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An Updated Comparative Study on the Impact of COVID-19 Infection and Vaccination in Patients with Inflammatory Bowel Disease and Irritable Bowel Syndrome

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ABSTRACT

Background & Aims: This study assessed the differences in swabbing rates, vaccine uptake, COVID-19 infection, hospitalization rates and outcomes in patients suffering from inflammatory bowel disease (IBD) on immunomodulation and patients diagnosed with irritable bowel syndrome (IBS).
Methods: A population consisting of 250 IBD and 250 IBS patients was randomly selected from the local database. Apart from demographic data, the following data was collected: number of COVID-19 swabs taken, vaccination rates, type of vaccine administered, infection secondary to COVID-19, hospitalization and outcomes.
Results: IBD patients performed significantly more swabs tests for SARS-CoV-2 detection compared with IBS patients in both phases of the study. Whilst the IBS cohort recorded a larger number of COVID-19 infection and less hospitalisations whilst infected, IBD patients had a better outcome whilst infected since hospitalisation reason in the latter was not related to COVID-19 infection. IBD patients had a larger uptake of COVID-19 vaccines.
Conclusions: This study was the first of its nature locally and internationally as it compared two unrelated cohorts of patients followed up in gastroenterology. Vaccination rates in both cohorts were higher than those reported internationally. In concordance with international studies, IBD patients are not at an increased risk of worse outcomes from COVID-19 infection compared to non-IBD cohorts.

Key words: COVID-19 – hospitalization – vaccination – inflammatory bowel disease –irritable bowel syndrome.

Abbreviations: CD: Crohn's disease; COVID-19: coronavirus disease 2019; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; UC: ulcerative colitis.

INTRODUCTION

Towards the end of 2019, a novel respiratory beta coronavirus originated in China and spread globally, being named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Whilst symptomatology may range from respiratory and gastrointestinal tract symptoms to life-threatening pneumonia, its physical and economic impact led WHO to declare a pandemic in March 2020 [1]. Several logistical analyses have attempted to identify risk factors for developing adverse outcomes from coronavirus disease 2019 (COVID-19), including mortality. Chronic conditions, including respiratory, cardiovascular, and renal diseases increase the risk of ICU admission and mortality in patients hospitalised for COVID-19 infection [2].

Inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) are chronic gastrointestinal disorders which differ in pathophysiology. Inflammatory bowel disease is a relapsing, remitting inflammatory disorder which includes Crohn's disease (CD) and ulcerative colitis (UC). The development of IBD is multifactorial, including genetic and environmental elements, which may alter gut architecture and predispose to malignancy if left untreated. Irritable bowel syndrome is the commonest functional gastrointestinal disorder which may also cause debilitating symptoms affecting the quality of life. It is widely thought to be related to a disorder

of the gut-brain axis causing neuroimmune interactions which leads to symptomatology.

Patients with IBD on immunomodulatory therapy are known to be at an increased risk of respiratory illness, such as influenza and pneumococcal disease [3]. This has raised the question if patients with IBD are at a higher risk of acquiring COVID-19 and of subsequent complications. Until the time of writing, IBD patients have not shown increased susceptibility to COVID-19 [3].

With regards to IBS patients, studies have shown that they had experienced a greater deterioration in their well-being during the pandemic compared to non-IBS individuals. The lack of knowledge regarding COVID-19, it being a novel threat, was a contributory factor towards anxiety and IBS flares [4].

One of the best ways to mitigate the COVID-19 pandemic is the development of safe and effective vaccines whilst ensuring equitable vaccine access to achieve herd immunity. Unfortunately, patients on immunosuppressive treatment, including IBD patients, were grossly excluded from phase 1 and 2 trials of COVID-19 vaccine studies resulting in uncertainty into the effectiveness and risks of the vaccine in this cohort. Furthermore, vaccine uptake for other viral illnesses is low amongst IBD patients, despite vaccination being recommended in European IBD guidelines [5].

The use of immunomodulatory drugs in IBD brings about a level of concern among patients, which increased during the pandemic. Patients on immunomodulatory treatment have voiced their concerns regarding both risk of infection with COVID-19 as well as the risk and effectiveness of the vaccine. Similarly, patients with IBS may have concerns about the effect of infection and vaccine on their wellbeing. COVID-19 infection may also contribute to chronic gastrointestinal symptoms, aptly termed post-infectious functional gastrointestinal disorder, which is a condition of multifactorial etiology [6].

The aim of this study was to assess for any differences in swabbing rates, vaccine uptake, COVID-19 infection, hospitalization rates and outcomes in patients with IBD on immunomodulatory treatment and patients with IBS. In the second phase of the study, the aim was to re-assess the above differences, as well as determine any discrepancy in the third COVID-19 vaccine uptake.

METHODS

Patients were randomly selected through the local database with the timeframe being from the start of the pandemic in March 2020, until August 2021 in the first phase of the study. The second phase of the study, which evaluated the same parameters but also included the third vaccine dose, was conducted in June 2022. All IBD patients had a histological diagnosis through endoscopic biopsies as per Copenhagen diagnostic criteria, while IBS patients were diagnosed according to the ROME IV criteria. All patients were offered vaccination as part of the national vaccine campaign. Apart from demographic data, the following was collected: number of COVID-19 swabs taken, vaccination rates, type of vaccine administered, infection secondary to COVID-19, hospitalization and outcomes.

Statistical analyses used the unpaired t-test. A p-value less than 0.5 was considered significant.

RESULTS

In total, 250 IBD patients (43.6% female) and 250 patients with IBS (78.4% female) were recruited. The mean patient age in the IBD cohort was 40.7 years (SD±15.7) whilst the average age of the IBS cohort was 40.6 years (SD ± 11.99). One patient suffering from IBS and 4 patients from the IBD cohort passed away between the first and second phase of the study from unrelated causes.

Patients with IBD were receiving the following biological therapy: infliximab 62.8%, adalimumab 24.8%, vedolizumab 10% and ustekinumab 2.4%.

Within the first phase of the study, patients with IBD underwent significantly more SARS-CoV-2 swab tests (n=759) than patients with IBS (n=615) (p=0.02). There was no significant difference in COVID-19 infection rate between the IBS cohort (22 patients, 8.8%; 2 patients not vaccinated) and the IBD cohort (16 patients, 6.4%; 3 patients not vaccinated) (p=0.3). The vaccine uptake rate was similar (IBD: 91.2%, IBS: 90%) (p=0.6) (Table I). The types of vaccine administered to both cohorts are shown in Table II.

Table I. Difference in swabbing, infection, vaccination rates in IBD and IBS cohorts – phase 1

	IBS	IBD	p
Swabs performed, n	615	719	0.02
COVID-19 infection, n (%)	22 (8.8)	15 (6)	0.2
Hospitalizations, n (%)	1 (0.4)	3 (1.2)	0.3
Vaccinations, n (%)	226 (90.4)	229 (91.6)	0.6

IBS: irritable bowel syndrome; IBD: inflammatory bowel disease; COVID-19: coronavirus disease 19.

Table II. Vaccine type administered in IBD and IBS cohorts – phase 1

Cohort	Pfizer-BioNTech	AstraZeneca	Johnson & Johnson	Moderna
IBD	43%	54%	1%	2%
IBS	57%	31%	7%	5%

For abbreviations see Table I.

During the second phase of the study, the cumulative number of swabs taken rose from 615 to 904 (+289) in the IBS cohort and from 719 to 1149 (+430) in the IBD cohort. The cumulative number of COVID-19 infection increased from 22 to 42 (+20) in the IBS cohort and from 15 to 25 (+10) in the IBD cohort. Unvaccinated patient numbers decreased in both cohorts: from 24 to 19 in the IBS group, and from 21 to 15 in the IBD group. 203 patients with IBS and 214 patients with IBD received the vaccine.

With regards to infection outcome in both study phases, in the IBS cohort, 2 female patients (unvaccinated) were admitted to hospital in view of symptomatic hypoxemia. A computed tomography pulmonary angiogram was performed to rule out a pulmonary embolism in view of hypoxemia and tachycardia, which demonstrated a COVID-19 pneumonia and superimposed bacterial infection. The patients were both treated with oxygen, antibiotics and dexamethasone. They did not require ventilatory support or transfer to the intensive

care unit. Another female vaccinated patient presented to Accident and Emergency Department due to headache and fever attributed to COVID-19 infection but was discharged home as she was respiratory and hemodynamically stable with satisfactory bloods results. Within the IBD cohort in the first phase, 3 patients (all vaccinated) tested positive asymptomatically on pre-admission COVID-19 screening, with the admission being required for treatment of IBD flare-ups. All had an uneventful outcome from the COVID-19 point of view. One further IBD patient was noted to be COVID-19 positive during the second phase of the study when he was admitted for an elective change of ureteric stent – he was also asymptomatic from COVID-19 and remained well.

Table III. Cumulative swabbing, infection, vaccination rates in IBD and IBS cohorts – phase 2

	IBS	IBD	p
Swabs performed, n	904	1149	0.017
COVID-19 infection, n (%)	42 (16.9)	25 (10.2)	0.03
Hospitalizations, n (%)	2 (0.8)	4 (1.6)	0.317
Vaccination, n (%)	231 (92.8)	231 (93.9)	0.615
Third dose, n (%)	203 (81.5)	214 (87)	0.095

For abbreviations see Table I.

DISCUSSION

This study has focused on the impact of COVID-19 on two cohorts of patients suffering from chronic gastrointestinal conditions: IBD and IBS. Locally, IBD patients amount up to 2,000, of whom approximately 420 receive regular biological treatment according to the hospital's IBD registry. IBD incidence in the Maltese population was documented formally as mean incidence of UC in males of 8.16 per 100,000 per year and for females 7.59 per 100,000 per year. Incidence of CD in males was 0.96 per 100,000 per year and for females 1.622 per 100,000 per year. Therefore, there is a higher incidence of UC in males and of CD in females locally. Furthermore, using linear regression, in UC there is an almost significant (p=0.069) increasing trend with time but no difference by gender, whilst in CD there is an almost significant trend by gender (p=0.078) but not with time [7]. Whilst an official statistic for IBS prevalence within the general population is lacking on a national level, the prevalence of IBS amongst local medical students and junior doctors is 17.7% according to a recent study [8].

IBD patients in our study underwent significantly more swab tests than patients with IBS in both phases of the study. A possible reason could be the patient concern of acquiring COVID-19 while being on immunosuppressive medications. This is compounded by the fact that national and international data on outcomes of infection in such a cohort is limited. This new added psychological burden might further impact the patients psychological state and thus their quality of life. Within the IBD population, COVID-19 infection whilst on treatment with immunomodulators such as anti-tumour necrosis factor [anti-TNF], anti-integrins and anti-interleukin 12/23 [anti-IL12/13] agents was not linked to increased mortality [9]. The ECCO position statement concludes that immunomodulatory drugs should be maintained in IBD patients without COVID-19 infection during the pandemic [10].

As previously discussed, the health, financial and social challenges posed by the emergence of COVID-19 led to a collective effort in research aimed not only at treating the virus, but also at preventing serious infection and chronic effects. The mRNA and viral vector vaccines were developed and have been recommended by several international associations for patients with gastrointestinal disorders.

With respect to the actual vaccination rate, COVID-19 vaccine uptake among patients with IBD on biologic therapies in a Kuwaiti center was lower than that of the general population. Female patients, patients above the age of 50, and expatriates were more likely to receive the vaccine. There was no observed statistical difference in the vaccination rate between patients on infliximab and vedolizumab [11]. On the other hand, in Europe around 80% of IBD participants in an international survey had received at least one dose of the vaccine by June 2021. This figure supersedes not only studies regarding intent or hesitancy to obtain the COVID-19 vaccine, but also vaccine uptake for other viral illness such as influenza, as mentioned earlier [12].

In our study, both IBS and IBD cohorts supersede these figures, with vaccination rates at 90.4% and 91.6% respectively. In Malta, 80% of the population had been fully vaccinated by August 2021 (90.4% until April 2022) [13], thus showing that IBD and IBS patients were more likely to get vaccinated compared to the general population. There was no observed gender difference for vaccine uptake in the IBD cohort; however, there was a female predominance in the unvaccinated IBS cohort.

One question which may arise is whether the COVID-19 vaccine has reduced efficacy in IBD patients. It is widely known that vaccines have lower efficacy rates in IBD patients, due to single nuclear polymorphisms in the genome of IBD patients resulting in altered expression of toll-like receptors which contribute towards the adaptive immune response and thus results in modified response to vaccines [14]. Altered immune response may also occur secondary to IBD treatment used to induce and maintain remission in IBD, especially immunosuppressive treatment. Three studies have offered insight to this question so far. One study of 48 IBD patients, most of whom were on immunosuppressants, measured their antibody response to mRNA COVID-19 vaccines as compared to a control group. Those who received both vaccine doses obtained the highest antibody titers, whilst those with previous COVID-19 infection who took a single vaccine dose still achieved increased antibody levels in comparison to those achieved by infection alone. Furthermore, this study confirmed that patients on biological therapy achieve lower antibody titers than those off biological therapy [15]. The UK CLARITY study was a large-scale, multi-center trial comparing antibody response rates after a single dose of a COVID-19 vaccine. Patients with IBD on vedolizumab or infliximab were vaccinated with either the viral vector vaccine or the mRNA vaccine. Results demonstrate that the mean antibody concentrations were lower in patients treated with inflixmab than vedolizumab for both vaccine types. Furthermore, age over 60 years, immunomodulator use, non-white ethnicity

and smoking emerged as independent variables associated with lower antibody concentrations for both vaccines [16].

A multicenter, prospective, case-control study in the UK was in concordance with the previous study, in that patients with IBD being treated with infliximab or tofacitinib had lower anti-SARS-CoV-2 spike protein antibody concentrations after two doses of vaccine than did healthy controls. No significant decrease in antibody responses were observed in patients with IBD being treated with thiopurines, ustekinumab, or vedolizumab in relation to control participants [17]. Despite the insight offered by these studies, the question on how vaccine-induced antibody concentrations translate clinically is yet to be answered, and this may present a barrier in patient-doctor interactions. Antibody concentration was not an objective of our study, yet this may present an interesting recommendation or follow-up study. Our clinical study has, however, shown that patients with IBD who received the vaccine did not have worse outcomes than patients with IBS who also received the vaccine, suggesting that there is a strong element of vaccine efficacy. These findings can reassure patients that, though *in-vitro* studies may demonstrate lower antibody concentrations, this does not necessarily translate to increased susceptibility or worse outcomes. Further longitudinal studies are required to assess this finding [18].

Patients with IBD may also be concerned that vaccination for COVID-19 may affect disease activity. Despite a paucity of data on the matter, an observational cohort study in the US observed that amongst reported gastrointestinal side effects such as increased bowel frequency and abdominal pain, only 2.1% of patients had symptoms meeting the criteria for an IBD flare post-vaccination. Moreover, participants who became infected with COVID-19 reported mild COVID-19 symptoms and none required hospitalization [19]. In Europe, 1.8% of the cohort reported an IBD relapse post-vaccination, with only 3 patients with moderate disease at baseline requiring hospitalisation for medical treatment [12]. Our study did not show any relapses post-vaccination, and this is significant as it will encourage more patients to get vaccinated and therefore prevent adverse outcomes if infected with COVID-19.

As regards the third vaccine dose, the UK Joint Committee on Vaccination and Immunisation (JCVI) issued guidance recommending a third primary dose of a SARS-CoV-2 vaccine in individuals who received targeted therapy for an autoimmune disease in the previous 3 months, administered at least 8 weeks after the second dose [20]. All 85 patients with IBD in a multicentre trial who received a third COVID-19 mRNA vaccine dose demonstrated a humoral immune response. Median antibody concentrations were higher following a third dose than after the 2-dose series. As previously stated, clinical correlation of this antibody response is yet to be determined [21]. In Canada there was higher uptake of third doses of SARS-CoV-2 vaccines among patients with IBD compared to the general population, yet the rate was still low at around 58% [22].

A survey including patients with functional dyspepsia, IBS and functional dyspepsia–IBS overlap noted that 11.9% of respondents endured worsening of gastrointestinal symptoms during the pandemic, and respondents with FD-IBS overlap sustained the worst gastrointestinal and psychological symptoms [23]. These symptoms may also be exacerbated in patients having IBS and co-morbid anxiety or depression [24]. Unfortunately, until the time of writing there have not been any studies regarding post-vaccination gastroenterological symptoms in IBS patients.

The stress associated with COVID-19, lockdown and financial concerns are similar in both IBS and non-IBS sufferers, but the psychological impact and detriment in quality of life are both higher in IBS patients. Whilst the univariate analysis shows that teleworking, solitary confinement, and low household resources influence the psychological well-being of both groups, the multivariate analysis brought out IBS as the single factor contributing towards a decline in the quality of life [25].

One limitation of the study was that the low hospitalization rate observed in both groups which may not be representative of the whole Maltese IBD and IBS population, although there have not been any cases of intubation or mortality due to COVID infection in the local IBD population. Another drawback of the study was the lack of inclusion of IBD patients on non-immunosuppressive treatment, as this would have added a third comparative group to assess for differences in infection and vaccination effects.

Our recommendations are for clinicians to approach patients with IBD and IBS in an empathetic manner, especially during the pandemic, and strive to address concerns in a scientific and honest approach. This may involve the recruitment of the multidisciplinary team, including specialist nurses and psychological support, to reduce anxiety and encourage safe measures whilst avoiding IBD or IBS flares. Furthermore, a nation-wide effort to protect these vulnerable groups from infection and pandemic-related anxiety must be taken.

CONCLUSIONS

Our study was the first of its nature comparing the impact of COVID-19 infection, sequelae, swabbing and vaccination rates between two groups of patients with gastrointestinal disorders. This study demonstrates that vaccine uptake, COVID-19 infection rates, hospitalization and outcomes were similar in patients with IBS compared to IBD patients on immunosuppressive therapy.

Conflicts of interest: None to declare.

Authors' contribution: All authors equally contributed to this study and agree to be responsible for the content of this paper.

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