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Post COVID-19 hospitalizations in patients with chronic inflammatory diseases – A nationwide cohort study☆

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ABSTRACT

Objective: To study long term consequences of hospitalization for COVID-19 in patients with chronic inflammatory diseases. We studied the risk of subsequent hospitalizations in patients with chronic inflammatory diseases, who survived a hospitalization for COVID-19, compared to other patients who had been hospitalized for COVID-19.

Design and Setting: Population based cohort study based on Danish nationwide health registers. The study population included all adult patients in Denmark who had been discharged alive after a hospitalization with COVID-19 from March 1, 2020 to July 31, 2021.

Population: From the study population, the exposed cohort constituted patients who had inflammatory bowel diseases (IBD), rheumatoid arthritis (RA), spondyloarthropathy (SpA), or psoriatic arthritis (PsA) prior to hospitalization for COVID-19, and the unexposed cohort constituted those without these diseases.

Main outcome measures: We estimated the adjusted Hazard Rate (aHR) for the following outcomes: overall risk of hospitalization, cardiovascular diseases, respiratory diseases, blood and blood-forming organs, nervous system diseases, infections, sequelae of COVID-19, and death.

Results: A total of 417 patients with IBD/RA/SpA/PsA were discharged alive after COVID-19, and 9,248 patients without these diseases. Across the different outcomes examined, the median length of follow up was 6.50 months in the exposed cohort (25–75% percentiles: 4.38–8.12), and among the unexposed the median time of follow up was 6.59 months (25–75% percentiles: 4.17–8.49). Across different analyses, we consistently found a significantly increased risk of hospitalizations due to respiratory diseases (aHR 1.27 (95% CI 1.02–1.58)) and infections (aHR 1.55 (95% CI 1.26–1.92)). In sensitivity analyses, the overall risk of hospitalization was aHR 1.15 (95% CI 0.96–1.38) and the risk of hospitalization due to cardiovascular diagnoses was aHR 1.14 (95% CI 0.91–1.42). During the time of follow up, the risk of nervous system diagnoses or death was not increased in patients with IBD/RA/SpA/PsA.

Conclusions: After hospitalization with COVID-19, patients with IBD/RA/SpA/PsA had an increased risk of subsequent hospitalizations for a number of categories of diseases, compared to other patients who have been hospitalized with COVID-19. These results are disturbing and need to be examined further. The implication of our results is that clinicians should be particularly alert for post COVID-19 symptoms from several organ systems in patients with IBD/RA/SpA/PsA.

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1. Introduction

The coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which is responsible for the disease COVID-19 (coronavirus disease 2019), has caused morbidity and mortality at an unprecedented scale [1,2]. For this new disease, the immediate problems have been related to emergency treatment options of COVID-19 and development and distribution of vaccines. An urgent question, however, is raised all over, "what are the long-term consequences for COVID-19"? Evolving literature has added to the evidence that COVID-19 has long-term effects on multiple organ systems [1–6]. Although COVID-19 is mostly well-known for causing substantial respiratory pathology, it can also result in several extrapulmonary manifestations, and post COVID-19 symptoms have been related to many organ systems (pulmonary, hematologic, cardiovascular, neuropsychiatric, endocrine, etc.). It is a matter of discussion how to define "long-term", and there is no strict definition of "long-term" in terms of post COVID-19 symptoms. For those who were survivors among the first infected in the start of 2020, we now have approximately 1½ years of follow-up data (as of August 2021). This length of follow up provides us at least with some evidence related to post COVID consequences, but of course not on consequences after many years. Therefore, in this paper we prefer to use the term "post COVID-19".

In the era of COVID-19 there have been special concerns about patients with chronic inflammatory diseases, about their risk of hospitalization for COVID-19 and their risk of severe adverse in-hospital outcomes. These concerns have been related to a possible negative impact of the underlying chronic diseases and because immunosuppressive therapies are used in the management of inflammatory disorders such as chronic inflammatory bowel disease (IBD), rheumatoid arthritis (RA), spondyloarthropathy (SpA), and psoriatic arthritis (PsA) [7]. Among such therapies, steroids have been associated with both an increased risk of hospitalization [8,9] and severe COVID-19 [10].

We aim to add to the evidence on post COVID-19 hospitalizations in patients who have underlying chronic inflammatory diseases. Based on Danish nationwide data, on patients with IBD/RA/SpA/PsA who were discharged alive after a COVID-19 hospitalization, we aim to examine the risk of hospitalizations and death, compared to discharged patients without these diseases. We examine post COVID-19 hospitalizations according to diagnoses of the cardiovascular system, the respiratory system, diseases of the blood and blood-forming organs, the nervous system, infections, and sequelae of COVID-19.

2. Methods

2.1. Setting and data

All citizens in Denmark have free access to a tax-supported health care system. The total population is approximately 5.8 million inhabitants and more than 90% are Caucasians. We were able to perform a nationwide population-based cohort study due to a uniform organization of the health care system and we had access to nationwide registries. In this study we used data from the following Danish health registries: the National Patient Registry, the Nationwide Prescription Registry, and the Civil Registration System [11–13].

2.2. Study population and study period

The study population included all patients in Denmark, who had been discharged alive after hospitalization due to COVID-19 in the period March 1, 2020 to July 31, 2021. The patients were ≥18 years of age at the time of COVID-19 hospitalization. Only patients hospitalized for more than 12 h with COVID-19 were included (primary diagnoses according to COVID-19 without localization [ICD-10 B342A] or COVID-19 with severe respiratory syndrome [ICD-10 B972A]). Multiple registered hospitalizations with COVID-19 in one patient were considered as the same course if the date of exit in one registration was the same as the date of entry in the next. Our study population is thus not based on PCR positive patients but on patients who were in fact hospitalized with COVID-19 [9,14].

2.3. Exposed cohort

The exposed cohort constituted all patients with IBD, RA, SpA, or PsA who had been discharged alive after hospitalization with COVID-19. Patients with IBD/RA/SpA/PsA had been diagnosed at Danish hospitals with specific ICD10 codes, and the patients with IBD/RA/SpA/PsA had their diagnoses within 10 years before hospitalization 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).

2.4. Unexposed cohort

The unexposed cohort constituted all other patients from the study population, i.e. patients without IBD/RA/SpA/PsA who had been discharged alive after hospitalization with COVID-19. None of the patients in the unexposed cohort had had any of the mentioned diagnoses of inflammatory diseases within 10 years before hospitalization with COVID-19.

2.5. Outcomes

The selected outcomes were chosen based on The International Classification of Diseases, ICD10 version:

i) Hospitalization with diseases of the cardiovascular system (ICD-10: I*, * indicates that all subgroups are included)
ii) Hospitalization with diseases of the respiratory system (ICD-10: J*)
iii) Hospitalization with diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (ICD-10: D5*, D6*, D7*, D8*)
iv) Hospitalization with diseases of the nervous system (ICD-10: G*)
v) Hospitalizations with infections, overall (except coronavirus). Supplementary table 1 for types of infections.
vi) Overall hospitalization (outcome within group i, ii, iii, iv, or v)
vii) Sequelae of COVID-19 (ICD-10: B948A)
viii) Death after discharge with COVID-19

2.6. Confounders

Gender, date of birth and death were retrieved from the Civil Registration System. The age at first hospitalization with COVID-19 was calculated as the date of birth subtracted from the date of the relevant COVID-19 hospitalization. The length of hospitalization with acute COVID-19 was calculated and used as a proxy measurement of severity of COVID-19. Oral steroids could have been used in both exposed and unexposed cohorts. Therefore, using the Nationwide Prescription Registry, we extracted information on the use of steroid prescriptions within 6 months prior to hospitalization with COVID-19 as a proxy measurement of severity of underlying diseases (ATC codes H02AB02, H02AB04, H02AB06, H02AB07 and H02AB09). For our entire study population, we identified those who had had the previous diagnoses within the same organ system as our outcomes of interest, i.e. patients who had diseases in the cardiovascular system, respiratory system, diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, diseases of the nervous system, and infections in a period of 10 years prior to COVID-hospitalization for acute COVID-19 were identified. This information was extracted from the National Patient Registry.

2.7. Statistics

A contingency table was constructed for the main study variables according to the exposed and unexposed cohorts. In our main analyses, the follow up of the patients started on the date after hospital discharge with COVID-19 and ended on the date of the first diagnosis of the specific outcomes of interest, emigration, death, or July 31, 2021, whichever came first. In case of multiple COVID-19 hospitalizations, the follow up started on the date after the last discharge. In order to analyze whether hospitalizations after COVID-19 discharge were different between the exposed and unexposed cohort in a standardized model, we used Cox proportional hazard regression models estimating the hazard ratio (HR) for each specific outcome. The HR with 95% confidence intervals (CI) was reported, and the Cox proportional hazards assumption was inspected graphically using Schoenfeld residuals. In the model we adjusted for age at the time of COVID-19 hospitalization, sex, length of hospitalization due to COVID-19 (continuous variable), and steroid prescriptions within 6 months prior to hospitalization due to COVID-19 (proxy measurement of severity of underlying diseases). We also adjusted for whether the patients had former diseases related to the specific outcome of interest, for example, when we assessed the risk of hospitalization for cardiovascular diseases, we took into account whether the patients had former diagnoses of cardiovascular diseases (i.e. hospitalizations for cardiovascular diseases within 10 years prior to COVID-19 hospitalization). A similar approach was used in the analyses for outcome groups ii) - vi). In all analyses, we further displayed the comparison of failure in the exposed and unexposed cohorts using the Kaplan-Meyer estimator, plotting the cumulative proportion for the specific outcome groups.

In sensitivity analyses 1 and 2, we repeated all analyses, and started the time of follow up 14 days and 28 days, respectively, after hospital discharge with COVID-19, and ended the follow up time on the date of the first diagnosis of the specific outcomes of interest, emigration, death, or July 31, 2021, whichever came first. It may be argued that a rapid re-admission after discharge for COVID-19 is not really a post COVID problem, but merely related to the disease course of the acute COVID-19 hospitalization, and this was the rationale behind changing the start of follow-up in the sensitivity analyses. As in the main analyses, we calculated HRs according to outcomes i)-viii).

In sub-analyses 1 we examined infections at various sites (respiratory tract infections, infections of the gastrointestinal tract, urological/gynecological infections, infections of the skin/subcutaneous tissue, bacteremia and other infections). In these analyses the HRs were adjusted for sex, age, length of hospital stay with COVID-19, previous steroid prescriptions, and previous infections of the same kind. In sub-analyses 2 we stratified our main analyses according to IBD or RA/SpA/PsA. In case of diagnoses within both IBD and RA/SpA/PsA in one patient, the last given diagnosis before COVID-19 hospitalization determined the group.

2.8. Patient and public involvement

Patient representatives are part of the research committee at our department, and the patient representatives have been involved in specific parts of the research process. They have been part of the discussion about the study outcome measurements. The patient representatives were not involved in the design of the study or in the writing of the paper.

2.9. Approvals and ethics

This study follows all currently applicable Danish laws regarding scientific research. The study was non-interventional and did not require direct patient contact or influence on the 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).

2.10. Data availability

According to Danish legislation, we have approvals to use these register data for this study, but we are not allowed to make patient data available to other parties. Any interested researchers can apply for access to data through an application to the Danish Health Data Authority (forskerservice@sundhedsdata.dk). Also, access to data from the Danish Health Data Authority requires approval from 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

Our study population included 9,665 patients who were discharged alive after hospitalization for acute COVID-19. Of these, 417 patients had underlying diseases of IBD/RA/SpA/PsA (exposed cohort), and 9,248 patients did not have IBD/RA/SpA/PsA (unexposed cohort). Most patients in the exposed cohort had diagnoses of RA (48.9%) and IBD (37.2%). Table 1 shows the basic characteristics for the study cohorts. The median age at hospitalization with COVID-19 was 71 years in the exposed cohort and 65 years in the unexposed cohort, and in both cohorts 25% were aged ≥77. Regarding comorbidity, former hospitalizations for diseases in different organ systems were frequent in both the exposed and the unexposed. The most frequent causes of former hospitalizations in both cohorts were due to infections and cardiovascular diseases. In the exposed cohort, 30.2% received steroid prescription

Table 1
Descriptive characteristics of study cohorts of patients with inflammatory bowel disease (IBD)/rheumatoid arthritis (RA)/spondyloarthropathy (SpA)/psoriatic arthritis (PsA) who have been discharged alive after hospitalization for COVID-19, and for those without IBD/RA/SpA/PsA (study period of March 01, 2020 through July 31, 2021).

	Exposed cohort (IBD/RA/SpA/PsA) N = 417	Unexposed cohort (without IBD/RA/SpA/PsA) N = 9248
Age at time of hospitalization for COVID-19		
Median (25%–75% percentiles)	71 (59–78)	65 (52–77)
Patient's age in categories (years)		
≥18–40, N (%)	22 (5.3)	978 (10.6)
41–60, N (%)	96 (23.0)	2809 (30.4)
61–80, N (%)	218 (52.3)	3757 (40.6)
≥81, N (%)	81 (19.4)	1704 (18.4)
Gender		
Female, N (%)	231 (55.4)	4042 (43.7)
Male, N (%)	186 (44.6)	5206 (56.3)
Length of hospitalization due to COVID-19		
Median (25–59% percentiles)	4.8 (2.3–9.0)	4.6 (2.0–7.9)
Comorbidity: Former hospitalizations within		
Cardiovascular system, N (%)	273 (65.5)	4606 (49.8)
Respiratory system	227 (54.4)	3656 (39.5)
Blood/blood-forming organs, N (%)	70 (16.8)	938 (10.1)
Nervous system, N (%)	150 (36.0)	2296 (24.8)
Infections, N (%)	366 (87.8)	6854 (74.1)
Steroid prescription within 6 months prior to COVID-19 hospitalization		
	126 (30.2)	887 (9.6)
Types of disease[a]		
IBD, N (%)	155 (37.2)	–
RA, N (%)	204 (48.9)	–
SpA, N (%)	51 (12.2)	–
PsA, N(%)	21 (5.0)	–

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

prior to hospitalization with COVID-19, versus 9.6% in the unexposed cohort.

Fig. 1 shows the cumulative proportion of our different outcomes from the day after hospital discharge after acute COVID-19. Compared to the unexposed cohort, more patients with IBD/RA/SpA/PsA had outcomes according the cardiovascular system, respiratory system, blood system, and infections. There were no major differences according to the nervous system, code for sequela COVID-19, or death.

In the exposed cohort, the median length of follow up was 6.50 months (25–75% percentiles: 4.38–8.12), and among the unexposed, the median length of follow up was 6.59 months (25–75% percentiles: 4.17–8.49). Table 2 shows crude and adjusted HRs for the examined outcomes where the observation period starts the day after hospital discharge for COVID-19. The adjusted HR of hospitalization due to respiratory diseases was 1.27 (95% CI 1.02–1.58), and for hospitalization due to infections 1.55 (95% CI 1.26–1.92). Regarding respiratory diseases, 54% of the patients with IBD/RA/SpA/PsA had more than one hospitalizations due to respiratory diseases during follow up. Regarding infections, 67% of the patients with IBD/RA/SpA/PsA had more than one hospitalizations due to infections during follow up. The overall risk of hospitalization, and the risk of hospitalization due to diseases of the blood/blood-forming organs/certain disorders involving the immune mechanism, was also increased, but not statistically significantly increased (adjusted HR 1.14 (95% CI 0.98–1.33) and 1.20 (95% CI 0.73–1.99), respectively). The new code for sequelae for COVID-19 was used similarly in the exposed and unexposed cohort (9.6% versus 9.0%, respectively). In patients with IBD/RA/SpA/PsA there was no increased risk of death.

Table 3 shows the results from the sensitivity analyses 1 and 2, where the observation time started 14 days and 28 days after hospital discharge, respectively. These results were consistent with the overall finding of an increased risk of hospitalization due to respiratory diseases and infections. Also, the sensitivity analyses showed that the overall risk of hospitalization, and the risk of hospitalization due to cardiovascular diagnoses, was also increased, although not statistically significantly increased. When we initiated the start of follow up 4 weeks after discharge for COVID-19, we found no increased risk of hospitalization with diseases of the blood/blood-forming organs/certain disorders involving the immune mechanism in patients with IBD/RA/SpA/PsA.

Sub-analyses 1 showed that the risks of several types of infections were increased. We found a significantly increased risk of hospitalization due to respiratory tract infections, infections of the gastrointestinal tract, and "other" infections, adjusted HR 1.63 (95% CI 1.21–2.20), 2.12 (95% CI 1.23–3.66), and 1.79 (95% CI 1.15–2.77), respectively. The two most common types of infections in the category "other" infections were bacterial infection unspecified (A499) and Candidasis in the mouth (B370). The risk of bacteremia was increased but not statistically significantly increased (1.47 (95% CI 0.81–2.66)). Supplementary table 2 shows crude and adjusted HR for the specific types of infections.

In sub-analyses 2 we stratified our main analyses according to IBD or RA/SpA/PsA. In these analyses we did not have the same statistical power as in the main analyses. For patients with RA/SpA/PsA we found an increased risk of respiratory diseases (aHR 1.51 (95% CI 1.17–1.95), and infections (aHR 1.63 (95% CI 1.26–2.10)), and for patients with IBD the analogous risks were aHR 1.34 (95% CI 0.89–2.01) and aHR 1.76 (95% CI 1.24–2.50), respectively.

4. Discussion

4.1. Principal findings

Our study presents important information on post COVID-19 risk of hospitalizations in patients with underlying diseases of IBD/RA/SpA/PsA in the entire Danish population. We followed 417 patients with IBD/RA/SpA/PsA discharged alive after COVID-19 hospitalization, and the patients were followed for a median of 6.50 months (25% of the patients with IBD/RA/SpA/PsA were followed for more than 8.12 months). Across different analytic approaches, we found that patients with IBD/RA/SpA/PsA had an increased risk of hospitalizations for respiratory diseases and infections. The overall risk of hospitalization, and the risk of hospitalization due to cardiovascular diagnoses, was also increased although not statistically significant. Contrary, patients with IBD/RA/SpA/PsA did not have an increased risk of hospitalization due to diseases in the nervous system and no increased risk of death.

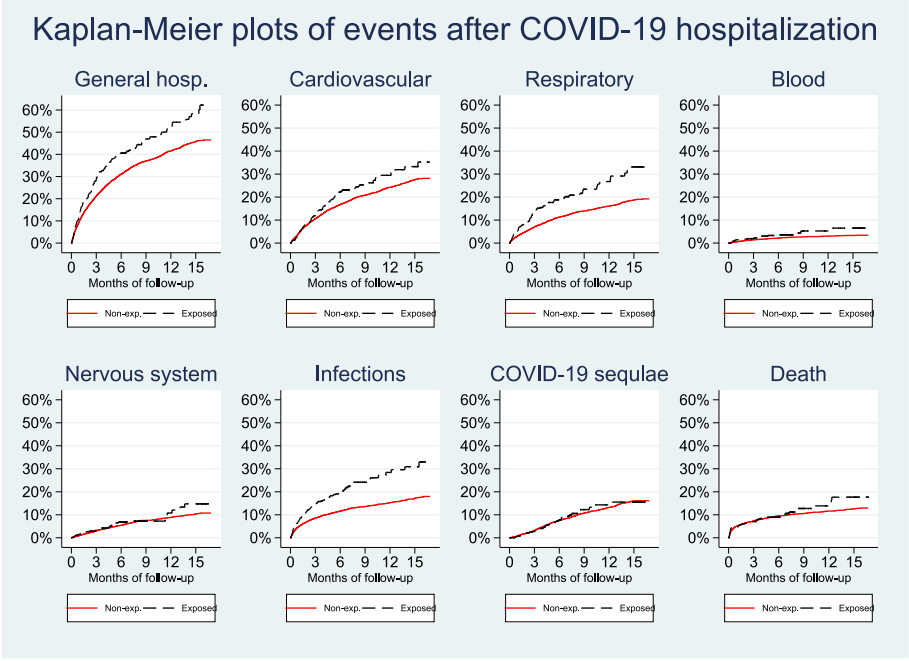

Fig. 1. The cumulative proportion of different outcomes (specific types of hospitalizations and death) after discharge for COVID-19 in patients with chronic inflammatory bowel disease/rheumatoid arthritis/spondyloarthropathy/psoriatic arthritis (exposed), and patients without these diseases (non-exposed).

Table 2
Hazard ratios for hospitalizations and death after COVID-19 discharge in patients with chronic inflammatory bowel disease (IBD)/rheumatoid arthritis (RA)/spondyloarthropathy (SpA)/psoriatic arthritis (PsA), relative to other patients who have been discharged from hospital after COVID-19. Cox proportional hazard models with crude and adjusted estimates with 95% confidence intervals (CI). Observation time starts on the date after discharge for COVID-19.

	Exposed cohort (patients with IBD/RA/SpA/PsA) N = 417	Unexposed cohort (patients without IBD/RA/SpA/PsA) N = 9,248	Hazard ratios (95% CI)	
Outcomes	N, events	N, events	Crude	Adjusted[a]
Hospitalization, overall	182 (43.6)	3,068 (33.2)	1.40 (1.20–1.62)	1.14 (0.98–1.33)
Hospitalization with diseases of the cardiovascular system (ICD-10: I*)	99 (23.7)	1,713 (18.5)	1.29 (1.05–1.57)	1.06 (0.86–1.30)
Hospitalization with diseases of the respiratory system (ICD-10: J*)	90 (21.6)	1,147 (12.4)	1.80 (1.45–2.23)	1.27 (1.02–1.58)
Hospitalization with diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (ICD-10 D5, D6, D7, D8)	17 (4.1)	219 (2.4)	1.71 (1.04–2.79)	1.20 (0.73–1.99)
Hospitalization with diseases of the nervous system (ICD-10: G*)	33 (7.9)	594 (6.4)	1.22 (0.86–1.73)	0.95 (0.67–1.35)
Hospitalization with infection	95 (22.8)	1,157 (12.5)	1.90 (1.54–2.35)	1.55 (1.26–1.92)
Sequelae of COVID-19 (ICD-10: B948A)[b]	40 (9.6)	835 (9.0)	1.04 (0.76–1.43)	1.08 (0.79–1.49)
Death[b]	47 (11.3)	908 (9.8)	1.14 (0.85–1.53)	0.96 (0.71–1.29)

[a] Adjusted for sex, age, length of hospital stay, previous hospitalization of the same kind and steroid prescription within 6 months prior to COVID-19 hospitalization.
[b] Not adjusted for previous hospitalization.

4.2. Strengths and weaknesses

This study has several strengths. We have access to valid data in our Danish registries which are important tools for clinical epidemiological studies [11,12,15–17]. The Danish national registries comprise unique data with which to study long-term health outcomes in COVID-19 individuals. The most important strength is the nationwide design providing an unselected cohort of all patients with IBD/RA/SpA/PsA who have been hospitalized because of COVID-19, and therefore our results can be generalized to the overall population of Danish patients with IBD/RA/SpA/PsA discharged alive after COVID-19. No patients were lost to follow-up, thereby preventing selection bias, and we had independent ascertainment of exposure and outcomes. Furthermore, we have valid outcome measurements from the Danish National Patient Registry, and we were able to adjust the analyses for the patients' underlying morbidity (other than IBD/RA/SpA/PsA), as well as other important confounders [11]. We believe that we have taken into account important confounders including age, sex, former morbidities prior to COVID-19 hospitalization, and proxy measurements of the severity of COVID-19 (length of hospital stay), and the severity of underlying diseases (use of steroids). In an observational study like this, one can never be certain that all possible confounders have been considered, and therefore an impact of unknown confounding can never be ruled out. It is an important strength that our analyses were robust across the different analytic approaches. In a nationwide study like this it is not possible to review all medical records, and we did not have information on clinical details such as severity of comorbid diseases or disease activity of IBD/RA/SpA/PsA. A critical factor, when wanting to examine "long-term" consequences after COVID-19, is of course the length of follow-up. At present, it is only possible to observe long-term outcomes for a period of 1½ years after hospital discharge due to COVID-19, and we cannot comment on the consequences in patients with IBD/RA/SpA/PsA in a longer perspective. Our current data can therefore only provide some initial results on selected health outcomes. This study includes the study population of patients who have been discharged alive after hospitalization with COVID-19 disease, and we thus estimate the risk of subsequent hospitalizations in only those who have had severe COVID-19 requiring hospitalization. The patients with IBD/RA/SpA/PsA who had COVID-19 but were not hospitalized for COVID-19 were not included in this study. This study specifically estimates the risk of severe outcomes after hospital discharge for acute COVID-19, i.e. to be captured as an outcome, patients in our study population had to have rather severe symptoms requiring referral to a hospital for a diagnosis/treatment. Patients with mild symptoms after recovery from acute COVID-19 were not included in this study. In Denmark we have no general access to data from the general practitioners, and therefore we cannot assess the risks for only mild post COVID-19 symptoms.

4.3. Other studies

To our knowledge, there have been no studies on post COVID-19 hospitalizations in patients with IBD/RA/SpA/PsA who have been discharged due to COVID-19. Consequently, our results cannot be compared to other studies. Our study adds to early evidence on post COVID-19 outcomes in patients with IBD/RA/SpA/PsA. Initial studies in patients with chronic inflammatory/autoimmune diseases have concentrated on the risk of having coronavirus SARS-CoV-2, and severe COVID-19 [8,9,14,18–23]. None of these studies, however, have examined the risk of post COVID-19 adverse outcomes.

There have been initial reports on symptoms in the general population who have survived hospitalization because of COVID-19. A case-series study from the United States evaluated the outcomes of 1,250 patients discharged alive at 60 days and 6.7% died, while 15.1% required re-admission [24]. Another study on 593 patients showed that among symptomatic individuals, persistent symptoms were common: 52.5% had not recovered 30 days post COVID-19 onset and 35.0% had not recovered after 60 days [25]. A case-series study from Italy on 143 patients showed that 87.4% reported persistent symptoms at a mean follow up of 60 days from onset of the first symptoms [26], and similar findings were reported in a study from France [27]. A cohort study from China assessed the consequences in 1,733 patients at 6 months from symptom onset, and showed that 76% of the patients reported at least one symptom [28]. Six months after acute infection, patients who were severely ill during their hospital stay had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations, compared to those who were less severely affected [28]. When evaluating earlier literature, it is important to realize that the definition of long-term consequences is debated, and the National Institute of Health has suggested the research term "post-acute sequelae of SARS-CoV-2 infection (PASC)" [25]. Several other terms are, however, used and post COVID conditions are currently being referred to a wide range of overlapping entities, including post-acute COVID-19, long-term effects

Table 3
Hazard ratios for hospitalizations and death after COVID-19 discharge in patients with chronic inflammatory bowel disease (IBD)/rheumatoid arthritis (RA)/spondyloarthropathy (SpA)/psoriatic arthritis (PsA), relative to other patients who have been discharged from hospital after COVID-19. Cox proportional hazard models with crude and adjusted estimates with 95% confidence intervals (CI). Observation time starts 14 days after discharge for COVID-19 (left panel) and 28 days after discharge for COVID-19 (right panel).

	Observation time starts 2 weeks after discharge for COVID-19				Observation time starts 4 weeks after discharge for COVID-19			
	Exposed cohort (IBD/RA/SpA/PsA) N = 417	Unexposed cohort (without IBD/RA/SpA/PsA) N = 9,248	Hazard ratios (95% CI)		Exposed cohort (IBD/RA/SpA/PsA) N = 417	Unexposed cohort (without IBD/RA/SpA/PsA) N = 9,248	Hazard ratios (95% CI)	
Outcomes	N, events	N, events	Crude	Adjusted[a]	N, events	N, events	Crude	Adjusted[a]
Hospitalization, overall	154 (40.0)	2,589 (29.9)	1.42 (1.20–1.67)	1.16 (0.98–1.36)	132 (36.9)	2,225 (27.0)	1.42 (1.19–1.70)	1.15 (0.96–1.38)
Hospitalization with diseases of the cardiovascular system (ICD-10: I*)	94 (23.0)	1,527 (17.1)	1.37 (1.11–1.69)	1.13 (0.91–1.39)	85 (21.6)	1,366 (15.6)	1.39 (1.11–1.73)	1.14 (0.91–1.42)
Hospitalization with diseases of the respiratory system (ICD-10: J*)	77 (19.3)	988 (11.0)	1.80 (1.43–2.27)	1.25 (0.99–1.59)	71 (18.3)	885 (10.0)	1.86 (1.46–2.36)	1.29 (1.01–1.65)
Hospitalization with diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (ICD-10 D5, D6, D7, D8)	14 (3.4)	195 (2.1)	1.58 (0.92–2.71)	1.11 (0.64–1.92)	11 (2.7)	172 (1.9)	1.40 (0.76–2.58)	1.00 (0.54–1.86)
Hospitalization with diseases of the nervous system (ICD-10: G*)	29 (7.1)	551 (6.1)	1.16 (0.80–1.68)	0.89 (0.61–1.30)	27 (6.7)	509 (5.7)	1.16 (0.79–1.71)	0.90 (0.61–1.33)
Hospitalization with infection	77 (19.5)	910 (10.2)	1.98 (1.57–2.50)	1.62 (1.28–2.05)	64 (17.0)	751 (8.7)	2.01 (1.56–2.59)	1.63 (1.26–2.11)
Sequelae of COVID-19 (ICD-10: B948A)[b]	40 (9.7)	806 (8.9)	1.08 (0.78–1.48)	1.14 (0.83–1.57)	38 (9.4)	774 (8.6)	1.06 (0.77–1.47)	1.12 (0.80–1.55)
Death[b]	29 (7.1)	580 (6.6)	1.09 (0.75–1.59)	0.88 (0.60–1.28)	28 (6.9)	456 (5.3)	1.34 (0.91–1.96)	1.07 (0.72–1.57)

[a] Adjusted for sex, age, length of hospital stay, previous hospitalization of the same kind and steroid prescription within 6 months prior to COVID-19 hospitalization.
[b] Not adjusted for previous hospitalization.

of COVID, long COVID, post-acute COVID syndrome, chronic COVID, and others. The appropriate time windows for post COVID-19 symptoms are also part of this discussion: whether to consider symptoms of COVID-19 for up to 4 weeks after disease onset? Symptoms from 4 to 12 weeks, or symptoms that develop or persist for more than 12 weeks, etc.? We have analyzed our data according to different time windows due to a lack of strict post COVID-19 definitions.

4.4. The meaning of our results and implications for clinicians

It is disturbing that we find an increased risk of hospitalizations in patients with IBD/RA/SpA/PsA who have been discharged after COVID-19, compared to other patients discharged after COVID-19. A consistent finding is an increased risk of respiratory diseases and infections. Some of our other point estimates, however, also suggest an increased risk (overall hospitalization and cardiovascular diseases), but were not statistically significantly increased. The absence of significant associations, however, does not provide evidence that the risk is not increased. Therefore, the implication of these results is that clinicians should be particularly alert for post COVID-19 symptoms from several organ systems in patients with IBD/RA/SpA/PsA.

With initial reports from all over the world, there is no doubt that COVID-19 causes post-acute COVID-19 symptoms [2]. The critical question is to what degree COVID-19 affects the long-term health and which patient categories are at special risk. As the pandemic is still new, we only have few solid data on post COVID-19 consequences, and our first data on "long-term" consequences in patients with IBD/RA/SpA/PsA should be seen in this perspective.

It is also worth considering whether our results reflect what normally occurs in patients with autoimmune diseases, but so far, it is not possible to answer that question in the context of COVID-19. Nevertheless, our study showed that the IBD/RA/SpA/PsA patients had an increased risk of several outcomes, but not all outcomes, compared to the other patients discharged alive after COVID-19.

4.5. Future research

There are still very few data on long-term outcomes after COVID-19 survival, and there is a huge need to conduct well-designed studies on the consequences after COVID-19 in populations of patients with underlying diseases. Identifying high risk groups for severe post COVID-19 outcomes is critical for risk stratification in order to plan targeted preventive measures. Therefore, there is an obvious need to study the long-term outcomes in patients with chronic autoimmune diseases, who have been discharged alive after hospitalized for COVID-19. Other studies have to confirm our findings and examine the underlying mechanisms behind which patients with IBD/RA/SpA/PsA have an increased risk of hospitalization after COVID-19. Future studies should, however, also examine the long-term outcomes in COVID-19 patients with chronic autoimmune diseases who have not been hospitalized for COVID-19, because even people with only a mild disease can experience persistent symptoms or long-term effects.

5. Conclusion

After hospital discharge for COVID-19, patients with IBD/RA/SpA/PsA had an increased risk of subsequent hospitalizations for several categories of diseases, compared to other patients discharged after COVID-19. They had an increased risk of a hospitalization due to respiratory diseases and to infections. Our results also showed an increased risk of overall hospitalization and cardiovascular diseases although these results were not statistically significant. It was reassuring that patients with IBD/RA/SpA/PsA did not have an increased risk of hospitalization due to diseases in the nervous system, nor had an increased risk of death.

Contributors

BMN: funding, conception, design, assistance with data analysis,

interpretation of results, manuscript editing, approved the final version. **FDZ**: design, 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. **JK**: funding, conception, assistance with data analysis, interpretation of results, manuscript writing and editing, approved the final version.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2021.102739.

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