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Outcome of COVID-19 in hospitalized patients with chronic inflammatory diseases. A population based national register study in Denmark

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ABSTRACT

Objective: COVID-19 has substantial morbidity and mortality. We studied whether hospitalized patients with COVID-19 and chronic inflammatory diseases experienced worse outcomes compared to patients hospitalized with COVID-19 without chronic inflammatory diseases.

Methods: Danish nationwide registers were used to establish a cohort of hospitalized patients with COVID-19 and inflammatory bowel diseases (IBD), rheumatoid arthritis (RA), spondyloarthropathy (SpA), or psoriatic arthritis (PsA) (exposed), and a control cohort without these diseases (unexposed) between March 1, 2020, and October 31, 2020. We compared median length of hospital stay, used median regression models to estimate crude and adjusted differences. When estimating crude and adjusted odds ratio (OR) for continuous positive airway pressure (CPAP) and mechanical ventilation, in-hospital death, 14-day and 30-day mortality, we used logistic regression models.

Results: We identified 132 patients with COVID-19 and IBD, RA, SpA, or PsA, and 2811 unexposed admitted to hospital with COVID-19. There were no differences between exposed and unexposed regarding length of hospital stay (6.8 days vs. 5.5 days), need for mechanical ventilation (7.6% vs. 9.4%), or CPAP (11.4% vs. 8.8%). Adjusted OR for in-hospital death was 0.71 (95% CI 0.42–1.22), death after 14-days 0.70 (95% CI 0.42–1.16), and death after 30-days 0.68 (95% CI 0.41–1.13).

Conclusion: Hospitalized patients with COVID-19 and chronic inflammatory diseases did not have statistically significant increased length of hospital stay, had same need for mechanical ventilation, and CPAP. Mortality was similar in hospitalized patients with COVID-19 and chronic inflammatory diseases, compared to patients hospitalized with COVID-19 and no chronic inflammatory diseases.

1. Introduction

With the occurrence of the Coronavirus disease 2019 (COVID-19), a pandemic has swept across the globe starting in China and now affecting all parts of the world [1]. Patients with symptomatic COVID-19 will primarily present with clinical findings compatible with a mild upper airway tract infection, in the form of fever and cough. However, a substantial portion of the patients will have a more severe disease course, with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which may lead to admission to a hospital. They may require ventilatory support (continuous positive airway pressure (CPAP) or mechanical ventilation) and the mortality is substantial [2]. Thus, the

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spectrum of COVID-19 is broad from a majority of asymptomatic carriers over mild symptoms to a severe respiratory condition with a need for hospitalization and intensive care therapy. The mortality is varying, in particular, related to age. In hospitalized patients, mortality is ranging from less than five percent in patients below the age of 40 years and up to 35% in patients above the age of 70 years [3,4]. Various predictors for a severe course of COVID-19 have been suggested, including older age, male gender, comorbidity burden. The impact of overweight and obesity is not completely clear [4–6]. Furthermore, it has been suggested that various medical conditions could be associated with a risk of a complicated disease course. In recent studies including a meta-analysis, hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease, chronic liver disease, and cerebrovascular disease were independent risk factors associated with the course of COVID-19 [4,7,8]. Studies so far, in patients with chronic inflammatory bowel disease (IBD), rheumatoid arthritis (RA), spondyloarthropathy (SpA), and psoriatic arthritis (PsA) have give conflicting results with regard to risk of and outcome of COVID-19, and data regarding medical therapies have suggested an increased risk in patients using glucocorticoids to a reduced risk during treatment with biologics including anti-TNFαagents [6,9–20] [21-23].

Thus, the handling of the COVID-19 pandemic in specific patient groups and in patients using immunomodulatory drugs may still not be based upon substantial evidence [24,25]. The variation in the outcomes of patients with COVID-19 may reflect different study types – ranging from small case series to larger cohort studies [6,16,20]. In the current study, we present results based on national registries in Denmark and have examined the length of in-hospital stay and the risk of a severe disease course including the need for mechanical ventilation and CPAP in patients with chronic inflammatory bowel disease (IBD), rheumatoid arthritis (RA), spondyloarthropathy (SpA), and psoriatic arthritis (PsA), compared to other patients hospitalized for COVID-19. Finally, we have estimated the in-hospital death, the 14-days and 30-days mortality of COVID-19 in these patient groups.

2. Methods

2.1. Study population and setting

In Denmark, citizens have free access to a tax-supported and uniform organized health care system. The total population is approximately 5.8 million inhabitants [26]. We were able to perform an unselected nationwide population-based study because of access to nationwide Danish health registries [27]. We used the National Patient Registry, the National Prescription Registry, and the Central Personal Registration system [28,29]. We created a study population of Danish patients hospitalized with COVID-19 between March 1, 2020, and October 31, 2020.

2.2. Data material

The Danish National Patient Registry includes records of all discharges from Danish hospitals since 1977 and all outpatient visits since 1994 [27]. Basic data includes dates of admission and discharge, information on the hospital, information on procedures and treatments given at the hospital, and discharge diagnoses based on the International Classification of Diseases (In Denmark, ICD-8 was used before 1994 and ICD-10 from 1994 and onward). Data on mechanical ventilator use and CPAP was retrieved from the Danish National Patient Registry. In Denmark, biologic agents are solely administered in hospitals or in hospital-based outpatient settings in accordance with the National Board of Health, and all treatments with biologics are registered in the Danish National Patient Registry. The Nationwide Prescription Registry provides information on all prescriptions of drugs in Denmark since January 1, 1995 and is maintained by the Danish Medicine Agency [28]. All pharmacies in Denmark are equipped with computerized accounting systems which send key data on out-patient drug prescriptions directly to the Nationwide Prescription Registry. All medications are classified according to the Anatomical Therapeutical Chemical (ATC) system.

2.3. Exposed and unexposed cohorts

Hospitalization for COVID-19 in the period from March 1 to October 31, 2020, was retrieved from the Danish National Patient Registry. We included only patients who had a COVID-19 diagnosis code as the primary reason for the hospitalization (COVID-19 without localization (ICD-10 B342A) or COVID-19 with severe respiratory syndrome (ICD-10 B972A)), and if the patient had a hospital admission with a duration of at least 12 h. The study population is thus not based on PCR positive patients but on patients who were in fact hospitalized because of COVID-19 [21].

The *exposed cohort* was defined as patients who had a discharge diagnosis within 10 years before admission for COVID-19, in one of the following categories: IBD (ICD-10: K50 and K51), RA (ICD-10: M05; M06), SpA (ICD-10: M459, M468), and PsA (ICD-10: M07).

The *unexposed cohort* (controls) was patients admitted with COVID-19 who did not have any of the above-mentioned diagnoses of inflammatory diseases within 10 years before admission for COVID-19.

2.4. Outcome

The length of hospital stay was defined as the total time from admission to discharge. Patients who received CPAP or mechanical ventilator treatment, had a respective procedure code during their admission for COVID-19, CPAP (procedure code: BGFC32), and mechanical ventilator treatment (procedure code: BGDA0). In-hospital death was registered. 14-day and 30-day mortality were defined as death within 14 days or 30 days after discharge, respectively.

2.5. Data on confounders

From the Danish National Patient Registry, we obtained data on comorbid diseases for the study population and we calculated the Charlson Comorbidity Index (CCI) based on data 10 years back from March 1, 2020 [30]. The CCI covers 19 major disease categories weighted according to their prognostic impact, and three index levels were defined, no comorbidity (CCI: 0), moderate comorbidity (CCI: 1–2), and severe comorbidity (CCI:≥3).

Patients were considered as exposed to medications if they had at least one filled prescription or one treatment procedure at the hospital within six months before the COVID-19 hospitalization. The following categories of medications were used: thiopurines (azathioprine/mercaptopurine), methotrexate, systemic corticosteroids, or anti-TNFα agents.

2.6. Statistics

Contingency tables were constructed for the main study variables according to the exposed cohort and unexposed cohort. To analyse whether the length of hospital stay was different for the exposed and unexposed cohorts we compared the median length of admission. We used Wilcoxon rank sum test to the crude difference and median regression models to estimate the two adjusted differences and reported the difference with 95% confidence intervals (CI). In the first model, we adjusted for gender, age, and CCI. In the second model, we adjusted for gender, age, CCI, and the different categories of medications (thiopurines, methotrexate, systemic corticosteroids, anti-TNFαagents).

To analyse whether the risk of receiving CPAP, use of mechanical ventilation, death during hospitalization, 14-days and 30-days mortality was different between the exposed and unexposed cohort, we used a logistic regression model estimating the odds ratio (OR) for each outcome, and reported the OR with 95% CI. We calculated the crude OR, and adjusted ORs according to two models. In the first model, we

adjusted for gender, age, and CCI. In the second model, we adjusted for gender, age, comorbidity, and the different categories of medications.

In sub-analyses, we did stratified separate analyses for IBD and rheumatoid diseases (RA + PsA + SpA) compared to the unexposed cohort.

2.7. Patient and public involvement

Patient representatives are part of the research council at our department, and patient representatives have been involved in the process of this study.

2.8. Approval/ethical considerations and data availability

This study followed all currently applicable Danish laws regarding scientific research. The study was not interventional and did not require direct patient contact or influence on patient's treatment. According to Danish law, no ethical approvals of register-based studies are necessary. The study was approved by the Danish Data Protection Agency (j.nr. 20/16,376).

2.9. Data availability

Our approvals to use these register data for the current study do not allow us to distribute or make patient data available to other parties. Any interested researchers may apply for access to data through an application to the Research Service at the Danish Health Data Authority (forskerservice@sundhedsdata.dk). Access to data from the Danish Health Data Authority requires approval form the Danish Data Protection Agency. The authors of this paper do not have special access privileges to the data used in the current study.

3. Results

We identified 132 patients with one of the following chronic inflammatory diseases: IBD, RA, SpA, or PsA, who had been admitted to the hospital for COVID-19 (the exposed cohort), from March 1 to October 31, 2020, for at least 12 h. For comparison, we identified all patients admitted to hospital for COVID-19 in the same period of interest, but without any of the mentioned chronic inflammatory diseases (the unexposed cohort) identified in the Danish National Patient Registry. Data on the patients (Table 1) showed that patients with COVID-19 and chronic inflammatory disease (exposed) were slightly older, than the patients with COVID-19 without chronic inflammatory disease (unexposed), above 60 years 108 of 132 patients (82%) and 1834 of 2811 patients (65%), respectively. There was a slight preponderance of females in the exposed group (61%), which was the opposite in the unexposed group (44%). In the exposed group of patients, the majority had either IBD (n = 52, 39.4%) or RA (N = 69, 52.3%). Twenty-six patients (19.7%) had received systemic corticosteroids, a minority of the patients had received anti-TNFα agents or thiopurines/methotrexate within six months before the COVID-19 hospitalization. The CCI was higher in the exposed group compared to the unexposed group of patients (RA is included in the Charlson comorbidity index).

For the exposed group, the hospital stay had a median length of 6.8 days (25 and 75 quartiles 2.6–13.3), the median length was 5.5 days (25 and 75 quartile 2.6–9.9) for the unexposed group. This difference, 1.3, was borderline statistically significant (p=0.09), however, after data were adjusted for gender, age, and CCI the difference was non-significant. When data were adjusted for medication categories, gender, age, and CCI the difference was also non-significant. For the exposed group with COVID-19, 10 (7.6%) needed mechanical ventilation, for the unexposed group with COVID-19 this figure was 265 (9.4%), and the corresponding adjusted OR (adjusted for medications, gender, age, and CCI) was 0.75 (95% CI 0.36–1.56), Table 2. The use of CPAP was not different between the exposed group (11.4%) and the

Table 1

Characteristics of study population: Hospitalized COVID-19 patients with IBD, RA, SpA or PsA (exposed group), and hospitalized COVID-19 patients without any of these diagnoses (unexposed group). COVID-19 hospitalizations from March 1 to October 31, 2020.

	Patients with chronic inflammatory diseases (exposed cohort) N = 132	Patients without chronic inflammatory diseases (unexposed cohort) N = 2811
Age (years) at admission		
Median (25–75 percentiles)	74 (63–80)	69 (54–80)
Patient's age in categories (years), N (%)		
< 19	0 (0)	21 (0.7)
20-39	2 (1.5)	238 (8.4)
40-59	22 (16.4)	718 (25.3)
60-69	27 (20.1)	466 (16.4)
70-79	48 (35.8)	675 (23.8)
≥ 80	33 (24.6)	693 (24.4)
Gender, N (%)		
Female	80 (60.6)	1227 (43.6)
Male	52 (39.4)	1584 (56.4)
Comorbidity[a],N (%)		
0	15 (11.4)	1341 (47.7)
1-2	61 (46.2)	897 (31.9)
≥3	56 (42.4)	573 (20.4)
Disease[b]		
IBD, N (%)	52(39.4)	
RA, N (%)	69 (52.3)	
SpA, N (%)	3 (2.3)	
PsA, N (%)	12 (9.1)	
Categories of medication[c], N (%)		
Thiopurines	3 (2.3)	4 (0.1)
Methotrexate	12 (9.1)	5 (0.2)
Systemic corticosteroids	26 (19.7)	207 (7.4)
Anti-TNF α agents	8 (6.1)	5 (0.2)

[a] Charlson's comorbidity index (CCI) is based on ICD-10 disease history within the last 10 years.

[b] Patients can have more than one disease, hence the sum is larger that the total.

[c] Patients can have used medication in more than one of these categories within six months before the COVID-19 hospitalization.

unexposed group (8.8%), corresponding to an adjusted OR of 1.09 (95% CI 0.60–2.00), Table 2. In-hospital mortality, death after 14-days, and death after 30-days in the exposed group with COVID-19 was 17.4%, 20.5% and 21.2%, respectively - these figures for patients in the unexposed group with COVID-19 were 15.2%, 18.1%, and 19.1%. The corresponding adjusted ORs for mortality in-hospital, death after 14-days, and death after 30-days were 0.71 (95% CI 0.42–1.22), 0.70 (95% CI 0.42–1.16), and 0.68 (95% CI 0.41–1.13), respectively (Table 2).

After stratification for the subtype of the underlying chronic inflammatory diseases, IBD (Table 3) or RA/SoA/PsA (Table 4), there was no statistically significant increased risk for mechanical ventilation, CPAP, or death.

4. Discussion

This study is to our knowledge, the first study which upon complete national population-based data, has assessed the impact of several chronic inflammatory diseases, including IBD, RA, SpA, and PsA on adverse in-hospital and post-discharge outcomes in patients who have been infected and hospitalized with COVID-19. The data shows reassuringly that having a chronic inflammatory disease does not seem to adversely affect the outcome in patients infected with COVID-19 compared to patients admitted to hospital with COVID-19 but without

Table 2
Crude and adjusted median difference and odds ratios (ORs) for different outcomes during COVID-19 hospitalizations from March 1 to October 31, 2020, with corresponding 95% confidence intervals (CI), for patients with IBD, RA, SpA, or PsA (exposed group), relative to patients without any of these prior diseases (un-exposed group).

Outcome	Exposed cohort N = 132 Median (p25-p75)	Unexposed cohort N = 2811 Median (p25-p75)	Difference	P-value	Adjusted Difference[a]	95% CI	Adjusted Difference[b]	95% CI
Hospital stay duration	6.8 (2.6–13.3)	5.5 (2.6–9.9)	1.3	0.09	0.48	(-0.76-1.72)	−0.16	(-1.51-1.18)
	Events (%)	Events (%)	Crude OR	95% CI	Adjusted OR[a]	95% CI	Adjusted OR[b]	95% CI
Mechanical ventilator	10 (7.6)	265 (9.4)	0.79	(0.41–1.52)	0.81	(0.41–1.59)	0.75	(0.36–1.56)
CPAP	15 (11.4)	247 (8.8)	1.33	(0.77–2.31)	1.14	(0.65–2.01)	1.09	(0.60–2.00)
In-hospital death	23 (17.4)	426 (15.2)	1.18	(0.74–1.87)	0.89	(0.55–1.45)	0.71	(0.42–1.22)
14-days mortality	27 (20.5)	508 (18.1)	1.17	(0.76–1.80)	0.85	(0.53–1.35)	0.70	(0.42–1.16)
30-days mortality	28 (21.2)	537 (19.1)	1.14	(0.74–1.75)	0.82	(0.52–1.30)	0.68	(0.41–1.13)

Adjustment for: a) gender, age, and Charlson's comorbidity index, b) medication categories (thiopurines, methotrexate, systemic corticosteroids, anti-TNFalfa agents), gender, age, and Charlson's comorbidity index.

Table 3
Crude and adjusted median difference and odds ratios (ORs) for different outcomes during COVID-19 hospitalisations from March 1 to October 31, 2020, with corresponding 95% confidence intervals (CI), for patients with IBD, relative to patients without any of these prior diseases.

Outcome	Exposed IBD patients N = 52 Median (p25-p75)	Unexposed patients N = 2811 Median (p25-p75)	Difference	P-value	Adjusted Difference[a]	95% CI	Adjusted Difference[b]	95% CI
Hospital stay duration	6.8 (2.3–13.6)	5.5 (2.6–9.9)	1.3	0.24	0.40	(-1.47-2.27)	0.43	(-1.48-2.35)
	Events (%)	Events (%)	Crude OR	95% CI	Adjusted OR[a]	95% CI	Adjusted OR[b]	95% CI
Ventilator	4 (7.7)	265 (9.4)	0.80	(0.29–2.24)	0.67	(0.23–1.91)	0.66	(0.23–1.94)
CPAP	5 (9.6)	247 (8.8)	1.10	(0.44-2.80)	0.91	(0.35–2.33)	0.90	(0.35–2.33)
In-hospital death	8 (15.4)	426 (15.2)	1.02	(0.48–2.18)	0.76	(0.34–1.69)	0.68	(0.30–1.53)
Death 14 days	10 (19.2)	508 (18.1)	1.08	(0.54-2.17)	0.82	(0.39–1.72)	0.74	(0.35–1.58)
Death 30 days	11 (21.2)	537 (19.1)	1.14	(0.58–2.23)	0.85	(0.41–1.77)	0.79	(0.38–1.64)

Adjustment for: a) gender, age, and Charlson's comorbidity index, b) medication categories (Thiopurines, Methotrexate, Systemic corticosteroids, anti-TNFalfa agents), gender, age, and Charlson's comorbidity index.

Table 4
Crude and adjusted median difference and odds ratios (ORs) for different outcomes during COVID-19 hospitalizations from March 1 to October 31, 2020, with corresponding 95% confidence intervals (CI), for patients with RA,SpA, or PsA, relative to patients without any of these prior diseases.

Outcome	Exposed RA, SpA, PsA patients N =83 Median (p25-p75)	Unexposed patients N = 2811 Median (p25-p75)	Difference	P-value	Adjusted Difference[a]	95% CI	Adjusted Difference[b]	95% CI
Hospital stay duration	6.0 (2.7–12.2)	5.5 (2.6–9.9)	0.4	0.26	0.09	(-1.44-1.61)	−0.59	(-2.25-1.07)
	Events (%)	Events (%)	Crude OR	95% CI	Adjusted OR[a]	95% CI	Adjusted OR[b]	95% CI
Ventilator	6 (7.2)	265 (9.4)	0.75	(0.32–1.73)	0.89	(0.38–2.12)	0.77	(0.29–2.05)
CPAP	11 (13.3)	247 (8.8)	1.59	(0.83–3.03)	1.40	(0.72–2.73)	1.31	(0.63–2.74)
In-hospital death	15 (18.1)	426 (15.2)	1.23	(0.70-2.18)	0.92	(0.50–1.67)	0.65	(0.33–1.31)
Death 14 days	17 (20.5)	508 (18.1)	1.17	(0.68–2.01)	0.82	(0.46–1.46)	0.59	(0.30–1.15)
Death 30 days	18 (21.7)	537 (19.1)	1.17	(0.69–1.99)	0.82	(0.46–1.45)	0.61	(0.32–1.18)

Adjustment for: a) gender, age and Charlson's comorbidity index, b) medication categories (Thiopurines, Methotrexate, Systemic corticosteroids, anti-TNFalfa agents), gender, age and Charlson's comorbidity index.

chronic inflammatory diseases when evaluated on the length of hospital stay, the need for mechanical ventilation (around 10% in both groups), and CPAP. More importantly, chronic inflammatory diseases did not seem to affect the in-hospital mortality nor the mortality after 14-days or after 30-days. The 30-days mortality was 21.2% in chronic inflammatory diseases patients and 19.1% in the control patients without chronic inflammatory diseases. However, the data also stresses the fact that COVID-19, also in patients with chronic inflammatory diseases has substantial mortality when admitted to hospital. These data are comparable with results obtained in studies from the early part of the pandemic [4]. Thus, hospital admission in itself is a severe prognostic factor in evaluating the outcome of COVID-19, irrespective of comorbidity.

It has been speculated that, apart from already identified adverse prognostic factors, patients with chronic inflammatory diseases could be particularly susceptible to suffer a severe COVID-19 course - and in

particular ongoing immunomodulatory therapy (biologics), immunosuppressive drugs (methotrexate and azathioprine), and glucocorticoids could be of importance for the outcome [7,22]. In this context, we have recently presented results also on a national level, identifying glucocorticoids and cyclosporine as risk factors for admission due to COVID-19 [21]. A Danish study by Attauabi et al. examined a nationwide cohort of IBD patients including 76 patients and found that 19 (25%) required hospitalization, and secondly they found that patients with immune-mediated inflammatory disorder, including IBD, had significantly lower susceptibility to COVID-19 than patients without immune-mediated inflammatory disorders [20]. In this study we did not aim to examine the susceptibility to COVID-19 or to estimate the risk of hospitalization for COVID-19 in patients with IBD, RA, SpA, and PsA. On the contrary, we assessed whether hospitalized patients with IBD, RA, SpA, and PsA had more adverse outcome compared to hospitalized patients without these underlying diseases. Adverse in-hospital outcomes have also been studied in a Danish population based study on patients with inflammatory rheumatic disease, and the result showed a not significantly increased risk for intensive care, acute respiratory distress syndrome, or death compared to the general population [31]. In another recent paper by Attauabi et al. it was concluded that a more severe disease course was found in patients with various immune-mediated inflammatory disease and that glucocorticoids and other immunosuppressant were associated with a more severe coruse [22]. There are several important discrepencies compared to the current study. Our study was based on data on the entire Danish population, and our study population was based on all patients who were actually hospitalized due to Covid-19. Also, in contrast to our study population, Attuauabi et al. included a large variety of immune-mediated inflammatory diseases (subgroups of rheumatological immune-mediated inflammatory diseases, connective tissue diseases, vasculitis, dermatologic immune-mediated inflammatory diseases, any gastro-intestinal/hepatological/pancreatic immune-mediated inflammatory diseases and neurological immune-mediated inflammatory diseases).

The medications used to treat chronic inflammatory diseases have been a special focus of interest during the pandemic, both regarding the risk of hospitalization and regarding adverse in-hospital outcomes. Data on the risk of COVID-19 and the association with medication was presented in a meta-analysis including observational studies and case-control studies in patients with autoimmune diseases including IBD, PsA, rheumatic diseases, and systemic lupus erythematosus. It was documented that the prevalence of COVID-19 was significantly higher than in control patients and furthermore an overall mortality of 6.6% was documented [32]. The increased risk of hospitalization and mortality was associated with glucocorticoids and with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and biologic or targeted synthetic DMARDs (b/tsDMARDs)-csDMARDs combination therapy. However, b/tsDMARDS alone reduced the risk of a severe outcome. In the SECURE-IBD study, an international registry created to monitor outcomes in IBD cases with confirmed COVID-19, including 1439 patients, combination therapy and thiopurines seemed to be associated with an increased risk of a severe COVID-19 disease course compared to monotherapy with tumour necrosis factor (TNF) antagonist [33]. In a case study in patients with rheumatic diseases, from the C19-GRA registry glucocorticoid exposure of ≥ 10 mg/day was associated with a higher odds ratio of hospitalization (OR 2.05, 95% CI 1.06 to 3.96) and anti-TNFα therapy with a decreased odds of hospitalization (OR 0.40, 95% CI 0.19 to 0.81) [34].

Our results on the risk of adverse outcomes in patient with chronic inflammatory diseases did not statistically significant differ when adjusted for selected categories of medication. The strengths of the current study is the cohort design, based on comprehensive valid nationwide data, and our ability to follow-up all patients with no dropouts, thus preventing selection bias. We have complete information on the entire Danish population, and thus, due to The Central Personal Registration System, we have information on death that have occurred during follow-up (in- or outside hospitals). It is an advantage that we can perform analyses on a large group of patients with chronic inflammatory diseases to increase the robustness of our analyses, and that we have included all patients regardless of their disease severity. The data from The National Patient Register and The Danish National Prescription Register are well-known tools for clinical epidemiological studies, used in multiple studies, and are known for high data quality and with high coverage [27,28,35,36].

Our outcome assessments were obtained independently of the exposure and the hypothesis examined, and thus prevents differential misclassification of the outcome. We believe that we have taken into account important confounders as age, gender, CCI, and use of thiopurines, methotrexate, systemic corticosteroids, and anti-TNFα agents.

Our study has limitations. A limited number of patients with chronic inflammatory diseases had been admitted to the hospitals in Denmark during the study period of eight months, and therefore we lack statistical precision when we perform stratified analyses into IBD and RA/SpA/PsA subgroups, respectively. Also, we had no further information on clinical details such as the severity of the underlying disease, body-weight, in-hospital medications for COVID-19 or information from laboratory systems. Furthermore, it was not possible to address the daily doses of the various immunomodulatory drugs.

In an observational study like this, one can never be sure that all possible confounders have been considered, and therefore an impact of unknown confounding can never be ruled out.

Also, it could be speculated that increased awareness of COVID-19 due to the underlying inflammatory condition and immunosuppressive treatment may have reduced both patients and doctors delay in testing for COVID-19 and perhaps the hospital admission process. In the recent population based Danish study an increased hospitalization rate for patients with inflammatory rheumatic disease was documented [31].

5. Conclusion

We found reassuring results regarding the adverse in-hospital outcomes, and according to 14- and 30- days mortality, in patients with underlying inflammatory diseases compared to all other Danish patients with hospital admission for COVID-19. However, COVID-19 with SARS-Cov-2 is a severe disease with substantial mortality - also evident in the current study and in accordance with earlier studies [3–5,8,34]. Despite our nationwide approach, the number of patients with COVID-19 and chronic inflammatory diseases was relatively low, and further studies, applying the same national and register-based methods, should examine the suggested long-term effects [37]. Future studies on in-hopital outcomes and long-term effects in patients with chronic underlying inflammatory diseases are especially important when more detailed dataset are available, and perhaps dataset that have additional information on disease activity, laboratory values, regular use of immunosuppressive and immunomodulating treatment, systemic corticosteroids, biologics, and other interventions used during hospital stay.

Contributors

JK: funding, conception, design, data collection, assistance with data analysis, interpretation of results, manuscript writing and editing, approved the final version. BMN: funding, conception, design, assistance with data analysis, interpretation of results, manuscript editing, approved the final version. JN: conception, design, data collection, data analysis, interpretation of results, manuscript editing, approved the final version. RGN, TK, MDL, KL, TE: Assistance with data analysis, interpretation of results, manuscript editing, approved the final version.

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Declaration of competing interest

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