GM, Soberman US, Eberhart CG, Duh EJ. ACE2 and TMPRSS2 are expressed on the human ocular surface, suggesting susceptibility to SARS-CoV-2 infection. bioRxiv. 2020:2020.05.09.086165.

191. Gianotti R, Veraldi S, Recalcati S, Cusini M, Ghislanzoni M, Boggio F, et al. Cutaneous Clinico-Pathological Findings in three COVID-19-Positive Patients Observed in the Metropolitan Area of Milan, Italy. Acta Derm Venereol. 2020; 100[8]:adv00124. https://doi.org/10.2340/00015555-3490 PMID: 32315073

192. Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for dengue. J Am Acad Dermatol. 2020; 82[5]:e177. https://doi.org/10.1016/j.jaad.2020.03.036 PMID: 32213305

193. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. Journal of the European Academy of Dermatology and Venereology. 2020; 34[5]:e212–e3.

194. van der Voort P, Moser J, Zandstra DF, Muller Kobold AC, Knoester M, Calkhoven CF, et al. A clinical and biological framework on the role of visceral fat tissue and leptin in SARS-CoV-2 infection related respiratory failure. medRxiv. 2020:2020.04.30.20086108.

195. Healy SA, Hachim M, Senok A, Tayoun AA, Hamoudi R, Alsheikh-Ali A, et al. Regulation of angiotensin converting enzyme 2 (ACE2) in obesity: implications for COVID-19. bioRxiv. 2020:2020.04.17.046938.

196. Nakagawa K, Lokugamage KG, Makino S. Viral and Cellular mRNA Translation in Coronavirus-Infected Cells. Adv Virus Res. 2016; 96:165–92. https://doi.org/10.1016/bs.aivir.2016.08.001 PMID: 27726223

197. Forrester JV. Ebola virus and persistent chronic infection: when does replication cease? Ann Transl Med. 2018; 6[Suppl 1]:S39–S. https://doi.org/10.21037/atm.2018.09.60 PMID: 30613614

198. Smith JC, Sausville EL, Girish V, Yuan ML, Vasudevan A, John KM, et al. Cigarette Smoke Exposure and Inflammatory Signaling Increase the Expression of the SARS-CoV-2 Receptor ACE2 in the Respiratory Tract. Developmental Cell. 2020; 53[5]:514–29.e3. https://doi.org/10.1016/j.devcel.2020.05.012 PMID: 32425701
200. Rao S, Lau A, So H-C. Exploring Diseases/Traits and Blood Proteins Causally Related to Expression of ACE2, the Putative Receptor of SARS-CoV-2: A Mendelian Randomization Analysis Highlights Tentative Relevance of Diabetes-Related Traits. Diabetes Care. 2020;dc200643. https://doi.org/10.2337/dc20-0643 PMID: 32430459

201. Jacobs M, Van Eeckhoutte HP, Wijnant SRA, Janssens W, Joos GF, Brusselle GG, et al. Increased expression of ACE2, the SARS-CoV-2 entry receptor, in alveolar and bronchial epithelium of smokers and COPD subjects. medRxiv. 2020:2020.05.27.20114298. https://doi.org/10.1183/13993003.02378-2020 PMID: 32675207

202. Bénêteau-Burnat B, Baudin B, Morgant G, Baumann FC, Giboudeau J. Serum angiotensin-converting enzyme in healthy and sarcoidotic children: comparison with the reference interval for adults. Clin Chem. 1990; 36[2]:344–6. PMID: 2154343

203. Chen J, Jiang Q, Xia X, Liu K, Yu Z, Tao W, et al. Individual variation of the SARS-CoV-2 receptor ACE2 gene expression and regulation. Aging Cell. 2020; 19[7]:e13168. https://doi.org/10.1111/acel.13168 PMID: 32558150

204. Ciaglia E, Vecchione C, Puca AA. COVID-19 Infection and Circulating ACE2 Levels: Protective Role in Women and Children. Frontiers in Pediatrics. 2020; 8[206]. https://doi.org/10.3389/fped.2020.00206 PMID: 32391299

205. Jefferson T, Spencer E, Brassey J, Heneghan C. Viral cultures for COVID-19 infectivity assessment. Systematic review. medRxiv. 2020:2020.08.04.20167932.

206. Goldsmith CS, Miller SE, Martines RB, Bullock HA, Zaki SR. Electron microscopy of SARS-CoV-2: a challenging task. Lancet. 2020; 395[10238]:e99.

207. Lakdawala SS, Menachery VD. The search for a COVID-19 animal model. Science. 2020; 368[6494]:942–3. https://doi.org/10.1126/science.abc6141 PMID: 32467379

208. Ehaideb SN, Abdullah ML, Abuyassin B, Bouchama A. A systematic review uncovers a wide-gap between COVID-19 in humans and animal models. medRxiv. 2020:2020.07.15.20147041.