RESEARCH ARTICLE

SARS-CoV-2: Possible Factors Contributing to Serious Consequences of COVID-19?

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Abstract:

Background and objectives: The recently discovered coronavirus, SARS-CoV-2 has infected over 170 million people (as of 31st May 2021) since it was elucidated in December 2019. The number of SARS-CoV-2 cases and mortality rates vary from country to country, and unfortunately, the United Kingdom ranks in the top 5 countries with the most deaths as of 31st May 2021.

Methods: A literature review was conducted during May 2021 to examine if factors such as gut microbiome, ethnic diversity, high cancer rates, obesity and alcohol consumption may have contributed to the higher number of cases and mortality due to SARS-CoV-2 in the UK.

Results: The western diet is associated with a less diverse gut microbiome, as well as obesity, and contributes to the severity of SARS-CoV-2 infection. Moreover, people belonging to Black and South Asian ethnic groups in the UK have an increased risk of death due to SARS-CoV-2 infection. Given the high number of cancer patients in the UK, as well as excess consumption of alcohol, higher mortality rates were observed, most likely due to people possessing a less diverse gut microbiome and/or weakened immune system.

Conclusion: Targeting the gut microbiome in developing potential therapeutics against SARS-CoV-2 is of value, and further studies are needed to understand the specific role of the gut microbiome.

Keywords: Severe acute respiratory syndrome, Coronavirus, Cancer, Ethnicity, Obesity, Gut microbiome.

1. INTRODUCTION

The recently discovered coronavirus, SARS-CoV-2, is the seventh affiliate of the coronavirus family that can cause disease in humans and has infected over 170 million people (as of 31st May 2021) since it was elucidated in December 2019 [1, 2]. Coronaviruses, are a sizeable family of enveloped single-stranded, positive-sense RNA viruses, and are known to cause respiratory, neuronal, hepatic, gastrointestinal diseases. Until recent times, Middle East respiratory syndrome-CoV (MERS-CoV), HCoVs-OC43, HCoVs-HKU1, HCoVs-NL63, HCoVs-229E, and severe acute respiratory syndrome-CoV (SARS-CoV) were the six coronaviruses that were known to affect humans [3].

The number of SARS-CoV-2 cases and mortality rates have varied from country to country (Fig. 1). As such, the United Kingdom represents a striking case since it ranks in the top 5 countries with the most deaths and is the country with the highest mortality per population and with the highest number of mortalities as of 31st May 2021 [4]. Some may argue that the high number of deaths may be due to the inefficacity of the government to tackle the pandemic with issues such as its decision to delay lock-down, the stuttering test-and-trace network and protection of the care home residents [5]. However, there may be other factors involved, such as the high obesity rate in the UK [6] and the high rates of conditions such as diabetes, kidney disease and respiratory problems that...
increases the risk of death due to COVID-19 [5]. Therefore, herein, we debate additional factors that may play a role and conducted a literature review (as of 31 May 2021) pertaining to the diverse ethnicity of the population, alcohol consumption, high cancer rates and the gut microbiota of the UK population that may affect the infectivity and/or mortality due to SARS-CoV-2.

2. GUT MICROBIOME PLAYS A KEY ROLE IN HEALTH AND DISEASE

It is well known that the human microbiome is a key factor in human physiology and disease, since humans consist of approximately 10% human cells and 90% microorganisms, many of which colonize the gastrointestinal tract and have evolved alongside humans [7, 8]. Nearly all aspects of human biology are affected by gut microbes through interactions between the microbes and the host [8]. Gut microbiota can both affect and be affected by invading viruses and hence can either facilitate the suppression or stimulation of the viruses [9].

Diarrhoea, anorexia and other gastrointestinal symptoms are typically observed in patients with COVID-19 and a study of 204 patients revealed lack of appetite in 78.6% of cases, diarrhoea in 34% of cases, vomiting in 3.9% of cases, and abdominal pain in 1.9% of cases [10]. Reports also linked gastrointestinal symptoms to more severe cases of COVID-19 and higher incidence of hospitalizations and indicated that in some cases of COVID-19, patients experienced only gastrointestinal symptoms without fever, shortness of breath or cough [11]. The presence of infectious SARS-CoV-2 virus in faeces further affirms that the gastrointestinal tract may play a role in COVID-19 cases [12].

Gastrointestinal symptoms are accompanied by intestinal damage or by inflammation, leading to a loss in the integrity of the intestinal barrier and gut microbes triggers systemic inflammation by releasing proinflammatory cytokines into the circulatory system [13]. It has also been suggested that diarrhoea may be secondary to inflammation induced by SARS-CoV-2, which is linked to the entry of inflammatory cells into the intestinal mucosa and hence disruption of the gut microbiota [13]. The gut microbiome may impact SARS-CoV-2 cases through the microbiomes’ impacts on cytokines, since microbiota can increase chronic phase proteins and interferon signalling in lung cells and that in some patients, the immune response against SARS-CoV-2 works by releasing excessive levels of cytokines, leading to multi-organ failure [14].

A vital step in elucidating the relationship between SARS-CoV-2 and the gut microbiome is to investigate the possibility of the virus interacting with each of the 1500 species of microbiota in the gut [14]. An indication of the relationship between the microbiota and the virus is in the fecal samples, where samples with high SARS-CoV-2 infectivity had more bacterial species Collinsella tanakaei, Collinsella aerofaciens, Streptococcus infantis, and Morganella morganii and samples with low-to no SARS-CoV-2 infectivity had more short-chain fatty acids producing bacteria namely: Bacteroides stercoris, Parabacteroides merdae, Lachnospiraceae bacterium and Alistipes onderdonkii [13]. Moreover, studies have linked certain bacteria, such as Coprobacillus in the gut, as a strong up-regulator of angiotensin-converting enzyme 2 (ACE2), the receptor that allows entry of SARS-CoV-2 to establish infection, with higher severity of COVID-19 cases, while a lower severity of COVID-19 has been linked to Faecalibacterium prausnitzii, known for its anti-inflammatory properties [11].

![Fig. (1). Countries with most cases of COVID-19. The figure depicts the number of deaths per million population (as of 31st May 2021) in the countries with the highest reported number of COVID-19 cases.](image-url)
In another interesting study, it was demonstrated that COVID-19 disease severity can be predicted by determining the oral or stool composition more accurately than with traditional clinical scoring methods that utilize various clinical biomarkers and comorbidities. The study enrolled 69 patients suffering from severe or moderate symptoms and analysis was performed. In particular, the presence of Porphyromonas endodontalis in the oral microbiota or Enterococcus faecalis in the intestinal microbiota may indicate the severity of SARS-CoV-2 infections [15]. In accord with this study, another pilot study revealed similar findings where in 15 patients with COVID-19, persistent alterations in their faecal microbiome were detected, compared with controls. The study found that faecal microbiota alterations were associated with fecal levels of SARS-CoV-2 and COVID-19 severity, thus suggesting that strategies to alter the intestinal microbiota may reduce disease severity [16].

A plethora of studies have shown that the Western diet is associated with a less diverse gut microbiome, metabolic disease and obesity [17]. Given the UK population consume a high fat, ultra-processed Western diet, this may be a factor contributing to the higher numbers of COVID-19 cases observed, as well as higher mortality. Interestingly another recent study has revealed that ethnicity can influence the diversity of the gut microbiome [18]. The study revealed less diverse microbiome in South-Asian Surinamese, compared to the Dutch population suggesting that ethnicity is an important factor that may affect gut microbiome diversity and thus play a role in the overall health of the population. This is in agreement with another study which revealed that patient geography and ethnicity may considerably impact the taxonomic composition of the microbiome and the existence of geographic signatures in the gut microbiome has been reported [19]. Thus, the gut microbiota of the UK’s population might play a role in the elevated mortality rate in SARS-CoV-2 cases.

3. ETHNICITY

United Kingdom is known for its ethnically diverse and densely packed urban population [5]. In 2011, while 80.5% of the population are White British and 4.4% are Other White, 2.5% and 2.0% are Indians and Pakistanis, and the rest of the population consisted of Irish, Gypsy, Bangladeshi, Chinese, African, Caribbean, Arab, other Asians, Other Black, mixed groups and 0.6% were classified as other ethnic group [20]. Trends clearly indicate that England is becoming more ethnically diverse [20]. According to the CDC, the rate of hospitalization and death is higher in other ethnic groups as compared to White, Non-Hispanic persons [21]. A review of 50 studies covering over 18 million cases revealed that people of Asian and Black ethnicity have a higher risk of SARS-CoV-2 infection and Asians may have an increased risk of intense care unit admission and death, as compared to White individuals [22].

More specifically, the office of national statistics of the UK revealed that considering death linked to COVID-19 up to July 2020, as compared to people of White background, males and females belonging to the Black and South Asian ethnic groups have increased risk of death [23]. In general, in the UK, other than people of Chinese background, males and females of all ethnic groups had a higher mortality rate due to COVID-19 as compared to the White ethnic population [23]. Males of Black African ethnic background had 2.7-times higher mortality rate linked to COVID-19 as compared to males of White ethnic background while females belonging to Black Caribbean ethnic background had twice the mortality rate linked to COVID-19 as compared to females of White ethnic background [23]. Moreover, using a statistical model adjustment for age and excluding the care home residents revealed that all ethnic groups, excluding female Chinese, had a higher mortality rates as compared to the White ethnic group for COVID-19 cases in England and that males and females of Black African ethnic background had 3.8- and 2.7-times higher mortality rates linked to COVID-19, respectively, as compared to males and females of White ethnic background [23].

Considering that SARS-CoV-2 affects individuals of varying ethnicity differently and that the UK has an ethnically diverse population, the ethnical diversity may partially account for the elevated number of deaths. However, the reason that SARS-CoV-2 causes more mortality in ethnic minorities is not well understood and may be due to various reasons, such as lifestyle and cultural factors, socioeconomic disparities, genetic predisposition, or even because of pathophysiological differences in susceptibility or response to the infection [24]. Additionally, as indicated in the previous section, some studies have shown that the gut microbiome composition can be less diverse in ethnically diverse populations [18] and also that human genetics can shape the gut microbiome [25]. In addition, the disparity in severity of cases due to SARS-CoV-2 affecting ethnic minorities may also be due to the increased number of ethnic minorities undertaking more frontline roles [26].

4. ALCOHOL CONSUMPTION

Alcohol misuse is the biggest risk factor for death, disability and ill-health among 15- to 49-year-olds in the UK [27]. In England from 2018 to 2019, 1.26 million hospital admissions related to alcohol consumption was recorded and 82% of adults consume alcohol during the year while 49% of adults drink once a week [28].

Consumption of alcohol has been linked to over 230 diseases and illnesses due to the psychoactive, immunosuppressive, carcinogenic, reinforcing and toxic effects of alcohol, making it one of the main causes of preventable mortality worldwide, causing about 3 million deaths yearly [29]. Excessive consumption of alcohol weakens the immune system, hence decreasing the ability of the body to fight viral infectious diseases, such as COVID-19 [29]. It has been demonstrated that the incidence of acute respiratory distress syndrome is significantly higher in patients with a history of alcohol abuse as compared to those without a history of alcohol abuse [30].

A study conducted by Cambridge University revealed that over one-third of adults drank more alcohol during the first lockdown in the UK [31]. Considering the rise in alcohol consumption in the UK and the fact that alcohol consumption increases the incidence of acute respiratory distress syndrome,
which is one of the most severe complications of COVID-19, this could be contributing to the high number of mortality. In addition, various studies have shown that alcohol-related disorders are also associated with changes in the gut microbiota and increased inflammation in the gastrointestinal tract has been observed [32]. Studies have revealed that chronic consumption of alcohol leads to gut dysbiosis in humans as well as rodent models (Engen et al., 2015). Thus, alcohol consumption may also play a role in high mortality rate of COVID-19 in the UK.

5. CANCER RATES

Patients suffering from cancer may be more susceptible to COVID-19, since the malignancy and anticancer treatments may weaken their immune system, leading to severe illness due to SARS-CoV-2 [33]. Data collected by the American Institute for Cancer Research shows that the UK is among the top 15 countries with the highest rates of cancer [34].

Immune systems of cancer patients are altered as a result of specific cancer therapies and the extent of disease leading to lymphopenia in 20% of patients [35]. Interestingly, laboratory findings revealed that the majority of patients suffering from SARS-CoV-2 infections had lymphopenia that increased in severity in cases that resulted in mortality [35]. It has been shown that cancer patients have a higher chance to contract community acquired respiratory viral infections, including coronaviruses [36]. Also, patients who have undergone treatments, such as hematopoietic stem cell transplant, and then contracted parainfluenza viruses, had 40% increased chance of mortality due to respiratory failure [37].

A recent study comprised of 17456515 people in UK, showed that out of 17063 deaths linked to COVID-19, 16.15% of the patients whose cases resulted in mortality suffered from cancer [38]. Out of the patients, COVID-19 patients suffering from cancer and COVID-19 whose cases resulted in death, 11% had been diagnosed with cancer for less than a year, 24% had been diagnosed for more than one year but less than five years and 65% had been diagnosed with cancer for more than 5 years [38]. A study in which autopsies were performed to determine the exact causes of death of COVID-19 patients revealed that causes of death were directly linked to COVID-19 in most cases and that deaths were not a direct result of pre-existing health conditions, including cancer [39].

Considering that cancer patients are at a higher risk of suffering from severe illness due to SARS-CoV-2, the relatively high number of cancer cases in the country and the fact that more than 16% of COVID-19 patients that died due to COVID-19 were suffering from cancer, it seems reasonable to assume that the high cancer rates in the UK might be partly responsible for the high number of deaths in the country.

CONCLUSION

In conclusion, while delayed lock-down, the stuttering test-and-trace network and lack of protection of the care home residents may have contributed to the high mortality rate of COVID-19 in the UK, the situation is much more complex than it seems. An interplay with several important factors, such as the gut microbiome composition in those with severe COVID-19 outcomes, ethnicity of patients, health conditions, such as cancer, as well as alcohol consumption, and obesity may be contributing overall to the high mortality rates. These factors are all issues of clinical importance in their own right. Further quantitative and qualitative research that investigates gut microbiome composition, ethnicity and alcohol consumption as well as their interconnectivity with each other and effects on COVID-19 susceptibility and severity needs to be accomplished, especially since gut microbiome diversity is known to impact overall human health. Targeting the gut microbiome in developing potential therapeutics against SARS-CoV-2 will be of value, and further studies are needed to understand the role of the gut microbiome.

CONFLICT OF INTEREST

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

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