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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Virology* (*WJV*, *World J Virol*) is to provide scholars and readers from various fields of virology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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REVIEW

Gastrointestinal tract and viral pathogens

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Abstract

Viral gastroenteritis is the most common viral illness that affects the gastrointestinal (GI) tract, causing inflammation and irritation of the lining of the stomach and intestines. Common signs and symptoms associated with this condition include abdominal pain, diarrhea, and dehydration. The infections commonly involved in viral gastroenteritis are rotavirus, norovirus, and adenovirus, which spread through the fecal-oral and contact routes and cause non-bloody diarrhea. These infections can affect both immunocompetent and immunocompromised individuals. Since the pandemic in 2019, coronavirus gastroenteritis has increased in incidence and prevalence. Morbidity and mortality rates from viral gastroenteritis have declined significantly over the years due to early recognition, treatment with oral rehydration salts, and prompt vaccination. Improved sanitation measures have also played a key role in reducing the transmission of infection. In addition to viral hepatitis causing liver disease, herpes virus, and cytomegalovirus are responsible for ulcerative GI disease. They are associated with bloody diarrhea and commonly occur in immunocompromised individuals. Hepatitis viruses, Epstein-Barr virus, herpesvirus 8, and human papillomavirus have been involved in benign and malignant diseases. This mini review aims to list different viruses affecting the GI tract. It will cover common symptoms aiding in diagnosis and various important aspects of each viral infection that can aid diagnosis and management. This will help primary care physicians and hospitalists diagnose and treat patients more easily.

Key Words: Virus diseases; Gastroenteritis; Enterocolitis; Rotavirus infections; Norovirus; Adenoviridae infections; Digestive system diseases

Core Tip: Viral gastroenteritis is a common condition that affects the gastrointestinal (GI) tract. These viruses can affect people of all ages and are a significant public health concern. Dehydration resulting from the infection is the primary reason for emergency department visits in both children and adults. Our review discusses other GI viruses such as cytomegalovirus, herpes simplex virus, and hepatitis virus that cause manifestations such as hepatitis, gastritis, and bloody diarrhea. Both immunocompetent and immunocompromised individuals can be affected by these GI viral pathogens. Understanding the various viruses that cause GI manifestations can help with early diagnosis and appropriate management. This is a concise review of GI viral pathogens.

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INTRODUCTION

Viral pathogens cause gastrointestinal (GI) manifestations such as watery diarrhea, bloody diarrhea, and various other manifestations like hepatitis, ulcerative diseases, motility disorders, and neoplastic diseases of the GI tract in both immunocompetent and immunocompromised individuals. Infectious gastroenteritis is a major illness worldwide, especially in developing nations and viruses account for most of the illnesses. Globally, Norovirus is the leading cause of acute gastroenteritis outbreaks. Besides diarrhea, viruses are also responsible for causing diseases like hepatitis and ulcerative diseases. Asymptomatic and symptomatic co-infections with these pathogens listed are also mentioned in prior literature. Our paper is the first-of-its-kind mini-review summarizing most of the GI viral pathogens and their varied manifestations to update existing reviews[1,2]. We consolidated information on viruses that cause both diarrheal illness and non-diarrheal manifestations. Our paper will concisely summarize each entity to equip clinicians with accurate information and aid in correct diagnosis and management. As gastroenteritis is the most common disease caused by these viruses, we will be categorizing the paper based on this presentation. This categorization may also help with forming a differential diagnosis when patients present to health care centers and hospitals with the infection. We categorized the manuscript into: (1) Diarrheal illnesses further subdivided into non bloody diarrhea and bloody diarrhea; and (2) viruses associated with other non-diarrheal illnesses-hepatitis, ulcerative disease, and neoplasms (Table 1 shows common viruses that affect the GI system).

NON-BLOODY DIARRHEA FROM VIRAL GASTROENTERITIS

Norovirus

Norovirus is an RNA virus belonging to the *Caliciviridae* family and consists of forty-nine genotypes. According to Centers for Disease Control and Prevention (CDC), Norovirus is the leading cause of acute gastroenteritis among all age groups in the United States[3]. However, high-risk groups include young children, the elderly, travelers, military personnel, and the immunocompromised. On average, each year in the United States, Norovirus causes 109000 hospitalizations. Outbreaks usually occur in congregant environments like healthcare centers, cruise ships, and restaurants *via* fecal-oral transmission through food, water, or person-to-person contact. It is typically a self-limiting disease with symptoms like diarrhea, nausea/vomiting, and abdominal cramps that resolve within two to four days. It is primarily a clinical diagnosis. However diagnostic modalities include electron microscopy, polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), and immunochromatographic testing[4]. Diagnostic testing for Norovirus is rarely used given the short-lived nature of the disease. Currently, no drug has been clinically approved to treat norovirus infection owing to its mild state of disease. Complications of this illness include electrolyte imbalances, chronic gastroenteritis, irritable bowel syndrome, inflammatory bowel disease, convulsions, and encephalopathy (especially in children)[5]. Vaccinations are not currently licensed for norovirus infection prevention, but many trials are underway to assess the impact and efficacy of vaccines on disease prevention and transmission.

Rotavirus

Rotavirus, an RNA virus, and a member of the Reoviridae family is the major cause of diarrhea in children younger than five years. Reports from the Global burden of disease showed that 128530 deaths occurred due to Rotavirus infection alone[6]. Rotavirus contributed to 29.3% of total diarrheal deaths in 2015[6]. Younger age groups (< 5 years) and lower socioeconomic status seem to be the targets of the

Table 1 Common viruses affecting the gastrointestinal system

Virus	Route of infection	Population affected	Type of disease	Diagnosis	Treatment
Norovirus	Fecal-oral, fomites	Children < 5 yr	Gastroenteritis	Self-limited	Supportive
Rotavirus	Fecal-oral, fomites	Children < 5 yr	Gastroenteritis	Self-limited	Supportive
Adenovirus	Fecal-oral, fomites	Any age group, especially children	Gastroenteritis	Self-limited	Supportive
Hepatitis A	Fecal-oral, fomites	Any age groups; international travelers to endemic countries, IV drug users, men who have sex with men	Gastroenteritis, acute viral hepatitis, and fulminant liver failure	Serology	Supportive
Astrovirus	Fecal-oral, fomites	Children < 5 yr	Gastroenteritis	Self-limited	Supportive
Sapovirus	Fecal-oral, fomites	Children < 5 yr	Gastroenteritis	Self-limited	Supportive
Coronavirus	Fecal-oral, fomites	Any age group	Gastroenteritis; respiratory infection	Self-limited, viral rapid antigen, PCR can be performed	Supportive; for COVID-19-antivirals (nirmatrelvir/ritonavir, remdesivir), steroids, biologics (tocilizumab, baricitinib)
Hepatitis E	Fecal-oral, Fomites	15-40 yr	Gastroenteritis, acute hepatitis, and acute liver failure	Serology	Supportive
Cytomegalovirus	Contact with bodily fluids and organ transplantation	All ages	Colitis, toxic megacolon, and peritonitis	Viral PCR	Ganciclovir, valganciclovir, ganciclovir resistant-foscarnet, cidofovir
Herpes simplex virus	Sexual contact	MSM	Proctitis and anal ulcerations	Viral PCR	Acyclovir, valacyclovir, and famciclovir
HIV	Contact through bodily fluids like sexual contact, injection drug use, perinatal transmission	All ages	Acquired immunodeficiency syndrome, HIV enteropathy-diarrhea	2-step testing-combination antigen-antibody test followed by HIV 1/2 differentiation assay	HAART-combination therapy with Tenofovir, Emtricitabine, raltegravir, and bictegravir
Hepatitis B and D	Contact through bodily fluids like sexual contact, injection drug use, perinatal transmission	Usually adults, but all age groups can be affected	Hepatitis, cirrhosis, hepatocellular carcinoma	Serology, DNA load	Acute infections usually resolve; in some cases, tenofovir, entecavir
Hepatitis C	Contact through bodily fluids like sexual contact, injection drug use, transfusion, or perinatal transmission	Usually adults, but all age groups can be affected	Hepatitis, cirrhosis, hepatocellular carcinoma	Serology, RNA load	Combination therapy specific for genotypes; includes sofosbuvir/velpatasvir, glecaprevir/pibrentasvir
Varicella Zoster	Droplet, and contact infection	Commonly in children but can occur in any age group. Reactivation common in immunocompromised	Erosive disease of the stomach and intestines, motility problems	Clinical diagnosis, but RNA PCR is used for atypical presentations	Acyclovir, valacyclovir, and brivudin
Epstein-Barr virus	Contact with bodily fluids, especially saliva; sexual transmission, blood transfusion, organ transplantation	Individuals aged 15-24 yr	Gastritis, Enteritis, esophageal disorders, and gastric cancer	Mostly clinical diagnosis but can be diagnosed by serology	Symptomatic treatment, acyclovir in some cases
HHV-8	Sexual transmission, contact with saliva, blood transfusion, and organ transplantation	All age groups	Maculopapular and polypoid lesions of the GI tract	Endoscopy and biopsy	Radiation, intralesional chemotherapy, or systemic chemotherapy with liposomal doxorubicin and paclitaxel
HPV	Sexual transmission-oral, vaginal, anal sex	15-49 yr	Oropharyngeal, esophageal, gastric, colorectal, and anal cancers	Cytology and viral testing	Cancer-specific treatment

HIV: Human immunodeficiency virus; HPV: Human papillomavirus; HHV: Human herpesvirus 8; MSM: Men who have sex with men; PCR: Polymerase chain reaction; GI: Gastrointestinal.

disease[7]. Diarrhea caused by the virus is thought to be *via* two mechanisms: (1) Osmotic diarrhea due to malabsorption secondary to enterocyte damage; and (2) secretory diarrhea from activation of the enteric nervous system and non-structural protein-4[7]. The disease is transmitted through fecal-oral routes and fomites. Clinical manifestations include diarrhea, vomiting, and fever. Clinical morbidity is due to severe dehydration requiring hospitalization and can sometimes also lead to necrotizing enterocolitis[8]. ELISA can detect the virus until 1 wk after the onset of diarrheal illness whereas real time PCR (RT-PCR), being more sensitive can detect the virus until longer periods[7]. Fluid and electrolyte resuscitation remains the mainstay of treatment. Symptomatic management with Antiemetics and Antidiarrheal drugs decreases fluid losses thus fastening recovery and preventing death. Routine use of antivirals is not recommended for this infection. The advent of Rotarix and RotaTeq around 2006-2008 brought about a notable change in the morbidity and mortality of rotaviral disease. Mortality among children younger than 5 years of age has decreased by more than 45% since the mid-2000s[6]. It is prudent to say that, although there has been a shift from rotaviral illness being a fatal disease to a non-fatal disease, continued efforts are necessary to widen vaccination coverage and improve water and sanitation facilities.

Adenovirus

Adenovirus is a double-stranded DNA virus belonging to the Adenoviridae family. HAdV-F40 and F41 are the enteric serotypes implicated in causing acute gastroenteritis[9]. According to the re-analysis done by Global Enterics Multicenter Study, adenovirus was the second most common cause of diarrheal illness after Rotavirus in infants[9]. Infections caused by Adenovirus include febrile respiratory illness, pharyngoconjunctival fever, keratoconjunctivitis, and gastroenteritis. Transmission routes include aerosols, fecal-oral, and fomites. Adenovirus infections occur in congregate settings like daycare centers, summer camps, college campuses, and military camps. Symptoms of adenoviral gastroenteritis are like any other gastroenteritis including diarrhea, vomiting, and abdominal cramps. However, a multicenter study done in 8 Low-resource countries showed that fever was more commonly associated with adenoviral infection compared to other viral infections other than rotavirus[10]. Diagnostic methods are not often used but consist of antigen detection, PCR, and serology. No specific treatment is available for the infection but measures like rehydration, adequate food intake, and zinc supplementation are essential, especially in low to middle-income countries. Complications of adenoviruses include intussusception, hepatitis of unknown cause (adenovirus type 41), chronic lung disease, meningoencephalitis, and cystitis[11,12]. Currently, vaccination against Adenovirus type 4 and 7 is FDA-approved to prevent febrile acute respiratory disease for military populations aged 17 years to 50 years.

Astrovirus

Astroviruses are single-stranded RNA viruses belonging to the family of Astroviridae. Astroviruses are responsible for 0.5%-15.0% of diarrheal outbreaks across the world[13]. Transmission is through the fecal-oral route and fomites. Like any other gastroenteritis-causing virus, outbreaks happen in communal settings like schools, nursing homes, and swimming pools[14]. The incubation period is long (4.5 d) and it causes mild diarrhea lasting for about 2 d to 3 d associated with symptoms like fever, anorexia, and vomiting[15]. Diagnostics include electron microscopy, cell culture, immunoassays, and RT-PCR, with the latter being the most commonly used modality[16]. This infection is self-limited and usually resolves with fluid and electrolyte replacements. Immunocompromised adults and the elderly have longer-lasting symptoms with rare occurrences of complications like meningitis and encephalitis [17].

Sapovirus

Sapoviruses are single-stranded RNA viruses belonging to the same family as Norovirus, *Caliciviridae*. According to the Etiology, Risk Factors, and Interactions of Enteric Infection and Malnutrition and the Consequences for Child Health and Development (MAL-ED) study, sapovirus had the second-highest incident rate of acute diarrhea after Shigella. The study attributed an incidence rate of 22.8 cases per 100 child years to sapovirus with a 95% confidence interval ranging from 18.9 to 27.5[18]. Transmission occurs through fecal-oral contact, contaminated food/water, and fomites[19]. They are known to cause gastroenteritis in humans, specifically aged < 5 years, and animals[20]. Outbreaks occur in communal settings like daycare centers, hospitals, nursing homes, and schools[21]. While the usual clinical symptomatology is the same as any gastroenteritis-causing virus, it has also been implicated in causing chronic diarrhea, especially in immunocompromised populations. Definitive diagnosis by PCR detection, however, is not indicated due to the self-limiting nature of the disease and the cost considerations[21]. No antivirals are warranted, World health organization (WHO) guided treatment for diarrhea viz rehydration, zinc supplementations, and adequate nutrition is considered the treatment of choice[22]. Interestingly, Nitazoxanide has been tried in transplant patients with some benefits[23]. Cases of Sapoviruses causing septic shock and intestinal obstruction have been reported in the literature[24,25].

Enterovirus

Enteroviruses are single-stranded RNA viruses belonging to the Picornaviridae family. Enterovirus

genus consists of viruses like Poliovirus, Coxsackie virus, Echovirus, rhinovirus, and other enterovirus subtypes. According to the CDC, it is estimated that around 10-15 million non-polio-enterovirus infections occur annually[26]. They can be transmitted *via* the fecal-oral route or through respiratory secretions. Infants, children, and teenagers are more likely to get affected than adults[27]. They generally have a secondary tissue tropism and spread to other target tissues after they infect the GI system[28]. Non-Polio enteroviruses are known to cause diseases like aseptic meningitis, hand-foot-mouth disease, flaccid paralysis, myocarditis, pancreatitis, *etc*[28,29]. Some non-specific GI manifestations are less common but include abdominal pain, vomiting, and diarrhea and are self-limited. Enteroviruses can be detected in stool, pharynx, blood, and CSF using techniques like PCR, serology, and cell culture. Treatment is usually symptomatic care and no targeted therapies have been developed yet. Some of the dreaded complications of enteroviruses include meningitis, encephalitis, myocarditis, and acute flaccid paralysis[30,31]. The only enteroviral vaccine is the polio vaccine to prevent poliomyelitis.

Coronavirus

Coronaviruses are single-stranded RNA viruses belonging to the Coronaviridae family. SARS-CoV-1 emerged in 2002-2003 and caused a global outbreak that affected over 8000 people in 26 countries, with a case fatality rate of approximately 10%[32]. MERS-CoV emerged in 2012 and has since caused sporadic outbreaks in the Middle East and other regions, with a case fatality rate of approximately 34%[33]. Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in late 2019 and has since spread globally, causing a pandemic that has affected millions of people worldwide. As of April 21, 2023, there have been over 435 million confirmed cases and over 5.8 million deaths reported globally[34]. Coronaviruses are transmitted through multiple routes, mainly through droplets, contact with infected persons, and contaminated surfaces.

Human Coronaviruses are known to cause respiratory infections, but they also cause GI symptoms including diarrhea, nausea, vomiting, and abdominal pain. The majority of HCoV infections like diarrhea occur in neonates, infants, and children. Also, they co-infect with other enteric viruses like norovirus and rotavirus. SARS-CoV and MERS-CoV, members of the coronavirus family have also been implicated in causing the above symptoms[35]. SARSCoV2 causing COVID-19 also presents as diarrhea, nausea, vomiting, and abdominal pain along with respiratory symptoms and sometimes even in the absence of respiratory manifestations[36]. GI manifestations were speculated to be caused due to the high expression of ACE2 receptors in the gut which is the binding site for SARS-CoV-2[37]. Changes in the gut microbiota have also been observed in COVID-19-infected patients. Although they are respiratory viruses, interestingly, the GI transmission of this group of viruses has also been proven as many studies have mentioned the detection of RNA in stool samples[35]. Currently, no specific antivirals are indicated in SARS and MERS infections, whereas COVID-19 treatment entails various therapies like antivirals, steroids, biologics, *etc*. The most common complications of COVID-19, caused by SARS-CoV-2, include pneumonia and acute respiratory distress syndrome (ARDS), which can lead to respiratory failure and death in severe cases[38]. COVID-19 can also cause a range of other complications, including cardiovascular and neurological complications, blood clots, and multisystem inflammatory syndrome in children[39]. MERS-CoV infections are also associated with severe respiratory illness and complications such as pneumonia, ARDS, and septic shock[40]. SARS-CoV-1 infections can cause similar respiratory complications, as well as complications such as liver and kidney failure[41]. Currently, several vaccines against the COVID-19 have been developed. Pfizer-BioNTech and Moderna mRNA vaccines have reported efficacies of over 90% in preventing symptomatic COVID-19[42,43].

Hepatitis E virus

Hepatitis E virus is a single-stranded RNA virus belonging to the family Hepeviridae. According to the WHO, there are an estimated 20 million HEV infections worldwide every year[44]. hepatitis E caused approximately 44000 deaths in 2015 (accounting for 3.3% of the mortality due to viral hepatitis)[44]. Hepatitis E is mainly transmitted through food and water contamination, also through perinatal transmission, and blood transfusions[45]. Pregnant women, especially those in their third trimester, and individuals with pre-existing liver disease are the most vulnerable groups for developing severe HEV infection[46-48]. Other groups that may be at increased risk of HEV infection include travelers to endemic areas, healthcare workers, and individuals who consume undercooked or raw pork[49]. It is usually a self-resolving illness but can sometimes occur with symptoms like fever, anorexia, jaundice, nausea, vomiting, hepatomegaly, and abdominal pain[50]. Diagnosis is by serology, enzyme immunoassay, or RNA detection by PCR. Acute hepatitis E does not require treatment, however, if liver failure occurs then liver transplantation is an option[51]. Chronic hepatitis E can be treated with Ribavirin for 12 wk[52]. In pregnant women, HEV infection can lead to fulminant hepatic failure, which has a mortality rate of up to 30%[46]. Other complications include acute liver failure, chronic HEV infection, and neurological complications like Guillain-Barre syndrome, myelitis, and neuropathy to name a few[53]. Vaccines are not yet commercially available for prevention except in China[54].

BLOODY DIARRHEA FROM VIRAL GASTROENTERITIS

Cytomegalovirus

Cytomegalovirus (CMV) is a double-stranded DNA virus and a member of the Herpesviridae family with a prevalence ranging between 40%-100% in the adult population[55]. Latent phase reactivation occurs in immunocompromised individuals, including transplant recipients, patients on immunosuppressive agents, and those with inflammatory bowel disease (IBD) treated with steroids[56]. CMV is transmitted by contact with infectious body fluids like saliva, urine, respiratory droplets, sexual contact, blood transfusion, and solid organ transplants. Symptomology of CMV colitis could range from bloody diarrhea, abdominal pain, fever, weight loss, and lymphadenopathy to toxic megacolon. Few studies show that the severity of CMV is related to age and could cause Toxic megacolon and pan peritonitis in the elderly[57]. Although histology of tissue analysis is considered the gold standard for diagnosis, RT-PCR has the highest sensitivity and detection rate for infection. The most used antivirals are intravenous ganciclovir and valganciclovir. Foscarnet and cidofovir are used in ganciclovir-resistant cases. Some studies showed that although CMV is reactivated in IBD patients, it spontaneously disappears even without antiviral treatment[58,59]. Complications associated with CMV colitis may include ischemic colitis, perforation of the large bowel, toxic megacolon, and formation of pseudomembranous. Currently, there are no vaccines available for CMV. As per European Crohn's and Colitis Organization guidelines, if severe systemic CMV is detected, immunomodulators should be discontinued and screening for CMV is not routinely performed before starting immunomodulators in IBD[60].

Herpes simplex virus

Herpes simplex virus (HSV) is a double-stranded DNA virus belonging to the Human Herpesviridae family. HSV proctitis is the second most common sexually transmitted cause of infectious proctitis in homosexual males and could be caused by HSV-1 or HSV-2, but 70% of cases are due to HSV-2[61,62]. Prevalence of HSV-1 and HSV-2 have decreased over time linearly from 59.4 % & 18.0% in 1999-2000 to 48.1% & 12.1% in 2015-2016[63]. HSV is transmitted by intimate person-to-person contacts like men who have sex with men (MSM), unprotected receptive anal, and oral sex. Clinical symptoms of HSV proctitis include rectal bleeding, tenesmus, anorectal pain, and mucous discharge. The absence of external HSV lesions should not diminish suspicion of HSV infection as only 32% of men with HSV proctitis have external anal ulcerations[64,65]. Due to the high seropositivity for HSV worldwide, serological analysis plays a minor role in the diagnosis. PCR has been used to accurately diagnose and quantify the HSV DNA from clinical biopsy specimens[66]. Immunofluorescence staining of colonic specimens with HSV-type specific monoclonal antibodies against glycoproteins is highly specific to confirm the diagnosis. CDC recommends antiviral treatment with acyclovir, valacyclovir, or famciclovir in acute proctitis if the HSV infection is suspected or confirmed. Complications of HSV proctitis can result in symptoms such as constipation, severe anorectal pain, difficulty urinating, sacral paresthesia's, and diffuse ulcerations of the distal rectal mucosa. Currently, there are no vaccines approved for the prevention of HSV. Infectious proctitis must be considered before starting immunosuppressant therapy for presumed IBD, as the immunosuppressive medications may result in a lack of improvement or symptomatic worsening of infectious proctitis. HSV-induced anogenital ulcers will lead to a 1.5 to 7.0-fold increase in human immunodeficiency virus (HIV) transmission due to associated mucosal barrier breach, hence HIV screening is important. Individuals with acute proctitis along with HIV and/or painful perianal ulcers should receive presumptive treatment for anogenital HSV[67].

VIRAL GASTROINTESTINAL PATHOGENS ASSOCIATED WITH DIARRHEA AND OTHER GASTROINTESTINAL MANIFESTATIONS

Hepatitis A virus

Hepatitis A virus (HAV) is an RNA virus and a member of the Picornaviridae family. According to a report published in 2017, the incidence of acute hepatitis A was 170 million cases globally[68]. It is commonly transmitted through the fecal-oral route *via* contaminated food and water consumption. Transmission through sexual contact, person-to-person contact, and illicit drug use also exist in the literature[69]. Case fatality was higher in males, older than 50 years, and coexisting chronic liver disease raised the risk of developing fulminant hepatitis after an HAV infection[69]. From prior literature, > 70% of children under six years of age do not develop symptoms whereas > 70% of adults manifest symptoms[70]. Symptoms include fever, malaise, nausea, vomiting, abdominal discomfort, and jaundice. Physical examination findings include hepatomegaly and jaundice[70]. Hepatitis A generally follows a benign course, however chronic relapsing hepatitis for as long as 1 year is a possibility. Diagnosis is through serology by measuring the IgM antibody. IgG detection is useful when the question of immune status arises. Owing to its self-limited nature, this infection does not require treatment. According to the CDC, Hepatitis A vaccination is recommended for all infants. It is also recommended for those at substantial risk of exposure to hepatitis A infection, those at risk of

progressing to fulminant hepatitis, those experiencing homelessness, and HIV-infected persons.

Human immunodeficiency virus

Human immunodeficiency virus (HIV) is an RNA virus, belonging to the family Retroviridae. According to recent statistics, around 1.5 million individuals acquired HIV in 2021[71]. High-risk groups include gay and bisexual populations of all races and ethnicities, African Americans, injection drug users, and transgender populations[72]. It is transmitted *via* body fluids through sexual contact, needle sharing, breast milk, and perinatal transmission. In addition to the wide range of clinical manifestations, it is interesting to note how this virus affects the GI system. A specific term, "HIV enteropathy" has been coined to define the GI manifestations caused by this virus[73]. It causes alteration of epithelial ionic balances and enterocyte apoptosis resulting in inflammation, change in permeability, and malabsorption[73]. Histologically, villous atrophy, crypt hyperplasia, and epithelial hyperproliferation ensue. All of this culminates in causing diarrhea secondary to HIV enteropathy. HIV also leads to other GI effects by the virtue of its immunodeficiency, thus paving the way for opportunistic infections. Antiretroviral therapy (ART), especially protease inhibitors itself, can also cause diarrhea in HIV[74]. GI complications range from Esophageal disorders, gastric illnesses to colitis, enteritis, and anorectal disease. Most of these are caused by secondary/opportunistic bacterial, fungal, and viral infections and HIV-induced neoplasia of the GI tract. Also, the GI tract is a favorable site for HIV replication and GI CD4 destruction[75]. Pancreatic and hepatobiliary complications include pancreatitis, exocrine pancreatic insufficiency, hepatitis, and non-alcoholic fatty liver disease[76]. Diagnosis is fourth generation antigen-antibody assay followed by HIV 1/2 differentiation assay. Stool samples for ova and parasite examination should be done to identify the causative pathogen given the high chance of opportunistic infections like Cryptosporidium, Isospora, Giardia, *etc*[74]. If a cause cannot be identified yet, endoscopy with biopsy is an option[74]. Highly ART (HAART) causes the reconstitution of peripheral circulating plasma CD4 cells, but studies have found that it is not successful in the replenishment of GI CD4 cells[77].

Hepatitis B and D virus

Hepatitis B virus (HBV) is a partially double-stranded DNA virus and belongs to the family of Hepadnaviridae. According to the CDC statistics, globally, 296 million people are infected with Hepatitis B. High-risk groups include veterans, healthcare professionals, MSM, injection drug users, persons with HIV, hepatitis C virus (HCV) co-infection[78]. hepatitis B can be transmitted perinatally, through sexual contact, percutaneous or person-to-person contact with infected body fluids[79]. The incubation period ranges from 1 mo to 4 mo. The acute phase of hepatitis B infection presents as a serum-sickness-like illness characterized by fever, rash, and arthralgia followed by jaundice, nausea and vomiting, and other constitutional symptoms[79]. It causes elevation of alanine aminotransferase (ALT) more than aspartate aminotransferase (AST) and bilirubin. Diagnosis is by serum viral biomarkers[79]. It is known that Hepatitis B is implicated in the causation of Hepatitis and its plethora of clinical manifestations including hepatocellular carcinoma (HCC). HCC contributes to 80% of global liver cancers in 2018[80]. Pathogenesis of HCC in hepatitis B is: (1) Direct-due to the oncogenic viral protein activating proto-oncogenes, transcriptional pathways (MAP kinase and JAK/STAT), and inhibition of tumor suppressor genes (p53); (2) chronic inflammation, cirrhosis, and regeneration[81,82]. It is also worth noting the other GI disorders caused by this virus. According to a cumulative analysis performed by Yang *et al*[83] involving 7027546 individuals across 13 studies-10 studies reported data on hepatitis and gastric cancer, and it was found that the risk of gastric cancer was 26 times higher in the hepatitis B population[83] (pooled HR, 1.26; 95%CI, 1.08-1.47; P = 0.003). This can be attributed to chronic inflammation, tumorigenesis, and alteration of the tumor suppression process due to oncogenic viral proteins [84,85]. Another study observed that Hepatitis B is associated with gut microbiota disturbance, especially in the cirrhosis population[86]. Acute HBV is self-limited and does not require treatment. Special cases like acute liver failure, complicated course (prolonged PT and marked elevation of jaundice are treated[87]. Treatment of chronic hepatitis B depends on factors like the presence or absence of cirrhosis, ALT level, and HBV DNA level. Therapy includes drugs like Tenofovir, Entecavir, and Interferon[87]. Complications of acute hepatitis B are mainly due to immune complex reactions occurring in various parts of the body manifesting as glomerulonephritis, polyarteritis nodosa, cryoglobulinemia[88], *etc.* Sequelae of chronic hepatitis B are well known including cirrhosis and HCC. Hepatitis B prevention is achieved with recombinant vaccines that require either three or two doses. Combined vaccination, along with diphtheria, pertussis, tetanus, and hepatitis A is also in use currently in the United States.

Hepatitis D virus (HDV) is a defective RNA virus requiring the presence of the Hepatitis B virus for its replication and assembly of virions. It belongs to the Kolmioviridae family. The global disease burden of hepatitis D/hepatitis B co-infection is 62-72 million[89]. HDV requires HBV to replicate and therefore the HBV population is the target group for this infection. The mode of transmission is the same as HBV infection. Hepatitis D infection can occur as a co-infection with hepatitis B occurring simultaneously which usually leads to spontaneous resolution[90]. On the other hand, superinfection in already infected HBV persons usually leads to conversion to chronic hepatitis D infection which is considered a severe form of chronic hepatitis. Symptoms of acute hepatitis D are indistinguishable from

other forms of viral hepatitis. However, superinfection with HBV can lead to fulminant liver failure[91]. In addition, the risk of progression to cirrhosis is 3 times higher in superinfection than in infection with HBV alone[92]. Diagnosis is through the detection of IgM and IgG Anti HDV antibodies and confirmed by testing for HDV RNA[93]. The current treatment strategy utilizes Pegylated interferon for at least 1 year[94]. However, several emerging therapies like myrcludex B and Lonafarnib are gaining popularity in the treatment of hepatitis D.

HCV

HCV is a hepatotropic, single-stranded RNA virus belonging to the family of Flaviviridae. The prevalence of Hepatitis C is 0.5%-2.5% with the highest being in the eastern Mediterranean region and Europe[95]. It was recorded that 399000 individuals died in 2016 due to complications from chronic hepatitis C[95]. Injection drug users, HIV, healthcare professionals, prior recipients of blood products (before 1992), and hemodialysis patients are at risk of acquiring HCV[96]. Modes of transmission include injection drug use, blood transfusion, sexual contact, and perinatal transmission[97]. Acute hepatitis C infection is usually asymptomatic and can consist of symptoms like fever, abdominal pain, and jaundice[97]. Only 15%-20% resolve completely whereas the remaining percentage of infected patients go on to have chronic hepatitis C[97]. Chronic hepatitis C is characterized by the presence of HCV RNA for more than 6 mo. Sequelae of chronic hepatitis C are liver fibrosis, Cirrhosis, and Hepatocellular Carcinoma. A decision analytical model done by Chen *et al*[98] predicted that the cumulative incidence of HCC among HCV-infected persons would be 583000 cases between 2012 to 2040. Several extrahepatic manifestations affect the quality of life in chronic hepatitis C like mixed cryoglobulinemia, glomerulonephritis, skin disease (porphyria cutanea tarda and lichen planus), thyroid disease (Hashimoto's disease and Grave's disease) to name a few[99]. Diagnosis is made by serology either by the presence of HCV RNA or anti-HCV antibody[100]. Guidelines suggest treatment with direct-acting antiviral agents (DAA) after acute infection to prevent progression to chronic infection and due to the high likelihood of loss to follow-up to test for spontaneous clearance of the virus[101]. Chronic hepatitis C is treated with DAA regimens based on the genotype and also the presence of advanced liver disease. Some of the pan-genotype regimens include Sofosbuvir and velpatasvir for 12 wk and glecaprevir and pibrentasvir for 8 wk[102]. Vaccination for hepatitis C is under development and prevention of hepatitis C solely depends upon the prevention of high-risk behavior like injection drug use and adopting safe sexual practices.

Varicella zoster virus

Varicella-zoster virus (VZV) is a double-stranded enveloped DNA virus belonging to the α-herpesviruses subfamily. Adults, young children, and immunocompromised are at risk of developing the severe disease with primary varicella infection[103]. According to the CDC report, 4 million cases occurred annually in the United States during the pre-vaccine era. After the introduction of vaccines, incidence declined by around 97%[104]. Transmission is through droplets, aerosols, and direct contact with respiratory secretions or zoster lesions[105]. Reactivation of latent VZV from dorsal root ganglia leads to herpes zoster (shingles), which presents as localized cutaneous eruption associated with neuralgic pain. GI VZV lesions could present as multiple erosions occurring in the stomach, duodenum, and small and large intestines[106]. Skin findings often precede visceral involvement. In a study, 42 of 131 patients with herpes zoster [not specified as bone marrow transplant (BMT) or malignancy patients] progressed to visceral involvement[107]. The mortality rate from GI VZV ranges from 28.6% to 50.0% in BMT recipients despite antiviral therapy[108]. GI manifestations of herpes zoster are extremely rare. Constipation secondary to motility issues (visceral neuropathy) has been reported in some case reports [106,109]. Skin findings and concomitant GI symptoms should raise suspicion in predisposed patients. Elevated liver enzymes and abnormal imaging findings also aid in diagnosis. Diagnosis can be confirmed through immunohistochemical staining of biopsy specimens VZV. Although shingles is a clinical diagnosis, PCR (highly sensitive) and immunoassays are used for the diagnosis, especially in atypical presentations[110]. Treatment options include IV Acyclovir, valacyclovir, famciclovir, and brivudine. If clinical resistance to Acyclovir is suspected, foscarnet could be used. Complications of primary varicella infection are bacterial infections of the skin and soft tissues, pneumonia, and cerebellar ataxia[111]. Reactivation of VZV (Herpes zoster) is complicated by chronic pain, encephalitis, post-herpetic neuralgia, myelopathy, *etc*[112]. Varivax, a two-dose vaccine, is licensed for children above 12 mo of age to protect against chicken pox. Shingrix is an FDA-approved recombinant vaccine to reduce the risk of shingles in people aged 50 years or more.

Epstein-Barr virus

Epstein-Barr virus (EBV) is a double-stranded DNA virus belonging to the Herpesviridae family. It is estimated that more than 90% of the worldwide population has been infected with EBV[113]. It is associated with a wide range of clinical manifestations, the most common one being infectious mononucleosis (IM), prevalent among teens and adults[114]. It is spread through saliva and presents with fever, malaise, sore throat, and lymphadenopathy[114]. Chronic active EBV (CAEBV) is a condition where IM symptoms persist for more than 3 mo and is commonly seen in Asia[115]. EBV has also been

implicated in the pathogenesis of multiple sclerosis and rheumatoid arthritis[115]. Also, chronic EBV has been linked with gastritis, enteritis, and esophageal disorders, oral hairy cell leukoplakia[116-119]. A separate clinical subset of diseases EBV has been strongly associated with is lymphoproliferative cancers like Burkitt's Lymphoma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, and post-transplant lymphoproliferative disorder. Besides lymphoproliferative cancers, EBV has been implicated in causing other cancers like gastric cancer, nasopharyngeal cancers, and breast cancer. Some key features of EBV-associated gastric cancers are they can occur in the gastric fundus, cardia, and body, unlike non-EBV-associated gastric cancers which happen in the antrum. EBV-associated cancer starts as a lesser fibrotic nodular ulcer compared to the non-EBV type[119]. Microscopically, EBV-associated gastric cancer shows a monoclonal proliferation infected latently with EBV, suggesting the role of the virus in the early stages of tumorigenesis[119]. IBD patients on immunosuppressants like thiopurines have a high incidence of EBV and some studies also showed that patients taking these medications also have a higher incidence of lymphoproliferative disorders than those who are not on treatment for IBD [120,121]. EBV can be diagnosed by the detection of antibodies against various antigens like viral capsid antigens, EBNA; enzyme immunoassays, Western blot, PCR, heterophile antibody agglutination, *etc* [122]. There is no targeted therapy for EBV. Symptomatic treatment has been a cornerstone for the treatment of EBV. Several anti-viral drugs including acyclovir, and cidofovir have been tried with good invitro activity and with no clinical benefit[123].

Human herpesvirus 8

Human herpesvirus 8 (HHV 8) is a double-stranded DNA virus belonging to the Human Gamma herpesvirus family. It is also commonly known as Kaposi Sarcoma-associated herpesvirus due to the disease it causes, Kaposi's Sarcoma (KS). It is common in HIV, MSM, Mediterranean, Ashkenazi jews, and sub-Saharan African populations[124,125]. According to seroprevalence, Uganda has the highest seroprevalence worldwide where KS is endemic. No more than 6% seroprevalence has been reported in the United States[126]. KS is a low-grade vascular tumor that involves mucocutaneous sites and visceral locations, predominantly the respiratory and GI systems[125]. GI Kaposi sarcoma is usually asymptomatic but on progression, can present as abdominal pain, nausea, vomiting, and GI bleeding. Diagnosis is through endoscopy and biopsy[127]. It is most common in the stomach and small intestine and endoscopically appears as a maculopapular lesion to a nodular or polypoid mass which can sometimes bleed on touch[127]. In HIV Kaposi, HAART is the mainstay of treatment with or without chemotherapy. In classic Kaposi's sarcoma, treatment options include local therapy with radiation or intralesional chemotherapy; systemic chemotherapy with liposomal doxorubicin or paclitaxel[124]. Besides KS, HHV 8 is implicated in the causation of lymphoproliferative disorders like primary effusion lymphoma and multicentric Castleman's disease[128].

Human papillomavirus

Human papillomavirus (HPV) is a double-stranded DNA virus belonging to the Papillomaviridae family. It is estimated that around 13 million persons acquired HPV infection in 2018 in the United States and over 77 million had a prevalent infection during the same year[129]. It is primarily a sexually transmitted disease (vaginal, anal, and oro-genital) but can also be transmitted through skin-to-skin contact and vertical transmission[130]. High-risk sexual behaviors, multiple sexual partners, and previous history of STDs increase the risk of HPV acquisition. Clinical manifestations of HPV include cutaneous warts, anogenital warts, and respiratory papilloma's caused by HPV 6,11 *etc* genotypes along with cancer precursor lesions (intraepithelial neoplasia's) and cancers caused by HPV 16,18 genotypes. HPV is an oncogenic virus and has been associated with a multitude of cancers including GI cancers like esophageal cancer, stomach cancer, colorectal cancer, anal cancer, and liver cancer[131]. The other cancers to which it has been linked are cervical, penile, vulvar, vaginal, and oropharyngeal cancers [132]. HPV causes cervical cancer near the transformation zone where there is a transitional/transformational zone (squamocolumnar junction). In the same fashion, HPV also causes cancerous lesions in the anal region because of the presence of a squamocolumnar junction which is a site of multipotent embryonic cells. However, the incidence rates of cervical cancer and anal cancer are much different (17:1). Colposcopy, Biopsy, HPV DNA detection, PCR, and pap smear are some of the methods by which HPV can be diagnosed[133]. Treatment depends on the type of disease. Warts can be treated with topical medications like salicylate, imiquimod, trichloroacetic acid, cryosurgery, and electrocautery. Precancerous and cancerous lesions require detailed workup and surgical excision of lesions[134]. Current FDA-approved vaccines are Bivalent (for types 16 and 18), quadrivalent (for types 6, 11, 16, and 18), 9 valent (for types 6, 11, 16, 18, 31, 33, 45, 52, and 58) protect against genital warts, precancerous lesions of vulva, cervix and anus, oropharyngeal cancers and are approved for males and females aged 9-45.

CONCLUSION

After conducting a comprehensive review of the literature on viruses and the GI tract, these pathogens

play a significant role in both acute and chronic GI diseases. While many viruses can cause mild symptoms, such as diarrhea and vomiting, some can lead to severe and even life-threatening conditions. The importance of early detection and appropriate management of viral gastroenteritis cannot be overstated.

Several studies have highlighted the need for better prevention and control measures, including improved hygiene practices and the development of effective vaccines. It is crucial to continue researching the relationship between viruses and the GI tract to better understand how these pathogens operate and to develop more targeted treatments.

Overall, this review provides clinicians with a differential diagnosis when they encounter patients with GI manifestations. It emphasizes the importance of recognizing the different presentations of viruses on the GI tract and understanding the prevention, diagnosis, and treatment of these illnesses.

FOOTNOTES

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REVIEW

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic caused by the novel beta coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) crippled the whole world and has resulted in large number of morbidity and mortality. The origin of the SARS-CoV-2 is still disputed. The risk of infection with SARS-CoV-2 is dependent on several risk factors as observed in many studies. The severity of the disease depends on many factors including the viral strain, host immunogenetics, environmental factors, host genetics, host nutritional status and presence of comorbidities like hypertension, diabetes, Chronic Obstructive Pulmonary Disease, cardiovascular disease, renal impairment. Diabetes is a metabolic disorder mainly characterized by hyperglycemia. Diabetic individuals are intrinsically prone to infections. SARS-CoV-2 infection in patients with diabetes result in β-cell damage and cytokine storm. Damage to the cells impairs the equilibrium of glucose, leading to hyperglycemia. The ensuing cytokine storm causes insulin resistance, especially in the muscles and liver, which also causes a hyperglycemic state. All of these increase the severity of COVID-19. Genetics also play pivotal role in disease pathogenesis. This review article focuses from the probable sources of coronaviruses and SARS-CoV-2 to its impacts on individuals with diabetes and host genetics in pre- and post-pandemic era.

Key Words: Coronavirus; SARS-CoV-2; Diabetes; MERS; SARS; Single nucleotide polymorphism

Core Tip: The coronavirus disease 2019 (COVID-19) pandemic caused by the novel beta coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) crippled the whole world and has resulted in large number of morbidity and mortality. The origin of the SARS-CoV-2 is still disputed. The risk of infection with SARS-CoV-2 is dependent on several risk factors as observed in many studies. The severity of the disease depends on many factors including the viral strain, host immunogenetics, environmental factors, host genetics, host nutritional status and presence of comorbidities like hypertension, diabetes, Chronic Obstructive Pulmonary Disease, cardiovascular disease, renal impairment. Diabetes is a metabolic disorder mainly characterized by hyperglycemia. Diabetic individuals are intrinsically prone to infections. SARS-CoV-2 infection in patients with diabetes result in β-cell damage and cytokine storm. Damage to the cells impairs the equilibrium of glucose, leading to hyperglycemia. The ensuing cytokine storm causes insulin resistance, especially in the muscles and liver, which also causes a hyperglycemic state. All of these increase the severity of COVID-19. Genetics also play pivotal role in disease pathogenesis. This review article focuses from the probable sources of coronaviruses and SARS-CoV-2 to its impacts on individuals with diabetes and host genetics in pre- and post-pandemic era.

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DIABETES AND PRE PANDEMIC ERA

The term “diabetes” first appeared in a medical text book around 1425 and was first suggested by a Greek scientist, Araetus of Cappodocia (81-133AD)[1]. Thomas Willis added the word "mellitus" (meaning "sweet taste of urine") to the word diabetes in 1675. Diabetes was referred to as Madhumeha in ancient Indian medicine[1,2]. In 1776, a British physician named Matthew Dobson identified excess sugar in urine and blood as the cause of their sweet taste, and glucose was identified as the responsible sugar[1,2]. The experimental creation of diabetes in 1889 in experimentally pancreatectomized dogs eventually confirmed that the pancreas is the causative organ of the disease followed by the isolation of insulin in 1922, which finally established that diabetes is an endocrine disorder due to deficiency of insulin[2-4].

Diabetes mellitus has been recognized as one of the major health concerns and is considered a global epidemic affecting 382 million people worldwide. According to the prediction of the World Health Organization, diabetes will be the seventh leading cause of death by 2030[5]. Diabetes is a metabolic disorder caused by hyperglycemia and characterized by polyuria, polyphagia, polydipsia, and weight loss. Diabetes mellitus causes macrovascular and microvascular complications. Macrovascular complications include coronary heart disease, cardiomyopathy, arrhythmias and sudden death, cerebrovascular disease and peripheral artery disease. Myocardial infarction, stroke, and peripheral artery disease are more prevalent in individuals with diabetes mellitus. Microvascular complications include retinopathy, nephropathy, and neuropathy. These complications are the major contributing factors to the increasing mortality rate in patients with diabetes and an estimated 4 million individuals are dying each year due to diabetes related complications.

American Diabetes Association classified diabetes into four categories: Type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and diabetes induced by or related to particular specific illnesses, pathologies, and/or syndromes are the four primary forms or categories of diabetes, respectively. T1DM, often referred to as type 1A diabetes mellitus (DM), insulin-dependent diabetes mellitus (IDDM), or juvenile-onset diabetes, accounts for around 5%-10% of all diabetes cases. It is an autoimmune condition marked by the T-cell-mediated apoptosis of pancreatic beta-cells, which causes an insulin shortage and ultimately leads to hyperglycemia. T2DM, also known as non-insulin-dependent diabetes mellitus accounts for 90%-95% of all cases of diabetes. This kind of diabetes is characterized by two main insulin-related abnormalities: Insulin resistance and β-cell dysfunction. Any degree of glucose intolerance or diabetes, typically discovered in the second or third trimester of pregnancy, is referred to as GDM. Other than T1DM, T2DM, and GDM, other types of diabetes although in smaller percentages relative to the overall diabetic incidence scenario, has been found to be linked to a number of other illnesses, including several pathologies[6].

Endocrinopathies, exocrine pancreatic diseases, diabetes caused by monogenic deficiencies in β-cell function, and diabetes caused by genetic abnormalities in insulin action are the most common types of diabetes. Type 1 diabetes is a chronic autoimmune disease that has both hereditary and environmental causes. In those who have a genetic predisposition to developing autoimmunity, viruses may affect the susceptibility of the infectious disease and trigger it. The most frequently studied viruses in relation to type 1 diabetes are enteroviruses. Pancreatic islet autoimmunity and the onset of type 1 diabetes clinical

symptoms have also been linked to respiratory viral infections. In animal models, the influenza virus can infect human pancreatic cell lines and result in pancreatitis and hyperglycemia. In case-report studies, influenza A virus infection has also been linked to acute pancreatitis and type 1 diabetes. There may be a connection between pandemic influenza and type 1 diabetes, according to two small retrospective investigations. These revealed a parallel rise in type 1 diabetes among kids throughout the pandemic influenza timeframe. It normally takes several years from the induction of islet autoimmunity to the clinical presentation of type 1 diabetes, hence studies with longer follow-up following influenza are necessary to clarify how pandemic influenza contributes to the development of diabetes.

Diabetes patients are up to six times more likely than healthy people to require hospitalization for influenza virus or flu-like infections, and they are also more likely to experience infection related complications. Diabetic individuals, especially those with uncontrolled diabetes, are more prone to fungal infections[7]. Community-based pneumonia was more frequent in those diagnosed with diabetes mellitus[8]. Increased mortality risk from cardiovascular disease, chronic lower respiratory illnesses, influenza and pneumonia, and kidney disease is linked to baseline diagnosed diabetes[9]. A regulated immune response that leads to more severe and prolonged lung pathology is most likely the cause of the higher disease severity seen in mice with REMS and co morbid type 2 diabetes[10]. According to a systematic analysis of 637 Middle East respiratory syndrome (MERS)-CoV cases, 50% of the patients had both diabetes and hypertension. Obesity was prevalent in 16% of cases, while cardiac problems were present in 30%[11].

SARS CORONAVIRUS AND THE PRE- PANDEMIC ERA

There are similarities between many epidemics and industrial revolutions that have occurred throughout history. No other virus, bacteria, or germ has ever produced as many pandemics and as many deaths on Earth in as little time as plagues and flu. Plague is a disease caused by a bacterium called Yersinia pestis, which is mainly transmitted by rats and one type of fly. History shows that the first plague occurred between 165 and 180 AD (also known as the Antonine Plague that brought the Roman Empire to the brink of destruction) and caused the deaths of 500000 people. Plague outbreaks followed in 541-542 AD, 1347-1351 AD, 1665 AD and 1629-1631 AD. At this time, the word “industrial” revolution did not appear in the world. But history tells us that the plague that occurred in 1885 between the first and second industrial revolutions caused the death of more than a million people in China and India alone. During the Second Industrial Revolution in 1889-1890 and 1918-1919, respectively, the Russian flu and the Spanish flu struck, which took the lives of about 60 million people in the world. During the Third Industrial Revolution, Asian flu (1957-1958), Hong Kong flu (1968-1970), and AIDS (still ongoing since 1981) killed over 40 million people. Among these, flu-like diseases are caused by different types of influenza viruses that belong to the same genus but differ in the structure of their genetic material. The genetic material of the influenza, swine flu viruses is formed by ribonucleic acid, or RNA.

Different types of wildlife frequently carry diseases or disease agents that are harmful, and in some cases fatal, to humans. Recent studies have shown that 60% of the infectious diseases that are currently occurring are zoonotic, that is, the bacteria responsible for these diseases spread from animals to humans. Although these bacteria are common in animals, they can also infect humans. Also 70% of infectious diseases originate from wildlife[12].

The study of Corman *et al*[13] revealed that bats are the natural host of the coronavirus. Even the age of corona virus found in bats is much longer than that of coronavirus found in other animals. This suggests that the virus has overcome the barriers that normally exist to spread from one species to another and has now adopted humans as its home[14]. Bats are also thought to be the source of two other strains HCoV-NL63 and HCoV-HKU1[15]. Every organism has a natural reservoir. The more we disturb nature, the more likely it is to deplete natural resources. As a result, the microbes are in crisis of existence and to adapt to the changing environment, they cause rapid change or mutation. The significant natural reservoirs of the coronavirus are bats, camels and palm civets. Because of its crown like shape, it is called the "coronavirus". Before making devastating impacts, the human race has always received signs of warnings for larger damage. For example, SARS in 2002-2003, swine flu (2009-2010) in 2009-2010 and MERS, MERS from 2015 to the present.

Coronavirus can be generally divided into four genera - alphacoronavirus, beta coronavirus, gamma and delta. Among these, the beta group is further divided into four groups – A, B, C and D. Human strains of coronaviruses include HCoV 229E (HCoV 229E) and HCoV NL63 of the alpha genus, and HCoV OC43 and HKU1 of the beta genus. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are also members of the beta genus. A study in 2003 found that the genome of SARS-CoV-1 in humans was 99.8% identical to that of SARS-CoV in palm civets. Later, the genome of human SARS-CoV-1 was found to be approximately 87%-92% similar to that of SARS-CoV recovered from Chinese bats. From this, it is assumed that the natural source of this virus is the Chinese bat. The virus is transmitted to humans using the palm civet as an intermediate vector.

Since the outbreak of MERS-CoV, scientists have begun more research on bat-borne coronaviruses. In line with this, a study in Saudi Arabia found that the genome sequence of human MERS-CoV is nearly 100% identical to a virus found in bats called Taphozous perforates. In addition, some preliminary studies have found viruses similar to this virus in several species of bats. The scientists then sequenced the replication gene of MERS-CoV and found that the virus resembled the HKU4 coronavirus of Tylonycteris bats. However, a 2013 study found that MERS-CoV is actually a member of the beta-coronavirus family and that camels are intermediate carriers of the virus.

NOVEL CORONAVIRUS OR SARS-COV-2

The Coronaviruses are enveloped virus. It is a positive sense, single-stranded RNA composed of about 29000 nucleotides. 229E (HCoV-229E) virus is a close relative of the currently prevalent CoV virus in humans due to several conformations. Their habitat was also known to be in the hipposideridae family of African bats. It is hypothesized that they may have used dromedaries as intermediate habitats between bats and humans[16].

The HCoV virus has also been found to be related to viruses in other animals. For example, HCV-OC43 has been shown to be highly homologous to mouse hepatitis virus and bovine respiratory coronavirus[13]. The habitats of these two viruses are rats and cows respectively. An enzyme called hemagglutinin esterase is found in all of them.

Pangolin is also another natural reservoir of coronavirus. Analysis of the Genome Sequence of the currently alarming virus has shown that some parts of the RNA of Novel Coronavirus 2019 or COVID-19 came from bats and some parts came from Pangolin, and this recombination process took place in a third animal. We are destroying these animals for food and medicine.

The genome of SARS-CoV-2 is similar to that of other beta coronaviruses. Most of the proteins that SARS-CoV-2 encodes are similar in length to those that SARS-CoV encodes[17]. From 5′ to 3′, the genomic structure contains leader sequence, ORF1/ab, Spike (S), ORF3a, Envelope (E), Membrane (M), ORF6a, ORF7a, ORF7b, ORF8, Nucleocapsid (N), ORF10 and lacks the hemagglutinin-esterase gene which is found in some β-CoVs. ORF1a/b is made up of 16 non-structural proteins (nsp1–16) and accounts for almost two-thirds of SARS-CoV-2 RNA. The replicase gene encodes a large polyprotein (pp1ab), which is involved in transcription and virus replication. It is fragmented by proteolysis into 16 non-structural proteins. The remaining one-third of the genome, at the 3′-terminus, contains ORFs that code for structural and auxiliary proteins of SARS-CoV-2[18]. With the exception of the S protein, which is different, the structural proteins (E, M, and N) of SARS-CoV-2 share around 90% of their amino acid composition[19,20]. The majority of SARS-CoV-2 non-structural proteins share more than 85% of their amino acid sequences with SARS-CoV[17].

ZOONOSIS OF CORONAVIRUSES

Endemic coronaviruses have animal origins: HCoV-NL63 and HCoV-229E are speculated to have originate in bats whereas; HCoV-OC43 and HKU1 are likely to have originated in rodents[21,22]. Bats are also considered as the natural reservoir of SARS-CoV, MERS-CoV and SARS-CoV-2[16,20,23]. Masked palm civet and dromedary camel are the intermediate hosts of SARS-CoV and MERS-CoV, respectively[23]. However, the intermediate host of SARS-CoV-2 is not clear till date. Pangolin, snakes, minks, turtles, ferret and companion animals are possible candidates for the intermediate hosts of SARS-CoV-2[24] (Figure 1).

Cohorts from The United States, Germany, Netherlands, Singapore and the United Kingdom that 20% to 50% individuals not exposed to SARS-CoV-2 previously had T cell activity against peptides that match the sequences of the SARS-CoV-2[25-29]. The T cell activity was mostly due to CD4+ T cells. This might be due to the presence of preexisting memory against endemic coronaviruses which share sequence homology with SARS-CoV-2.

COMORBIDITIES AND COVID-19

Despite the fact that risks are generally higher in men and rise with age, there is now compelling evidence that those who have a number of medical conditions—including chronic kidney disease, diabetes, lung and liver disease, cardiovascular disease, obesity, immunodeficiency, certain disabilities, and mental health conditions—are also at higher risk[30].

People with complex diabetes, obesity, and psychological disorders are at the highest risk (relative risk of about 1.3 compared to those without these illnesses), whereas those with cardiovascular disease are at a lower risk (relative risk roughly 1.1)[31]. The evidence is inconclusive for asthma, hypertension, and viral hepatitis, while it is scarcer for other illnesses like obesity, sickle cell disease, and substance

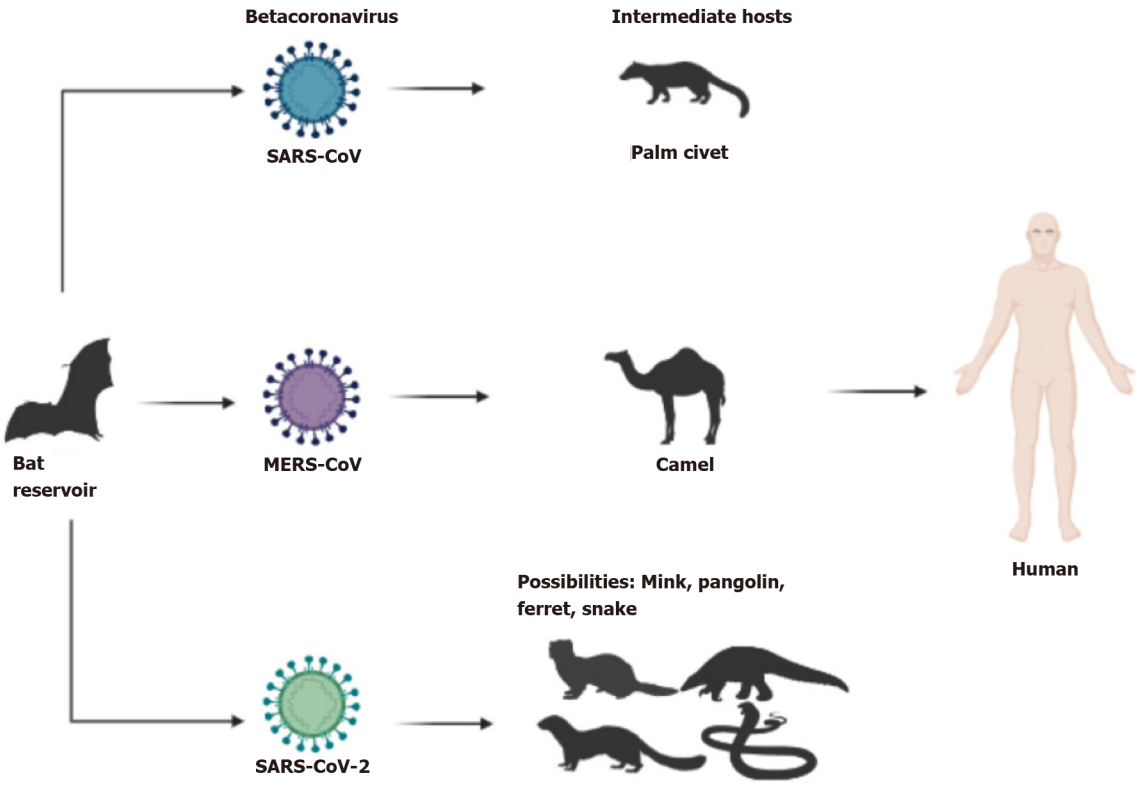

Figure 1 Possible intermediate hosts of severe acute respiratory syndrome coronavirus 2. Bat is considered as the natural reservoir of the pandemic-causing beta coronaviruses: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV. The intermediate hosts of SARS-CoV and MERS-CoV are palm civets and dromedary camels, respectively. Although mink, pangolin, ferret and snake have been considered as the intermediate hosts of SARS-CoV-2, however the issue is still unresolved. The figure was created using BioRender (https://biorender.com/).

use disorders. Inflammatory and hormonal routes, as well as social factors like being in a crowded or institutionalized environment, are proposed as possible disease susceptibility and severity processes, albeit the precise mechanisms remain unknown[32,33].

Based on the frequency of chronic diseases, it is projected that one in five people globally are at an increased risk of negative COVID-19 outcomes. Along with age, the risk rises when there are more underlying conditions[34]. Ages 50 to 64 have a fourfold rise in mortality risk compared to those under 40, and 85 and older see a more than tenfold increase[35]. Similar to this, those with one comorbidity or more than 10 comorbidities had a 1.5- and 3.8-times higher risk of dying than those without any underlying diseases[31]. To assist clinical judgments, a number of risk score calculators have been developed using these data[36,37]. Previous research has shown that individuals with H7N9 infection have a 3.4-fold higher chance of having acute respiratory distress syndrome when any comorbidity is present. Similar to the influenza virus, the coronavirus causing SARS-CoV and the MERS-CoV, Covid-19 more easily predisposes susceptible patients to respiratory failure and mortality[38].

A report consisting of 72314 cases in China, case fatality rate was observed to be increase in individuals with preexisting comorbidities like cardiovascular disease (10.5%), diabetes (7.3%), chronic respiratory disease (6.3%), hypertension (6.0%) and cancer (5.6%)[39]. In a study, 399 instances (25.1%) out of the 1590 reported having at least one comorbidity. The prevalence of specific comorbidities included hepatitis B infections (28; 1.8%), chronic obstructive pulmonary disease (24; 1.5%), chronic kidney disease (21; 1.3%), malignancy (18; 1.1%), and immunodeficiency (3; 0.2%). Hypertension (269; 16.9%), other cardiovascular diseases (53.7%), cerebrovascular diseases (30; 1.9%), diabetes (130; 8.2%), and diabetes-related complications were also common. None of the cases had asthma diagnosed by a doctor. In severe instances *vs* non-severe cases, at least one comorbidity was more frequently observed (32.8% *vs* 10.3%). Patients with at least one comorbidity tended to be older (mean: 60.8 *vs* 44.8 years), more likely to experience shortness of breath (41.4% *vs* 17.8%), nausea, or vomiting (10.4% against 4.3%), and to present abnormally on chest X-rays (29.2% *vs* 15.1%)[38].

DIABETES AND COVID-19

The world has experienced the devastating impact of infectious organism novel coronavirus or SARS-CoV-2 since it's inception in December 2019. Physicians faced enormous challenges to battle against the COVID-19 related complications especially determining or selecting the way of managing the disease *i.e.*, which group of individuals are at higher risk of worst severity[40]. Epidemiological evidences supported that comorbidities have added extra burden to the miseries of pandemic. Among the comorbidities, diabetes took the lead. Further, individuals with diabetes had greater risk of sufferings from the complications caused by this virus. The ongoing COVID-19 pandemic has once again emphasized the importance of preventing and managing type 2 diabetes. Complications even worsen in individuals with both heart disease and diabetes or macrovascular complications due to chronic diabetes.

Diabetic individuals are more prone to both primary and secondary infections caused by bacteria, viruses, fungus and as disease progresses, severity of the disease intensifies compared to their nondiabetic counterparts[10,41]. Obesity and poor control of blood glucose has been found to be directly linked to the clinical outcomes of COVID-19 and poor prognosis followed by increased mortality[42-45]. Zhu *et al*[45] in a cohort study comprised of 7337 confirmed COVID-19 cases demonstrated that the occurrence of ARDS (16.9% *vs* 7.2%), acute heart injury (7.3% *vs* 3.0%), acute kidney injury (3.9% *vs* 0.8%), septic shock (3.8% *vs* 1.0%), and DIC (0.5% *vs* 0.2%) were in individuals with T2D compared to the non-diabetic group. SARS-CoV-2 infects multiorgan system and pancreas is no exception as this organ also expresses angiotensin converting enzyme 2[46]. Previous findings reported presence of angiotensin converting enzyme 2 (ACE2) receptor in the pancreatic beta cells for SARS-CoV-1 virus that acts as the viral entry point leading to the destruction of β-cells and insulin insufficiency causes hyperglycemia[47]. Studies reported morphological, translational and functional modification of pancreas followed by impaired insulin secretion as SARS-CoV-2 is able to successfully infect different cell types of both exocrine and endocrine system which include pancreas[48,49]. SARS-CoV-2 infected patients with poor control of blood sugar had high mortality rate compared to those with well controlled blood glucose. Further investigation revealed that even individuals suffering from COVID-19 disease with a glucose range of 3.9 to 10.0 mmol/L had a lower mortality rate than that of their counterparts with blood glucose levels above 10.0 mmol/L[44]. Moreover, COVID-19 patients with poorly controlled blood glucose had to extend their hospital stay[44]. Thus, better management of blood glucose results in improved outcome in patients with multiple organ damage and reduced the mortality rate in COVID-19 patients[45,50].

In an investigation of two major health-care datasets, US CDC researchers discovered that COVID-19 was associated with a higher risk of diabetes than pre-pandemic acute respiratory infections and that non-SARS-CoV-2 respiratory infections were not. In the post-acute phase of COVID-19, those under the age of 18 who had SARS-CoV-2 infection had a higher probability of being diagnosed with diabetes than non-infected controls. Despite this, the study was unable to differentiate between type 1 and type 2 diabetes[51].

A Scottish study of individuals under the age of 35 found an overall 20% rise in the incidence of type 1 diabetes during the pandemic and an elevated risk of the disease within the first 30 days following SARS-CoV-2 infection, but not afterward[52]. Another study of 428650 individuals with COVID-19 and 428650 matched controls revealed a net increase in the incidence of diabetes in the first four weeks following COVID-19. This increase persisted from five to twelve weeks but not from thirteen to fifty-two weeks. The participants in this study had a median age of 35[53].

CYTOKINE STORM, COVID-19 AND DIABETES OR DIABETES, COVID-19 AND INFLAMMATION

Several advances have been made in understanding the pathophysiology of type 2 diabetes. Inflammation plays an important role in the pathogenesis of type 2 diabetes as it mediates hypoxia and cell death of adipose tissue, activation of important factors in signal transduction *i.e.*, nuclear factor-κB (NF-κB) and JUN N-terminal kinase, interleukin-1β and recruitment of immune cells. Factors associated with innate immune response are found to be in the circulation, insulin-sensitive tissues and pancreatic islets in type 2 diabetes. Obesity, one of the major causes of developing insulin resistance followed by type 2 diabetes, leads to elevated levels of C-reactive proteins, haptoglobin, fibrinogen, plasminogen activator inhibitor and serum amyloid A and sialic acid, as well as cytokines and chemokines.

Exaggerated immune response is responsible for the most of the fatalities in case of coronavirus infection. Release of inflammatory cytokines is contributing to the severity of the disease. The inflammatory cytokine release is primary thought to be due to macrophages[54-56]. Infection by the highly pathogenic respiratory viruses such as SARS-CoV-1, Middle East respiratory syndrome (MERS)-CoV, influenza, and respiratory syncytial virus results in the release of substantial amount of cytokine and chemokine by provoking a prolonged inflammatory macrophage phenotype, allowing for direct viral infection of infiltrating cells. This causes massive cell death and damage of alveolar lung tissue,

increasing morbidity for the patient[57]. Coronaviruses also induce macrophage mediated cytokine storm in patients with type 2 diabetes[58]. Coronavirus infection causes decrease expression of histone methyltransferase, SETDB2 that results in decrease of the repressive trimethylation of histone 3 Lysine 9 (H3K9me3) at NF-κB binding sites on inflammatory gene promoters of inflammatory genes which in turn effectively increases inflammation[58].

Diabetes is linked to a proinflammatory condition, which may increase the chance of developing severe COVID-19and a higher chance of suffering a cytokine storm. As part of the low-grade chronic inflammation, the proinflammatory cytokines and hazardous metabolites that are present in a cytokine storm are already chronically increased in people with diabetes[59-61]. One of the most significant pathophysiological mechanisms that contribute to higher risk in diabetic patients is believed to involve the proinflammatory NF-kappa-B pathway, which is chronically activated in patients with diabetes[59, 62]. Although the underlying pathogenesis of low-grade inflammation leading to a more rapid progression of COVID-19 and the associated cytokine storm is unclear, it is thought to be one of the most important pathophysiological mechanisms. Interleukin-6, interleukin-8, and tumor necrosis factor- may have the worst prognosis or may be fatal for diabetes individuals among the cytokines that have been studied in research. Increased cytokines are linked to risk factors and comorbidities such hypertension and cardiovascular disease and are associated with greater mortality. In diabetic individuals with COVID-19 who had at least one prior comorbidity, especially hypertension and CVD, management of diabetes by insulin treatment may reduce the rate of mortality among diabetic patients, but it may also be contraindicate[63]. The interplay between SARS-CoV-2 infection and diabetes is shown in Figure 2.

GENETICS OF DIABETES

Diabetes, an endocrine system disease marked by exceptionally high blood glucose levels, is one of the most common diseases in the world. Vascular problems of both the macrovascular system (cardiovascular disease, or CVD) and the microvascular system are the main causes of morbidity and mortality in patients with diabetes (diabetic kidney disease, diabetic retinopathy, and neuropathy)[64]. Despite the complexity and lack of complete knowledge of the precise mechanisms underlying hyperglycemia-induced vascular damage, increased intracellular glucose are thought to result in increased reactive oxygen species production, altering a number of significant downstream pathways, including the flux of the polyol pathway, the formation and activation of advanced glycation end products, the activation of protein kinase C, and the flux of the hexosamine pathway[65].

The HLA has received the majority of attention. in genetic studies of the diabetes, despite the fact that genome-wide association study (GWAS) have so far identified more than 50 Loci that affect Type I Diabetes (T1D) risk[66-69]. PTPN22 possesses a cluster of unusual variants that disrupt mRNA splicing, according to targeted sequencing of known locus, even though no large-scale sequencing projects have been successfully completed in T1D patients[70]. The largest GWAS on T2D to date is a meta-analysis of 32 European cohorts with roughly 74000 cases and nearly 824000 controls. 243 Loci reached genome-wide significance. Together, these top GWAS signals account for more than 17% of the variation in T2D phenotypes, and 73 signals supporting a single causative variable were discovered by thorough fine-mapping research on these loci[71]. People with polygenic scores in the top 2.5% do have a lower probability of getting the condition, despite the fact that these scores, which combine the genetic risk for T2D across numerous genetic loci, are not any more reliable than clinical markers for T2D prediction [72].

The Diabetic Nephropathy Collaborative Research Initiative, led by the GENIE collaboration, published the largest GWAS on diabetic kidney disease (DKD) to date in 2019[73]. The sample size was increased by three times for European Americans with T1D compared to the prior study, and 16 additional significant genome-wide loci connected to multiple illness definitions were found[73]. The missense variant SNP rs55703767 of the type IV collagen alpha 3 chain gene (COL4A3frequent), whose minor allele (T) guards against DKD and numerous other albuminuria-related symptoms, was the one with the highest correlation. Notably, Alport syndrome is caused by loss-of-function mutations in COL4A3[74]. The mutation was also associated with a reduction in glomerular basement membrane (GBM) thickness in a normoalbuminuric cohort for whom ultrastructural data were available for analysis. The SNP rs55703767 had a significantly greater impact in women. In addition, the protective association in an observational study and in those randomly assigned to a conventional *vs* intensive glycemic control in the Diabetes Control and Complications Trial was most pronounced in people with higher hemoglobin A1c (HbA1c) levels, which is noteworthy and might be expected for genetic effects expressed in the context of diabetes[73]. In dissected human glomerulus samples from Pima Indians with DKD and glomerulosclerosis, COL4A3 expression levels were discovered to be negatively correlated with GBM surface density. Furthermore, this study project identified three additional genetic loci that exceeded a strict threshold after controlling multiple correction testing (rs144434404 in intron 1 of BMP7, rs142823282 near TAMM41 and rs145681168 in intron 3 of HAND2-AS1)[73]. The SNP rs144434404 in intron 1 of BMP7, a gene involved in renal morphogenesis that is almost exclusively

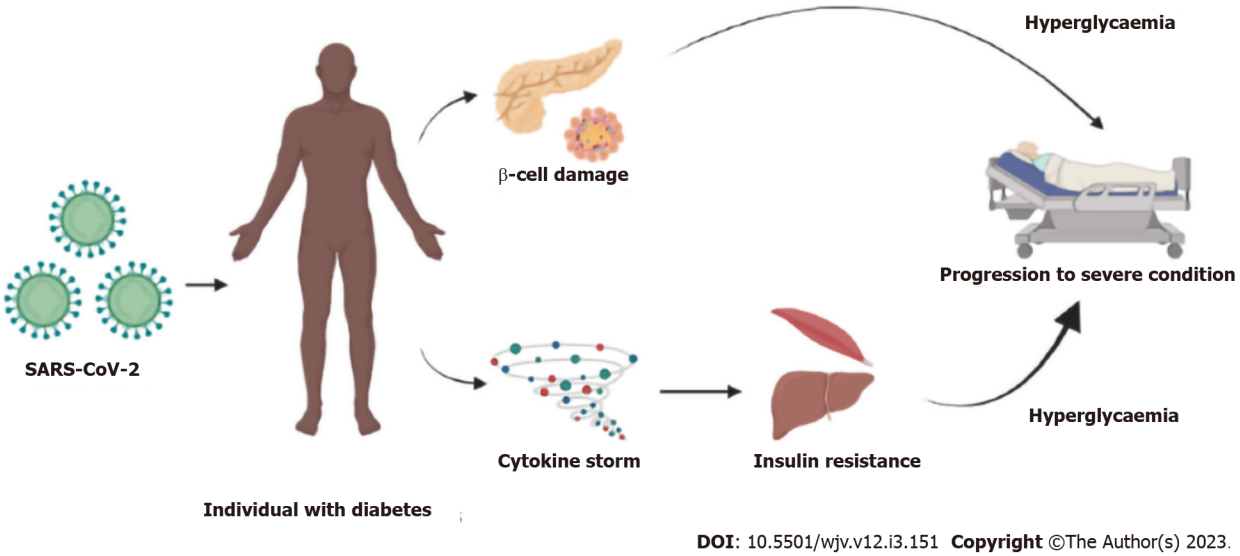

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Figure 2 Interplay between severe acute respiratory syndrome coronavirus 2 and Diabetes. Severe acute respiratory syndrome coronavirus 2 infection in diabetic individuals result in β-cell damage and cytokine storm. β-cell damage deteriorates the glucose homeostasis resulting in hyperglycemic condition. The resulting cytokine storm causes insulin resistance particularly in liver and muscles which also results in hyperglycemic condition. These altogether deteriorates the condition of the diabetic individual ensuing increased severity of coronavirus disease 2019. The figure was created using BioRender (https://biorender.com/).

expressed in mouse podocytes, was found to be associated with microalbuminuria. The SNPs rs142823282 and rs145681168, which are located close to TAMM41, as well as rs145681168, which is located in intron 3 of HAND2-AS1, were both substantially linked to microalbuminuria across the entire study. The expression of the neighboring gene PPARG (an expression quantitative trait locus), which is a known T2D GWAS gene but has not been previously studied, was also connected to the TAMM41 signal[74].

With respect to diabetic retinopathy, significant result was found by only one study[75] at the discovery and replication meta-analysis stages by merging two T2D cohorts, one T1D cohort of European ancestry, and one T2D Indian cohort. The genotypes linked to sight-threatening diabetic retinopathy were significantly correlated with genotypes at SNP rs9896052, a variant 17 kb upstream of the *GRB2* gene. This gene encodes an epidermal growth factor receptor-binding protein that is expressed in healthy human retina and is elevated in the retina of a transgenic mice model of retinal stress[76]. Since then, there have been two further comprehensive GWAS of diabetic retinopathy, but at the meta-analysis stage, they have not yet been able to provide definitive proof of a genetic relationship. The genome-wide significant intronic variant SNP rs3913535, which affects NOX4, was discovered by the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) discovery cohort.

Regarding diabetic neuropathy, the two main GWAS carried out in the GoDARTS project discovered three signals nominally associated with diabetic nerve pain (rs71647933 in ZSCAN20 in female cases and sex-combined analyses only, rs6986153 at chr8q23 in male cases only, and rs17428041)[77,78]. The presence of foot ulcers in people with diabetic neuropathy was compared to two different groups of control people with diabetes and without foot ulcers in a third GWAS using the same GoDARTS dataset. Comparing cases and controls with diabetic neuropathy, the authors discovered the intronic SNP rs80028505 in MAPK14 related with foot ulcers. These studies are from a single cohort, which is significant.

GENETICS OF COVID-19 DISEASE

The COVID-19 is caused by the novel SARS-CoV-2 and was first reported in Wuhan, China. The clinical manifestation of this disease ranges from an asymptomatic to severe disease outcome. Considering the broad spectrum of COVID-19 disease severity, risk factors that predict the disease severity might play a crucial in improving the clinical outcome of COVID-19 patients. Older age, male gender, increased BMI, pre-existing comorbidities and ethnicity are some of the risk factors that are relevant in the context of COVID-19 disease severity and susceptibility. The host genetic predisposition has also been recognized as the crucial risk factor for COVID-19 which is evident by the large number of genome wide association studies, Whole exome sequencing and candidate gene studies conducted by different consortia (COVID-19 Host Genetics Initiative (HGI), Genetics of Mortality In Critical Care (GenOMICC), COVID human genetic effort, independent academic working groups, and commercial genomics service providers such as 23 and Me and Ancestry DNA) regarding the COVID-19 disease to decipher the disease susceptibility

and severity[79].

Human Leukocyte Antigen (HLA) are encoded by the most polymorphic MHC genes. Several HLA alleles have been found to be associated with COVID-19 severity and susceptibility. In a study comprising of 82 Chinese individuals, HLA-C*07:29 and B*15:27 were significantly higher in COVID-19 patients compared to control population after correcting the *P* value[80]. HLA-DRB1*15:01, -DQB1*06:02 and HLA-B*27:07 were significantly higher in 99 severe or critical COVID-19 patients compared to 1017 reference individuals previously analyzed by the research team after applying Bonferroni's multiple test correction[81]. HLA-DRB1*08 was found to be significantly higher in COVID-19 positive individuals and it was also correlated with mortality[82]. HLA-A*11:01, B*51:01, and C*14:02 alleles were found to be significantly associated with worst COVID-19 outcome[83]. In a study comprising of 619 healthy Sardinian controls and 182 SARS-CoV-2 patients, the haplotype HLA-A*02:05, B*58:01, C*07:01, DRB1*03:01 was absent in the patients. The HLA allele HLA-C*04:01 allele and the three-loci haplotype HLA-A*30:02, B*14:02, C*08:02 were significantly more frequently in COVID-19 patients[84].

The cytokine storm has been implicated in severe COVID-19. Seven *IL-6* (rs140764737, rs142164099, rs2069849, rs142759801, rs190436077, rs148171375, rs13306435) variants and five *IL-6R* variants (rs2228144, rs2229237, rs2228145, rs28730735, rs143810642) can be implicated in the pathogenesis and severity of COVID-19[85]. Patients with no previous history of severe infection may develop life-threatening COVID-19 pneumonia due to inborn defects of type I IFN immunity that are TLR3- and IRF7-dependent[86]. None of the asymptomatic patients and 2.1% of severely affected males had the TLR7 deleterious variants[87]. Interferon-alpha and -beta receptor subunit 2 (IFNAR2) variant rs2236757 was associated with critical COVID-19[88].

The ACE2 gene is located at position Xp22.2. The S1 subunit of the spike protein (S) of SARS-CoV-2 binds with the ACE2 on the surface of the host cell. The entry into the host cell requires the cleavage at the S1/S2 site by a cellular serine protease, TMPRSS2[89]. The TMPRSS2 variants rs12329760 was found to have deleterious effect on the protease activity and protective role in COVID-19 patients[90]. The T allele of rs2285666 of ACE2 gene was found to be a risk factor for critical COVID-19 especially for men [91]. The splice site variant rs2285666 was also found to be overrepresented in SARS-CoV-2 positive individuals compared to the 100K genome project controls and in hospitalized European patients compared to outpatients. This variant increases the expression of ACE2. The eQTL rs12006793 was found to be more prevalent in patients in this study[92]. The ACE2 variant (rs190509934:C; a rare X-linked variant) was found to reduce the risk of COVID-19 but not the risk according to a meta-analysis [79].

Ellinghaus *et al*[93] found the 3p21.31 Locus (rs11385942) was associated with severe COVID-19 and respiratory failure in a GWAS study. 3p21.31 spans the gene cluster containing the genes sodium-amino acid transporter 1 (SLC6A20), human leucine zipper transcription factor like 1, CC motif chemokine receptor 9, FYVE and coiled-coil domain-containing protein 1, C-X motif chemokine receptor 6, and X-C motif chemokine receptor 1 genes. A second locus 9q34.2 (rs657152) overlapping with the ABO locus was also found to be significantly associated with severe COVID-19[93]. The GenOMICC (Genetics of Mortality In Critical Care) genome-wide association study involving 2244 critically ill COVID-19 patients from 208 United Kingdom intensive care units, identified significant associations on chromosome 12q24.13 (rs10735079), chromosome 19p13.2 (rs74956615), chromosome (rs2109069) and on chromosome 21q22.1 (rs2236757)[88].

The rs35705950 of the MUC5B was found to be associated with hospitalization in COVID-19. rs35705950 is a promoter specific mutation (https://www.covid19hg.org/results/r6/). The association of rs1886814 in the transcription factor FOXP4 was found to be associated with hospitalization by HGI [94]. Independent of pre-existing dementia, cardiovascular illness, or type 2 diabetes, the ApoE e4e4 homozygous genotype was observed to increase the risk of severe COVID-19[95].

LONG-TERM EFFECTS OF COVID-19 DISEASE

It has been demonstrated that COVID-19's clinical presentation varies greatly, frequently exhibiting substantial respiratory problems. A number of patients with SARS-CoV-2 have gone on to experience long-term problems from the virus, making it notable. Long-haul COVID-19 has evolved to represent a wide range of problems and sequelae of symptoms that may occur, beyond the original reports of individuals feeling weary for months following initial infection[96]. Lung fibrosis, venous thromboembolism (VTE), arterial thromboses, heart thrombosis and inflammation, stroke, "brain fog," dermatological issues, and general mood dysfunctions are some of the potential late consequences that could result from COVID-19 infection, according to prior investigations[97]. Despite the wide range of these long-term problems, certain patient characteristics have been proven to predict which symptoms they would experience and for how long[98].

COVID-19 is mostly a respiratory disease, despite the fact that SARS-CoV-2 can have widespread effects throughout the body. Following COVID-19 infection, numerous long-term pulmonary problems have been reported. Dyspnea, ventilator dependency, oxygen dependence, pulmonary function test (PFT) abnormalities, and fibrotic lung disease are only a few of them. Dyspnea is the most frequent

pulmonary symptom associated with COVID-19, and it might last for two months in 22.9% to 53.3% of patients[99-101]. Infection with SARS-CoV-2 can lead to verifiable long-term alterations in pulmonary physiology in addition to subjective symptoms. Up to 6.6% of survivors who make it to hospital discharge have been found to be oxygen dependent[101]. Long-term weaning from ventilator use is not frequently successful in patients with respiratory insufficiency necessitating a tracheostomy. Only 48% of patients in Spain's 1890 tracheostomy patients were successful in weaning off artificial breathing at the 1-month follow-up[102]. Previous studies have also discussed abnormalities in lung function as determined by PFT. In a study of 55 non-critically ill COVID-19 patients in China, PFT evaluation over a three-month follow-up period indicated abnormalities in 25% of patients, with a decrease in DLCO being the most prevalent (16%)[103]. Salem *et al*[104] made similar observations with elevated incidence of restrictive lung findings when compared with matched controls.

After being released from the hospital following COVID-19, cardiac problems are a frequent complaint. As many as 21% of patients had chest pain 60 days after leaving the hospital, according to Carfì *et al*[99]. Palpitations have also been reported to occur often in as many as 9% of patients at the 60-day follow-up. Aside from the subjective cardiac symptoms listed among the long-term effects of SARS-CoV-2 infection, there have also been a number of quantifiable results. Investigation into the precise prevalence of postural tachycardia syndrome, which has been associated with SARS-CoV-2 infection, is still ongoing[105].

Acute COVID-19 has been linked to a higher risk of thrombotic events, particularly in patients who are severely sick[106,107]. The causes of this coagulopathy are multifaceted and include hypoxia's impact on the activation of hypoxia-inducible transcription factors, microvascular dysfunction, and enhanced expression of tissue factors in response to inflammatory cytokines[108,109]. The regular administration of intermediate-dose anticoagulation (enoxaparin 1 mg/kg) is recommended due to the elevated risk of thrombosis found in this patient population. Recently, a comparison of typical preventive anticoagulation (enoxaparin 40 mg daily) and severely ill individuals with a randomized controlled method in the INSPIRATION trial, COVID-19. Treatment with intermediate-dose anticoagulation did not appear to lower the composite endpoint of arterial or venous thrombosis. ECMO, or death at 30 days as compared to prophylactic anticoagulation at a standard dose[110]. Even though bleeding incidents do occur, most patients benefit more from inpatient VTE prevention than they risk due to the minimal risk of significant bleeding[111,112].

With SARS-CoV-2 infection came a number of long-term neurological and behavioral problems. Two months after the acute infection, patients continued to experience neurological symptoms as fatigue, muscle weakness, difficulty sleeping, myalgia, and headaches, according to long-term symptom data from numerous sources[99,113]. These signs and symptoms have come to represent the long COVID syndrome. In contrast to other viral infections, SARS-CoV-2 infection has also been associated with loss of taste and smell. At a 2-month follow-up, 11% to 13.1% of patients still had chronic loss of taste and smell[100,113]. Due to the considerable burden of severe, life-threatening illness and acute respiratory distress syndrome (ARDS) associated with COVID-19, cognitive disturbances comparable to those shown in ARDS patients in previous studies should be anticipated. At one year of follow-up, ARDS survivors from other causes have reported memory problems (13%), verbal fluency problems (16%), and executive function problems (49%)[114].

A review of the literature found that of the reported cutaneous manifestations of COVID-19 infection, the most prevalent cutaneous manifestation was maculopapular exanthem (morbilliform), which was reported by 36.1% of 72 documented patients in 18 studies. Other cutaneous manifestations included papulovesicular rash (34.7%), urticaria (9.7%), painful red acral purple papules (15.3%), and urticaria, with 19.4% of these manifestations[115]. Another international study of 2560 patients reported that the most prevalent cutaneous manifestation (51.5%) was pernio-like lesions, and that children had a 1.5-day latency period between upper-respiratory infections and cutaneous findings compared to adults, who had a 7.9-day latency period[116]. Only 47 of 1655 hospitalized patients in the Chinese post-acute COVID-19 study (3%) reported skin rashes six months after the infection started[113]; hair loss, on the other hand, was a symptom that was much more frequently reported for patients' months after the COVID-19 infection and was reported in 24 of 120 patients (20.0%) as a post-discharge symptom 110 days after hospital discharge. However, other, more uncommon presentations have been described in case reports, indicating that, although having the same virus in their bodies, the symptoms in various patients may change[117]. Vesicular rashes may be diagnostic of an initial diagnosis of COVID 19 and may be predictive of disease prognosis, although the particular use of these symptoms in this manner has not yet been proven and should be the subject of future prospective research[118].

Children often experience a milder disease during the acute phase of COVID-19 and receive diagnoses at a lesser rate than adults[119]. Multisystem inflammatory syndrome in children (MIS-C), which is characterized by fever and multiorgan dysfunction in the weeks following SARS-CoV-2 infection[120, 121], is one of the consequences and sequelae of infection. 316 cases per 1000000 infections are reported for MIS-C, which primarily affects youngsters from racial/ethnic minority backgrounds[122,123]. Nearly 75% of MIS-C patients require ICU admission, and the condition shares characteristics with both severe acute COVID-19 and Kawasaki illness[120-122]. The most typical symptoms include gastrointestinal issues, cardiovascular issues, respiratory issues, mucocutaneous issues, and neurological issues[122-124].

Poorer COVID-19 outcomes have been linked to pre-existing diabetic mellitus. Meanwhile, COVID-19 has been linked to both type 1 and type 2 diabetes patients' new-onset hyperglycemia and rapid decompensation of diabetes, including diabetic ketoacidosis[125]. In addition to iatrogenic hyperglycemia caused by steroid usage, other suggested mechanisms for hyperglycemia after infection include insulin resistance brought on by the inflammatory state and insulin secretory deficiencies from defective beta cells—caused either directly or indirectly by viral damage[125,126]. Unknown numbers of people with newly discovered diabetes following COVID-19 may have already had undiagnosed diabetes prior to infection, which was merely concealed or made worse by the infection. It's also not certain whether diabetes that develops after being hospitalized for COVID-19 is a lifelong condition. In order to better understand the relationship between COVID-19 and diabetes and to better define the length of post-COVID-19 diabetes, the global CoviDiab Registry was established[127].

Acute COVID-19 patients frequently experience acute kidney injury (AKI), and 5% of all hospitalized patients need inpatient renal replacement treatment[128]. The causes of AKI are multifactorial, and they include aberrant coagulation, systemic hypoxia, inflammatory cytokine effects, and direct virus harm [129]. The most frequent histological finding is acute tubular necrosis, however glomerulopathy[130] and microvascular thrombi[131] can also occur[132-136]. AKI is linked to an increase in hospital mortality, and those who make it out of the hospital[128].

SHARED VARIANTS RESPONSIBLE FOR DIABETES AND SEVERITY OF COVID-19 DISEASE

Frequencies of variations in human ACE2 receptor gene is not uniform rather varied considerably from population to populations. Mutations emerging within the SARS-CoV-2 genome and natural polymorphisms harbored within the ACE2 receptor gene are crucial for the binding of receptor binding domain of spike protein of SARS-CoV-2 followed by the entry and transmission of the virus[137]. Several studies have been conducted to evaluate the binding affinity of the novel SARS-CoV-2 variants to hACE2[138-140] and association of population specific ACE2 variants with disease susceptibility as well as severity has been reported[141-143]. Presence of ACE2 receptor polymorphisms can alter binding interaction with SARS-CoV-2 followed by COVID-19 disease susceptibility[144] on one hand while on the other side different mutations in SARS-CoV-2 revealed varied binding pattern to its host receptor, ACE2[145].

Studies on different population revealed linkage between the single nucleotide polymorphisms within the angiotensin converting enzyme 2 receptor gene and hypertension, diabetes, cardiovascular diseases[146,147]. The ACE2 variants rs2285666, rs879922, rs4646188, rs2106809, rs4240157, rs4830542, rs2158083, rs879922, rs1514283, rs2074192, rs4646155, rs4646176, rs4646174 and rs233575 have been reported to be associated with primary hypertension while rs2106809, rs2074192, rs4646156, rs879922, rs4240157 and rs233575 were found to be linked with left ventricular hypertrophy[148]. Incompatible results have been reported regarding association of *ACE2* gene variants with the risk as well as severity of COVID-19 disease. Studies conducted on Turkish, Italian and Spanish populations reported that *ACE2 receptor* gene rs2106809, and rs2285666 polymorphisms were not associated with the severity of COVID-19 infection[148-151] while ACE2 rs2285666 (AA allele) and ACE2 rs2074192 (TT allele), and for ACE2 rs4646174 (GG allele), ACE2 rs4646156 (TT allele) and ACE2 rs2158083 (TT allele) the most significant correlation with COVID-19 in Polish population[152]. On the other hand, in another study Cafiero *et al*[153] reported SNPs within the members of renin angiotensin system such as rs2074192 within ACE2, rs1799752 within ACE1 and rs699 within angiotensinogen, SNPs could potentially be a valuable tool for predicting the clinical outcome of SARS-CoV-2 infected patients.

Intronic variant rs228666 (located in intron 3) can cause change in mRNA splicing followed by altered ACE2 expression which ultimately results in higher binding affinity to novel coronavirus[152] and similar characteristics in case of rs2158083 was observed in patients with arterial hypertension[138]. Another intronic variant rs2074192 has been demonstrated to dysregulate SARS-CoV-2 binding to its host receptor by mediating imbalance in ACE2 transcription/translation through inducing changes in secondary structure of RNA[138,152]. Sienko *et al*[152] demonstrated significant correlation of the *ACE2 receptor* gene rs2074192, rs2158083, rs2285666, rs4646156, rs4646174 polymorphisms with the severity of COVID-19 in adult patients. Strong correlation of T allele and TT genotype with respect to of rs2074192 within *ACE2 receptor* gene has been shown with disease severity caused by SARS-CoV-2[151,152] and in French-Canadian and British patients (n = 1644) with COVID-19 disease in obese smoking males[154]. Recent research has demonstrated that persons with type 2 diabetes (T2D) experience COVID-19 with greater severity and mortality as compared to healthy individuals. Patients with T2D who are infected with SARS-CoV-2 are more prone to experience severe cytokine storm consequences and need to be hospitalized to high-dependency or intensive care facilities. Due to the severe activation of inflammatory cascades, some COVID-19 individuals are known to experience different types of acute respiratory distress syndrome and have a greater mortality risk.

Recently, Wu *et al*[155] tried to find the common genetic determinants between T2D and COVID-19. They analyzed the key pathways that were shared between T2D and COVID-19 in order to identify the common pathways between the two diseases. Using iGSEA4GWAS, they discovered chemokine binding, G-protein coupled chemoattractant receptor activity pathways (CCR2 and CCR3), TFAP2 family pathway (TFAP2B), and ventricular cardiac muscle cells differentiation (RARB and PROX1) pathways shared by T2D and COVID-19. Immunological cell recruitment to infection sites is aided by the chemokine binding pathway, and leukocyte chemotaxis and innate and adaptive host immune responses are mediated by the G-protein coupled chemoattractant receptor. Additionally, using PASCAL, 15 pathways that were common between T2D and COVID-19 were discovered. These pathways were linked to a number of biological functions and organs, including the heart, axons, and calcium channels. However, no shared pathways between the four pathway-based analytic programs were discovered. 394 genes were associated with T2D according to PASCAL analysis, while 58 genes were associated with COVID-19. Five were discovered to be common between T2D and COVID-19 after comparing the important genes in T2D and COVID-19: PTPRD, CSMD1, MAGI1, ASIC2, and DAB1.

Significantly positive genetic correlations between T2D and COVID-19 were found in genome-wide linkage disequilibrium score regression studies (R for genetic = 0.15, *P* value = 0.01). There is a slight polygenic overlap between COVID-19 and T2D, as evidenced by the enrichment of associations with COVID-19 across different degrees of association with T2D[22]. Wu *et al*[155] further revealed two loci shared between COVID-19 and T2D: ABO (rs505922, intronic) and NUS1 (rs3924604, intronic) based on a threshold of conjFDR<0.05. Both of these independent loci were displaying a consistent direction when the effect directions of the shared independent loci were compared (conjFDR<0.05). One locus (rs505922) has shown a favorable effect, whilst the other (rs3924604) demonstrated a detrimental effect. SNPnexus was used to identify these two genes from two separate SNPs. In the genes closest to the identified loci shared between COVID-19 and T2D, eight pathways were found to be significantly overrepresented, with the faulty DHDDs causing retinitis pigmentosa 59 pathway being the most significant (*P* value = 1.88×10^{-4}).

CONCLUSION

The world has overcome the devastating impact of COVID-19 by undergoing massive vaccination program against SARS-CoV-2. The pandemic has also showed us weaknesses of the health care system of both the developed and underdeveloped world. Also, we should think about preserving our forests, water reservoirs *i.e.*, the natural habitats of all living beings. To do so, we need to revisit the actions of climate change. Moreover, the world researchers, policy makers, health care providers should also consider the probable impacts of long COVID on human health. Understanding the genetics of hosts and disease pathophysiology could be one of the many steps towards better human health and well-being.

FOOTNOTES

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REVIEW

Viruses and autism: A Bi-mutual cause and effect

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Abstract

Autism spectrum disorder (ASD) is a group of heterogeneous, multi-factorial, neurodevelopmental disorders resulting from genetic and environmental factors interplay. Infection is a significant trigger of autism, especially during the critical developmental period. There is a strong interplay between the viral infection as a trigger and a result of ASD. We aim to highlight the mutual relationship between autism and viruses. We performed a thorough literature review and included 158 research in this review. Most of the literature agreed on the possible effects of the

viral infection during the critical period of development on the risk of developing autism, especially for specific viral infections such as Rubella, Cytomegalovirus, Herpes Simplex virus, Varicella Zoster Virus, Influenza virus, Zika virus, and severe acute respiratory syndrome coronavirus 2. Viral infection directly infects the brain, triggers immune activation, induces epigenetic changes, and raises the risks of having a child with autism. At the same time, there is some evidence of increased risk of infection, including viral infections in children with autism, due to lots of factors. There is an increased risk of developing autism with a specific viral infection during the early developmental period and an increased risk of viral infections in children with autism. In addition, children with autism are at increased risk of infection, including viruses. Every effort should be made to prevent maternal and early-life infections and reduce the risk of autism. Immune modulation of children with autism should be considered to reduce the risk of infection.

Key Words: Autism; Children; Rubella; Cytomegalovirus; Herpes simplex virus; Influenza virus; Zika virus; SARS-CoV-2; COVID-19; Viral infection

Core Tip: There is a mutual relationship between viral infections and autism. There is an increased risk of developing autism when contracting a viral infection during pregnancy or early postnatal life during the critical period of brain development. At the same time, children with autism have many co-morbidities that expose them to more risk of contracting infections, including viruses. Therefore, every effort should be made to prevent infections, especially during this critical period of neurodevelopment. Parents should also be educated about the importance of vaccination and immune modulation in children with autism to avoid further infections.

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INTRODUCTION

Autism is a group of heterogeneous, multi-factorial, neurodevelopmental disorders that occur during infancy and toddlerhood, best described as a spectrum rather than a disease. It is characterized by language, social communication, interaction problems with restricted, repetitive, or stereotyped behaviours or interests, and the inability to generate biologically determined, regular, emotional interaction with others[1]. Autism spectrum disorders (ASD) involve autism, pervasive developmental disorder not otherwise specified, and Asperger's disorder. In addition, ASD, childhood disintegrative disorder, Rett's disorder, and the overactive disorder accompanied by mental retardation and stereotyped movements form pervasive developmental disorders. The diagnosis of autism is made by identifying at least two domains (out of three) of impaired social interaction and/or communication and restricted, repetitive, or stereotyped behaviour, interests, and activities[2,3].

There is no one definite cause of autism. Several factors play together to increase the risk of development of autism, including genetic, epigenetic, and environmental factors that may work in combination to affect the brain during the crucial phases of early development. The genetic causes of autism could result from single-gene mutations or abnormal copy number variations (such as large deletions, duplications, inversions, or translocations of chromosomes)[4]. As autism is likely to run in families, specific genetic changes may increase the risk of autism development in children. Therefore, the risk of recurrence of pervasive developmental disorders ranges between 2% and 8% in siblings of children with autism[5]. Lichtenstein *et al*[6] showed that monozygotic twins had higher rates of ASD and other neuropsychiatric disorders than dizygotic twins. However, this increase in the risk is not only due to the shared genes but also could be related to the shared environment, as identified by several twin studies[6,7].

Therefore, specific environmental conditions may increase or decrease the risk of autism in genetically predisposed patients through epigenetic modification by affecting gene expression quantity and quality without altering the DNA sequence. The epigenetic modification of gene expression occurs through altering DNA methylation, changing histone proteins, or modifying the expression of noncoding RNAs[8]. According to Barbeau[9], three pathways trigger the development of autism. The

first pathway is activated by in-utero insult or injury, while obstetric complications at birth initiate the second pathway. The third pathway is triggered by various environmental triggers affecting infants in the first three years of life. The environmental factors include antennal factors (*e.g.*, parental age, especially the father's age, the mother's physical and mental health, prenatal drug use, and family socioeconomic status), prenatal factors (preterm delivery, abnormal presentation, cesarean section, fetal complications, neonatal hypoxia, respiratory distress, natal bleeding, low-birth weight, seizures at birth), and postnatal factors (*e.g.*, neonatal jaundice, early infection, sepsis, meningitis, encephalopathy, postnatal vitamin D deficiency, *etc.*)[10].

The sharp rise in ASD incidence observed worldwide is due to the increased prevalence of risk factors such as genetic predisposition, adverse environmental circumstances, and increased awareness about this disorder[11]. Infection is a common triggering factor in the three environmental pathways that affect autism development. Viral infection is widespread in all ages, including during the antenatal period. Viral infection during critical periods of early in-utero neurodevelopment may lead to an increased risk of autism in the offspring. On the other side, autism may be associated with impaired cellular and humoral immunity, which predisposes children with autism to encounter different types of infections, including viruses[12].

Meanwhile, some viruses may be used as a vector during gene therapy which could be a promising therapy for many diseases, including autism[13]. This review highlighted the mutual relationship between autism and viruses. The study focused on how viral infections may affect brain development and how this could be at play in some traits commonly associated with autism, such as difficulty communicating verbally or recognizing familiar faces. It also focused on how children with autism may have an increased frequency of infections, especially viral infections.

LITERATURE REVIEW

We conducted an inclusive literature review by searching different electronic databases, including Embase, PubMed, Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, Scopus, Web of Science, Library and Information Science Abstracts, the National Library of Medicine catalogue, Ovid/Medline, and google search until January 31, 2023, related to viral infections and autism using the terms autism, autism spectrum disorders, viral infections, rubella, cytomegalovirus, influenza virus, Zika virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19), vibrobiota, neurodevelopment, perinatal, antenatal, natal, and postnatal. Reference lists were inspected, and citation searches were done on the included studies. We included papers written in English and with open access. Figure 1 shows the flow chart of the reviewed articles. We reviewed 458 articles concerned with the viral infection and autism in children; 158 were included in the study.

PROPOSED UNDERLYING PATHOPHYSIOLOGY OF AUTISM

ASD pathogenesis is not fully recognized. Autism has different pathophysiological neuroanatomical, and neuropsychological changes in the affected patients' brains that affect many brain functions resulting in the characteristic cognitive and behavioural changes of autism. Different genetic and environmental factors activate pathological pathways that disrupt brain development[14,15]. Behaviour and social impairment are among the hallmarks of autism. ASD is diagnosed based on behavioural impairments in social communication, interest fixation, and repetitive behaviours. These social impairments may be related to the improper interpretation of social signals[16]. Evidence from healthy individuals suggests that potentially threatening situations, such as others' proximity, can trigger several physiological responses that help regulate the distance between themselves and others during social interaction. Vicarious fear learning critically impacts cognitive abilities, receiving a neutral image as threatening and frightening as phylogenetically innate negative and dangerous stimuli, consequently affecting the person's behavioural control[17,18]. Individuals with ASD have social impairments, potentially due to the lack of or improper social signal interpretation, resulting in the inability to interpret these signals to guide appropriate behaviours[19]. In utero or early life, disruption of normal brain development triggers the subsequent development of neuropsychiatric disorders during later life [20].

The brain volume and weight are usually more prominent in children with autism with larger head circumferences than in typically developed children. The brain overgrowth observed in children with autism is not precisely understood. However, it could be related to excess neurons that induce local overconnectivity in specific brain regions. It also could be related to abnormal neuronal migration during early pregnancy with abnormal synaptogenesis and formation of dendritic spines and disturbed excitatory-inhibitory networks[21-23]. Changes in the division rates of germinal cells induce abnormal daughter cells migration to their target regions, causing autism-associated sensory and motor deficits [24].

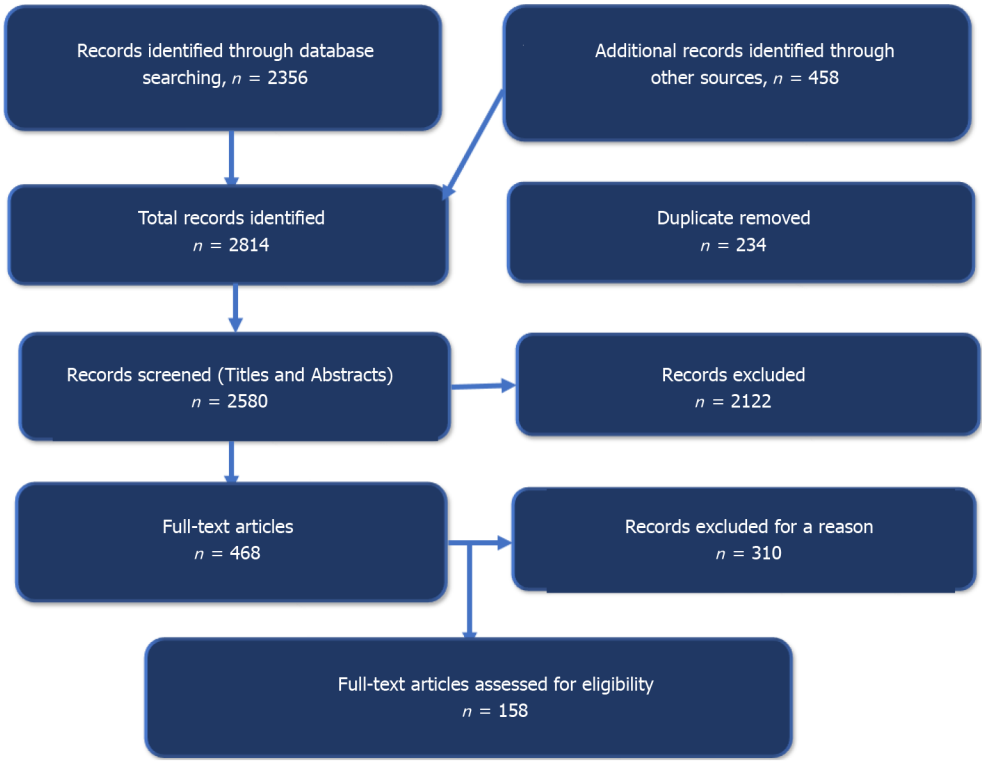

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Figure 1 Shows the flow chart of the reviewed articles.

Neuroinflammation is common in ASD with low-grade chronic inflammatory reactions and increased pro-inflammatory cytokines in cerebrospinal fluids (CSF) and specific brain areas due to microglial cells and innate neuroimmune system activation[25]. Altered immune function induces neuroinflammation, affecting many neurological processes, including neural development, brain structures, synapse plasticity, cognition, and behaviour[26]. This neuroinflammation may begin in early embryogenesis during the critical periods of neurodevelopment, resulting in unsuccessful neurodevelopment. Various antenatal factors, such as maternal vitamin D deficiency, medication use, such as valproic acids, prenatal infection, and neonatal hypoxia, can trigger autism-related neuroinflammation. Brain development during the perinatal period is critical and particularly vulnerable to the effects of abnormal immune activation with detrimental consequences on neurodevelopment and alterations in neural connectivity[27]. Gastrointestinal abnormalities, repeated infections with gut dysbiosis, and impairment of the gut-brain axis cause immune imbalance and trigger neuroinflammation[28]. The role of neuroinflammation in autism pathogenesis is proved by observing the raised reactive microglial and astrocyte numbers in postmortem tissue from patients with ASD and animal models[29]. Other evidence of neuroinflammation is frequent reporting of dysregulated immune responses, anti-brain antibodies in CSF and blood, and several neurotransmitter abnormalities, such as increased serotonin levels in children with autism. Neuroinflammation identification and other markers of immune profile abnormalities can hypothetically lead to more consistent diagnostic measures and options for treating ASD[30,31].

The mirror neuron system (MNS) is essential in developing social and communication skills by helping to understand other people *via* imitating their behaviour through personified simulation, intentions, action perceptions, and emotions. Children with autism were found to have structural abnormalities in MNS regions, causing impaired activation of the imitation core circuit in children with autism. Remarkably, the activity of MNS regions is inversely related to the severity of the deterioration of social domain communication, which can explain the social impairment in children with autism[32,33]. However, children with autism can still mimic goal-directed behaviours[34]. In addition to the impaired MNS observed in children with autism, they have impaired activation of many other brain circuits outside the MNS[35]. For example, patients with autism may have an altered functional organization of their large-scale task-negative brain network engaged in social and emotional processing. However, they have an intact organization of the task-positive brain network, which maintains attention and goal-directed thinking[36]. Therefore, it was unsurprising when Chiu *et al*[37] found different signalling patterns in the cingulate cortex using functional neuroimaging with severely reduced cingulate self-response when playing games in patients with autism from that observed in typically developed partners. Some studies showed that patients with autism might have local overconnectivity in the cortex with reduced functional connectivity between the frontal lobe cortex and the rest

of the cerebral cortices with poor high-level neural connectivity and synchronization and disordered association cortex[38,39].

Neuroinflammation of the brainstem causes brainstem dysfunction, including sensory processing abnormalities[40]. Since the thalamus is close to the brainstem, neuroinflammation could also affect it, augmenting autonomic nervous system dysfunction. Therefore, children with autism have intermittent autonomic nervous system dysfunction with enhanced sympathetic excitation and parasympathetic hypofunction causing chronic sensory hyperarousal state in children and sleep disorders. Autonomic dysfunction also affects heart rate, blood pressure, respiratory rhythm, gastrointestinal motility, gastric acid, and intestinal enzyme secretion[41,42]. Immune dysregulation and autoimmunity can induce neuroinflammation, cytokine dysregulation, and inducing anti-brain antibodies, significantly impacting brain development, causing neurodevelopmental deficits and playing a role in autism progression[43]. Vargas *et al*[44] showed the presence of neuroinflammatory markers and elevated cytokines, and enhanced activity of microglia and astrocytes in postmortem autopsies from patients with autism between 5 to 44 years, indicating permanently activated immune status in patients with autism. Table 1 summarizes the possible underlying mechanisms and triggering factors for autism.

VIRAL INFECTION AS A TRIGGER OF AUTISM

Increased susceptibility to infection is a common problem during pregnancy due to various pathophysiological and mechanical changes and immune system adaptation necessary to keep the fetus in utero and prevent expulsion. Therefore, there is an increased chance of asymptomatic and symptomatic viral infection during pregnancy[45]. Some viruses can cross the placental barrier, reaching the fetus and causing devastating developmental fetal effects[46]. Infection is an important trigger for immune activation. Viruses can directly infect the brain, causing neuron cell death by cell lysis, the release of free radicals, or apoptosis induction, inducing a systemic inflammatory response that affects the brain or alters the maternal or their offspring's immune status, which could influence autism development. Viral-induced immune activation causes elevated levels of pro-inflammatory cytokine IL-6, which changes brain gene expression in the offspring, driving abnormal behaviour development[47]. Maternal immune activation increases maternal pro-inflammatory cytokines, activates maternal T-helper-17 cells, and increases IL-6 mRNA and protein in the fetal brain and the placenta making specific placental tissue changes commonly observed in patients who developed ASD[48-51]. Some viruses, such as rubella and cytomegalovirus, may have a teratogenic effect on the fetus, impairing brain functions and causing autism[46]. The brain and immune system are not fully developed in fetuses and young infants, so they are at high risk of viral-induced brain damage. Therefore, maternal viral infection and inflammation during critical periods of pregnancy could result in an unfavourable intrauterine environment and alter the brain structure and function, raising the risks of having a child with autism[52]. The effects of maternal infections depend on many factors, including genetic susceptibility, the time of infection in pregnancy (early or late), and the severity of the infection [53]. Figure 2: General mechanism of viral infection in the induction of autism.

More than 50 years had elapsed since the link between viral infection and autism development appeared on the surface when Chess *et al*[54] observed the development of autism in 7% of children suffering from congenital rubella. One year later, Deykin and MacMahon[55] hypothesized that direct exposure to or getting infected with prenatal rubella, measles, mumps, or postnatal mumps might have a causal role in developing autism. After that, many studies documented the link between other viral infections, such as polyomaviruses, cytomegalovirus, and influenza, with the increased risk of autism [56,57]. Many animal studies have shown the role of prenatal or early postnatal exposure to infections, including viruses, in developing permanent neurological and behavioural abnormalities in offspring involving autism features[57,58]. Shi *et al*[57] showed that pregnant mice infected with the human influenza virus give up offspring with significant behavioural abnormalities as adults, including schizophrenia and autism, with deficits in prepulse inhibition in the acoustic startle response. Moreno *et al*[59] showed that antenatal mice-adapted influenza virus infection could induce behavioural changes by altering serotonin and glutamate systems *via* upregulating serotonin 2 A receptors and downregulating metabotropic glutamate receptor 2 in the frontal cortex of the born mice.

There is increasing evidence that a prenatal infection can lead to autism. Maternal infection by DNA or RNA viruses that can cross the maternal-fetal interface may induce neurodevelopmental problems in the developing fetus[60]. A study published in the American Journal of Perinatology 2017 Looked at data from more than 100000 children who were a part of the Kaiser Permanente health system in California from 1991 to 2009. It showed that women who developed an infection in the third trimester were at an increased risk for developing autism in their children[61]. Another study by Croen *et al*[62] showed that the risk of autism is double in mothers with second-trimester infections and fever, suggesting that the infection-induced inflammation during a specific temporal window of pregnancy may be an etiological factor. Fang *et al*[63] studied 4184 children with ASD, and 16734 healthy, controlled-matched children over seven years between 2000 and 2007 to evaluate the link between prenatal infections and the risk of developing autism across three trimesters. They showed that

Table 1 The possible underlying mechanisms and triggering factors for autism

Possible mechanism	Effects
Immune dysregulation and autoimmunity	Neuroinflammation, cytokine dysregulation, and inducing anti-brain antibodies
Neuroinflammation	**Neuroinflammation of the Cortex:** Raised reactive microglial and astrocyte numbers → excess neurons → local overconnectivity in specific brain regions, abnormal neuronal migration during early pregnancy → abnormal synaptogenesis and formation of dendritic spines and disturbed excitatory-inhibitory networks, prominent brain volume and weight volume
	Neuroinflammation of brainstem → brainstem dysfunction → sensory processing abnormalities → enhanced sympathetic excitation and parasympathetic hypofunction
	Neuroinflammation of thalamus → autonomic nervous system dysfunction
Abnormalities in mirror neuron system regions	→ Impaired activation of the imitation core circuit → social impairment
Impaired signaling patterns in the cingulate cortex	→ Severely reduced cingulate self-response → social impairments
Autonomic nervous system dysfunction	Chronic sensory hyperarousal state in children and sleep disorders
	Affects heart rate, blood pressure, and respiratory rhythm
	Impaired gastrointestinal motility, gastric acid, and intestinal enzyme secretion
Underlying triggering factors	Maternal vitamin D deficiency, use of medication such as valproic acids during pregnancy, prenatal infection, neonatal hypoxia, preterm delivery, abnormal presentation, cesarean section, fetal complications, neonatal hypoxia, respiratory distress, natal bleeding, low-birth weight, seizures at birth, neonatal jaundice, early postnatal infection, sepsis, meningitis, encephalopathy, postnatal vitamin D deficiency
Augmenting factors	Gastrointestinal abnormalities, repeated infections with gut dysbiosis, and impairment of the gut-brain axis cause immune imbalance and trigger neuroinflammation

contracting infections in the third trimester was slightly associated with a raised risk of ASDs. However, the effects of infection in the third trimester on the risk of autism development demands further exploration. Zerbo *et al*[64] showed that maternal infections during pregnancy, especially bacterial and multiple infections that need hospitalization, are associated with an increased risk of having a child with ASD. There is some evidence that boys are at a more increased risk of antenatal viral infection and, consequently, autism, primarily due to the noted sex bias seen in the placental immune response related to the viral infection[65]. The placenta in female babies can induce random X- chromosome reactivation, potentially increasing the gene dosage of specific X-linked genes at a very early or late pregnancy period, inducing enhanced protection against viral infection[66].

It should be noted that most of the included studies give evidence from an epidemiological perspective. It is essential to consider possible confounding factors and other disorders during pregnancy, such as preterm birth, low birth weight, maternal smoking, and seasonal variation. An interesting study showed that the risk of autism was highest in babies conceived in the winter and born in the fall, while the rate was lowest in babies conceived in the summer and born in the spring[67]. Could the rate be related to an increased incidence of infection during winter time or low exposure to sunlight during a period of critical neurodevelopment? This finding needs further exploration.

Not only does infection during pregnancy increases the risk of developing ASD, but infection in early postnatal life is also associated with increased risk. A study by Getahun *et al*[68] showed that preterm and term babies who encountered neonatal sepsis had a significantly increased probability of autism for both boys and girls and in all race-ethnic groups except Asian/Pacific Islanders compared with unexposed children. A case-control Danish study involving 414 children with ASD cases and 820 children as controls showed that children with autism had a higher risk of infection-related hospital admission during the first year of life than the controls[69]. However, another study by Rosen *et al*[70] showed an increased risk of autism with infection during the first 30 days postnatal and not the first two years of life.

On the other hand, some previous studies showed no relation between antenatal viral infection and the risk of autism. Anlar *et al*[71] found no association between antibody levels against Human parvovirus B19 and the risk of autism in 22 children with autism and 50 children with other neurological disorders as control. However, they did not compare children with autism with typically developed children, which is a substantial limitation of the study. In addition, Sylvester Jørgensen *et al*[72] found no significant differences in the prevalence of herpes simplex virus antibodies in 123 children with different psychiatric disorders, including autism, and 86 typically developed children. Meanwhile, Deykin and MacMahon[55] suggested that antenatal or early postnatal exposure to chickenpox, mumps, measles, or rubella did not increase the likelihood of developing autism. However, they proposed that combined infection of two or more of these viruses could increase the risk of autism, especially for antenatal mumps, measles, rubella, and postnatal mumps. However, there may be a limitation in these

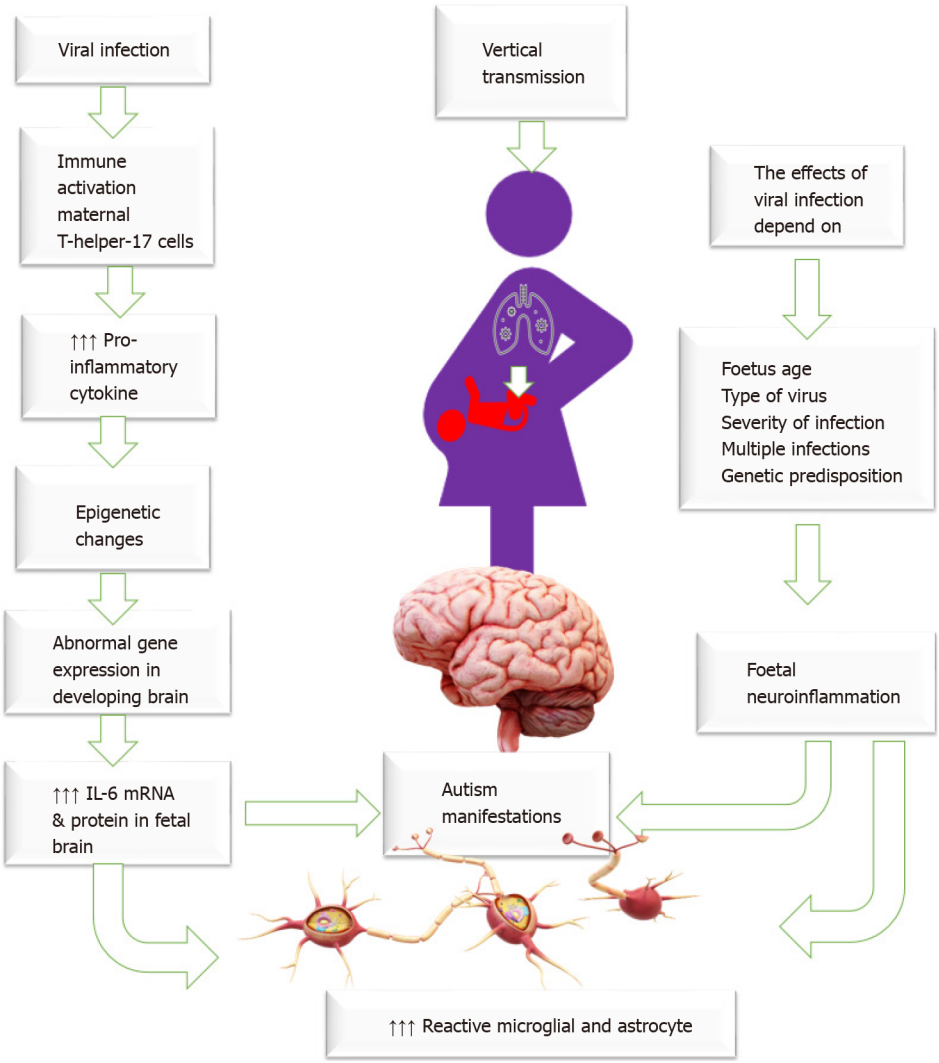

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Figure 2 General mechanism of viral infection in the induction of autism. The figure showed that maternal viral infection could reach the virus through vertical transmission and affect the placenta. It also causes maternal immune reactivation with activation of the maternal T-helper -17. This immune hyperactivation leads to a marked increase in the pro-inflammatory cytokines causing epigenetic changes in the fetus, which cause abnormal gene expression in the developing brain with overactivation of astrocytes and glial cells and the development of autistic manifestations.

studies' methodology that could explain the contradictory results with recent studies.

Specific viral infections and the risk of developing autism

Certain viruses are known to be more commonly associated with the development of autism.

Rubella: Rubella is a well-known RNA virus that can cause various congenital malformations when contracted, especially during the first trimester of pregnancy. Intellectual disabilities, including autism, are common among children with congenital rubella infection. The autism rate is 200 times more in these children than in the general population, reaching a rate of 8%-13% of children with congenital rubella syndrome[73]. Different mechanisms were proposed, including infection-induced hypervitaminosis A. Acute rubella infection induces mild liver dysfunction altering the liver metabolism of vitamin A with the spilling of the stored vitamin A complexes into the circulation, resulting in an endogenous type of hypervitaminosis A, which serves as a teratogen causing mitochondrial damage, DNA alteration, and apoptosis; inducing autism development[74] (Figure 3). In addition, the rubella virus can invade and replicate inside the brain cells. It also can cause cerebral vascular lesions and haemorrhages. It can also cause fulminant degeneration of leptomeninges with significant brain volume loss and destruction of white matter[73]. Therefore, many manifestations of congenital rubella syndrome, such as congenital heart defects, spasticity, deafness, and visual impairment, are common in children with autism. In addition, radiological findings, such as dilated perivascular spaces, periventricular leukomalacia, calcifications, and decreased perfusion to specific brain areas, are common for children with congenital rubella syndrome and those with autism[73]. Hence, rubella might still be a possible cause of autism, even in countries with well-vaccination policies.

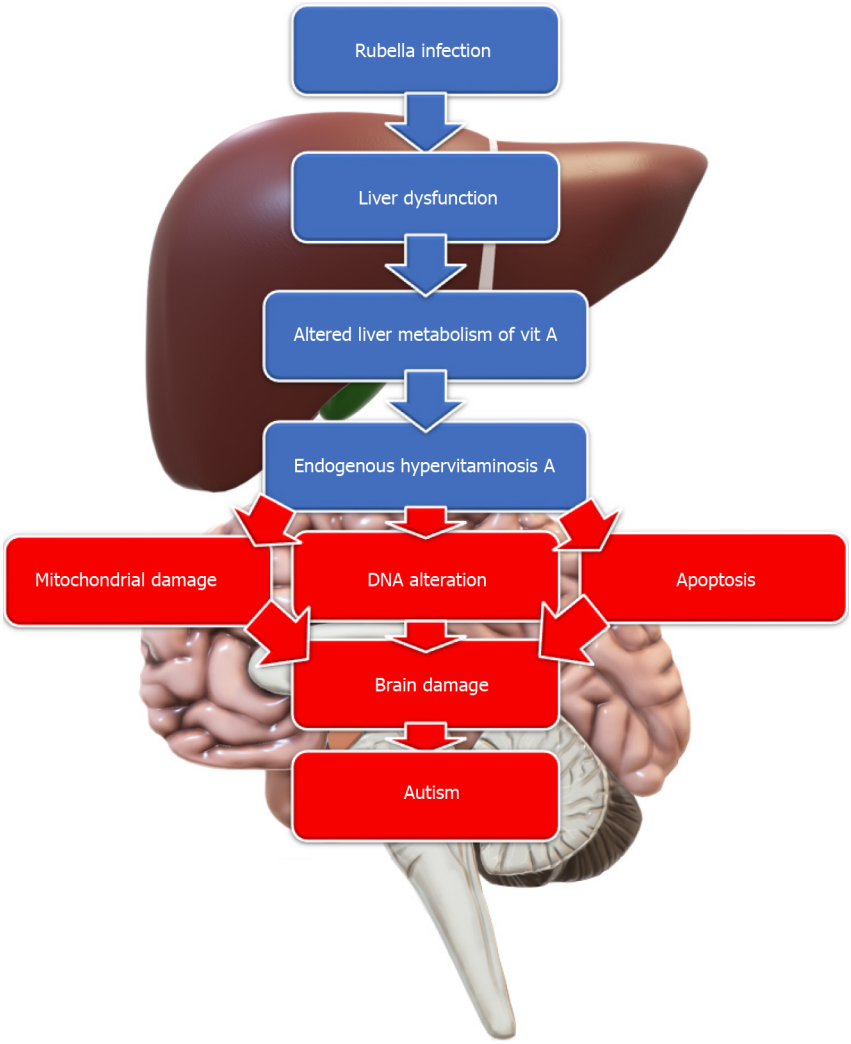

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Figure 3 The effect of antenatal Rubella Infection on the brain. Rubella virus causes liver dysfunction, which induces altered vitamin A metabolism and endogenous hypervitaminosis A. This hypervitaminosis A causes mitochondrial damage, DNA alteration, and altered apoptosis, resulting in brain damage and autism manifestations.

Due to the high incidence of autism in children with congenital rubella infection, they should be followed strictly for signs of autism. Symptoms of autism may not appear till adolescence. Conversely, clinicians should screen children with autism for possible signs of congenital rubella infection[75]. This delay in developing congenital rubella infection manifestations could be related to persistent rubella virus infection in the affected organs or developing autoimmune responses to an old infection[76]. Even though the United States of America was declared free from congenital rubella syndrome in 2004, the rate of autism is increasing in the USA, reaching a rate of 1:59[77]. The increased autism rate may indicate that subclinical rubella still plays a role, or at least rubella infection is just one of the players.

Cytomegalovirus: Human cytomegalovirus (CMV) is a double-stranded DNA neurotropic beta-herpes virus. It is the most prevalent member of the human herpesvirus family with high species-specificity as a human is the only host. Therefore, it is recently known as human herpes virus 5 (HHV-5)[78]. Congenital CMV infection is one of the leading infectious causes of neurological impairment in the new coming baby, with an infection rate between 0.5% and 1%. Congenital CMV infection can produce various clinical manifestations at birth in 10%–15% of the infected babies. However, asymptomatic infections can be reactivated anytime throughout life[79]. Engman *et al*[80] showed that congenital CMV infection is present in 3% of children with autism. CMV infection blocks interferon production and impairs CD8 T-cell function, thus inhibiting the antiviral defense mechanism of the host and inducing inflammation both in the maternal circulation and the placenta. In addition, it causes local infiltration of macrophage and T-cells at the site of infection *in vivo*, altering immune function and playing a significant role in perinatal brain injury[81,82]. CMV infection-associated alteration of the immune response causes disrupted development of particular regions or structures in the brain that lead to the development of autism[83].

CMV infection increases the circulating maternal pro-inflammatory cytokine levels, which is associated with an increased risk of autism and other mental disorders[84]. Children with congenital CMV infection may have many typical features of autism, including poor development of adequate interpersonal relationships, weak eye-to-eye contact, impaired language development, and non-thematic use of objects[85]. The presence of high CMV-IgM levels may indicate maternal infection with CMV[86]. Neonates with suspected congenital CMV could be diagnosed by detecting CMV-DNA in the cord blood or their urine in the first postnatal two weeks using real-time polymerase chain reaction[87,88]. Children with autism suspected of having congenital CMV infection may also have positive CMV-DNA in the urine and positive CMV- IgM antibodies in their serum[89,90]. Cranial ultrasound may show calcifications, increased periventricular echogenicity, ventriculomegaly, and intraventricular adhesions[91]. Magnetic resonance imaging (MRI) of their brain may reveal the presence of abnormal periventricular white matter intense areas, suggestive of disturbed myelination. MRI brain may also show an increased rate of hippocampal abnormality in children with congenital CMV infection. MRI may be normal in the first few weeks of life in children with congenital CMV; however, It may show the characteristic changes in white matter from temporal to posterior regions by one year of age[92,93]. Therefore, at birth, asymptomatic children might develop autism within the first few years of life[94].

In addition to congenital infection, CMV infection in infancy may raise the risk of developing autism. Postnatal CMV infection can impair overall cognitive functions and reduce intelligence during childhood and adolescence[58]. Lin *et al*[95] showed that CMV infection in infancy might raise the risk of consequent autism and epilepsy but not attention deficit hyperactivity disorder, particularly in infants under two years old. Yang *et al*[96] also showed that postnatal CMV infection might raise the predisposition to tuberous sclerosis and autism spectrum disorders. Both epilepsy and tuberous sclerosis are associated with an increased risk of autism[97].

Herpes simplex virus: The herpes simplex virus (HSV) is divided into two main types; HSV-1 and HSV-2. HSV-1 is mainly transferred through the oral route, while HSV-2 is principally transmitted through sex. About 67% of the global population has HSV-1 infection, while 13% have HSV-2 infection worldwide. About 15% of women of childbearing age are seropositive against HSV-2 globally[98]. HSV induces the release of inflammatory molecules and immune system activation that alter the brain structure with abnormal growth of the cerebral neocortex, a common finding in children with autism, especially during the first 6-12 mo of life[99]. A Norway study between 1999 and 2008 showed that active infection with HSV-2 in early pregnancy doubles the risk of developing autism in the male fetus. They found that increasing HSV-2 IgG levels in maternal mid-pregnancy plasma from 240 to 640 arbitrary units/mL doubles the risk of developing autism in male fetuses after adjusting for parity and the child's birth year. There were few female fetuses included in the study to conclude similar results. The presence of high mid-pregnancy antibody levels against HSV-2 might indicate an active maternal infection during early pregnancy[100]. However, a study by Gentile *et al*[101] showed no significant differences in the seropositivity rates and levels of anti-HSV-1 or anti-HSV-2 between children with autism and the controls. Another study by Slawinski *et al*[88] showed that the antenatal infection with CMV and not HSV-2 increases the risk of autism in the coming children. We still need more research to prove or disprove the effect of antenatal infection with HSV-2 on the risk of developing autism in the offspring.

Varicella-zoster virus: Varicella-zoster virus is s an alpha herpes DNA virus known as human herpesvirus 3 that causes chickenpox and herpes zoster (shingles). It is a neurotropic virus that can cause latent infection in the sensory nerve ganglia. It also induces neuroinflammation and is implicated in many central nervous system disorders, such as multiple sclerosis, that can share some common pathophysiologic features with ASD[102]. There is not much evidence about its role in the pathogenesis of autism. Gentile *et al*[103] showed an increased seropositivity rate for Varicella Zoster Virus in children with autism than in controls. They hypothesized that exposure to Varicella Zoster Virus and high titers of specific anti- Varicella Zoster Virus antibodies had a significant association with ASD. However, this association could be a cause or, on the other side, be due to increased susceptibility to infection with Varicella Zoster Virus due to vaccinophobia to MMR. Therefore, we need more studies to prove or disprove its causal relation. Some anti-varicella medications that are used to prevent or treat latent varicella infection can improve the symptoms of autism, establishing the causal relation of varicella infection with autism[104].

Influenza viruses: Influenza is caused by a group of enveloped negative-sense RNA Orthomyxoviridae viruses categorized into four main subgroups; Influenza types A, B, C, and D; among them, types A and B cause the well-known respiratory influenza disease. Influenza affects about 5%-15% of the world's population yearly, with more than three million people encountering severe infections and large numbers of hospitalization and deaths[105]. Influenza is associated with increased morbidity and mortality in high-risk groups, including pregnant women, and during the first two postpartum weeks, reliant on pre-existing immunity[106]. Some studies showed an increased risk of adverse neurodevelopmental outcomes such as autism or schizophrenia when pregnant ladies encounter influenza during pregnancy[107]. Mahic *et al*[108] found a statistically non-significant increase in the risk of autism in the offspring of seropositive mothers with symptoms of influenza during mid-pregnancy compared to

seronegative mothers. The chance may be responsible for this difference. Other biological factors, such as maternal immune system activation, could also be responsible. In addition, the influenza virus can trigger a cascade of acute-phase reactions, including fever which by itself increases the risk of autism, together with a systemic increase in cytokine expression[109].

However, many recent studies showed no increased risk of developing autism with influenza infection or vaccination during pregnancy in the offspring. In addition, Zerbo *et al*[110] showed no significant association between influenza infection and the risk of autism in the offspring. Meanwhile, they found a statistically non-significant increased risk of autism in the offspring when pregnant ladies received influenza vaccination during the first trimester. However, they emphasized that this observation should not call for any change in vaccination policy or practice. A more recent study by Becerra-Culqui *et al*[111] reported the same finding when they found no association between prenatal influenza infection or vaccination and increased risk of autism in offspring. They strongly recommended influenza vaccination to pregnant ladies to protect themself and their offspring. In addition, treatment of or prophylaxis against influenza during pregnancy did not pose a significant risk of autism. We should not ignore that influenza infection during pregnancy could increase the rate of complications such as preterm labor and encountering high-grade fever, which by itself increases the risk of autism. In addition, the discrepancies in the results of different studies could be related to methodological or population differences or the changes in the influenza virus structures across generations. Therefore, we need to perform more analyses on a broad scale.

SARS-CoV-2 viruses: COVID-19 is caused by infection by SARS-CoV-2, one of the beta coronaviruses, which caused the pandemic coronavirus COVID-19, posing a severe threat worldwide. SARS-CoV-2 can spread from the respiratory tract to the central nervous system through the olfactory bulb. COVID-19 induces brain structural changes that cause various neurologic complications that could last long[112]. There is a rising concern about the potentially harmful effects of SARS-CoV-2 on pregnancy that could affect the pregnant lady and her fetus[113]. Currently, there is no proof of SARS-CoV-2 vertical transmission from the mother to her fetus, which could be due to the preventive effect of placental lactoferrin. However, the virus could be transferred postnatally *via* the mother's air droplets or during breastfeeding[114]. Severe gestational COVID-19 induces uncontrolled inflammatory cytokine storm release and maternal immune activation, causing possible fetal organ damage, including the brain, that could manifest later with autism symptoms[28]. The induced inflammation causes amygdala neurodegenerative changes by "short-circuiting the electrical system," producing emotional feeling ability impairment and abnormal fear regulation due to an abnormal hypothalamic-pituitary-adrenal axis system[115].

Gestational COVID-19 activates the maternal immune system, increasing the pro-inflammatory cytokine production that inhibits the synthesis of placental Insulin-like growth factor-1 (IGF-1). Decreased IGF-1 production impairs perinatal myelination and induces dysconnectivity of the developing brain with permanent neurological deficits[116]. IGF-1 deficiency causes reduced perinatal neo-neuronal myelination mediated by oligodendrocytes in the developing nervous system, which in turn causes the early death of cerebellar Purkinje cells and the development of autism[117]. Additionally, SARS-CoV-2 infection can activate mast cells which in sequence activate microglial cells, releasing excessive inflammatory molecules, stopping synapses "pruning," damaging neuronal connectivity, and reducing the fear threshold, disorderly the emotional expression detected in children with autism[118] (Figure 4).

These changes can explain the increase in the rate of autism during the COVID-19 pandemic. Edlow *et al*[119] showed that in-utero exposure to SARS-CoV-2 infection might be associated with increased neurodevelopmental disorder rates in some offspring. However, Brynge *et al*[120] showed that the increased association of autism and other intellectual disabilities in the offsprings of mothers infected with SARS-CoV-2 during pregnancy does not necessarily reflect the causal relationship but is more probable to be related to common familial conditions such as shared genetic and environmental factors. On the other hand, Dutheil *et al*[121] claimed that the COVID-19 pandemic might be a reason for a decrease in the incidence of autism in a paradoxical phenomenon due to decreased global air pollution, which is a significant environmental trigger for autism.

To lessen the influence of gestational COVID-19, pregnant women should have adequate amounts of n-3 polyunsaturated fatty acids, vitamin D, folic acid, and a high choline and luteolin supplement. These supplements benefit brain development and function in the offspring of women who encounter viral infections during early pregnancy. Luteolin is a potent natural flavonoid inhibitor of microglia and mast cell activation and prevents SARS-CoV-2 binding to ACE2 receptors[118,122].

Zika virus: Zika virus (ZIKV) is an anthropoid-borne positive-sense RNA Flavivirus that spreads mainly by biting infected Aedes species mosquitos (Ae. aegypti and Ae. albopictus). It poses a significant threat to human health worldwide[123]. The severity of ZIKV infection ranges from mild influenza-like infection to severe conditions with neurological complications such as seizures and Guillain–Barré syndrome. Some strains of ZIKV can cross the placental barrier and infect cortical progenitor cells to promote cell death *via* enhancement of apoptosis and autophagy, producing severe congenital malformations (ZIKV Congenital Syndrome)[124]. ZIKV Congenital Syndrome includes

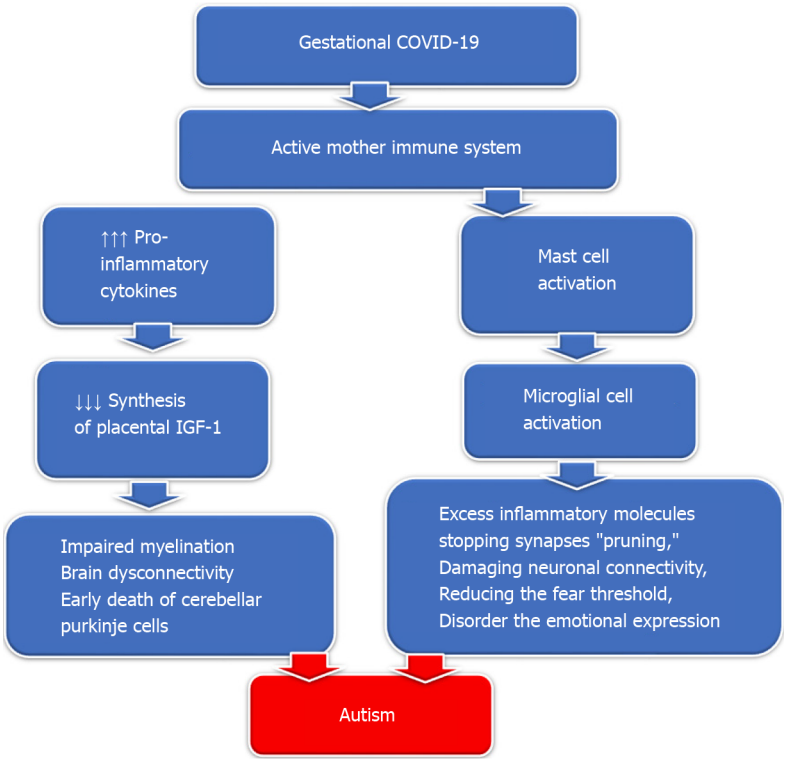

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Figure 4 The effect of gestational severe acute respiratory syndrome coronavirus 2 infection on the offspring brain. Maternal infection with severe acute respiratory syndrome coronavirus 2 activates the mother's immune system, releasing an excess of pro-inflammatory cytokines that decreases the placental synthesis of IGF-1, resulting in impaired myelination and brain dysconnectivity and early death of cerebellar Purkinje fibres. In addition, maternal immune activation causes mast cell activation, which activates microglial cell activation. Microglial cell activation causes excess inflammatory molecules, stopping synapses "pruning," damaging neuronal connectivity, reducing the fear threshold, and impairing emotional expression ending in the development of autism manifestations. COVID-19: Coronavirus disease 2019.

microcephaly, hypoplasia or atrophy of the cerebral cortex, cerebellum, brainstem, abnormal cortical formation, corpus callosum anomaly, other neurological abnormalities, cerebral palsy, severe developmental delay, and eye defects, which are one of the severe complications that occur when the mother gets infected during pregnancy[125]. Unfortunately, no specific antiviral medications or vaccines are available against ZIKV infection[126].

In a large population-based mother-child cohort study during the 2016-ZIKV outbreak in the United States, about 15.3% of toddlers with in-utero exposure to ZIKV had abnormal neurodevelopment findings at two years of age[127]. The inflammatory process generated by ZIKV during pregnancy has bi-mutual pathways. In one aspect, it helps to eradicate the virus, and in another aspect, it causes damage to the developing brain. The released inflammatory mediators, such as interleukin-6 and tumour necrosis factor-alpha, affect brain development, delay neuronal maturation, alter brain connectivity, and trigger autism symptoms[128]. There were some reports of increasing reported cases of autism in the offspring of mothers infected with ZIKV during pregnancy. Nielsen-Saines *et al*[129] observed 18 children who developed neurological symptoms out of 216 offspring from mothers infected with ZIKV during pregnancy. Six children out of 18 had autism manifestations. In addition, three children born asymptomatic developed autism manifestations at one year of age. In addition, Abtibol-Bernardino *et al*[130] showed that five children out of 26 who had antenatal exposure to ZIKV developed severe neurological disorders; two of them had autism. Therefore, children with a positive history of in-utero ZIKV exposure should have a serial follow-up for any neurological impairment, including autism, even when born asymptomatic.

ANTIVIRALS AND DRUGS WITH ANTI-AUTISM EFFECTS

Henderson[131] described a four-year-old child with a bipolar disorder associated with violent aggression and manifestations of autism and attention deficit hyperactivity disorder resistant to conventional treatment, including anticonvulsants, methylphenidate, guanfacine, lithium, and neuroleptics. After the failure of multiple regimens to stabilize the mood, the patient received a trial of valacyclovir 1000 mg twice till improved, then with half the dose to complete three years. The patient improved

dramatically in irritability, volatile mood, social reciprocity, concentration, and overall personality. The potential benefit of valacyclovir could be related to improving subclinical herpes simplex. Meanwhile, Kimberlin *et al*[132] found that oral acyclovir (300 mg/square meter/dose taken three times daily for six months a) can improve the neurodevelopmental outcomes in children who survived neonatal herpes simplex disease with central nervous system involvement. In addition, naltrexone therapy may benefit children with autism, particularly in the presence of self-injurious behaviour, failure of other treatments, and "high opioid tone" autism[133]. Naltrexone has immune-modulating effects and prevents the activation of grey and white matter astrocytes in specific brain areas, especially frontal cortical tissues, causing a reduction of injurious behaviour[134]. Intravenous immunoglobulins (IVIG) are one of the well-established treatment methods for severe systemic infections, including viral infections[135]. IVIG showed promising efficacy in treating autoimmune encephalopathy in children with autism, especially with high anti-dopamine D2L receptor antibodies[136]. Connery *et al*[137] showed that IVIG effectively alleviated the symptoms of irritability in children with autism who developed autoimmune encephalopathy. The presence of anti-dopamine D2L receptor antibodies is associated with improved responsiveness to IVIG therapy with modulation of behaviour. Therefore, we can use these antibodies to predict the responsiveness to IVIC therapy in these children.

N-acetylcysteine is derived from the amino acid L-cysteine and helps to regenerate glutathione with the release of glutamate into the extracellular space, reducing glutamatergic neurotransmission at synapses, correcting brain glutaminergic dysregulation, and consequently improving the autistic manifestations. It helps to reduce irritability and hyperactivity and improves social awareness in patients with autism[138,139]. Boris *et al*[140] found in a small cohort of children with autism that oral using 30 or 60 mg of Pioglitazone for three to four months might induce apparent clinical improvement of the behavioural symptoms in those children without significant side effects. Pioglitazone is an antidiabetic medication that modulates the effect of insulin. Pioglitazone can reduce IL4 production in CD4 cells and block IL10 and IL4 production by T cells. It also may help shift the T-cell response from Th2 to Th1 or decrease Th2 cytokine expression. Therefore, oral Pioglitazone may be of therapeutic advantage in children with autism[141].

INCREASED RISK OF VIRAL INFECTIONS IN PATIENTS WITH AUTISM

Children with autism have more chances of getting infected. Sabourin *et al*[142] showed that children with autism are more susceptible to infections in the first four postnatal weeks and the first three years of life than the typically developed children. In addition, they found that children with autism also have more infections in the first four weeks of life than children with other developmental disorders. Children with autism have multiple co-morbidities and behavioural problems that increase the risk of contracting various infections, including viruses[97]. Table 2 shows some important risk factors and co-morbidities that increase the risk of contracting diseases in children with autism.

Children with autism have a high rate of autoimmune diseases, immune dysregulation, and impaired levels of immune mediators, indicating continuing immune dysfunction[51]. Some genetic causes of autism are associated with an immune deficiency that increases the risk of infections, including viral disease, *e.g.*, Timothy syndrome[143]. Heuer *et al*[144] showed that children with autism have lower plasma IgG and IgM levels than typically developed children and children with developmental delays. The levels of these immunoglobulins were negatively correlated with the autism severity, as indicated by the Aberrant Behavior Checklist score. Children with autism commonly have mitochondrial dysfunction. Mitochondrial dysfunction is associated with reduced oxidative phosphorylation and burst in granulocytes which causes an impaired immune response and weak antioxidant defence[145].

Children with autism are subject to restrictive nutrition supplements either due to the restrictive and selective behaviour associated with autism, sensory-based feeding problems, relational sphere disorders, biological food intolerance, medically related feeding problems, and restrictive dietary management, that expose them to various nutritional deficiencies which further impair their immunity and susceptibility to infection[97]. Babaknejad *et al*[146] found statistically significantly lower plasma zinc levels in patients with autism than in healthy controls. Zinc deficiency negatively impairs children's mental development and physical growth and might damage their immune systems[147]. Vitamin C deficiency was also reported in some patients with autism due to the severely restricted diet or the associated gastrointestinal disorders that prevent adequate vitamin C intake or absorption[148,149]. Vitamin C is essential for the integrity of the mucous membrane and general immunity[147]. In addition, children with autism have the highest rate of vitamin A deficiency compared to other micronutrients, and the degree of deficiency is correlated with autism severity[150]. Vitamin A significantly impacts gastrointestinal functions and the skin's innate immunity. Therefore, vitamin A deficiency increases the risk of skin infections[151]. Vitamins A and D regulate microbial complexity, mucosal barrier function, and immune responses, ensuring intestinal homeostasis. Therefore, its deficiency induces gut dysbiosis and enhances the dysbiotic microbial communities, increasing susceptibility to infection and the risk of gastrointestinal tract injury[152].

Table 2 Important risk factors and co-morbidities that increase the risk of contracting infections in children with autism

Risk factors	Description
Immune system disorders	High rate of autoimmune diseases
	Immune dysregulation of T cell functions
	Impaired levels of immune mediators
	lower plasma IgG, and IgM
	Continuing immune dysfunction
	High rate of mitochondrial dysfunction
	Oxidative stress
	Neutrophils dysfunction
Medical co-morbidities	Genetic disorders: *e.g.*, fragile X syndrome, Down syndrome, Duchenne muscular dystrophy, tuberous sclerosis complex, and neurofibromatosis type I
	Neurological disorders: *e.g.*, cerebral palsy and congenital abnormalities
	Gastrointestinal disorders: Gastroesophageal reflux and inflammatory bowel disease
	Metabolic disorders: mitochondrial disorders, disorders of creatine metabolism, selected amino acid disorders, disorders of folate or vitamin B12 metabolism, and selected lysosomal storage disorders
	Allergic disorders: Such as asthma, nasal allergies, atopic diseases (IgE-mediated)
Behavioral problems	Stereotyping behavior: Affecting mouth and general hygiene
	Mouthing and pica behavior
	Faecal smearing
Feeding and nutritional disorders	Biological food intolerance
	Restrictive and selective behavior
	Sensory-based feeding problems
	Relational sphere disorders
	Medically-related feeding problems
	restrictive dietary management
	Nutritional deficiencies: *e.g.*, Vitamin A, D, C, and zinc
Gastrointestinal dysfunctions	Gastroesophageal reflux
	Autonomic dysfunction and Impaired intestinal motility
	Gastric hypoacidity and
	Impaired digestive enzyme production
	Gut dysbiosis
	Inflammatory bowel disease
Vaccinophobia	Lack of parental education and awareness
	Anti-vaccine movement

Normal intestinal motility is required for healthy gut microbiota by washing out any abnormal bacterial growth in the body. Children with autism have impaired intestinal peristalsis and digestive abilities due to autonomic dysfunction. They frequently get constipation resulting in abnormal proliferation and impaired clearance of the pathogenic intestinal bacteria. In addition, children with autism have gastric hypoacidity and impaired digestive enzyme production, which augments the resulting dysbiosis[153]. Conversely, gut dysbiosis correlates with the severity of autism, cytokine quantities, and tryptophan homeostasis. Therefore, gut microbiota modulation may alleviate the symptoms of autism [154].

Another critical risk factor that increases the risk of viral infections in children with autism is the reluctance of some parents to vaccinate their children with autism. Despite the marked progress in studying the epidemiology, aetiology, pathophysiology, and genetics of autism; many misguided scientists; politicians, and frustrated parent groups still resist vaccinating children with autism[155]. Since Andrew Wakefield and his 12 colleagues published their frauded paper in British Medical Journal

in 1998, the vaccination rate of children with autism significantly declined, especially for measles, mumps, and rubella[156]. The resultant antivaccine movements considered three main pillars for their action. They hypothesized that combining the measles-mumps-rubella vaccine can induce intestinal mucosal damage, allowing the entry of encephalopathic proteins that trigger autism. In addition, they suppose that the ethylmercury-containing vaccine preservative thimerosal is neurotoxic. They also suggest that concurrently administering multiple vaccines devastates or weakens the immune system [157]. Zerbo *et al*[158] found that the vaccination rate in children with autism and their younger siblings was significantly lower than in the typically developed children. Parents of children with autism were more reluctant to vaccinate at least one recommended vaccine for the child's younger sibling and to limit the number of vaccines given during the first year of life of the younger siblings.

Limitations and future direction

Many included studies were of a limited number of patients or were done in animal models. We need to have long-term, multicentered studies that include different races and populations to better judge the interplay between infections and autism as a cause or effect. Pregnant women should ensure their vaccination against influenza, as this can prevent them from getting the flu while pregnant, which can cause complications for the mother and the baby[105-108]. When women get vaccinated against influenza, they protect their unborn babies from getting this illness while in the womb. Studies have shown that influenza virus infection can cause severe problems for babies if infected during the first trimester of pregnancy, leading to preterm birth or stillbirth in some cases[109-111]. By getting vaccinated, pregnant women can protect themselves and their unborn babies from the flu while helping to reduce the spread of the disease in the community. Pregnant women could have enough vitamin D, folic acid, n-3 polyunsaturated fatty acids, and high choline and luteolin[117,122].

Early screening and possibly diagnosis to detect and may prevent autism are crucial for reducing the burden of this condition. Long-term follow-up is necessary for infants whose mothers report an inflammatory event due to viral infection at any time during pregnancy to monitor for signs of autism. In addition, children with autism should be screened for congenital rubella and cytomegalovirus infections [76,96]. Further research is needed to investigate whether specific vaccines or other measures taken during pregnancy can prevent the development of autism in children born to mothers whose certain viruses have infected them.

CONCLUSION

Autism is a group of heterogeneous, multi-factorial, neurodevelopmental disorders. Several factors play together to increase the risk of development of autism, including genetic, epigenetic, and environmental factors, together with antenatal and early-life infections. Viral infection during critical periods of early in-utero neurodevelopment may lead to an increased risk of autism. Maternal infection by DNA or RNA viruses that can cross the maternal-fetal interface may induce neurodevelopmental problems in the developing fetus. Viral infection induces neuroinflammation that affects many neurological processes, including neural development, brain structures, synapse plasticity, cognition, and behaviour; therefore, it may end in the development of autism. There are many shreds of evidence that rubella, cytomegalovirus, herpes simplex virus, influenza viruses, SARS-CoV-2 viruses, and zika virus infections during pregnancy and early life can trigger autism development. Conversely, children with autism are at increased risk of infections, including viruses. Every effort should be made to prevent maternal and early-life infections and reduce the risk of autism. Vaccination against common viral agents may help to reduce the prevalence of autism. Immune modulation of children with autism should be considered to reduce the risk of infection.

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MINIREVIEWS

Pediatric multisystem inflammatory syndrome associated with COVID-19: Insights in pathogenesis and clinical management

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Abstract

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been a major challenge to be faced in recent years. While adults suffered the highest morbidity and mortality rates of coronavirus disease 2019, children were thought to be exclusively asymptomatic or to present with mild conditions. However, around April 2020, there was an outbreak of a new clinical syndrome related to SARS-CoV-2 in children - multisystemic inflammatory syndrome in children (MIS-C) - which comprises a severe and uncontrolled hyperinflammatory response with multiorgan involvement. The Centers for Disease Control and Prevention considers a suspected case of MIS-C an individual aged < 21 years presenting with fever, high inflammatory markers levels, and evidence of clinically severe illness, with multisystem (> 2) organ involvement, no alternative plausible diagnoses, and positive for recent SARS-CoV-2 infection. Despite its severity, there are no definitive disease management guidelines for this condition. Conversely, the complex pathogenesis of MIS-C is still not completely understood, although it seems to rely upon immune dysregulation. Hence, in this study, we aim to bring together current evidence regarding the pathogenic mechanisms of MIS-C, clinical picture and management, in order to provide insights for clinical practice and implications for future research directions.

Key Words: Pediatric multisystem inflammatory disease; COVID-19 related; Multisystem inflammatory syndrome in children; COVID-19; SARS-CoV-2; Etiology; Disease management

Core Tip: Multisystem inflammatory syndrome in children (MIS-C) comprises a severe and out-of-control inflammatory response with multiorgan dysfunction following severe acute respiratory syndrome coronavirus 2 infection. Despite its severity, there are no definitive disease management guidelines for this condition. Conversely, the complex pathogenesis of MIS-C is still not completely understood, although it seems to rely upon immune dysregulation. Hence, in this study, we aim to bring together current evidence regarding the pathogenic mechanisms of MIS-C, clinical picture and management, in order to provide insights for clinical practice and implications for future research directions.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic has been a major challenge to be faced in recent years. With variable clinical manifestations, the disease mainly affects older people with comorbidities, whereas children were not initially considered a risk group for its severe form[1]. However, even though COVID-19 in children is generally milder when compared to adults, it was noticed that a small part of infected children are subject to a post-infectious severe condition presenting with multiorgan dysfunction and systemic inflammation, thus called multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19[2,3]. Several aspects of this syndrome are still unclear, given its recent discovery. Initially, the heterogeneous clinical picture of MIS-C was attributed to conditions such as Kawasaki disease (KD) or toxic shock syndrome, due to the existing similarities. However, as COVID-19 pandemic progressed, there was an urge to recognize MIS-C as a new clinical condition that needs to be thoroughly understood[4].

Epidemiological data, although not very robust, suggest that the incidence of MIS-C is higher in African, Afro-Caribbean and Hispanic countries, while the incidence in East Asian countries is lower[5]. Furthermore, factors such as age, viral load and chronic comorbidities are considered risk factors for severe manifestations of COVID-19 and therefore may be associated with the development of MIS-C[6-8].

MIS-C usually develops weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and, even though its pathophysiological mechanisms are still unclear, studies point to an exacerbated immune response that leads to a state of hyperinflammation, *i.e.*, an imbalance between host pro-inflammatory and anti-inflammatory mechanisms with the potential to affect multiple organs [9]. Regarding its presentation, MIS-C associated with COVID-19 has a broad clinical spectrum in which fever is the main symptom. In addition, patients may also manifest gastrointestinal disorders, such as diarrhea and vomiting, abdominal pain, shock and/or hypotension, respiratory symptoms such as cough and dyspnea, as well as cardiac and neurological symptoms[10].

There are differences between the main definitions of MIS-C made by the Royal College of Pediatrics and Child Health (RCPCH), Center for Disease Control and Prevention (CDC) and the World Health Organization (WHO). However, all three institutions agree on the presence of fever, laboratory findings indicative of active inflammation, multisystem organ involvement without a plausible underlying diagnosis, as well as proven infection by COVID-19 or recent exposure to a case of COVID-19[11]. In this sense, a well-established definition is essential for early diagnosis and exclusion of the main differential diagnoses.

Considering that MIS-C is a serious condition with numerous possibilities of complications and scarce scientific evidence on the subject, standardizing a therapeutic line to be followed has been a challenge[5]. The main guidelines advise that the treatment should be done individually, aiming to control hyperinflammation and recover organic function[12]. Some medications such as intravenous immunoglobulin (IVIG) and other anti-inflammatory and immunosuppressive therapies are considered the mainstay of treatment for MIS-C. In addition, other drugs such as steroids and immunobiologicals and aspirin have also been widely used with reservations[13]. This minireview aims to bring together current evidence regarding the pathogenic mechanisms of MIS-C, clinical picture and management, in order to provide insights for clinical practice and implications for future research directions.

PATHOGENESIS OF MIS-C

The pathogenesis of MIS-C is a complex event that has not yet been fully elucidated. To date, three hypotheses that may be associated with the development of the syndrome are highlighted: (1) SARS-CoV-2 spike protein superantigenic profile[14,15]; (2) Chronic response to viral antigen exposure[16]; or (3) Production of autoantibodies in response to the viral infection[17]. These may provide a subset for further understanding about the immunopathological features of MIS-C, which, in turn, apparently rely on autoreactivity, cytokine storm, and immune dysregulation[18]. Thus, we hereby discuss, in detail, the main findings regarding the immunological issues associated with MIS-C.

Immune dysregulation

A major factor that maintains the hyperinflammatory state of MIS-C is immune dysregulation[19]. Currently, several manuscripts have demonstrated the occurrence of disorders related to innate and adaptive immunity and to cytokine response[20-22]. In this regard, Huang *et al*[20] exploit some of these aspects. Apparently, classic monocytes and type 2 dendritic cells were found to be downregulated in MIS-C, while type 1 DCs were greatly activated. Interestingly, some findings also suggest that this syndrome presents with impaired antigen presentation, given the low levels of HLA-DR and CD86 in monocytes and dendritic cells[23]. Altogether, these data support a possible role for antigenic cross-presentation as one of the possible mechanisms of MIS-C, since this process is strongly related to the action of CLEC9A, a major marker of type 1 DCs[20]. Moreover, elevated expression of alarmin-related S100A genes is also documented[19]. These molecules are closely related to the triggering of inflammatory mechanisms in the innate immune response, *via* Toll-like receptors (TLRs), and play a role in apoptosis and organ damage[24].

As for T cells, Ramaswamy *et al*[19] describe an increased expression of perforins, granzyme A and H on natural killer cells and CD8+ T cells. These cytotoxic molecules greatly increase tissue damage characteristic of MIS-C. Also, skewed T cell receptor (TCR) repertoire with TRBV11-2 expansion, found in severe MIS-C patients may indicate exposure to a superantigen (SAg) or be related to the presence of autoreactive T cells, while γδ and CD4+CCR7+ T cells activation is highlighted by elevated HLA-DR expression[23]. On the other hand, B-cells show an intriguing pattern in MIS-C, characterized by increased numbers of plasmablasts. However, their role in the pathophysiology of the syndrome requires further investigation[25]. Additionally, MIS-C patients apparently present interferon-gamma (IFN-γ) response dysregulation, which is characterized by exacerbated production of CXCL9 in response to IFN-γ[22]. Of note, excessive production of this chemokine is related to increased disease severity[26].

Cytokine storm

Emerging evidence has highlighted MIS-C as a state of out-of-control release of cytokines - referred to as "cytokine storm" - and immune cell hyperactivation[27]. In fact, high levels of interleukin-1β (IL-1β), IL-6, IL-8, IL-10, IL-17, and IFN-γ, with raised C-reactive protein (CRP) and ferritin, were reported in the acute phase of MIS-C[23]. Carter *et al*[23] also demonstrated that MIS-C patients show raised fibrinogen levels, raised D-dimer, and low platelet count, which suggests a possible interplay between cytokine storm/hyperinflammation and pro-coagulant state development. This crosstalk has also been extensively explored in the pathophysiology of severe acute COVID-19[28-30]. Since the up-regulated cytokines IL-1β, IL-6, and IL-8 are critically involved in pro-inflammatory-induced coagulation in other conditions, their role in MIS-C-related hypercoagulable state should be further investigated[31-34].

Except for IL-1β and IL-17 elevations, these results are ratified by Diorio *et al*[35]. In that study, the authors report that the sum of IL-10 and tumor necrosis factor (TNF)-α levels was hypothesized to differentiate between MIS-C and severe COVID-19 patients [mean (95% confidence interval); severe: 30.06 (9.54-50.6) *vs* MIS-C: 82.25 (32.5-132.0), $P = 0.036$]. The significant and paradoxical elevation of IL-10 - a potent anti-inflammatory cytokine with immunoregulatory functions[36] - also differs from the cytokine profile seen in KD[37]. There were also noted increases in markers of endothelial dysfunction in both MIS-C and severe COVID-19 with elevated sC5b-9 concentrations. At last, univariate linear regression modeling revealed that sC5b-9 levels correlated in a statistically significant manner with IL-6, IL-8, and TNF-α[35].

Although Diorio *et al*[35] demonstrate that sC5b-9 was significantly elevated in patients with severe COVID-19 in comparison with those with minimal COVID-19, the observed elevated levels in MIS-C patients did not reach statistical significance. However, a subsequent study by Syrimi *et al*[21] revealed that complement protein C9 and C5b-9 were significantly increased in MIS-C patients at the acute stage of the disease. C5b-9 is a marker of the formation of the membrane attack complex, the final common pathway of complement activation[38]. The hyperactivation of complement components including C5a in sera and C5b-9 correlates with the out-of-control release of pro-inflammatory cytokines including TNF-α, IL-1, and IL-6[39]. These authors also demonstrated that MIS-C patients had significantly increased levels of the chemokine's monocyte chemoattractant protein 1 (MCP-1/CCL2) and interferon gamma-induced protein 10 (IP-10/CXCL10). Higher levels of IL-6, IL-18, and IL-10 were also observed [21]. On the other hand, in contrast with previous findings, no difference was observed in the levels of

IL-1β, IL-8 (CXCL8), IL-17A, IFN-α_2, IFN-γ, and TNF-α in MIS-C patients in comparison with the healthy donor controls.

Cytokine profiling also identified elevated signatures of inflammation (IL-18 and IL-6), lymphocytic and myeloid chemotaxis and activation (CCL3, CCL4, and CDCP1), and mucosal immune dysregulation (IL-17A, CCL20, and CCL28) in another report[40]. Gruber *et al*[40] suggested that elevations in unique chemokines (CXCL5, CXCL11, CXCL1, and CXCL6) and cytokines (including IL-17A, CD40, and IL-6) appear to distinguish MIS-C patients from pediatric COVID-19 patients. In another study, IL-6, IL-17A, and CXCL10 were also found to contribute the most to the cytokine storm. In contrast, the main negative contributors were adenosine deaminase, stem cell factor, and TWEAK[17] - a suppressor of production of IFN-γ and IL-12, that attenuates the innate response and its transition to adaptive Th1 immunity[41]. However, despite being raised in MIS-C patients, IL-17A seems to drive Kawasaki- but not MIS-C-associated hyperinflammation[17].

At last, more recent studies reiterate that a robust cytokine release might explain the severity and outcome of MIS-C. Abo-Haded *et al*[42] recently reported that mild MIS-C patients present higher levels of IFN-α, IFN-γ, IL-6, IL-8, IL-10, and CXCL10 in comparison with the control group. Conversely, there was an extremely significant difference regarding all measured cytokines when comparing both study groups (mild and severe) ($P < 0.0001$)[42]. Severe MIS-C patients showed higher levels of IFN-α, IL-1β, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), and HMGB1 ($P < 0.0001$), alongside less significant increases ($P < 0.05$) in IL-8, TNF, and GM-CSF. These findings suggest that the cytokine profile and its serum levels may be determining factors for the clinical outcome of patients with MIS-C.

Cytokine storm-induction mechanism

Despite these findings, the molecular features of the MIS-C-related cytokine storm have not been completely understood. One potential explanation for the out-of-control release of cytokines seems to be an antibody-dependent enhancement (ADE) mechanism[43,44]. In ADE - also called immune enhancement - pre-existing non-neutralizing or sub-neutralizing antibodies (nNAbs) bind to virus-derived antigens[43,44]. The resulting immunocomplexes may further interact with the immune cell's membrane harboring the immunoglobulin G (IgG) Fcγ receptor (FcγR) through the Fc domain of the immunoglobulin, thereby activating the immunoreceptor tyrosine-based activation motifs of these receptors[45-47]. When triggered, downstream signaling pathways induce the release of a variety of cytokines and immune cell recruitment[48,49]. The engagement of complement receptors could also represent a possible ADE-related mechanism. Once recognized by complement receptors, immunocomplexes bonded to complement-derived molecules could also trigger cytokine release and immune activation[49] (Figure 1). On the other hand, ADE may also promote SARS-CoV-2 epitope intake into the host cell cytoplasm[50]. nNAbs-antigen immunocomplexes interaction with FcγR facilitates the internalization of the virus into host cells by endocytosis[48]. At last, upon internalization, endocytic TLRs can then recognize these viral particles and also induce immune cell activation and recruitment[50].

In contrast, other studies have highlighted that MIS-C cytokine storm could also be attributed to a SAg-induced immune response. SAgs are highly potent immunostimulatory molecules that induce T cell activation through binding to specific β chains of TCRs at their variable domain in a complementarity-determining region 3-independent (CDR3-independent) manner[51,52]. This activation requires simultaneous interaction of the SAg with the Vβ domain of the TCR and HLA class II molecules on the surface of an antigen-presenting cell[53]. The specificity of SAg attachment to different TCR Vβ chains results in Vβ skewing, whereby the frequency of T cells responding to SAg exposure exceeds that of conventional peptide antigens[54].

It has been recently demonstrated that an insertion unique to SARS-CoV-2 spike glycoprotein exhibits a SAg-like sequence motif that possesses a high affinity for binding TCR, interacting closely with both the α- and β-chains variable domains' complementarity-determining regions[14,55]. In this sense, Porritt *et al*[15] showed that MIS-C patients present a profound expansion of TCRβ variable gene 11-2 (TRBV11-2), with up to 24% of clonal T cell space occupied by TRBV11-2 T cells. The author also found a significant correlation between TRBV11-2 usage and TNF-α, IFN-γ, IL-6, and IL-10 levels[14]. Therefore, it seems that the TRBV11-2 expansion and possible activation may be one of the main features in the MIS-C-related out-of-control cytokine release. These findings were ratified by Moreews *et al*[56], that observed a specific expansion of activated T cells expressing the Vβ21.3 T cell receptor β chain variable region in both CD4 and CD8 subsets, and this was also associated with the observed cytokine storm. Although multiple cytokine storm-induction mechanisms have been proposed, further research is needed to build a more reliable model of MIS-C-related immunopathophysiology.

Autoreactivity

The rapid resolution of disease following high-dose IVIG administration has raised the hypothesis that MIS-C could be an autoantibody-mediated condition[57]. IVIG is a usual approach to triggering inhibitory FcγR, thus exerting a multitude of immunomodulatory properties[58]. Upon FcγR engagement, IVIG may thereby preclude Th1 and Th17 differentiation, enhance CD4+FoxP3+ regulatory T cells expansion, and inhibit autoantibody release by B-cells, for example[59-61].

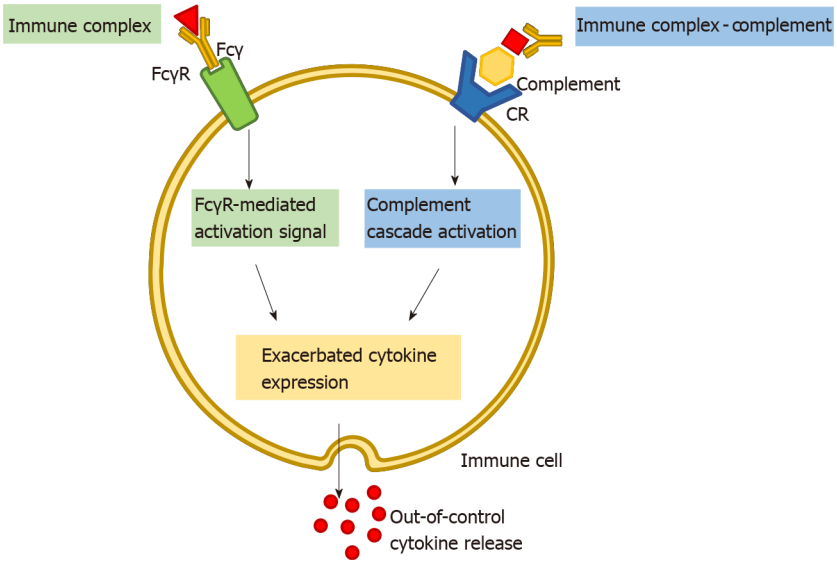

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Figure 1 Simplified scheme of antibody-dependent enhancement mechanism of multisystemic inflammatory syndrome in children-C-related cytokine storm. FcγR: Fcγ receptor; CR: Complement receptor.

Based on this, Gruber *et al*[40] tested the hypothesis that SARS-CoV-2 infection leads to a secondary autoreactive humoral response. These authors' differential autoantibody analysis returned 189 peptide candidates for IgG autoantigens and 108 IgA autoantigens. More interestingly, the majority of these antigens present enrichment in organ systems that play a central role in the pathophysiology of MIS-C. Possible autoantigens include peptides expressed in the gastrointestinal tract (MUC15, TSPAN13, and SH3BP1), the endothelial and cardiac tissue (P2RX4, ECE1, and MMP14), and, notably, in immune cells (CD244, IL-1A, IFNGR2, IL-6R, and LAMP1)[40]. Moreover, the analysis of MIS-C plasma also revealed well-known disease-associated autoantibodies - namely anti-La, and anti-Jo-1[40]. Similarly, Consiglio *et al*[17] found that 26 Gene Ontology (GO)-terms were enriched in MIS-C samples. Among these, there were autoantigen peptides involved in lymphocyte activation processes, immune cell signalling, and structural proteins in the heart and blood vessels[17]. In turn, Porritt *et al*[61] identified a number of IgG-target tissue-specific antigens from the gastrointestinal and cardiovascular tracts, skeletal muscle, and brain tissues. On the other hand, Burbelo *et al*[62] have failed to detect autoantibodies against the majority (16/18) of the most relevant autoantigens raised by previous studies in MIS-C patients who did not receive IVIG. These data have highlighted that the first-line IVIG therapy may be a confounding factor in autoantibody measurements in MIS-C[62]. Therefore, these results suggest that secondary autoreactive humoral response may play a pivotal role in MIS-C pathobiology; however, further studies, taking into account possible confounding factors, are necessary to elucidate this matter.

CLINICAL MANAGEMENT

Clinical and laboratory features

Regarding the clinical manifestations of MIS-C, we relied on recent meta-analyses to identify the most prevalent symptoms of the syndrome. Overall, fever was the most predominant reported symptom, being present in 82.4% to 100% of total cases and with median duration of approximately 5 d, followed by gastrointestinal symptoms including diarrhea, abdominal pain, and vomiting (82%-85.2%)[10,63-66]. Respiratory symptoms have also been reported (25%-50.3%), such as cough, dyspnea, and sore throat, although not as prevalent as expected, which diverges from the classical COVID-19 manifestations, especially in comparison to adults[63,64]. Thus, a greater vulnerability for children to develop gastrointestinal symptoms is apparent, which highlights the need to consider the possibility of MIS-C in infants with non-respiratory manifestations along with a hyperinflammatory profile.

In addition, cutaneous manifestations similar to KD are reported, especially, polymorphic maculopapular exanthema (63.7%), and non-purulent conjunctivitis (56%)[65]. Furthermore, neurological and cardiac involvement are also outlined and represent a relevant aggravating factor. In this sense, neurological symptoms are commonly expressed as headaches, in most cases, irritability and lethargy [10,64,66]. On the other hand, cardiocirculatory manifestations are more frequently observed, present in approximately 80% of cases, with a broad spectrum that includes from tachycardia (76.7%), hypotension (77%) and shock (52%-68.1%) to myocarditis (41.4%), aneurysms (10.3%) and mild dilatation of the coronary artery (11.6%)[63,64,66].

Consistent with the syndromic manifestations of MIS-C, the laboratory findings demonstrate an expected hyperinflammatory state. The most important laboratory findings demonstrate increased levels of inflammatory markers, such as CRP, ferritin and IL-6[63,66], along with increased erythrocyte sedimentation rate and procalcitonin[66,67]. Moreover, complete blood count often reveals leukocytosis, with increased neutrophil levels[67]. Lymphocytopenia is also a common finding, along with anemia and normal or reduced platelet count[63,64,66]. Regarding the coagulation panel, D-dimer and fibrinogen showed a considerable increase[64,65,67].

As for markers of myocardial injury, such as troponin, B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), evidence points to a frequent elevation, being current factors of concern in the management of children with MIS-C[63,64,67]. Troponin levels > 32 pg/mL are considered a major predictor of myocardial involvement in MIS-C[68]. Similarly, elevated levels of NT-proBNP are associated with myocardial dysfunction and severe MIS-C, being considered a useful biomarker for early identification of impaired cardiac function[69].

Diagnosis

Currently, MIS-C diagnosis is conducted through criteria established by important health institutions on characteristics such as age, clinical picture, inflammatory markers, and molecular or serological COVID-19 testing[70]. Of note, three distinct case definitions stand out in the diagnosis of MIS-C: That of the RCPCH[71], the WHO[72] and the CDC[73].

Overall, when faced with a suspected case of MIS-C, specific laboratory findings should be measured to assist the diagnosis[74]. In this regard, Gottlieb *et al*[75] points out the major parameters necessary for the evaluation of these cases, such as: Complete blood cell count; electrolytes; renal and liver function; inflammatory markers (CRP, D-dimer, albumin and coagulation panel); BNP; tests for SARS-CoV-2, such as polymerase chain reaction (PCR) and/or serologies; as well as troponin, ferritin, fibrinogen and procalcitonin.

In this context, the available case definitions serve as a guide for clinical practice, as they synthesize the main findings related to the diagnosis of MIS-C. According to the RCPCH, MIS-C is characterized by persistent fever > 38.5 °C, inflammation and single or multi-organ dysfunction, along with additional features such as abdominal pain, conjunctivitis, lymphadenopathy and rash and exclusion of any other microbial cause[71]. On the other hand, WHO case-definition of MIS-C includes individuals aged 0-19 years with fever ≥ 3 d, at least 2 concomitant systemic symptoms, elevated markers of inflammation, evidence of COVID-19 or contact with contaminated patients and no apparent other etiology for the inflammation[72]. Ultimately, CDC diagnosis of MIS-C includes: Individuals under 21 years of age presenting with fever ≥ 38.0 °C for ≥ 24 h; laboratory evidence of inflammation, presence of severe multisystemic disease; no other plausible alternative diagnosis; presence of reverse transcription PCR (RT-PCR), serology, or antigen test positive for COVID-19 currently or recently, or exposure to the virus within 4 wk prior to symptom onset[73]. Table 1 summarizes the major differences between these case definitions. Among these case definitions, Hoste *et al*[63] demonstrate a greater accuracy of the WHO MIS-C definition, comprising 97% of cases, followed by the CDC (62%) and lastly, the RCPCH.

Treatment

Treatment for patients with MIS-C relies on continuous monitoring of inflammatory markers to assess the progression of the condition[67]. Given the multisystemic involvement of MIS-C, its management should be performed with multidisciplinary team support, such as pediatric cardiologist, rheumatologist, and infectologist, and may require the assistance of other specialties, such as intensive care, neurology, nephrology, or gastroenterology[18]. Management of the condition follows a supportive approach and an immunomodulatory perspective. Thus, supportive care is crucial, including respiratory and circulatory support, ranging from intubation, intravenous fluids and inotropic support to extracorporeal membrane oxygenation[76]. In addition to supportive measures, immunomodulatory therapy with IVIG and steroids is established as first-line treatment for children with MIS-C, with a recommended dose of 2 g/kg IVIG[5,77]. In this regard, the American College of Rheumatology (ACR) prescribes IVIG alone in patients without shock or organ-threatening diseases, whereas the combination of IVIG combined with glucocorticoids in patients presenting with these conditions is recommended[5]. Furthermore, in patients in whom IVIG and corticosteroid therapy is not successful, the ACR recommends treatment with anakinra or infliximab at high doses[5].

Some studies have compared the efficacy of treatment with combined IVIG and methylprednisolone *vs* IVIG alone[78,79]. It is noted that the combined regimen is associated with significantly lower risk of poor outcome, such as treatment failure, acute myocardial dysfunction, need for hemodynamic support or second-line treatments. Furthermore, it is also established that in patients at high risk of thrombosis, anticoagulation therapy may be required[5], and that children with shock should be treated according to established guidelines for pediatric septic shock[80]. Given the complexity of management, children presenting with MIS-C-related symptoms should be quickly transferred to a pediatric intensive care center once stabilized[75].

Table 1 Case definition criteria for multisystemic inflammatory syndrome in children issued by the Royal College of Pediatrics and Child Health, World Health Organization and Centers for Disease Control and Prevention

Criteria	RCPCH[71]	WHO[72]	CDC[73]
Age	ND	< 21	< 19
Clinical	Persistent fever > 38.5 °C. Evidence of single or multi-organ dysfunction with additional features[1]	Fever ≥ 3 d; two of the following: (1) Mucocutaneous inflammation signs; (2) Hypotension or shock; (3) Cardiac issues[2]; (4) Evidence of coagulopathy; and (5) Acute gastrointestinal problems	Fever ≥ 38.0 °C for ≥ 24 h; multisystemic disease involving multiple (≥ 2) organs (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological). Requirement of hospitalization
Inflammatory markers	Neutrophilia, elevated CRP and lymphopenia	Elevated markers (such as ESR, CRP or procalcitonin)	Elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, neutrophils, LDH, or IL-6 or reduced albumin and/or lymphocytes
COVID-19 test	Positive or negative SARS-CoV-2 RT-PCR test	Evidence of COVID-19 (*via* RT-PCR, antigen test, or serology) or probable contact with patients contaminated with SARS-CoV-2	RT-PCR, serology or antigen test positive for COVID-19 (currently or in recent period) or exposure to the virus within 4 wk prior to symptom onset
Exclusion factors	Exclusion of any other microbial cause	No other obvious etiology for the inflammation	Absence of other plausible alternative diagnoses

[1]Additional features: Abdominal pain, confusion, conjunctivitis, cough, diarrhoea, headache, lymphadenopathy, mucus membrane changes, neck swelling, rash, resp symptons, sore throat, swollen hands and feet, syncope, vomiting.
[2]Cardiac issues: Myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP).
RCPCH: Royal College of Paediatrics and Child Health; WHO: World Health Organization; CDC: Centers for Disease Control and Prevention; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; IL-6: Interleukin 6; RT-PCR: Reverse transcription-polymerase chain reaction; ND: Not described; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019.

CONCLUSION

In this study, we have brought together the current evidence regarding the pathogenic mechanisms of MIS-C, clinical picture and disease management. Emerging evidence has highlighted this condition as a state of out-of-control release of cytokines, immune cell recruitment and activation, and production of auto-reactive peptides. However, there is still much to be clarified regarding the mechanisms behind the induction of this response profile. Treatment for patients with MIS-C currently relies on continuous monitoring of inflammatory markers to assess the progression of the condition and IVIG administration. However, despite MIS-C severity, there are still no definitive disease management guidelines for this condition.

FOOTNOTES

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MINIREVIEWS

Etiopathogenic theories about long COVID

Luis Del Carpio-Orantes

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Abstract

The main etiopathogenic theories of long coronavirus disease (COVID) are listed and a conjunction of them is carried out with the objective of deciphering the pathophysiology of the entity, finally the main lines of treatment existing in real life are discussed (Paxlovid, use of antibiotics in dysbiosis, triple anticoagulant therapy, temelimab).

Key Words: Long COVID; Viral persistence; Amyloid microthrombosis; Dysbiosis; Weakened immune system; Paxlovid; Triple therapy

Core Tip: List the main etiopathogenic theories of long coronavirus disease (COVID) and evaluate their interrelation as pathophysiological agents of long COVID syndrome.

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INTRODUCTION

Long coronavirus disease (COVID) is broadly defined as signs, symptoms, and conditions that continue or develop after initial COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The signs, symptoms, and conditions are present four weeks or more after the initial phase of infection; may be multi-systemic; and may present with a relapsing– remitting pattern and progression or worsening over time, with the possibility of severe and life-threatening events even

months or years after infection; this being the definition adjusted by the Centers for Disease Control and Prevention's, since the previous definition of the World Health Organization mentioned persistent symptoms after 12 wk[1].

However, for all these etiopathogenic processes that define long COVID to occur, there is still no specific evidence on it and various theories have been created that try to decipher the pathophysiology of said entity, some are independent, but others have strong ties between them. And depend on each other, the main etiopathogenic theories of long COVID are mentioned below:

Theory of viral persistence or viral particles: There is evidence that after an acute episode of COVID-19, there is persistence of viral particles in various organs up to one year after the episode and the organs mainly affected are: Brain, Gastrointestinal and Hemolymphatic; Similarly, they have been detected in blood, feces and urine[2,3].

Theory of endothelial dysfunction: This theory deals with the damage to the vascular endothelium that leads to endothelitis which, in turn, will favor platelet increase and activation, increased risk of thrombus formation with subsequent damage to organs and tissues by a mechanism of tissue ischemia that can affect the main organs and systems of the human body[4,5].

Theory of platelet hyperactivity: Which is related to the previous theory and mentions that this hyperactivity favors the formation of microthrombi which have the characteristic of being amyloid and in this area, is linked to the theory of viral persistence which mentions that protein S has amyloidogenesis potential, which makes these amyloid thrombi more resistant to degradation and more hard, which ensures occlusion of the microvasculature with subsequent diverse organic damage (highlights tissue destruction and damage to central and peripheral nerves)[6-8].

Crucial nerve damage theory: This theory ties in with the previous one and refers to damage to nerves crucial to the functioning of the autonomic nervous system, such as damage to the vagus nerve, which controls various functions of the cardiovascular systems, gastrointestinal and pulmonary, so damage to it can cause many symptoms in these systems[9].

Theory of immune abnormalities: After an acute COVID-19 case, there is evidence of persistent inflammation that feeds the inflammasome of each person, in addition to the presence of autoimmunity that adds various comorbidities to the patients and even the *de novo* appearance of rheumatological diseases such as lupus, dermatomyositis, rheumatoid arthritis, *etc.* In addition, the production of antibodies against the angiotensin converting enzyme-2 (ACE2) receptor has been demonstrated that could decrease the activity of ACE2, both in the soluble part and in the membrane-bound part, which would finally activate the immune system, which can act as immunological priming by molecular mimicry. In the same way, an "exhaustion of the immune system after an acute COVID-19 condition has been demonstrated, which conditions a decrease in lymphocyte subpopulations and the subsequent risk of opportunistic diseases[10-14].

Theory of interaction with subclinical viruses: This theory mentions that after the maladjustment of the immune system produced by acute COVID-19, some viruses that tend to remain in a subclinical form (mainly those of the herpesviridae family), can be activated again by adding morbidity to the long COVID picture, with various symptoms according to the viral type[15-17].

Dysbiosis theory: This theory mentions that patients with Long COVID present a dysbiosis which would hinder the relationships between the microbiota and the virome, favoring symptoms of the main organ systems and systems, highlighting the involvement of the respiratory system and the gastrointestinal system (Which have a large number of ACE2 and transmembrane serine protease 2 receptors that favor viral entry into cells), which are the main ones that harbor the microbiota, conditioning dysbiosis[18,19].

Theory of aggravation of chronic diseases or de novo appearance of chronic diseases: in this etiopathogenic theory it is mentioned that diseases previously diagnosed with an acute picture of COVID-19 can get out of control or worsen concomitantly, which adds greater comorbidity to the patient both in the acute stage as in long COVID; It has also been seen that after the acute picture, many patients develop chronic degenerative diseases such as: Diabetes, Hypertension, various Cardiopathies, Dementias, Thyroid diseases, *etc*[20-26].

Once the main theories have been described, we will try to put them together in order to be able to describe pathophysiology.

In recent times, viral persistence has stood out, mainly of the S and N proteins that greatly affect the central and autonomic nervous system, coupled with the neurotropism of SARS-CoV-2 that causes damage to the nervous system and the vagus nerve, hence the main manifestations are neuropsychiatric; protein S has the particularity of conditioning amyloidogenesis together with the presence of amyloid peptide A product of inflammation in the acute stage, which could lead to the presence of amyloid microthrombi, perpetuating both inflammation and thrombotic risk; in aggregate form, these characteristics can condition both positive and negative immune deregulation; positive deregulation would increase the activity of the immune system conditioning autoimmunity while negative deregulation is associated with completeness of the system with disorder of B, T and NK cell lines, the latter reveals the reactivation of latent viruses that increase morbidity as well as the virome, causing an imbalance between it and the intestinal microbiota, giving way to the theory of dysbiosis, which is associated, in addition to gastrointestinal symptoms, to neuropsychiatric and cardiovascular disorders, even leading to dysautonomia and hormonal changes, leading to a vicious circle.

Table 1 Diagnosis and treatment based on the theories of long coronavirus disease

Pathological condition to study	Clinic	Basic diagnostic method	Extension studies	Treatments
Neuropsychiatric manifestations	Anxiety depression headache; brain fog; early dementia fatigue/weakness/myasthenia mitochondriopathy suspected	Psychological tests; clinical questioning neurological examination	Cranial CT head MRI brain PET scan CSF analysis; electroencephalogram EMG/CNV; serum lactate-pyruvate/CSF	Psychological therapy psychiatric treatment pacing; brain electrostimulation; speech therapy; behavioral therapy
Viral persistence	Leukopenia, lymphopenia virus reactivation (herpes, EBV); persistently positive COVID tests	Nasal COVID antigen (or PCR-RT); IgM-IgG serology for herpes, CMV, EBV	Total body PET to viral reservoirs, RT-PCR for Sars Cov2: Serum; urinary; stool	Antivirals: Paxlovid (Yale trial); oral remdesivir; acyclovir, ganciclovir
Immunothrombosis	Clinical data of inflammation or thrombosis: Arthralgias/arthritis; myalgias; arterial/venous thrombosis	D-dimer ferritin; C reactive protein reactive thrombocytosis DHL; creatine phosphokinase myoglobin	Intentional search for amyloid microthrombi: Immunofluorescence microscopy; flow cytometry; alpha 2 antiplasmin; serum amyloid A platelet hyperactivation; platelet aggregometry	Triple therapy: Oral anticoagulants; dual antiplatelet; gastric protection. Fibrinolytics chelators vitamins
Immune dysregulation	Frequent infections; de novo appearance of autoimmune diseases	Leukopenia, lymphopenia reactive lymphocytosis	Lymphocyte subpopulation; CD4/CD8/natural killers; miscellaneous and specific antibodies	Immunomodulators immunostimulants biological therapy; monoclonal antibodies (temelimab)
Vagus nerve injury	Brain fog dysautonomias	Electrocardiogram holter; ambulatory blood pressure monitoring	Vagus nerve ultrasound tilted table test	
Dysbiosis	Brain fog depression/anxiety irritable colon chronic diarrhea	Coprological stool culture	Intestinal dysbiosis test stool calprotectin dysbiosis specific kits: Gastrotest; GI effects; healthy gut	
Miscellany	Hepatic steatosis chronic kidney failure dysthyroidisms; chronic lung disease		Kidney, liver, thyroid function female hormonal profile spirometry, chest X-ray, chest CT	Specific treatments
Commercial kits for persistent COVID diagnosis			CheqUp; IncellKINE	

CT: Computed tomography; CMV: Cytomegalovirus; EMG: Electromyography; EBV: Epstein-Barr virus; GI: Gastrointestinal; MRI: Magnetic resonance imaging; PET: Positron emission tomography; PCR-RT: polymerase chain reaction reverse transcriptase; IgM: Immunoglobulin M; IgG: Immunoglobulin G; COVID: Coronavirus disease.

There are currently many researcher-led treatment efforts and initiatives, notably the following:

Dr. Iwasaki from Yale University, leads a clinical study using Paxlovid in these patients affected by Long COVID, based on the theory of viral persistence, who receive the antiviral for 15 days waiting for symptomatic improvement, the study is still recruiting participants and promising results are expected (ClinicalTrials.gov Identifier: NCT05668091)[27].

Other researchers led by Dr. Etheresia Pretorius, are addressing the theory of immunothrombosis, in which they have demonstrated the presence of amyloid microthrombi and initiated a special therapy called Triple therapy, which uses direct oral anticoagulants, dual antiplatelet therapy, and gastric protection, from which encouraging results are expected[28,29].

Other research efforts fall on two researchers, Tamara Romanuk and Ale Frost, who address the theory of dysbiosis secondary to long COVID and that it conditions a gut-brain axis disorder with subsequent neuropsychiatric dysfunction (@remissionbiome on twitter); In their study, they have implemented the study of the microbiota and are using a treatment scheme with the antibiotics doxycycline and amoxicillin with clavulanate, taking advantage of properties against neuroinflammation and neuroimmunology; something similar occurs with the study of dectin-1 as a therapeutic target for the treatment of stress-induced behaviors[30,31].

In Spain, researchers address the theory of damage to the vagus nerve in patients with long COVID, based on the prevalence of inappropriate sinus tachycardia in these patients, they have devised an ultrasound protocol to identify vagus nerve disorders, which would corroborate the viral neurotropism that affects to said nerve, conditioning dysautonomia and disorders in other spheres such as neuropsychiatric, cardiopulmonary, gastrointestinal and endocrinological (Table 1)[32].

Finally, in Switzerland, a research protocol has begun with a monoclonal antibody called Temelimab focused on chronic fatigue and cognitive alterations, whose target is a protein called HERV-W-End, which has been associated with autoimmune diseases and chronic fatigue; encouraging results are expected for long COVID patients. The investigation has been extended to Spain and Italy (ClinicalTrials.gov Identifier: NCT05497089)[33].

CONCLUSION

There is still much to be deciphered in the etiopathogenesis and pathophysiology of long COVID, however current efforts clarify these conditions on which treatments are tested in the real world, in order to limit the pathological manifestations that affect the population affected by long COVID. With the study of etiopathogenic theories, diagnostic and treatment strategies can begin to be created.

FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

Re-analysis of hepatitis B virus integration sites reveals potential new loci associated with oncogenesis in hepatocellular carcinoma

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Abstract

BACKGROUND

Hepatitis B virus (HBV) is a major cause of hepatocellular carcinoma (HCC). HBV DNA can get integrated into the hepatocyte genome to promote carcinogenesis. However, the precise mechanism by which the integrated HBV genome promotes HCC has not been elucidated.

AIM

To analyze the features of HBV integration in HCC using a new reference database and integration detection method.

METHODS

Published data, consisting of 426 Liver tumor samples and 426 paired adjacent non-tumor samples, were re-analyzed to identify the integration sites. Genome Reference Consortium Human Build 38 (GRCh38) and Telomere-to-Telomere Consortium CHM13 (T2T-CHM13 (v2.0)) were used as the human reference genomes. In contrast, human genome 19 (hg19) was used in the original study. In addition, GRIDSS VIRUSBreakend was used to detect HBV integration sites, whereas high-throughput viral integration detection (HIVID) was applied in the original study (HIVID-hg19).

RESULTS

A total of 5361 integration sites were detected using T2T-CHM13. In the tumor samples, integration hotspots in the cancer driver genes, such as *TERT* and *KMT2B*, were consistent with those in the original study. GRIDSS VIRUSBreakend detected integrations in more samples than by HIVID-hg19. Enrichment of integration was observed at chromosome 11q13.3, including the *CCND1* pro-

moter, in tumor samples. Recurrent integration sites were observed in mitochondrial genes.

CONCLUSION
GRIDSS VIRUSBreakend using T2T-CHM13 is accurate and sensitive in detecting HBV integration. Re-analysis provides new insights into the regions of HBV integration and their potential roles in HCC development.

Key Words: Carcinoma; Hepatocellular; Hepatitis B virus; Virus integration

Core Tip: To understand the role of hepatitis B virus (HBV) in hepatocellular carcinoma (HCC) development, we re-analyzed HBV integration sites using publicly available data. We found that chromosome 11q13.3 is a frequently observed HBV integration site. This region contains important cancer driver genes, such as *CCND1* and *FGF19*, which are amplified in HCC. This finding supports a mechanism of carcinogenesis promoted by HBV-induced genomic instability in the liver and provides insights into treating a subset of liver cancers.

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INTRODUCTION

The hepatitis B virus (HBV) is a major cause of hepatocellular carcinoma (HCC). When HBV infects liver cells, HBV DNA can be integrated into the human genome. Integration events typically occur during the early stages of an infection[1,2], and are known to promote carcinogenesis *via* several mechanisms: (1) Increasing the expression levels of neighboring genes; (2) induction of genomic instability and somatic copy number alterations of genes; (3) deletion of tumor suppressor genes through structural mutations [3]; and (4) inducing expression of HBV X protein (HBx) or HBx fusion proteins that contribute to carcinogenesis.

To investigate the effect of HBV on hepatocarcinogenesis, several studies have been conducted using next-generation sequencing technology to identify integration sites of HBV DNA. Examples of such technologies include whole genome sequencing[4] and HBV capture sequencing[5]. These studies revealed frequent integration into the promoter regions of *TERT* and *KMT2B* in tumor tissues and *FN1* in normal tissues. In an examination of an HBV-infected human-hepatocyte chimeric mouse model, mitochondrial DNA (mtDNA) was thought to be a frequent site of integration[1]. A European study reported a lower frequency of *KMT2B* insertion and a higher frequency of integration into *ADH* genes in normal tissues[6].

Most previous studies have used Genome Reference Consortium Human Build 37 (GRCh37) or human genome 19 (hg19) as the reference genomes. In GRCh37/hg19 and Genome Reference Consortium Human Build 38 (GRCh38)[7], tandem repeats, microsatellites, and minisatellites found in telomeres and centromeres remained unresolved. The complete human genome sequence, Telomere-to-Telomere Consortium CHM13 (T2T-CHM13 (v2.0))[8], was released in 2022.

Various methods have been used to detect integration breakpoints. High-throughput viral integration detection (HIVID), a detection method based on a pair-read assembly strategy[9], was applied in the analysis of 426 HCC cases[5]. GRIDSS is a multithreaded structural variant caller from a combination of assembly, split read, and read pair support[10]. VIRUSBreakend utilizes a virus-centric variant calling and assembly approach to identify viral integrations with high sensitivity and low false discovery rate, allowing the identification of integrations in repetitive host regions[11].

Here, we report new features observed by re-analyzing the published data using GRIDSS VIRUSBreakend based on GRCh38 and T2T-CHM13.

MATERIALS AND METHODS

Sequence data were obtained from the Sequence Read Archive (SRA) with accession number SRA335342

[5]. The dataset consisted of 426 tumor samples and 426 paired adjacent non-tumor samples.

All reads in the dataset were aligned to the GRCh38 and T2T-CHM13 reference genomes using bwa-mem2[12,13]. VIRUSBreakend was used to detect integration sites (Supplementary Figure 1), and the analysis was performed using Nextflow[14] on Amazon Web Service. HBV integration sites were detected using GRIDSS VIRUSBreakend[11]. Integration sites were compared with the count of fragments providing breakend for the variant allele (BVF) in the variant call format files. Statistical analysis and visualization were performed using R software, and statistical significance was set at $P < 0.05$.

RESULTS

Comparison of HBV integration sites

In total, 5361 and 5198 integration breakpoints were detected with T2T-CHM13 and GRCh38, respectively. The breakpoints were similar between the references using GRCh38 and T2T-CHM13 (Figure 1A and B). Consistent with previous studies, integration breakpoints were enriched in the *TERT* promoter region in tumor samples. In contrast, integration into *FN1* was frequently observed in non-tumor samples.

Compared with the original study, our analysis detected integrations in more samples (357 *vs* 328 in tumors; 288 *vs* 160 in non-tumors) (Table 1). In addition, we detected integration in the *TERT* region in 105 tumor samples, whereas the original study observed integration in 95 tumor samples (Table 2). In contrast, the number of breakpoints detected in tumors was lower than that in the original study (Table 1). In our study, only breakpoints validated by VIRUSBreakend were counted (Supplementary Figure 2). Integration of *DDX11L* was frequently detected in the original study, but no integration breakpoints were detected in our study (Table 2). The *DDX11L* gene family is frequently detected as a target for integration using a capture sequencing approach, but it is possible that fragments were mapped incorrectly owing to repetitive sequences[15,16]. In the non-tumor samples, our study detected more integrations, both in the number of samples and breakpoints. For example, we detected 97 integration breakpoints in the *FN1* gene from 56 non-tumor samples. The earlier analysis detected only 19 breakpoints from 17 non-tumor samples (Table 2). Few oncogenic regions were affected in the non-tumor samples. Breakpoints were most frequent around direct repeat 1 of the HBV genome (Figure 1C).

Chromosome 11q13.3 is a frequent site for HBV integration

When the chromosome region was explored, we found that the integration breakpoint at 11q13.3 was enriched with T2T-CHM13 and GRCh38 (Figures 2A-C). Breakpoints at 11q13.3 were more frequent in the tumor samples than in the non-tumor samples (16 (3.8%) of tumor samples compared to 1 (0.02%) of non-tumor samples, Figure 2B). 11q13.3 is characterized by the evolutionarily well-conserved genes *CCND1*, *FGF19*, *FGF4*, and *FGF3*[17], where copy number amplification frequently occurs in tumors (Figure 2D)[18,19]. Some breakpoints were within the genic and promoter regions of the genes, including *CCND1* and *FGF4*. Integration appeared to be distributed more in the non-genic regions (Figure 2B). When fragments from the integration site were counted using BVF, the values were higher in tumor samples than in non-tumor samples (Figure 2E). High BVF value formed a peak in the 11q13.3 in addition to the peak in the *TERT*, *KMT2B*, and *CCNE1* genes in the tumor samples (Figure 2E and Supplementary Figure 3).

Mitochondrial DNA has sites where HBV DNA is frequently integrated

There is some debate regarding whether mtDNA is a frequent site of HBV integration. A study using a mouse model by Furuta *et al*[1] found that mtDNA was frequently integrated early in infection. More recently, a preprint suggested that mtDNA is indeed a site for integration[20,21]. Although the original paper on which this study was based did not mention integration into mitochondria, we detected many integration breakpoints into mtDNA and identified repeat integration sites (Table 3 and Figure 3)[22]. Integration breakpoints in mtDNA were observed in both tumor and non-tumor samples. Recurrent integration events were observed in *ND4*. Of these, eight events were from non-tumor samples, and two from tumor samples. Microhomologous sequences were observed in some regions. For example, the GCCNTTCTCATC sequence, where N represents any nucleotide or gap, was observed at the junction of the *ND4* gene (Chromosome M:11079) and the HBV genome (HBV:1559). In contrast, the GCTTCACC sequence was observed at the junction of the *ND4* gene (Chromosome M:11104) and the HBV genome (HBV:1590). It is also possible that these integration breakpoints exist in nuclear-mitochondrial segments.

Table 1 Comparison of hepatitis B virus integration breakpoints among reference genomes

	GRCh38	T2T-CHM13	Original
Tumor			
Number of breakpoints	2439	2487	3486
Number of samples	357	355	328
Non-tumor			
Number of breakpoints	2759	2874	739
Number of samples	288	288	160

Table 2 Comparison of frequent integration breakpoints in the samples

Gene	GRCh38		Original	
	Breakpoints (*n*)	Samples (*n*)	Breakpoints (*n*)	Samples (*n*)
Tumor				
TERT	150	105	160	95
KMT2B	56	33	55	30
DDX11L1	0	0	36	23
CCNA2	12	7	14	8
CCNE1	13	9	14	7
Non-tumor				
FN1	97	56	19	17
TERT	12	10	8	3
IQGAP2	7	5	1	1
KMT2B	7	4	5	3

DISCUSSION

In this study, GRIDSS VIRUSBreakend, with an updated human reference genome, was used to detect HBV integration using public sequencing data from liver tumor and non-tumor samples. HBV integration was detected in more samples than in the original analysis (Table 1). The difference in methods could account for the discordant results. We investigated an example of HBV integration sites in the *TERT* region detected by GRIDSS VIRUSBreakend, but not in the original study (Supplementary Figures 4 and 5). In the original study, the HIVID pipeline, based on paired-end read assembly, was applied to detect integration[9]. In the sequencing data, some paired-end reads could not be assembled because of the absence of overlapping bases. These reads were also included in our analysis to detect integration sites more accurately. It should be noted that the GRIDSS VIRUSBreakend uses genotype D HBV for viral genome reference, whereas genotype C HBV is dominant in the current dataset, which may affect the sensitivity of virus detection.

We found HBV integration clusters in the 11q13.3 region (Figure 2). Unlike previously known single gene integration sites, such as *TERT* and *KMT2B*, 11q13.3 spans multiple gene regions. Although these clusters can be observed in the supplemental data of the original paper, to our knowledge, it has not been previously mentioned. Enrichment of 11q13.3 was more significant in tumors than in non-tumor tissues. *CCND1*, *FGF19*, *FGF4*, and *FGF3* are located at 11q13.3, where copy number amplification frequently occurs in tumors.

Integration into *CCND1*, located at 11q13.3, is a potential driver event[23], but its frequency is not high. Although recent studies have not detected integration at 11q13.3[1,6], several studies have detected these events only as supplementary data[4,5,24] and they have been reported since 1988[25,26]. According to a study by Bok *et al*[27], the expression levels of cancer-related genes, including *CCND1* and *FGF19*, are elevated near the viral integration site on 11q13.3 in an HCC cell line. HBV integration at this locus may be linked to cancer gene activation, as *FGF19* amplification was associated with chronic HBV infection[28,29].

HBV integration may be associated with copy number alterations[3]. Chromosomal instability often leads to copy number alterations in the short and long arms of the chromosome. However, 11q13.3

Table 3 Hepatitis B virus integration breakpoints in mitochondrial DNA

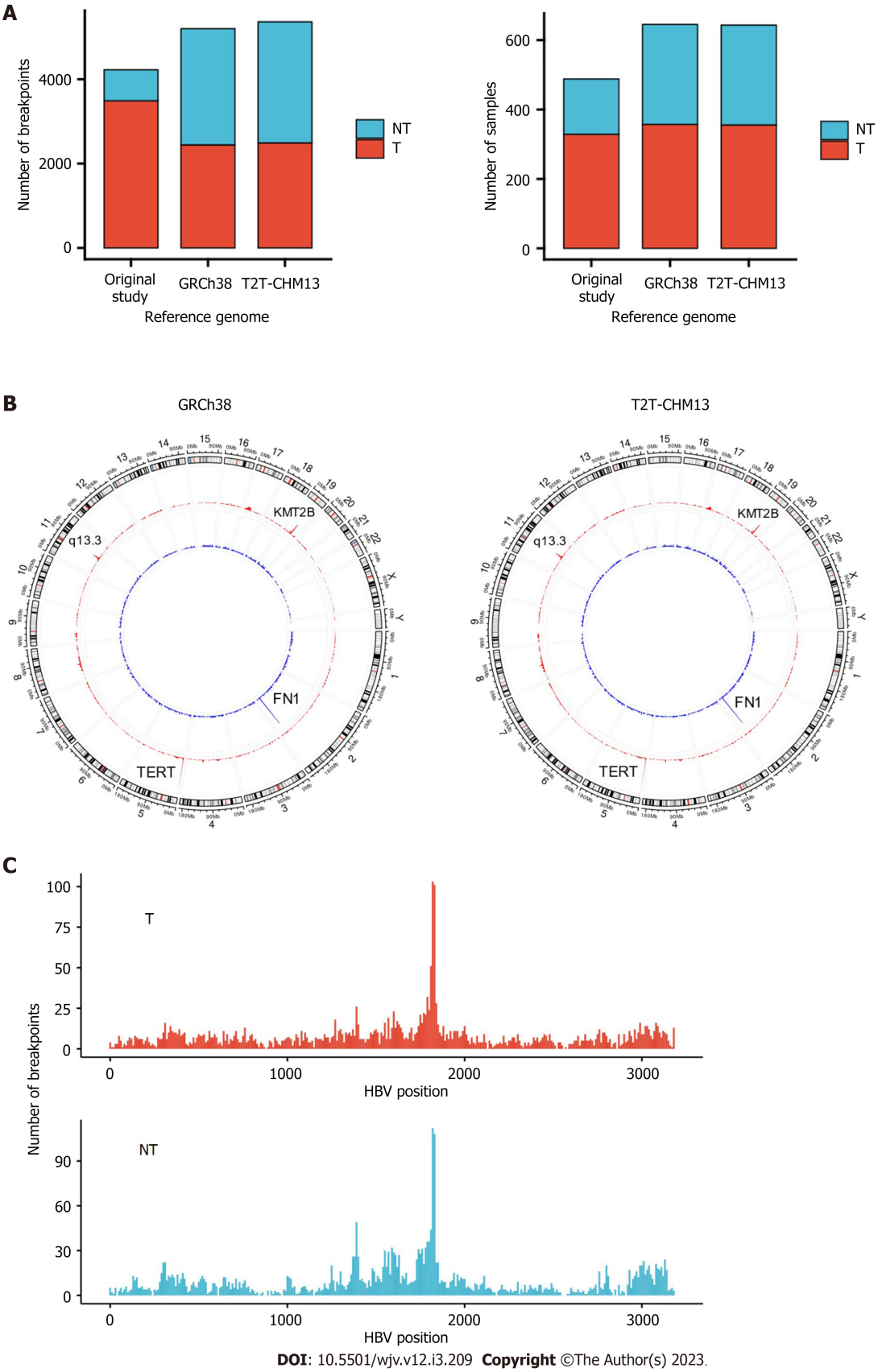
Sample	Tumor/Non-tumor	Chromosome	Position	HBV	Quality score
SRR3104746	NT	chrM	5367	1247	6933.33
SRR3105143	NT	chrM	5682	1513	11817.58
SRR3105012	T	chrM	8220	112	2080.04
SRR3104491	NT	chrM	8524	2482	33322.16
SRR3105095	NT	chrM	8694	471	4209.06
SRR3105101	NT	chrM	11079	1559	2937.33
SRR3105143	NT	chrM	11079	1559	14876.83
SRR3105001	NT	chrM	11104	1590	45538.21
SRR3105149	NT	chrM	11104	1590	16156.63
SRR3105251	NT	chrM	11104	1590	2276.31
SRR3105293	NT	chrM	11104	1590	24562.69
SRR3104643	T	chrM	11104	1590	13683.16
SRR3105172	T	chrM	11126	1621	2610.44
SRR3105251	NT	chrM	11130	1625	6793.43
SRR3104939	NT	chrM	11139	1729	30830.54
SRR3105149	NT	chrM	12453	323	2345.03
SRR3104636	NT	chrM	12735	1381	26840.64
SRR3105083	NT	chrM	13273	1755	4230.85
SRR3104696	NT	chrM	13433	363	2963.36
SRR3104643	T	chrM	13964	2809	2222.86
SRR3104823	NT	chrM	14052	1017	1788.18
SRR3105049	NT	chrM	14892	1768	21102.87
SRR3104982	T	chrM	15679	1768	32371.78
SRR3105185	NT	chrM	16319	1788	2013.53

HBV: Hepatitis B virus.

causes strong copy number amplification in a localized region in the middle of the chromosome (Figure 2D). Previous results using whole genome sequencing indicated that the integration allele frequency was high in the tumor samples, especially in the recurrent integration in tumors such as *TERT* [4]. By comparing fragment counts from the integration site using BVF, the values were found to be higher in the tumor samples than in the non-tumor samples. Some of the integration breakpoints at 11q13.3 had extremely high fragment counts (Figure 2E and Supplementary Figure 3). If BVF correlates with the integration allele frequency, it is possible that these events reflect the clonal expansion of tumors with integration breakpoints or the amplification of integrated genes. *CCND1-FGF19* amplification occurred at later points in the evolution of HCC[30]. Further research is needed to investigate the relationships between integration, copy number alteration, and cancer gene activation at 11q13.3.

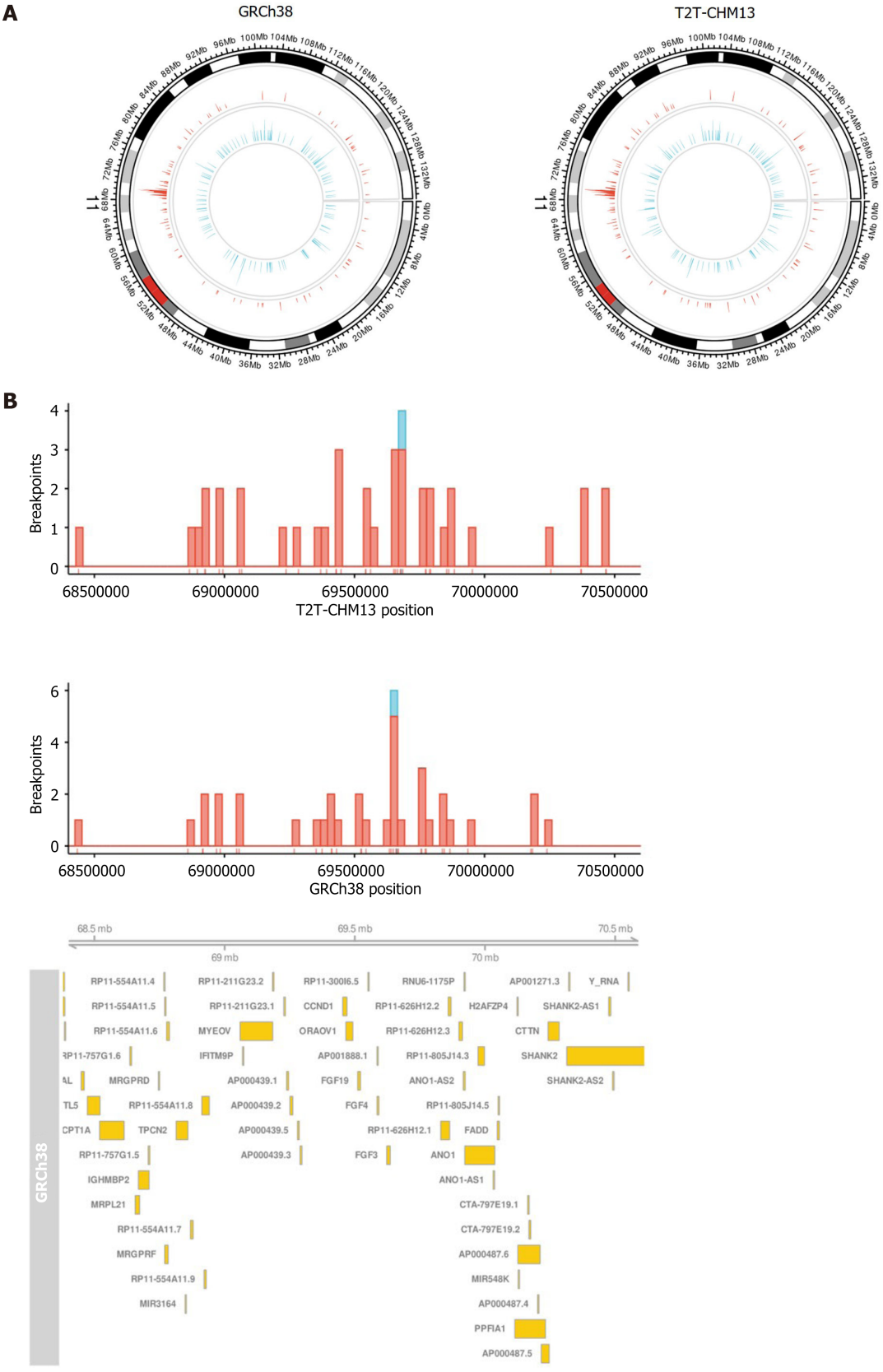
In our analysis, HBV integration in the mtDNA was observed in 2.3% (20/852) of the samples, and the *ND4* gene was a frequent target of HBV integration (Table 3). According to a previous study, HBV integration into mtDNA has occurred in only 0.1% of human clinical liver tissues[1]. Mouse model experiments have suggested that this integration primarily occurs during the early stages of HBV infection through microhomology-mediated end joining[1]. It is also possible that HBV integration occurs in nuclear copies of mtDNA sequences rather than in the mitochondria. Giosa *et al*[21] detected HBV integration in DNA isolated from mitochondria. The D-loop region is the target of HBV integration. Our analysis suggests that *ND4* genes may also be targeted for integration through microhomology-mediated mechanisms.

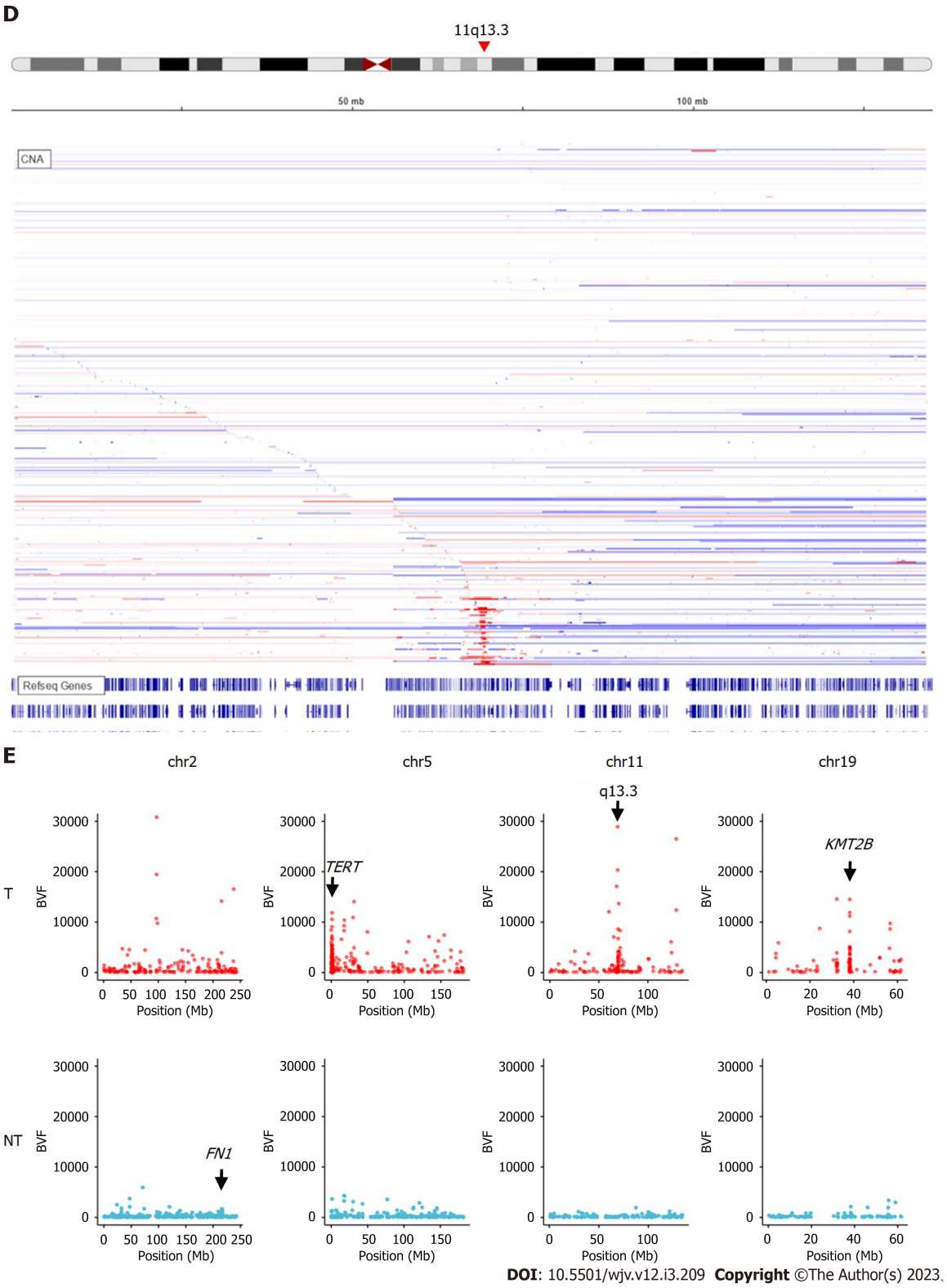
This study has several limitations. First, the analysis was conducted using existing data and the findings were not validated using independent data. Second, the original data were based on HBV



DOI: 10.5501/wjv.v12.i3.209

Figure 1 Hepatitis B virus integration breakpoints across the reference genomes. A: Integration breakpoints in the human reference genomes in tumor and non-tumor samples; B: Circos plot of integration breakpoints. Red represents tumor samples, and blue represents non-tumor samples; C: Hepatitis B virus genome integration breakpoints. T: Tumor; N: Non-tumor.

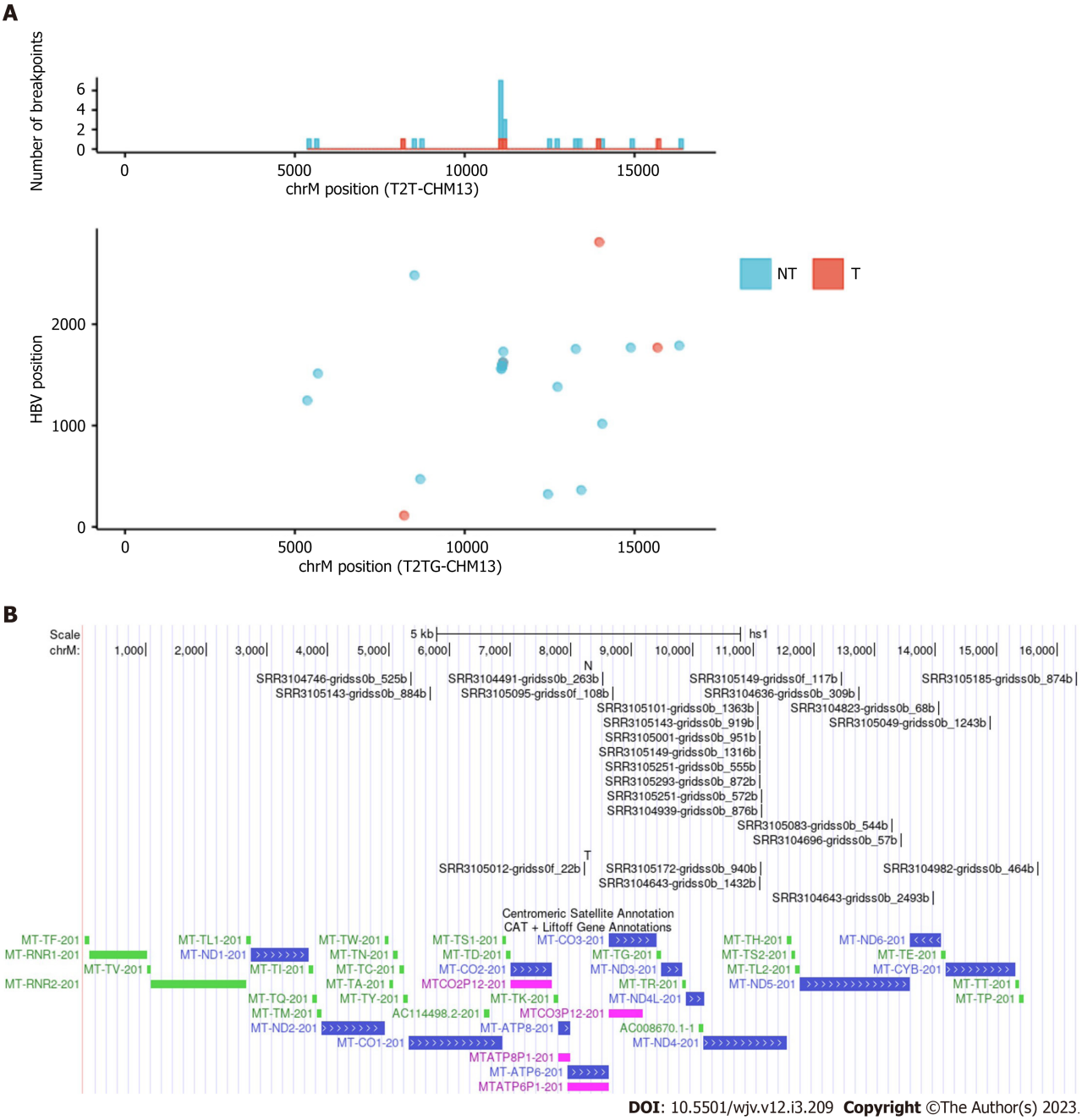

A
GRCh38
T2T-CHM13
B
Breakpoints
T2T-CHM13 position
GRCh38 position
68.5 mb
69.5 mb
70.5 mb
69 mb
70 mb
GRCh38
C
Number of breakpoints
3.07e-35
1.21e-38
Actual
Expected
GRCh38 11q13.3
T2T-CHM13 11q13.3



DOI: 10.5501/wjv.v12.i3.209

Figure 2 Integration breakpoints at chromosome 11. A: Circos plot of breakpoints at chromosome 11 in the human reference genomes; B: Integration breakpoints around 11q13.3 in relation to coding genes retrieved from Ensembl. Red represents tumor samples, and blue represents non-tumor samples; C: Comparison of integration breakpoints around 11q13.3 in the tumor samples. Actual represents actual number of integration breakpoints. Expected represents expected number of integration breakpoints assuming random distribution; D: Copy number of liver cancer samples from cBioPortal[18,19]. Red represents amplification, and blue represents deletion. E: Distribution of the number of fragments that provide breakend for the variant allele. T: Tumor; NT: Non-tumor.

capture sequencing, and gene copy numbers were not available. Finally, the integration data were obtained from short-read sequencing and have not been validated using long-read sequencing data.



DOI: 10.5501/wjv.v12.i3.209

Figure 3 Integration breakpoints in the mitochondrial genome. A: The upper panel displays integration breakpoints across mitochondrial genomes according to tumor and non-tumor samples, and the lower panel shows integration breakpoints along the human and hepatitis B virus genomes. Red represents tumor samples, and blue represents non-tumor samples; B: Integration breakpoints on the mitochondrial genome annotated using UCSC genome browser (NT: Non-tumor; T: Tumor)[22].

CONCLUSION

HBV integration in HCC samples has been characterized using the complete human reference. GRIDSS VIRUSBreakend using T2T-CHM13 is accurate and sensitive in detecting HBV integration. HBV frequently integrates at the 11q13.3 region, where the *CCND1* gene is located, and this region is frequently amplified in several types of cancer, including HCC. Further research is needed to examine how HBV integration interacts with driver gene expression and copy number alteration.

ARTICLE HIGHLIGHTS

Research background

Many hepatitis B virus (HBV)-infected patients suffer from hepatocellular carcinoma (HCC), but a little focus is given to detect HBV integration pattern in the treatment of HCC. Detection of HBV integration can be improved by introducing a reliable detection method.

Research motivation

HBV frequently integrates at the 11q13.3 region, where the *CCND1* gene is located, and this region is frequently amplified in several types of cancer, including HCC.

Research objectives

We aimed to analyze the features of HBV integration in HCC using a new reference database and integration detection method.

Research methods

Published data, consisting of 426 liver tumor samples and 426 paired adjacent non-tumor samples, were re-analyzed to identify the integration sites. Updated human reference genomes, Genome Reference Consortium Human Build 38 (GRCh38), and Telomere-to-Telomere Consortium CHM13 (T2T-CHM13 (v2.0)) were used. In addition, GRIDSS VIRUSBreakend, which utilizes a virus-centric variant calling and assembly approach, was used to detect HBV integration sites.

Research results

A total of 5361 integration sites were detected using T2T-CHM13. In the tumor samples, integration hotspots in the cancer driver genes, such as *TERT* and *KMT2B*, were consistent with those in the original study. GRIDSS VIRUSBreakend detected integrations in more samples than original analysis. Enrichment of integration was observed at chromosome 11q13.3, including the *CCND1* promoter, in tumor samples. Recurrent integration sites were observed in mitochondrial genes.

Research conclusions

GRIDSS VIRUSBreakend using T2T-CHM13 is accurate and sensitive in detecting HBV integration and provides new insights into the regions of HBV integration and their potential roles in HCC development.

Research perspectives

Further research is needed to examine how HBV integration interacts with driver gene expression and copy number alteration.

FOOTNOTES

Author contributions: Kojima R and Nakamoto S contributed to the conception, design, and writing of the manuscript; Kojima R contributed to data management and analysis; Kogure T, Ma Y, Ogawa K, Iwanaga T, Qiang N, Ao J, Nakagawa R, Muroyama R, Nakamura M, Chiba T, Kato J, and Kato N contributed to manuscript review and editing; Kato N contributed to the project administration.

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