PROTECT-ASUC: COVID-19 pandemic response of assessment, endoscopy and treatment in acute severe ulcerative colitis. A multi-centre observational case-control study

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Abstract

Background: There is a paucity of evidence to support safe and effective management of acute severe ulcerative colitis (ASUC) in the COVID-19 pandemic period. We sought to identify alterations in treatment paradigms of ASUC during the early COVID-19 pandemic, the impact on ASUC outcomes and any associations with SARS-CoV-2 infection and severe COVID-19 outcomes.

Methods: A multicentre observational case control study of ASUC patients during the first wave of the COVID-19 pandemic in the United Kingdom, with comparison to a 2019 pre-pandemic historical cohort.

Findings: We included 782 patients (398 in the pandemic period cohort and 384 in the historical control cohort) meeting the Truelove and Witts criteria for ASUC. The primary outcome of rescue therapy (including primary induction) or surgery was higher during the pandemic (55·2% [217/393] vs 41·8% [159/380] p=0·00024) and the time to the primary outcome was shorter (p = 0·0026). During the pandemic more patients received ambulatory (outpatient) intravenous steroids (13·2% [51/385] vs 5·3% [19/360] respectively, p=0·00023). During the pandemic, more patients received induction biologic therapy (either as rescue or primary therapy), ciclosporin or tofacitinib (45·7% [177/387] vs 35·9% [134/373], p=0·0064), there was lower use of thiopurines (7·3% [29/398] vs 12·0% [46/384], p=0·029) and 5-aminosalicylic acids (5-ASAs) (16·8% [67/398] vs 25·5% [98/384], p=0·0037). Whilst colectomy rates were similar between the pandemic and historical control groups (16·5% [64/389] vs 13·3% [50/375], p=0·26), laparoscopic surgery was less frequently performed during the pandemic period (53·1% [34/64] vs 76·0% [38/50], p=0·018). During the ASUC episode and by 3 months respectively, only 1·98% (5/253) and 1·94% (2/103) of patients were diagnosed with COVID-19 and none had serious COVID-19 outcomes (mechanical ventilation, ICU admission or death).

Interpretation: The COVID-19 pandemic altered practice patterns of gastroenterologists and colorectal surgeons in the management of ASUC but was associated with similar ASUC outcomes to a historical cohort. Despite continued use of high dose corticosteroids and biologics the incidence of COVID-19 within 3-months was low and not associated with adverse COVID-19 outcomes.

Funding: None

Research in context

Evidence before this study

- Expert consensus exercises have indicated a lack of evidence to support safe and effective management of acute severe ulcerative colitis (ASUC) in the COVID-19 pandemic period.
- Based on the immunomodulatory properties of standard treatments for ASUC, there are theoretical concerns around vulnerability of patients to SARS-CoV-2 infection and poorer outcomes from COVID-19.
- Potential risk factors relevant to ASUC included severely active mucosal inflammation, nosocomial infection, as well as the use of corticosteroids and immunosuppressants.

Added value of this study

- During the first COVID-19 pandemic wave there were adaptations to ASUC practice including use of ambulatory pathways, greater use of rescue therapy and lower use of laparoscopic surgery.
- Outcomes from medical and surgical management of ASUC during the first wave COVID-19 pandemic were similar to a pre-pandemic control cohort.
- There was low incidence of COVID-19 in hospitalised and ambulant ASUC patients treated with steroids +/- biologics or small molecules during the acute episode and up to 90 days from ASUC diagnosis.
- In this group of patients with a high inflammatory burden treated with powerful immunosuppression no severe COVID-19 outcomes were observed.

Implications of all the available evidence

- This data provides reassurance for clinicians during subsequent waves of the COVID-19 pandemic regarding the conventional management of ASUC using immune modifying drugs including use of intravenous corticosteroids and rescue therapies.
- Adaptations to care pathways and the impact of SARS-CoV-2 have not been seen

to be detrimental to overall patient outcome in ASUC and support the shaping of future care pathways in subsequent waves of this pandemic. Prospective studies are recommended embedding current and innovative changes to care pathways during the pandemic to determine pathway utility in ASUC treatment in the post-pandemic period.

Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has challenged conventional treatment strategies of inflammatory bowel disease (IBD) including the management of patients with acute severe ulcerative colitis (ASUC). ASUC is most commonly defined by the Truelove and Witts criteria,[1] which combines frequency of bloody stools (≥6 per day) with markers of systemic toxicity. Approximately 20–30% of patients with ulcerative colitis (UC) require hospitalization at some point in their disease course for an acute severe flare[2,3] and prior to the COVID-19 pandemic, ASUC was associated with a mortality of 1-2·9%.[2,4]

Data from small cohorts in the first wave of the COVID-19 pandemic suggested that disease activity may be a predictor for adverse COVID-19 outcomes in IBD patients.[5,6] Despite this, clinicians may have used a higher clinical threshold to determine which patients required emergency hospital admission due to concerns regarding nosocomial spread of SARS-CoV-2,[7] particularly in those thought to be most vulnerable to severe COVID-19 outcomes in whom 'shielding' and isolation was recommended. These concerns were shared by patients, whose reluctance for hospitalization may have led to failure in attendance for infusions and delayed presentation even in the presence of severe IBD symptoms.[8,9]

Pandemic-related challenges persisted after presentation to secondary care with ASUC; recommended early endoscopic mucosal assessment may have been impacted by uncertainty and delays regarding potential viral shedding in faeces, pre-endoscopic viral screening, availability of personal protective equipment (PPE), endoscopic capacity and staffing shortages.[10,11]

Conflicting evidence on the impact of high dose steroids in SARS-CoV-2 infection and COVID-19[12,13] challenged conventional steroid treatment dosing strategies. Data to inform discussions and decisions regarding risk:benefit of drugs used as rescue therapy, such as infliximab and ciclosporin in the pandemic era are still emerging.[13,14] Furthermore, early evidence from the pandemic identified that contracting COVID-19 in the peri-operative period increased mortality substantially, and this may subsequently have encouraged surgeons to set higher thresholds for considering colectomy[15] and also debate the role of laparoscopic surgery.[16]

Many of the current guidance documents relating to IBD care during the COVID-19 pandemic, including ASUC are based on expert consensus supported by few, if any, published data.[17,18] The impact of potential changes to conventional management pathways on ASUC outcomes is uncertain. A RAND consensus panel from the British Society of Gastroenterology (BSG) issued an expert consensus[19] pending evidence, acknowledging that there are considerable areas of uncertainty in relation to risk stratifying and managing ASUC patients in the era of the COVID-19 pandemic. The panel also suggested that this may contribute to variability in practice patterns and differences in patient outcomes.

The aim of this study was to identify alterations to established conventional evidence-based management of ASUC as a consequence of the first wave of the COVID-19 pandemic in the UK, and to evaluate the impact on patient outcomes and COVID-19 acquisition and severity.

Methods

Study Cohorts

PROTECT-ASUC (COVID-19 Pandemic Response Of assessmenT, EndosCopy and Treatment in Acute Severe Ulcerative Colitis) was a multi-centre observational case-control study conducted in acute secondary care hospitals throughout the United Kingdom (UK). We included adult patients (age ≥ 18 years) with either ulcerative colitis (UC) or inflammatory bowel disease unclassified (IBD-U) presenting with ASUC who fulfilled the Truelove and Witts criteria.[1]

Cases and controls were identified as either admitted or managed in emergency ambulatory care settings between 1st March 2020 and 30th June 2020 (COVID-19 pandemic period cohort), or between 1st January 2019 and 30th June 2019, (historical control cohort) respectively. Sites were asked to identify consecutive patients. Patients with Crohn's disease, infective colitis, cytomegalovirus (CMV) or *Clostridium difficile* infections were excluded from the study. Patients were identified from the participating site admission clinical records and IBD databases.

Data collection

We collected baseline clinical information including demographics (age, gender, ethnicity, body mass index and smoking status), disease characteristics (disease duration, disease extent, prior treatments including steroid, immunomodulatory and biologic therapies), disease severity markers (C-reactive protein, serum albumin, haemoglobin, C-reactive protein–albumin ratio, endoscopic severity) and testing for SARS-CoV-2.

Following diagnosis of ASUC, details of steroid therapy including preparation, dose duration, and clinical setting where instituted and continued (ambulatory outpatient care or inpatient), need for, and drug(s) prescribed as rescue therapy, as well as need for emergency colectomy during index admission were recorded. Data on therapies including 5-ASAs, steroids, immunomodulators either discontinued or initiated during the ASUC admission/period were recorded. Follow-up data were collected at 3 months with day of initial admission marked as day 0, and included clinical and biomarker remission status of IBD (where available), change in therapy during follow up and need for colectomy.

COVID-19 diagnoses at the point of ASUC diagnosis, nosocomial development of COVID-19 and COVID-19 acquisition between hospital discharge and 3-month follow up were recorded, including whether a diagnosis was based on symptoms, SARS-CoV-2 serology or quantitative Polymerase Chain Reaction (qPCR).

All clinical data were collected pseudo-anonymised and entered into a secure central REDCap server hosted at the Royal Devon and Exeter NHS Foundation Trust, UK.

Outcomes of interest

The primary outcome was the proportion of patients with ASUC receiving rescue therapy (including primary induction) and/or colectomy. Secondary outcome measures, both during ASUC episode and at 3-month follow up, included: time to rescue therapy or surgery, time to colectomy, new drugs prior to discharge, length of hospital admission, death during ASUC episode, adverse events (post-operative complications and mortality), positive PCR for SARS-CoV-2 and serious outcomes from COVID-19 (defined as the need for mechanical ventilation, intensive care unit [ICU] treatment or death).

Statistical analysis

The study was analysed and reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) methodology[20] and Statistical Analysis and Methods in the Published Literature (SAMPL).[21] Non-parametric data were summarised as medians and interquartile ranges (IQR) and differences between current pandemic cohort cases and historic cohort controls analysed using the Mann-Whitney *U* test. Categorical variables were summarised as proportions and analysed by Fisher's exact test or chi-squared test as appropriate; firstly, for initial outcomes after ASUC and secondly for 3-month follow up data.

Kaplan-Meier survival curves were plotted for i) rescue therapy or colectomy, and ii) colectomy rates in the cases and controls in the first 30 days after ASUC diagnosis. We used a combined outcome of rescue therapy or colectomy in preference of rescue therapy alone in order to avoid the incorrect assignment of patients who went straight-to-surgery as having `survived` without rescue therapy when no such therapy would be possible. All tests were two-sided and a *P* value of <0·05 was considered significant with no correction made

for multiple tests. Analysis was carried out using R 4·0·2 (R Foundation for Statistical Computing, Vienna, Austria) and the survival package.

Clinically plausible and previously reported markers of disease severity[22] in acute severe colitis (stool frequency, C-reactive protein, haemoglobin, albumin, CRP/albumin ratio) were selected for univariable (UVA) and multivariable (MVA) logistic regression models for the primary outcome of interest: rescue therapy (including primary induction) or surgery. In the MVA we present all terms without a reductive model as our intention was to establish if case-control status influenced outcome independently of markers for disease severity. These findings informed a sensitivity analysis using complete cases and after propensity score matching using the MatchIt package.[23] The covariates included were day 0 stool frequency, log(CRP) and albumin.

Ethical considerations

This study was registered with research governance teams at all hospital sites to approve access to patient records. The study was approved by Leeds and Bradford ethics committee (IRAS No:284030, REC reference:20/HRA/2578) and the protocol listed at https://clinicaltrials.gov/ct2/show/NCT04411784). As no additional study procedures were carried out the need for written informed consent was waived by the ethics committee.

Role of the funding source

There was no funding for this study. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Results

Cohorts

A total of 834 consecutive patients fulfilling the criteria for ASUC were submitted by 60 UK centres. Fifty-two patients were excluded from the final analysis: COVID-19 at baseline (n=1); admission outside of the specified periods (n=6); patients received neither intravenous steroids nor rescue therapy (n=19); acute CMV colitis (n=10); and, *Clostridium difficile* associated diarrhoea (n=16). Seven hundred and eighty-two patients were used in the final analysis (398 COVID-19 pandemic period cases and 384 historical controls) (see **Supplementary Figure 1**).

Demographics

The baseline demographic, smoking and co-morbidities among the pandemic period cohort and the historical control cohort were comparable and are depicted in **Table 1**.

Disease characteristics and baseline medications

The disease characteristics in the two cohorts were comparable (**Table 1**). At the time of presentation with ASUC, a higher proportion of patients during the COVID-19 period were receiving oral steroids (38·7% [148/382] vs. 25·8% [95/368], respectively, p = 0·0015), rectal steroids (4·8% [19/398] vs. 2·1% [8/384], respectively, p = 0·049) and biologic/small molecule therapies (26·9% [107/398] vs. 18·2% [70/384], p = 0·0047) than patients in the historic cohort. The median (IQR) duration of oral steroids prior to meeting ASUC criteria was 14·0 days (IQR 7·0 - 28·2) vs. 13·5 days (IQR 7·0 – 25·0) for the COVID-19 and historic cohorts, respectively (p = 0·21). No difference was observed in the use of oral (p = 0·94) or topical mesalazines (p = 0·67) or thiopurines (p = 0·55). Additionally, among patients receiving oral steroids, no difference in the type of steroid (prednisolone vs. poorly bioavailable steroid [budesonide CR, budesonide MMX or beclomethasone dipropionate]) used was observed between the cohorts (p = 0·17).

Disease severity indicators

There was no difference at day 1, day 3 or day 5 in any established markers of ASUC severity (stool frequency, CRP, haemoglobin, albumin, CRP/albumin ratio) between the two cohorts with the exception of serum albumin levels, which were lower in the COVID-19 pandemic period cohort (**Supplementary Table 2**).

Hospital Care

A greater proportion of patients in the COVID-19 pandemic cohort in comparison to patients in the historic control cohort were managed initially on an ambulatory pathway (13·2% [51/385] vs. 5·3% [19/360], respectively, p = 0·00023; **Table 2**). However, 43 of 51 (84.3%) and 18 of 19 (94.7%) ambulatory patients in the COVID-19 and historic cohort respectively, required inpatient admission (p = 0.43). Patients were less likely to present emergently to the Accident & Emergency department (74·9% [295/394] vs. 84·5% [322/381], respectively, p = 0·00095) in the COVID-19 period as compared with the historic cohort.

Primary and secondary outcomes

The ASUC outcomes including outcomes from medical and surgical treatments the two cohorts are depicted in **Table 3,** and **Supplementary Figure 2.** The proportion of patients receiving rescue therapy (including primary induction) or surgery was higher during the pandemic relative to the historical period (55.2% [217/393] vs 41.8% [159/380] p=0.00024). This difference was driven by a greater use of rescue and primary induction therapies with biologics, ciclosporin or tofacitinib (45·7% [177/387] vs 35·9% [134/373], respectively, p = 0·0064) in the COVID-19 pandemic period cohort as compared to the historical control period cohort. In comparison there was no difference in the requirement for emergency surgery between the cohorts (16.5% [64/389] vs 13.3% [50/375] respectively, p = 0.26).

Medical treatment

Response to intravenous corticosteroid in the pandemic period cohort was not statistically different to those in the control period cohort (68·8% [264/384] vs 74·8% [282/377], respectively, p = 0·065). Of patients requiring rescue or induction therapies, the choice of agents differed among the two cohorts with a greater use of non-infliximab and non-

ciclosporin based treatments (23.7% [42/177] vs 12.7% [17/134], respectively, p = 0·019) in the pandemic period cohort (**Table 4**). Time to rescue therapy or surgery was significantly different between the pandemic and historic cohorts (p = 0.0026)(**Figure 1A**); rescue therapy or surgery happened both at a higher rate and more quickly during the COVID-19 pandemic as compared to historic control period. The overall response to rescue therapy was similar within the two cohorts (81·3% [139/171] cases and 79·5% [105/132] controls, p = 0·77). High first infliximab dose (10mg/kg) induction loading was used in 23·5% [27/115] and 18·5% [17/92] of patients in the pandemic period cohort and historical control period cohort respectively (p = 0·40) and an accelerated infliximab dosing schedule with a second dose administered before discharge (prior to 2-weeks) was used in 19·2% [23/120] and 23·1% [24/104], respectively (p = 0·51).

Surgery

In addition to there being no difference in colectomy rates there was no difference in time-to-surgery in the two cohorts (p = 0·24) (**Figure 1B**). However, laparoscopic surgery was less often performed in the pandemic period cohort when compared to the control cohort (53·1% [34/64] vs 76·0% [38/50], p = 0·018). There was no significant difference in the need for postoperative intensive care unit stay (31.6% [18/57] vs 31.1% [14/45], p = 1.0) nor in overall complications rates 37·3% [22/59] vs 29·2% [14/48] (p = 0·42) or specific complications (**Supplementary Table 3**). Furthermore, there was no difference in mortality between the two cohorts (p = 1.0)

In a multivariable logistic regression analysis, the odds of rescue therapy or surgery were lower in the historic than the COVID-19 pandemic cohort (OR 0·63, 95%CI [0·44 to 0·89], p = 0·0083) – this is independent of day 1 biomarkers for disease severity including: stool frequency, CRP, haemoglobin, albumin and albumin/CRP ratio (**Supplementary Table 4** for univariate and multivariable analysis). Therefore, in order to ascertain if cohort type influenced our primary and secondary endpoints, we performed propensity score matching using stool frequency, CRP, haemoglobin, albumin and albumin/CRP ratio. This analysis demonstrates that our primary outcomes remained significant after matching for these variables. In the matched cohort of 281 cases and 266 controls, day 0 albumin was no longer significantly different (p = 0·080). In univariable logistic regression of the primary outcome

in the matched cohort, the univariable odds ratio for being in the historic cohort was 0·62 (95% CI 0·44 to 0·87; p = 0·006).

There were differences in the type of new drugs initiated during hospitalization and at discharge during the two periods. In particular there was higher rates of initiation of biologics and small molecules and lower rates of initiation of azathioprine and mesalazine. (**Table 4, Figure 2**).

3-month outcomes

Three-month follow up data were available on 697 patients (322 from the COVID-19 period and 375 from the control period) (**Table 5**). At three months, there was no difference in the proportion of cases or controls in clinical (43·1% [125/290] vs 42·1% [143/340], respectively, p = 0·96), biomarker (63·9% [163/255] vs 62·2% [191/307], respectively, p = 0·73) or endoscopic remission (33·3% [15/45] vs. 30·9% [25/81], respectively, p = 0·85). Nor was there a difference in the proportion of patients in the two cohorts who suffered a flare of their IBD (25·7% [79/307] vs. 27·4% [100/365], respectively, p = 0·29). The proportions in each cohort being initiated on oral or topical mesalazines (p = 0·67 and p = 0·23, respectively), oral steroids (p = 0·45) - including which type of oral steroid was prescribed (prednisolone vs. poorly bioavailable steroids [p = 0·67]) - and thiopurines (p=0·33) did not differ. Furthermore, with regards key ASUC outcome measures, the proportion of patients requiring re-admission for active disease (24·4% [75/307] vs. 22·3% [81/363], respectively, p = 0·32), IV steroids (5.9% [19/322] vs 6.1% [23/375], respectively, p = 1·0) and surgery (8·6% [26/301] vs. 5·3% [19/358], respectively, p = 0·12) was not significantly different between the two cohorts.

COVID-19 in ASUC patients

SARS-COV-2 nasopharyngeal swab testing was undertaken in 253 (63·6% [253/398]) of the included patients. Five patients tested PCR positive during their ASUC hospitalization (1.98% [5/253]). There were no serious COVID-19 outcomes. One hundred and three patients were re-tested for COVID-19 PCR during 3-month follow up period and 2 patients tested positive (1.94% [2/103]) 5 and 12 days after discharge from index admission for ASUC and both

recovered without serious outcomes. The details of COVID-19 PCR positive patients and therapies are included in **Supplementary Table 5.**

Shielding data following discharge from hospital was available in 292 patients included in the pandemic period cohort **(Supplementary Table 6)**. Among these 51 (17.5% [51/292]) confirmed to have shielded and 31 (10·6% [31/292]) confirmed not to have shielded. A further 102 (34.9% [102/282]) were advised to shield but not confirmed to have followed the advice.

Discussion

We report the largest series of patients diagnosed with ASUC to date in the COVID-19 pandemic period. We identify adaptations to treatment pathways during the first pandemic wave relative to a 2019 pre-pandemic cohort in the UK. During the COVID-19-era we observed more frequent use of biologics and tofacitinib as rescue or primary induction therapy. We also observed a reduction in use of immunomodulators and 5-ASAs during both the acute episode and at the point of discharge. Our study identifies an increased use of ambulatory (outpatient) pathways for initial administration of intravenous steroids although most of these patients were still admitted to hospital. Importantly we confirm that conventional use of corticosteroids during the early pandemic remained prevalent and was not associated with either a high incidence of SARS-CoV-2 infection, nor with adverse outcomes in those diagnosed with COVID-19. The incidence of surgery for ASUC was not higher during the pandemic. However, surgical practice for medically refractory patients during the pandemic was modified with a reduction in laparoscopic colectomy rates. Reassuringly, the immediate and 3-month outcomes of ASUC during the pandemic were comparable to the historical control cohort. Furthermore, during a 3-month follow up period, there was no increase in risk of flares, readmissions or colectomies and in the pandemic cohort, only two COVID-19 diagnoses among 103 tested patients.

Consensus statements and expert opinion in the early stages of the COVID-19 pandemic cautioned against use of high dose corticosteroids (≥20mg of prednisolone/day) in IBD patients due to concerns regarding adverse outcomes in COVID-19 infection.[17,18,24] This was largely based on extrapolation and lessons from historical cohorts in the previous coronavirus pandemics.[25] It is known that IBD patients have a higher seasonal flu risk and corticosteroids are an independent risk factor.[26] Steroids are also a risk factor for serious or opportunistic infection, particularly when combined with thiopurines.[27,28,29] Conversely, both dexamethasone and hydrocortisone with potent immune modifying effects have been shown as beneficial in severe COVID-19, an infection characterised by an exaggerated systemic inflammatory response in some patients.[12,30]

Steroids were also reported to be a risk factor for adverse COVID-19 outcomes in the SECURE-IBD registry,[13,14] which includes physician reported cases of COVID-19, and also from a small cohort from Italy;[5] both of which hold potential for reporting bias and neither

systematically controlled for disease activity. These reports have understandably led to concerns regarding the management of ASUC patients where intravenous high dose corticosteroids remain the cornerstone of first line management.[19] However, despite intense immunosuppression including use of intravenous and high dose oral corticosteroids, we report very low numbers of patients with concurrent COVID-19 during admission or during the follow up period of 90 days. Importantly, in our study there was no reduction in the use of intravenous steroids in ASUC patients during the COVID-19 era in comparison to the historical cohort, and in longitudinal follow up we did not notice an increase in risk of SARS-CoV-2 infection or an increased risk of serious adverse outcomes secondary to COVID-19 in this cohort.

There is increasing interest on the role of cytokine-directed therapies as a treatment for severe COVID-19 outside of the IBD setting.[31,32] Furthermore, a recent report suggests low prevalence of SARS-CoCV-2 seroconversion in patients with immune-mediated inflammatory diseases on cytokine therapies including IBD.[33] In the present study we have shown an overall increase in the use of rescue therapies during the COVID-19 pandemic, in particular, the use of Janus kinase inhibition and biologics (anti-TNF, anti-IL12/23 and anti-α4β7 integrin). The reasons for the increase use noted is likely to be multifactorial and could relate to delayed presentation and advanced disease,[34] concerns regarding prolonged steroid use in early expert consensuses,[18] but also wider availability and physician confidence in use of newer biologics over time. Importantly, the initial SECURE-IBD registry data[13] potentially supported the use of biologics in ASUC by showing an inverse association with risk of hospitalization and death in COVID-19 IBD patients on anti-TNF monotherapy (aOR 0·9, 95% CI 0·4-2·2). Furthermore, a recent update from the SECURE-IBD registry[14] suggests increased risk of severe COVID-19 outcomes with thiopurine monotherapy and in combination with anti-TNFs. Consistent with concern regarding thiopurine use and susceptibility to viral infection, we observed lower azathioprine use in the pandemic study period. Additionally, and perhaps in response to the as yet unclear mechanisms underpinning the association with 5-ASA and severe COVID-19 outcomes in the SECURE-IBD registry,[13,14] we also witnessed lower use of 5-ASA at the point of discharge during the pandemic study period. It is plausible that in addition to these safety concerns, logistical issues such as infusion unit capacity and the need for regular blood monitoring during the

pandemic[35] may have had a role to play in the reduction in the use of thiopurines, combination therapy and infusion-based biologics.

There is increasing debate about the timing of rescue therapy in patients who are refractory to intravenous corticosteroids as current practice is guided by a criterion[36] developed before the era of biologics. Our study suggests increasing and more varied use of rescue therapy and primary induction agents, although there no difference was observed in overall colectomy rates. The use of early risk stratification tools and their impact to guide timing of rescue therapy is being evaluated in an ongoing study (ELEVATE ASUC- NCT03907631).

It is plausible that enhanced adherence to well publicised public health measures including patient access to a self-risk identification tool[18] in our cohort (see **Supplementary Table 6** for shielding data) may have reduced the risk of SARS-CoV-2 acquisition, nevertheless our data provide some reassurance regarding the use of intravenous corticosteroids and induction doses of biologics during subsequent waves of the pandemic. While we did not systematically analyse the seroconversion rates in all our patients in this study (the subject of the recently launched UK CLARITY programme www.clarityibd.org), the very low rates in the tested patients and low rates of serious COVID-19 outcomes in the 90-day longitudinal follow up period is reassuring and in line with other observations.[37,38] We will seek to extend this follow up period in a forthcoming amendment to the existing study to capture longer-term COVID-19 risk, IBD outcomes and surveillance for the emergence of long-COVID/IBD immunological phenomena.

In the non-COVID-19 setting, clinically active IBD is reported to be an independent risk factor for serious viral or opportunistic infections.[28,29] Importantly our study does not support the assumption that inflamed mucosa in in the setting of ASUC is associated with increased risk of SARS-CoV-2 infection. In addition, although the number of patients with COVID-19 was small in our cohort, our study does not support data from small cohorts that active IBD is a risk factor for serious COVID-19 outcomes.[5,6] The impact of disease activity in IBD on risk of COVID-19 acquisition in different IBD phenotypes is being evaluated in another study from our group (www.preparedibd.org).

Colectomy is required in up to 20% of patients with ASUC.[3,4] Emerging data from the COVIDSurg cohort[15] indicates significant mortality in patients who acquired SARS-CoV-2 in

the perioperative period, with an understandable increase in the threshold to undertake surgery. COVIDSurg has not reported outcomes in emergency surgery for IBD patients. In the present study there was no difference in colectomy rates in the pandemic study period and there were no new infections with SARS-CoV-2 in the patients requiring colectomy. In addition, there was no difference in mortality rates. We observed a reduction in the number of colectomies undertaken using a laparoscopic approach in the pandemic period reflecting initial concerns of transmission risk to healthcare professionals.[16]

We observed an increase use in ambulatory patient pathways during the COVID-19 period compared with the control group. This likely reflects concern regarding nosocomial transmission of COVID-19 during hospital admission particularly in patients needing surgery.[15] More frequent use of ambulatory ASUC pathways using single daily dose methylprednisolone with close monitoring by the specialist teams in day care centres or infusion units[39] in the COVID-19 cohort potentially mitigate this risk, but a large proportion of patients subsequently still required hospital admission and so this practice should be further evaluated in randomised studies in the future.

Our study has a number of strengths: to the best of our knowledge, we report the largest cohort of ASUC patients treated in the early COVID-19 pandemic worldwide. We collected detailed metadata on clinical and biochemical disease activity markers to assess association with COVID-19 outcomes and recruited a matched cohort of patients treated for ASUC prior to the pandemic onset. However, we concede our study also has a number of limitations in relation to study design. PROTECT-ASUC was retrospective and whilst requested patient selection was consecutive, it is possible that not all ASUC patients from each centre were captured. This may lead to selection bias. However, baseline patient and clinical disease phenotypic data as well as disease severity indices apart from serum albumin levels and steroid intake were all well matched, and therefore justify comparison across the two time periods. Furthermore, using univariable and multivariable analyses we identified potential confounding factors associated with the need for rescue therapy or colectomy among the two cohorts - we then used nearest neighbour matching to confirm our principal findings remained significant. While the proportion of patients on steroids before ASUC was similar in the two cohorts, we did not have data on the dose or duration of steroids. Importantly, only 5 of 385 (1·3%) of the cohort were diagnosed with COVID-19. Whilst severe outcomes

were not identified, larger cohorts to further study associations are desirable. Due to the retrospective nature of this study, we acknowledge there is some missing data. It is also possible that adverse events from rescue therapy, surgery and post-operative infections may not have been captured if not systematically recorded in local electronic recorded data. Therefore, our results may underestimate the incidence of adverse events.

Conclusion

Despite theoretical concerns regarding ASUC treatments and risk of SARS-CoV-2 acquisition and/or severe COVID-19 outcomes, our data identifies two reassuring important conclusions. Firstly, while there have been some adaptations to the conventional management of patients during the pandemic with regards to setting for intravenous steroids, choice and frequency of biologic and small molecule induction/rescue therapy and surgical approaches to colectomy, this did not lead to different ASUC outcomes for patients. Secondly, the use of cornerstone medications such as high dose intravenous steroids and biologics in ASUC appear to pose a low risk of nosocomial and post-discharge acquisition of SARS-CoV-2 and of developing severe COVID-19.

Additional large-scale prospective studies during the COVID-19 pandemic are recommended to confirm the low incidence of COVID-19 in this disease group and to further study COVID-19 outcomes. The challenges faced during the pandemic may also provide the impetus for more formal randomised studies to evaluate the safety and effectiveness of alternative ASUC treatment strategies, including the use of ambulatory pathways and non-conventional biologic rescue therapy.

Figure and Table Titles and Legends

Figure 1: A. Time to initiation of rescue therapy or surgery for ASUC within the first 30 days. **B.** Time to surgery

Figure 2: Maintenance treatments started during acute admission

Table 1: Summary of baseline characteristics and baseline therapies

Table 2: Hospital care pathways for ASUC

Table 3: Principle outcomes: medical, surgical, ICU and mortality

Table 4: Treatments during admission and prior to discharge

Table 5: Changes to treatment at 3-month follow up

Data sharing statement

De-identified participant data will be made available to others for meta-analysis upon request following Study Steering Group discussion and signing of a data access agreement. Requests for access to data should be made to the corresponding author and the first authors via the corresponding email given. The clinical protocol is available at https://clinicaltrials.gov/ct2/show/NCT04411784.

Author contributions statement

SS, NAK, GW, TC, KVP, SrS, AJK, JPS, NJB, NB, HAG, LCH, SJM and CAL formed the study steering group. SS was responsible for initial study design which was further developed by the steering group. NAK led methodological development and all members of the steering group contributed to subsequent protocol development. SS led regulatory approvals and study co-ordination. The PROTECT-ASUC study group and steering group were responsible for local site approvals, data acquisition and data entry. NAK and GW verified the data and led the statistical analysis supported by all members of the steering group. SS, GW and CAL led the writing group. SS, GW, NAK and CAL verified the underlying data. All members of the steering group contributed to manuscript redrafting, editing and review and approved the final version.

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Declarations of interest

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References

1. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955; 2:1041-8. DOI: 10.1136/bmj.2.4947.1041
2. Bitton A, Buie D, Enns R, et al. Treatment of hospitalized adult patients with severe ulcerative colitis: Toronto consensus statements. Am J Gastroenterol 2012; 107:179-94. DOI: 10.1038/ajg.2011.386
3. Lamb CA, Kennedy NA, Raine T*, et al* British Society Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults *Gut* 2019;68: s1-s106. doi:10.1136/gutjnl-2019-318484
4. Lynch RW, Lowe D, Protheroe A, et al. Outcomes of rescue therapy in acute severe ulcerative colitis: data from the United Kingdom inflammatory bowel disease audit. Aliment Pharmacol Ther 2013; 38:935-45. https://doi.org/10.1111/apt.12473
5. Bezzio C,Saibeni S, Variola A et al. Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study Gut 2020; 0:1–5. doi:10.1136/gutjnl-2020-321411
6. Lukin DJ, Kumar A, Hajifathalian K, et al Baseline disease activity and steroid therapy stratify risk of COVID-19 in patients with inflammatory bowel disease. Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.05.066.
7. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585
8. D`Amico F, Rahier JF, Salvo L, et al Views of patients with inflammatory bowel disease on the COVID-19 pandemic: a global survey Lancet Gastroenterol Hepatol2020 Published OnlineMay 13, 2020 https://doi.org/10.1016/ S2468-1253(20)30151-5
9. Wang H-G, Xie R, Ma TH et al. Excessive anxiety in IBD patients is unnecessary for COVID-19. Clin Res Hepatol Gastroenterol (2020), https://doi.org/10.1016/j.clinre.2020.0
10. Zuo T, Liu Q, Zhang F*, et al* Depicting SARS-CoV-2 faecal viral activity in association with gut microbiota composition in patients with COVID-19. *Gut* Published Online First: 20 July 2020. doi: 10.1136/gutjnl-2020-322294
11. Occhipinti V, Saibeni S, Sampietro GM, Pastorelli L, Impact of COVID-19 outbreak on the management of patients with severe IBD: a domino effect, Gastroenterology (2020), doi:https://doi.org/10.1053/j.gastro.2020.05.027.

12. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. N Engl J Med 2020; DOI: 10.1056/NEJMoa2021436
13. Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, but not TNF Antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: Results from an International Registry, Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.05.032
14. Ungaro RC, Brenner EJ, Gearry RBet al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. Gut 2020 (Epub ahead of print:doi:10.1136/gutjnl-2020-322539.
15. COVIDSurg collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. Lancet 2020 Jul 4;396(10243):27-38. doi: 10.1016/S0140-6736(20)31182-X
16. Simone BD, Chouillard E, Savarion SD, et al. Emergency surgery during the COVID-19 pandemic: what you need to know for practice. Ann R Coll Surg Engl 2020; 102: 323–332. 323–332. doi 10.1308/rcsann.2020.0097.
17. Allez M, Fleshner P, Geary R, et al. Care of the Patient with IBD Requiring Hospitalization During the COVID-19 Pandemic. *Journal of Crohn's and Colitis*, 2020;14(supplement 3,S775-S779. https://doi.org/10.1093/ecco-jcc/jjaa150
18. Kennedy NA, Jones GR, Lamb CA et al. British Society of Gastroenterology guidance for management of inflammatory bowel disease during the COVID-19 pandemic Gut 2020;0:1–7. doi:10.1136/gutjnl-2020-321244
19. Din S, Kent A, Pollok RC, et al. Adaptations to the British Society of Gastroenterology guidelines on the management of acute severe UC in the context of the COVID-19 pandemic: a RAND appropriateness pane Gut Epub ahead of print: [please include Day Month Year]. doi:10.1136/ gutjnl-2020-321927.
20. Gharaibeh A, Koppikar S, Bonilla-Escobar FJ: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) in the International Journal of Medical Students. Int J Med Stud 2014; 2:36-37, 2014. DOI: https://doi.org/10.5195/ijms.2014.76
21. Lang TA, Altman DG: Basic statistical reporting for articles published in biomedical journals: The “Statistical Analyses and Methods in the Published Literature” or the SAMPL Guidelines. Int J Nurs Stud 52:5-9, 2015. DOI: 10.1016/j.ijnurstu.2014.09.006

22. Sebastian S, Myers S, Nadir S, Subramanian S. Systematic Review: Efficacy and Safety of Accelerated Induction Regimes in Infliximab Rescue Therapy for Hospitalized Patients with Acute Severe Colitis. Dig Dis Sci 2019 ;64(5):1119-1128. doi: 10.1007/s10620-018-5407-7. Epub 2018 Dec 7
23. Ho DE, Imai K, King G, Stuart EA. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. Journal of statistical software 2015;42(8):22-29. DOI 10.18637/jss.v042.i08
24. Rubin DT, Abreu MT, Rai V, et al Management of patients with Crohn's disease and ulcerative colitis during the Coronavirus Disease-2019 Pandemic: Results of an international meeting. Gastroenterology 2020;159(1):6-13.e6. doi: 10.1053/j.gastro.2020.04.002
25. Sebastian S, Gonzalez HA, Peyrin-Biroulet L. Safety of drugs during previous and current coronavirus pandemics: Lessons for IBD. *Journal of Crohn's and Colitis*, jjaa120, https://doi.org/10.1093/ecco-jcc/jjaa120
26. Tinsley A, Navabi S, Williams ED, et al. Increased risk of influenza and influenza-related complications among 140,480 patients with inflammatory bowel disease. Inflamm Bowel Dis 2019;10;25(2):369-376. doi: 10.1093/ibd/izy243.
27. Naganuma M, Kunisaki R, Yoshimura N, et al. A prospective analysis of the incidence of and risk factors for opportunistic infections in patients with inflammatory bowel disease. J Gastroenterol 2013;48(5):595-900. doi: 10.1007/s00535-012-0686-9.
28. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. Am J Gastroenterol 2012;107(9)1409-22. doi: 10.1038/ajg.2012.218
29. Wisniewski A, Kirchgesner J, Seksik P, et al. Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines. United Eur Gastroenterol J 2019. DOI:10.1177/2050640619889763.
30. Angus CD, Derde L, Al-Beidh F, et al. Effect of Hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA2020;324(13):1317-1329. doi: 10.1001/jama.2020.17022.

31. Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. The Lancet 2020.395;1407-1409. doi: 10.1016/S0140- 6736(20)30858-8
32. Robinson PC, Richards D, Tanner HL, Feldman M. Accumulating evidence suggests anti-TNF therapy needs to be given trial priority in COVID-19 treatment. Lancet Rhematol 2020; 2(11): e633-e655. https://doi.org/10.1016/S2665-9913(20)30309-X
33. Simon D, Tascilar K, Kronke G, et al. Patients with immune-mediated inflammatory diseases receiving cytokine inhibitors have low prevalence of SARS-CoV-2 seroconversion Nat Commun. 2020;11(1):3774. doi: 10.1038/s41467-020-17703-6.
34. Occhipinti V, Patorelli L. Challenges in the Care of IBD Patients During the CoViD-19 Pandemic: Report From a "Red Zone" Area in Northern Italy. *Inflammatory Bowel Diseases*, Volume 26, Issue 6, June 2020, Pages 793–796, https://doi.org/10.1093/ibd/izaa084
35. Kennedy NA, Hansen R, Young L et al. Organisational changes and challenges for. inflammatory bowel disease services in the UK during the COVID-19 pandemic. Frontline Gastroenterology 2020; 11:343-350. doi:10.1136/flgastro-2020-101520
36. Travis SP, Farrant JM, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. Gut 1996; 38:905-10. http://dx.doi.org/10.1136/gut.38.6.905.
37. Fumery M, Matias C, Brochot E. Seroconversion of immunoglobulins to SARS-CoV2 in patients with inflammatory bowel disease patients treated by biologics. J Crohns and Colitis 2020; jjaa154, https://doi.org/10.1093/ecco-jcc/jjaa154
38. Norsa L, Cosimo P, Indriolo A, et al. Asymptomatic SARS-CoV-2 infection in patients with inflammatory bowel disease under biologic treatment. Gastroenterology (2020). https://doi.org/10.1053/j.gastro.2020.08.046
39. Townsend T, Fiske J, Collins P, et al. Ambulatory Management of acute severe ulcerative colitis: A pandemic-driven initiative. *Inflammatory Bowel Diseases*, Volume 26, Issue 10, October 2020, Pages e112–e113, https://doi.org/10.1093/ibd/izaa231

Table 1: Summary of baseline characteristics and baseline therapies

Baseline variable	**N**	**COVID-19 pandemic period cohort (n = 398)**	**Historical control cohort (n = 384)**	**Significance *P* value**
Age in years (Median, IQR)	782	38·0 (27·0 - 54·8)	36·0 (26·0 - 52·0)	0·12
Gender				
Male	782	48·5% (193/398)	49·5% (190/384)	0·83
Female		51·5% (205/398)	50·5% (194/384)	
BMI median (IQR)	436	24·4 (21·9 - 27·4)	24·4 (20·9 - 28·4)	0·90
Smoking status				
Non-smoker	595	67·9% (212/312)	65·7% (186/283)	0·69
Ex-smoker		25·0% (78/312)	25·4% (72/283)	
Current smoker		7·1% (22/312)	8·8% (25/283)	
Ethnicity				
White	686	81.0% (294/363)	78.3% (253/323)	0·18
Asian		11.6% (42/363)	13.6% (44/323)	
Black		3.9% (14/363)	3.7% (12/323)	
Arab		1.1% (4/363)	1.2% (4/323)	
Mixed		0.3% (1/363)	2.2% (7/323)	
Other		2.2% (8/363)	0.9% (3/323)	
Comorbidities				
Hypertension	782	10·1% (40/398)	9·6% (37/384)	0·90
Diabetes	782	6·5% (26/398)	7·8% (30/384)	0·49
Cardiovascular disease	782	5·5% (22/398)	6·5% (25/384)	0·65
Chronic kidney disease	782	0·8% (3/398)	1·3% (5/384)	0·50
COPD	782	3·0% (12/398)	1·3% (5/384)	0·14
Asthma	782	8·8% (35/398)	8·3% (32/384)	0·90
Chronic liver disease	782	0·8% (3/398)	0·8% (3/384)	1.0
Current malignancy	782	1·0% (4/398)	0·8% (3/384)	1.0
Solid organ transplant	782	0·0% (0/398)	0·3% (1/384)	1.0
Stroke	782	1·3% (5/398)	0·5% (2/384)	0·45
Number of comorbidities				
0	782	70·1% (279/398)	72·1% (277/384)	0·81
1		21·4% (85/398)	18·8% (72/384)	
2		5·3% (21/398)	6·0% (23/384)	
>2		3·3% (13/398)	3·1% (12/384)	
Disease duration				
Years since diagnosis (median, IQR)	739	1·0 (0·0 - 5·0)	2·0 (0·0 - 6·0)	0·14
IBD subtype				
Ulcerative colitis	782	4·5% (18/398)	4·7% (18/384)	1·0
Inflammatory Bowel Unclassified		95·5% (380/398)	95·3% (366/384)	
Disease extent				
Proctitis	709	7·4% (25/338)	8·9% (33/371)	0·57
Left Sided Colitis		50·0% (169/338)	46·4% (172/371)	
Extensive Colitis		42·6% (144/338)	44·7% (166/371)	
Therapies prior to ASUC				
No treatment	782	26·4% (105/398)	29·7% (114/384)	0·34
Oral mesalazine	782	50·3% (200/398)	49·7% (191/384)	0·94

Rectal mesalazine	782	13·8% (55/398)	12·8% (49/384)	0·67
Rectal steroids	782	4·8% (19/398)	2·1% (8/384)	**0·049**
Any oral steroid	750	38·7% (148/382)	25·8% (95/368)	**0·0015**
Type of oral steroid*				
Poorly bioavailable steroids	239	15·6% (23/147)	8·7% (8/92)	0·17
Prednisolone		84·4% (124/147)	91·3% (84/92)	
Thiopurines	782	16·3% (65/398)	14·6% (56/384)	0·55
All biologics /small molecules	782	26·9% (107/398)	18·2% (70/384)	**0·0047**
Anti-TNFs	782	16·3% (65/398)	12·5% (48/384)	0·15
Vedolizumab	782	6·8% (27/398)	4·4% (17/384)	0·16
Ustekinumab	782	0·8% (3/398)	0·0% (0/384)	0·25
Tofacitinib	782	3·0% (12/398)	1·6% (6/384)	0·23
Number of previous admissions with ASUC				
0	673	52·7% (192/364)	56·3% (174/309)	0·70
1		25·3% (92/364)	25·2% (78/309)	
2		13·2% (48/364)	10·7% (33/309)	
>2		8·8% (32/364)	7·8% (24/309)	

Cardiovascular disease = coronary artery disease, heart failure, arrythmia; Chronic liver disease = primary sclerosing cholangitis, non-alcoholic fatty liver disease, cirrhosis; COPD = chronic obstructive pulmonary disease; ASUC = Acute Severe Ulcerative Colitis; BMI = body mass index; TNF = tumour necrosis factor; Poorly available corticosteroids = Beclometasone dipropionate (Clipper), Budesonide CR (Enterocort CR, and Budesonide MMX (Cortiment CR); Thiopurines = azathioprine, mercaptopurine or tioguanine; all biologics/small molecules = infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab; Anti-TNFs = infliximab, adalimumab and golimumab.
P value = Fisher's exact test or Mann-Whitney U test for discrete and continuous variables continuous, respectively. Values are displayed % (n/N) unless otherwise stated.

Table 2: Hospital care pathways for ASUC

Hospital care % (n/N)	**N**	**COVID-19 pandemic period cohort (n = 398)**	**Historical control cohort (n = 384)**	**Significance *P* value**
Patient initially managed on an ambulatory pathway for IV steroids*	745	13·2% (51/385)	5·3% (19/360)	**0·00023**
Attended accident & emergency department with ASUC	775	74·9% (295/394)	84·5% (322/381)	**0·00095**
Ward patient first managed when diagnosed with ASUC				
Dedicated GI ward		52·9% (200/380)	56·1% (212/378)	**0·42**[+]
Non-GI ward		38·6% (148/380)	43·9% (166/378)	
GI ward converted to general medicine during COVID-19 period		8·5% (32/380)	-	
Reviewed by consultant gastroenterologist within 24 hrs of hospitalization	761	80·7% (314/389)	77·2% (287/372)	0·25
Clinician responsible for patient after first 24 hrs				
IBD specialist	766	61·0% (238/390)	57·4% (216/376)	0·35
Non-IBD gastroenterologist		24·1% (94/390)	25·0% (94/376)	
Non-gastroenterology physician		10·5% (41/390)	14·4% (54/376)	
Colorectal surgeon		3·8% (15/390)	2·4% (9/376)	
Other general surgeon		0·5% (2/390)	0·8% (3/376)	
Patient discussed at IBD MDT	759	38·2% (150/393)	38·3% (140/366)	1.0

*ambulatory pathway = daily outpatient visits for intravenous steroids instead of admission to hospital. [+] p value for comparison of GI vs. non-GI ward. GI = gastrointestinal; IBD = inflammatory bowel disease; MDT = multidisciplinary team meeting; ASUC = acute severe ulcerative colitis.

Table 3: Principle outcomes: medical, surgical, ICU and mortality

Outcomes % (n/N)	**N**	**COVID-19 pandemic period cohort (n = 398)**	**Historical control cohort (n = 384)**	**Significance *P* value**
Primary endpoint				
Rescue (including primary induction) or surgery	773	55.2% (217/393)	41.8% (159/380)	**0.00024**
Medical Therapy Outcomes				
Received Intravenous Steroids	768	96·7% (380/393	98·4% (369/375)	0·16
Responded to intravenous steroids	761	68·8% (264/384)	74·8% (282/377)	0·065
Received rescue or primary induction therapy	760	45·7% (177/387)	35·9% (134/373)	**0·0064**
Responded to rescue therapy	303	81·3% (139/171)	79·5% (105/132)	0·77
Surgical Outcomes				
Required emergency surgery for ASUC	764	16·5% (64/389)	13·3% (50/375)	0·26
Surgery type:				
Subtotal colectomy	116	96·9% (62/64)	100·0% (52/52)	0·50
Diversion		3·1% (2/64)	0·0% (0/52)	
Surgery method:				
Open	114	46·9% (30/64)	24·0% (12/50)	**0·018**
Laparoscopic		53·1% (34/64)	76·0% (38/50)	
Post-operative complications	107	37.3% (22/59)	29.2% (14/48)	0.42
ASUC Outcomes:				
Length of stay Median (IQR)	673	7·0 (5·0 - 13·0)	7·0 (5·0 - 12·0)	0·99
ICU admissions[+]	762	3·1% (12/382)	2·9% (11/380)	0·32
Invasive ventilation	782	0·7% (3/398)	0·7% (3/384)	1
NIV	764	0·5% (2/384)	1·1% (4/380)	0·45
ECMO	782	0% (0/398)	0% (0/384)	NA
Death	771	1·3% (5/392)	0·8% (5/379)	1
Composite ICU/NIV/Death/ECMO	782	4·3% (17/398)	3·6% (14/384)	0·72

ASUC: Acute Severe Ulcerative Colitis; IQR: Inter Quartile Range; ICU: Intensive Care Unit; NIV: Non-Invasive Ventilation; ECMO: Extracorporeal Membrane Oxygenation. [+] Not including planned post-operative ICU admission.

Table 4: Treatments during admission and prior to discharge

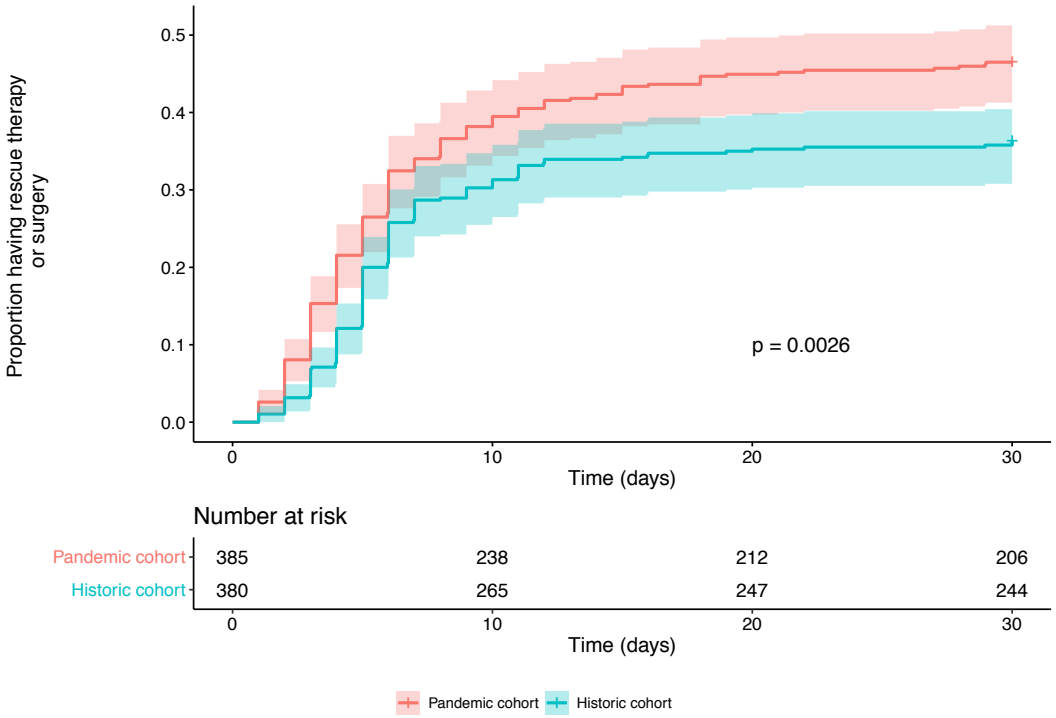
Treatments during admission and prior to discharge	**COVID-19 pandemic period cohort (n = 398)**	**Historical control cohort (n = 384)**	**Significance *P* value**
Any rescue therapy	45·7% (177/387)	35·9% (134/373)	**0·0064**
Infliximab	70·5% (124/176)	79·7% (106/133)	**0·021**
Adalimumab	0·6% (1/176)	2·3% (3/133)	
Ciclosporin	6·2% (11/176)	8·3% (11/133)	
Tofacitinib	7·4% (13/176)	2·3% (3/133)	
Ustekinumab	4·0% (7/176)	0·0% (0/133)	
Vedolizumab	11·4% (20/176)	7·5% (10/133)	
Dose of Infliximab			
10mg/kg	23·5% (27/115)	18·5% (17/92)	0·40
5mg/kg	76·5% (88/115)	81·5% (75/92)	
Was second dose Infliximab given prior to discharge	19·2% (23/120)	23·1% (24/104)	0·51

Table 5: Changes to treatment at 3-month follow up

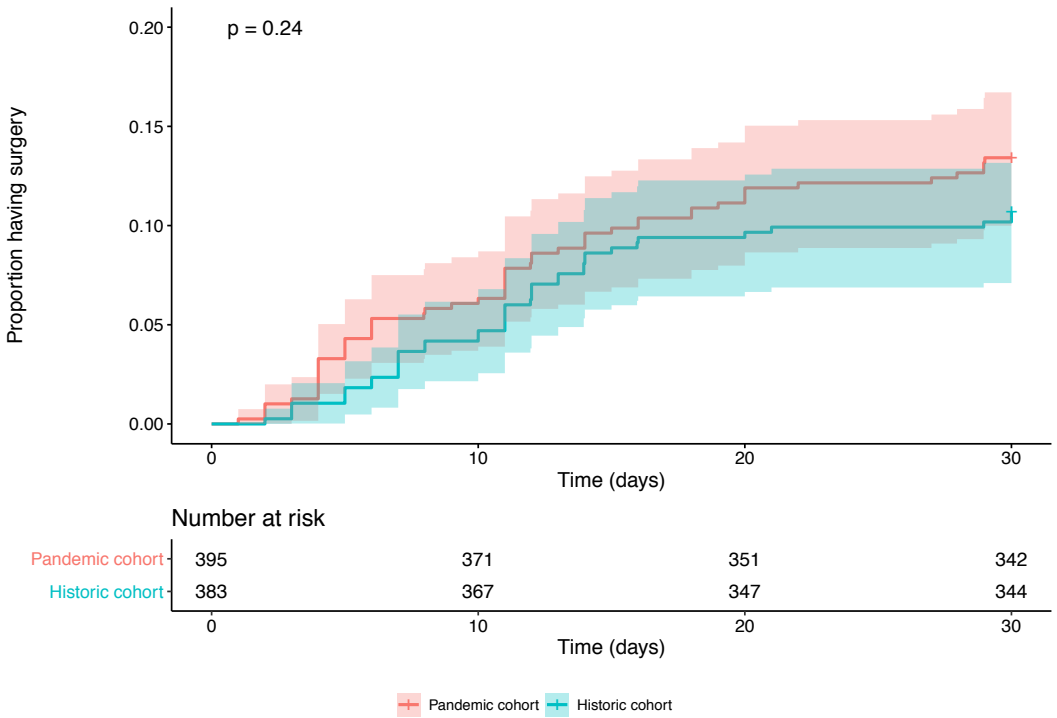
Variable % (n/N)	N	**COVID-19 pandemic period cohort** (n = 322)	**Historical control cohort** (n = 375)	**Significance** ***P* value**
Patient's disease status:				
Symptomatic remission	630	43·1% (125/290)	42·1% (143/340)	0·96
Biochemical remission	562	63·9% (163/255)	62·2% (191/307)	0·73
Endoscopic remission	126	33·3% (15/45)	30·9% (25/81)	0·85
Flare in last 3-months	672	25·7% (79/307)	27·4% (100/365)	0·29
New IBD therapies:				
Oral mesalazine	697	2·8% (9/322)	3·5% (13/375)	0·67
Topical mesalazine	697	4·0% (13/322)	6·1% (23/375)	0·23
Topical steroids	697	1·9% (6/322)	1·9% (7/375)	1.0
IV steroids	697	5·9% (19/322)	6·1% (23/375)	1.0
Oral steroid:	697	10·9% (35/322)	9·1% (34/375)	0·45
Oral prednisolone	69	88·6% (31/35)	94·1% (32/34)	0·67
Poorly bioavailable steroid		11·4% (4/35)	5·9% (2/34)	
Thiopurine monotherapy	697	4·7% (15/322)	6·7% (25/375)	0·33
Anti-TNF monotherapy	697	5·3% (17/322)	7·2% (27/375)	0·35
Anti-TNF and IMM	697	2·2% (7/322)	2·7% (10/375)	0·81
Vedolizumab	697	5·9% (19/322)	4·5% (17/375)	0·49
Ustekinumab	697	0·6% (2/322)	0·2% (1/375)	0·60
Tofacitinib	697	1·9% (6/322)	1·9% (7/375)	1.0
Readmitted to hospital with active disease	670	24·4% (75/307)	22·3% (81/363)	0·32
Active IBD and COVID-19 symptoms	160	5·1% (4/79)	NA	NA
Active IBD AND no COVID-19 symptoms		89·9% (71/79)	100.0% (81/81)	
COVID-19 symptoms AND no active IBD		5·1% (4/79)	NA	
Surgery	659	8·6% (26/301)	5·3% (19/358)	0·12
Emergency surgery	659	61·5% (16/26)	47·3% (9/19)	0·38
Elective surgery		38·4% (10/26)	52·6% (10/19)	

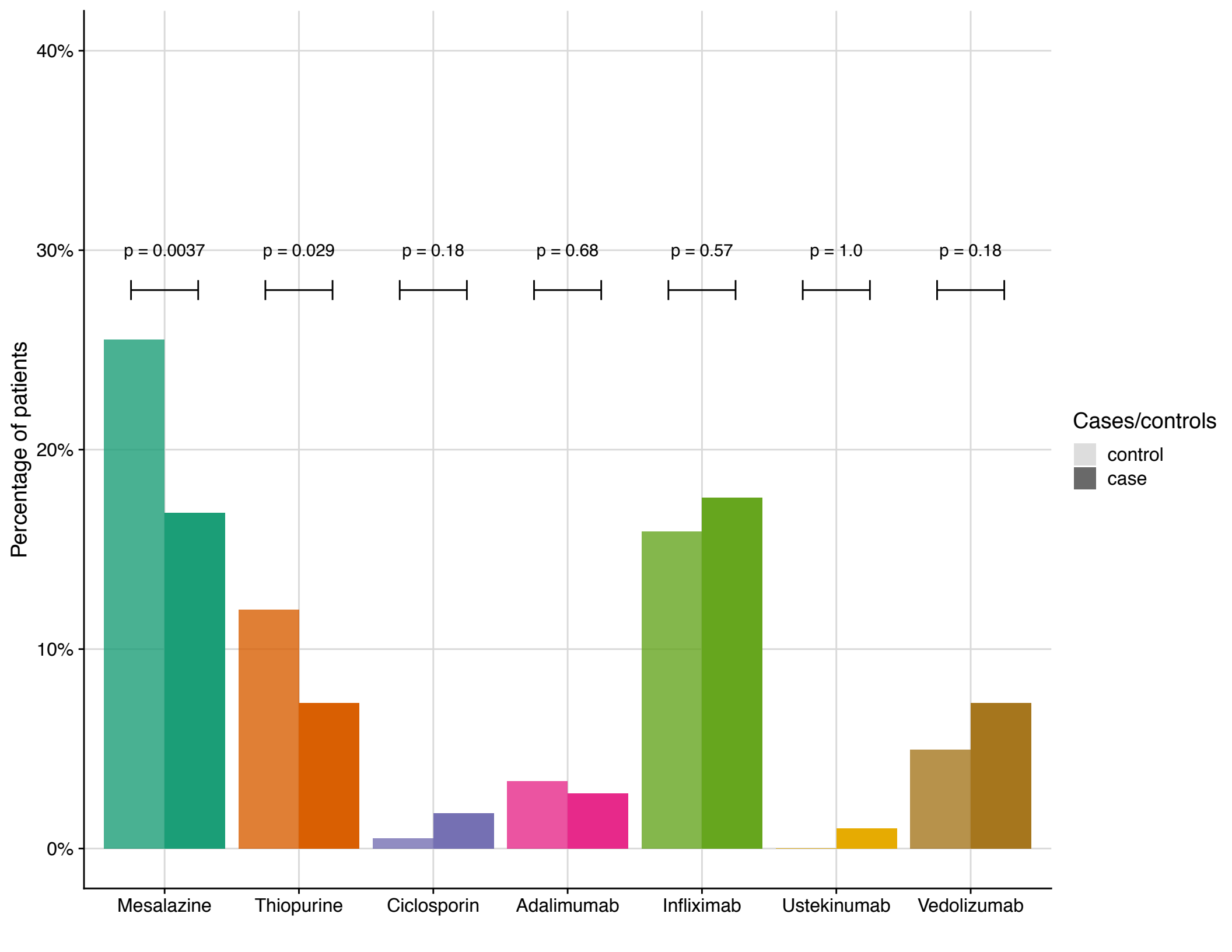
IMM = immunomodulator (thiopurine or methotrexate); thiopurine = azathioprine, mercaptopurine or tioguanine; anti-TNF = anti-tumour necrosis factor; IV = intravenous; poorly available corticosteroids = Beclometasone dipropionate (Clipper), Budesonide CR (Enterocort CR), and Budesonide MMX (Cortiment CR). *P* value = Fisher's exact test or Mann-Whitney U test for discrete and continuous variables continuous, respectively.

A


Proportion having rescue therapy or surgery
0.5
0.4
0.3
0.2
0.1
0.0
p = 0.0026
0
10
20
30
Time (days)
Number at risk
Pandemic cohort
Historic cohort
385
238
212
206
380
265
247
244
0
10
20
30
Time (days)
Pandemic cohort
Historic cohort

B


Proportion having surgery
0.20
0.15
0.10
0.05
0.00
p = 0.24
0
10
20
30
Time (days)
Number at risk
Pandemic cohort
Historic cohort
395
371
351
342
383
367
347
344
0
10
20
30
Time (days)
Pandemic cohort
Historic cohort


40%
30%
20%
10%
0%
Percentage of patients
p = 0.0037
p = 0.029
p = 0.18
p = 0.68
p = 0.57
p = 1.0
p = 0.18
Mesalazine
Thiopurine
Ciclosporin
Adalimumab
Infliximab
Ustekinumab
Vedolizumab
Cases/controls
control
case

Supplement

Supplementary Table 1: PROTECT-ASUC study contributors and institutions

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Supplementary Table 2: Disease severity indicators

Disease Severity Markers Median (IQR) [a]	**N**	**COVID-19 pandemic period cohort (n = 398)**	**Historical control cohort (n = 384)**	**Significance *P* value**
Day 1				
Day 1 stool frequency	613	10·0 (8·0 - 15·0)	10·0 (8·0 - 15·0)	0·57
Day 1 CRP	707	52·0 (17·0 - 120·0)	54·0 (23·0 - 110·0)	0·86
Day 1 haemoglobin	706	123·0 (106·0 - 136·0)	123·0 (109·0 - 137·0)	0·28
Day 1 albumin	666	35·0 (29·0 - 39·0)	37·0 (31·0 - 41·0)	**0·0036**
Day 1 CRP/albumin ratio	662	1·6 (0·5 - 3·6)	1·6 (0·6 - 3·3)	0·70
Day 3				
Day 3 stool frequency	450	7·0 (4·0 - 10·0)	6·0 (4·0 - 9·0)	0·21
Day 3 CRP	613	31·9 (11·0 - 72·0)	31·0 (14·5 - 60·0)	0·70
Day 3 haemoglobin	617	112·0 (98·0 - 125·0)	116·0 (101·0 - 128·2)	0·12
Day 3 albumin	527	31·0 (26·0 - 35·5)	33·0 (29·0 - 37·2)	**0·0048**
Day 3 CRP/albumin ratio	519	1·1 (0·3 - 2·7)	1·0 (0·4 - 2·2)	0·25
Day 5				
Day 5 stool frequency	438	5·0 (3·0 - 8·0)	4·0 (3·0 - 8·0)	0·72
Day 5 CRP	570	14·0 (5·0 - 35·0)	15·0 (6·0 - 31·5)	0·82
Day 5 haemoglobin	577	110·0 (97·8 - 125·0)	115·0 (100·0 - 127·0)	0·063
Day 5 albumin	499	31·0 (25·0 - 35·0)	32·0 (28·0 - 36·0)	**0·028**
Day 5 CRP/albumin ratio	493	0·5 (0·2 - 1·4)	0·5 (0·2 - 1·0)	0·60
Endoscopic assessment				
Flexible sigmoidoscopy	758	75·5% (289/383)	79·2% (297/375)	0·23
Day of endoscopic assessment median (IQR)	568	1·0 (0·0 - 3·0)	2·0 (0·0 - 3·0)	0·10
Endoscopic Severity % (n/N) Mayo 1 Mayo 2 Mayo 3	541	 4·9% (13/265) 33·2% (88/265) 61·9% (164/265)	 6·2% (17/276) 36·6% (101/276) 56·9% (157/276)	0·50

All values median (interquartile range) unless otherwise stated. IQR = interquartile range; CRP = C- Reactive Protein. *P* value = Fisher's exact test or Mann-Whitney U test for discrete and continuous variables continuous, respectively.

[a] Units for variables: CRP - mg/L; albumin – g/L; haemoglobin - g/L; stool frequency - stools per 24 hours.

Supplementary Table 3: Table of post-operative complications

Variable	N	COVID-19 pandemic period cohort (n= 398)	Historic control cohort (n= 384)	Significance P value
Required emergency surgery for ASUC	764	16·5% (64/389)	13·3% (50/375)	0·26
Post-operative ITU stay required	102	31·6% (18/57)	31·1% (14/45)	1·0
Post-operative complications?	107	37·3% (22/59)	29·2% (14/48)	0·42
Gastrointestinal complication(s)	782	2·0% (8/398)	1·8% (7/384)	1·0
Wound complication(s)	782	1·3% (5/398)	0·0% (0/384)	0·062
Infective complication(s)	782	2·3% (9/398)	1·3% (5/384)	0·42
Renal and Endocrine complication(s)	782	0·3% (1/398)	0·0% (0/384)	1·0
Cardiovascular disorder(s)	782	0·0% (0/398)	0·0% (0/384)	NA
Pulmonary complication(s)	782	0·5% (2/398)	0·3% (1/384)	1·0
Neurological disorder(s)	782	0·3% (1/398)	0·0% (0/384)	1·0
Small bowel obstruction	782	0·3% (1/398)	0·0% (0/384)	1·0
Anastomotic stricture (includes peritoneal adhesions)	782	0·0% (0/398)	0·0% (0/384)	NA
Pouch leak/Pouch failure	782	0·3% (1/398)	0·0% (0/384)	1.0
Bowel perforation	782	0·3% (1/398)	0·0% (0/384)	1.0
Ileus	782	0·8% (3/398)	0·8% (3/384)	1.0
Ischaemic bowel	782	0·0% (0/398)	0·0% (0/384)	NA
GI bleeding	782	0·0% (0/398)	0·3% (1/384)	0·49
Ileostomy / colostomy complication or malfunction	782	0·3% (1/398)	0·8% (3/384)	0·37
Digestive organ disorders (includes acute hepatic failure and acute pancreatitis)	782	0·0% (0/398)	0·0% (0/384)	NA
Fistula	782	0·0% (0/398)	0·0% (0/384)	NA
Hematoma/seroma	782	0·0% (0/398)	0·0% (0/384)	NA
Wound dehiscence and Delayed wound healing	782	1·3% (5/398)	0·0% (0/384)	0·062
Iatrogenic injuries (includes foreign body accidentally left during procedure)	782	0·0% (0/398)	0·0% (0/384)	NA
Sepsis and bacteraemia	782	1·3% (5/398)	0·8% (3/384)	0·73
Abscess	782	1·0% (4/398)	0·8% (3/384)	1·0
Wound infection	782	0·3% (1/398)	0·0% (0/384)	1·0
Urinary tract infection	782	0·0% (0/398)	0·0% (0/384)	NA
Pneumonia and empyema	782	0·8% (3/398)	0·0% (0/384)	0·25
Acute renal failure	782	0·0% (0/398)	0·0% (0/384)	NA
Fluid and electrolyte disorders (includes hypokalaemia)	782	0·0% (0/398)	0·0% (0/384)	NA
Severe endocrine disorders (includes adrenal disorders, hypoglycaemic coma)	782	0·3% (1/398)	0·0% (0/384)	1·0
Retention of urine	782	0·0% (0/398)	0·0% (0/384)	NA
Thrombosis/embolism	782	0·0% (0/398)	0·0% (0/384)	NA
Myocardial infarction	782	0·0% (0/398)	0·0% (0/384)	NA
Cardiac arrest	782	0·0% (0/398)	0·0% (0/384)	NA
Hypotension or shock	782	0·0% (0/398)	0·0% (0/384)	NA
Cardiac arrhythmias (excludes tachycardia)	782	0·0% (0/398)	0·0% (0/384)	NA
Heart failure	782	0·0% (0/398)	0·0% (0/384)	NA
Bleeding	782	1·0% (4/398)	0·3% (1/384)	0·37
Haematoma	782	0·3% (1/398)	0·0% (0/384)	1·0
Infection	782	3·5% (14/398)	1·3% (5/384)	0·061
Intestinal leak	782	0·3% (1/398)	0·5% (2/384)	0·62
Rectal stump blow out	782	0·5% (2/398)	0·0% (0/384)	0·50
Ileus	782	1·3% (5/398)	0·8% (3/384)	0·73
Thromboembolism (deep vein thrombosis or pulmonary embolus)	769	0·3% (1/385)	0·0% (0/384)	1
High stoma output	769	0·5% (2/385)	0·5% (2/384)	1

Supplementary Table 4: UVA and MVA for composite endpoint of rescue therapy (including primary induction) or surgery using Day 1 and Day 3 variables

Term	Day 1 variables UVA			Day 1 variables MVA			Day 3 variables UVA			Day 3 variables MVA		
	OR	**OR 95%CI**	**P value**	**OR**	**OR 95%CI**	**P value**	**OR**	**OR 95%CI**	**P value**	**OR**	**OR 95%CI**	**P value**
Cohort type: historic cohort	0·60	0·43 to 0·82	0·0015	0·63	0·44 to 0·89	0·0083	0·60	0·43 to 0·82	0·0015	0·72	0·45 to 1·16	0·18
Stool frequency	1·04	1·01 to 1·07	0·017	1·04	1·00 to 1·07	0·034	1·19	1·13 to 1·26	<0·0001	1·19	1·11 to 1·27	<0·0001
Log[CRP]	1·08	0·95 to 1·22	0·23	0·95	0·77 to 1·16	0·59	1·17	1·03 to 1·34	0·020	1·04	0·81 to 1·38	0·81
Haemoglobin	1·01	1·00 to 1·01	0·10	1·01	1·00 to 1·02	0·016	1·00	1·00 to 1·01	0·30	1·02	1·01 to 1·04	0·0085
Albumin	0·96	0·94 to 0·99	0·0035	0·96	0·93 to 0·99	0·023	0·95	0·92 to 0·97	0·00029	0·93	0·89 to 0·97	0·0023
CRP/albumin	1·11	1·04 to 1·18	0·0026	1·09	0·98 to 1·22	0·14	1·00	0·96 to 1·02	0·69	0·96	0·82 to 1·01	0·55

MVA = multivariable analysis; UVA = univariable analysis; OR = odds ratio; OR 95% = 95% confidence interval for odds ratio
Units for variables: CRP - mg/L; albumin – g/L; haemoglobin - g/L; stool frequency - stools per 24 hours

Supplementary Table 5: Details of ASUC patients testing positive for COVID-19 during or within 3 months of presentation

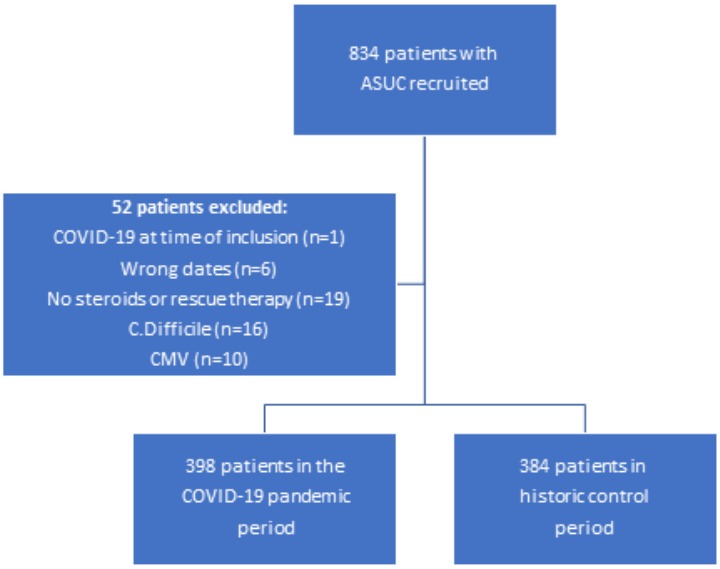
Age, gender, ethnicity	**Co-morbidity**	**Baseline medications**	**Treatments for ASUC**	**Rescue therapy**	**COVID-19 PCR days from index admission, imaging changes, outcomes**	**Treatment during follow up**
30 years, Male, Black	None	5-ASA oral 5-ASA topical	IV steroids, Oral 5-ASA	Nil	1 day, No imaging changes, No serious outcomes	Oral steroids, Azathioprine
53 years, Male, Asian	Current malignancy	No prior treatment	Oral 5-ASA, Rectal 5-ASA, IV steroids	Infliximab	1 day, No imaging changes, No serious outcomes	5-ASAs, Infliximab, Steroids
75 years, Female, White	Diabetes	No prior treatment	Oral 5-ASA, Rectal 5-ASA, IV steroids	Nil	7 days, No imaging changes, No serious outcomes	Oral steroids, Oral 5-ASAs
66 years, Female, White	Diabetes	No prior treatment	IV steroids, Oral -ASAs	Infliximab	2 days, No imaging changes, No serious outcomes	Oral 5-ASAs, Oral Steroids, Infliximab
37 years, Female White	Asthma	Oral 5-ASA Azathioprine Infliximab	IV steroids	Tofacitinib	1 day No imaging changes, No serious outcomes	Colectomy 31 days after index admission
75 years, Male, White	COPD, CVD, HTN, Obesity	Oral 5-ASA	IV steroids, Oral 5-ASA	Nil	28 days (12 days post discharge), Imaging changes, No serious outcomes	Oral steroids, Oral 5-ASAs
60 years, Male Asian	HTN Diabetes	Oral 5-ASA Azathioprine	IV steroids Oral 5-ASA	Nil	17 days (5 days post discharge) Imaging changes, No serious outcomes	Oral steroids Oral 5- ASA Infliximab

5-ASA = 5- aminosalicylic acid; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; HTN = hypertension

Supplementary Table 6: Pre-ASUC and post-ASUC COVID-19 shielding and risk assessment

Variable	COVID-19 pandemic period cohort (N = 398)
Social distancing measures pre-ASUC	
No social distancing measures	12·6% (49/388)
Social distancing	23·7% (92/388)
Stringent social distancing	9·8% (38/388)
Shielding	20·6% (80/388)
Unknown	33·2% (129/388)
COVID-19 risk according to British Society of Gastroenterology risk grid	
Lowest	34·3% (133/388)
Moderate	26·3% (102/388)
Highest	39·4% (153/388)
Shielding in the 3-month follow up period after ASUC	
No	10·6% (31/292)
Advised to shield - unclear whether advice followed	34·9% (102/292)
Yes, confirmed to have shielded	17·5% (51/292)
Unsure	37·0% (108/292)

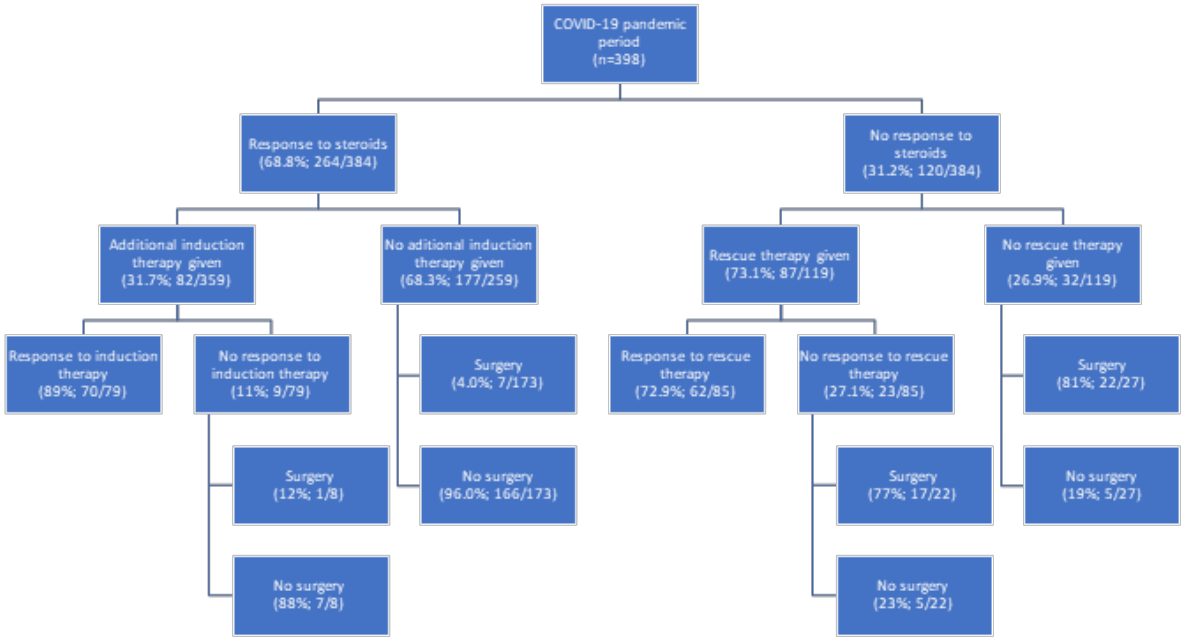
Supplementary Figure 1: Study cohorts



C. difficile = Clostridium difficile
CMVIgM positive and IgG negative inferred as acute CMV infection

Supplementary Figure 2: A. Outcomes in COVID-19 pandemic cohort and B. Historical control cohort

A



B