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Coronavirus disease 2019, immune-mediated inflammatory diseases and immunosuppressive therapies – A Danish population-based cohort study

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ABSTRACT

Background: Limited data exist regarding the disease course of coronavirus disease 2019 (COVID-19) and its relationship with immunosuppressants among patients with immune-mediated inflammatory diseases (IMIDs). Therefore, this study aims to investigate the association between COVID-19, frequent rheumatological, dermatological, gastrointestinal, and neurological IMIDs and immunosuppressants.

Methods: We conducted a Danish population-based cohort study including all residents living within Capital Region of Denmark and Region Zealand from January 28th, 2020 until September 15th, 2020 with the only eligibility criterion being a test for SARS-CoV-2 via reverse transcription–polymerase chain-reaction. Main outcomes included development of COVID-19, COVID-19-related hospitalization and mortality.

Results: COVID-19 was less common among patients with IMIDs than the background population ($n = 328/20,513$ (1.60%) and $n = 10,792/583,788$ (1.85%), $p < 0.01$, respectively). However, those with IMIDs had a significantly higher risk of COVID-19-related hospitalization (31.1% and 18.6%, $p < 0.01$, respectively) and mortality (9.8% and 4.3%, $p < 0.01$, respectively), which were associated with patients older than 65 years, and presence of comorbidities. Furthermore, systemic steroids were independently associated with a severe course of COVID-19 (Odds ratio (OR) = 3.56 (95%CI 1.83–7.10), $p < 0.01$), while biologic therapies were associated with a reduced risk hereof (OR = 0.47 (95%CI 0.22–0.95), $p = 0.04$). Patients suspending immunosuppressants due to COVID-19 had an increased risk of subsequent hospitalization (OR = 3.59 (95%CI 1.31–10.78), $p = 0.02$).

Conclusion: This study found a lower occurrence, but a more severe disease course, of COVID-19 among patients with IMIDs, which was associated with the use of systemic steroids for IMIDs and suspension of other immunosuppressants. This study emphasizes the importance of weighing risks before suspending immunosuppressants during COVID-19.

1. Introduction

The coronavirus disease 2019 (COVID-19) is a new form of acute infectious respiratory syndrome first reported in December 2019 in the Wuhan region of China [1]. The disease is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has rapidly become a pandemic [1]. As the disease continues to spread, more than 75 million infectious cases have been detected, along with over 1.6

million deaths, and it is considered a Public Health Emergency of International Concern. However, several large-scale studies, including population-based studies, have reported a highly heterogeneous disease course in the general population [1–3]. A large proportion of the worldwide population ranging up to 5–10% suffers from chronic immune-mediated inflammatory diseases (IMIDs) with increasing prevalence, incidence, morbidity and economic burden for society [4,5]. Many of these patients often require immunosuppressive therapies,

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which has raised concerns about a possible increased susceptibility to COVID-19, as well as to other infections [6,7]. If this is correct, these diseases and their treatments might increase the likelihood of a more severe COVID-19 disease course [8]. While studies to date indicate that there is no increased risk of COVID-19 among patients with IMIDs [9], other studies have warned about a more severe disease course, including a higher risk of respiratory failure [10], admission to intensive care units, and of requiring mechanical ventilation [11]. Other studies, while limited by their sample sizes, find no relationship between these outcomes and treatment with immunosuppressive therapies [12,13].

These data need to be validated in a population-based setting with a uniform COVID-19 registration system and should include an investigation of the potential modulation of COVID-19 by immunosuppressive therapies. The Danish health care system has recently adopted such a registration system within the Capital Region of Denmark and Region Zealand. Therefore, we aimed to conduct a population-based study (The Danish COVID-IMID Study) in these two regions, assessing both the overall risk and the disease course of COVID-19 among patients with and without IMIDs, stratified according to their use of immunosuppressive therapies.

2. Material and methods

2.1. Study design and population

We established a population-based cohort (The Danish COVID-IMID cohort) comprising all adult and pediatric patients living in the geographic area of Zealand, a region with 2.7 million residents (equal to 45.5% of the Danish population) that is governed by two administrative units, *Capital Region of Denmark* and *Region Zealand*. Within that population, we identified all inhabitants with an established diagnosis of at least one IMID and who tested positive for SARS-CoV-2 [14]. As the first tests for SARS-CoV-2 took place in Denmark on January 28th, 2020, we defined the study period as beginning on this date and lasting until September 15th, 2020. Following the development of the pandemic, and hence, changes in national guidelines regarding appropriate testing algorithms, testing was restricted to symptomatic patients as evaluated by a physician until May 18th. Afterwards, testing was available for anyone as part of a containment strategy. The presence of SARS-CoV-2 genomic material was, in all cases, laboratory-confirmed by reverse transcription-polymerase-chain-reaction (RT-PCR) analysis of a specimen from either a nasopharyngeal swab or tracheal suctioning. In these two geographical regions, the testing of COVID-19 was uniformly and automatically registered and coded by the patients' unique 10-digit identification number and integrated into the Epic Health Care System in which the medical records of all Danish patients are registered.

Patients with IMIDs were identified using International Classification of Diseases (Tenth Revision) codes, as listed in [Supplementary Table 1](#). We included all cases of rheumatological, gastrointestinal, dermatological and neurological IMIDs that might be treated with immunosuppressive therapies after manual screening of the medical records ensuring fulfillment of the specific diagnosis criteria. In this way we could investigate the frequency and disease course of COVID-19 among patients with IMIDs within a large, well-described population-based sample and compare them to the background population.

Data about symptoms of non-hospitalized patients with COVID-19 were collected from medical records at the time of COVID testing, either via a questionnaire at the test center or extracted from the medical record. Data from the background population of patients without IMIDs were provided by Statens Serum Institut, the institute responsible for monitoring and reporting COVID-19 occurrence and its disease course to the Danish Ministry of Health.

2.2. Outcomes, definitions, and data collection

We collected data on patient demographics, comorbidities, COVID-

19 symptoms and disease course (treatments, hospitalizations, admission to intensive care units, noninvasive or invasive respiratory support, and mortality) and IMID characteristics (type, clinical disease activity at diagnosis of COVID-19, including c-reactive protein (CRP), IMID-related treatments and changes in treatments). IMID-related disease activity was assessed using standardized clinical activity indices, including patient-reported outcomes and biochemical inflammatory markers, as appropriate. Remission of IMIDs was in all cases assessed by a specialist according to current guidelines prior to the COVID-19 episode ([Supplementary Table 2](#)).

The application of the nomenclature of COVID-19 and SARS-CoV-2 was according to the definition presented by World Health Organization (WHO) in the International Classification of Diseases (ICD) [15]. COVID-19-related mortality was defined as death occurring during active COVID-19, with the disease recorded as the primary or secondary cause of death; COVID-19-related hospitalization was defined as hospitalization due to COVID-19 and included hospitalizations related to acute pulmonary and general symptoms in relation to laboratory confirmed presence of SARS-CoV-2. Among patients already admitted to the hospital for other reasons, registration as a COVID-19-related hospitalization required an additional focus on the disease during the patient's stay. All biological and immunomodulatory therapies were considered for the treatment of IMIDs, and Janus kinase inhibitors were considered separately as small molecules. Suspension of immunosuppressants was defined as suspension following a positive test for SARS-CoV-2, and before development of clinical COVID-19.

The data were registered in the Research Electronic Data Capture system (REDCap) [16], and the present manuscript was prepared according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement ([Supplementary Table 3](#)) [17].

2.3. Statistical analysis

Statistical analyses were performed using R version 3.6.1, developed by R Foundation for Statistical Computing [18], with the use of descriptive statistics and regression analysis. Patients were grouped according to the presence or absence of gastrointestinal, dermatological, or rheumatological disease, and treatments with or without immunosuppressive therapies. Differences between the groups of patients were investigated by Fisher's exact test and chi-squared test, as appropriate. In addition, univariate and multivariate logistic regression models were used to investigate possible pre-defined variables as predictive factors for the disease course of COVID-19. Pre-defined endpoints included COVID-19 related hospitalization and mortality. In cases of overlapping data (e.g. "any comorbidity" and "hypertension"), multiple logistic regression analysis were conducted replacing the particular variables. *P*-values less than 0.05 were considered to be significant.

2.4. Ethics approval

According to Danish law, no permission from the National Committee on Health Research Ethics was required for this non-interventional study. This study is approved by the Danish Patient Safety Authority (R-20049371).

2.5. Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available, in adherence to Danish law, but are available from the corresponding author upon reasonable request. The study protocol and statistical code used to generate the results are available upon request.

3. Results

3.1. Occurrence of COVID-19 in patients with IMIDs and in the general population

Within the study population of 2,734,422 residents, a total of 71,733 (2.6%) individuals had at least one IMID. Of these, almost every third patient (n = 20,513; 28.6%) took a SARS-CoV-2 laboratory test, and 328 (1.6%) patients received a positive test result. As shown in Table 1, this rate was lower than that observed among residents without IMIDs (n = 10,792; 1.9%; p < 0.01). Both among patient with and without IMIDs, most cases of COVID-19 were diagnosed before the transition into free testing at May 18th, 2020 (243 (74.1%) and 7797 (72.2%), p = 0.46).

Looking at the age groups, SARS-CoV-2 occurred significantly less frequent among patients with IMIDs in the ages 30–70 compared to the corresponding patients without any pre-existing IMIDs (Supplementary Table 4). When grouped by specific IMIDs, the lower occurrence of COVID-19 was primarily confined to patients with dermatological (n = 60; 1.2%; p < 0.01) and gastrointestinal (n = 90, 1.5%, p < 0.01) IMIDs.

3.2. Baseline characteristics of patients with IMIDs infected with COVID-19

In total, 328 patients with an IMID and COVID-19 were followed for a median of 5.1 months (IQR 4.0–5.5). The median age at diagnosis of

COVID-19 was 55 (41–74) and half of the patients (n = 166, 50.6%) had comorbidities including hypertension (n = 59, 18.0%), diabetes (n = 35, 10.7%), current or previous cancers (n = 23, 7.0%), congestive heart failure (n = 18, 5.5%), and chronic kidney disease (n = 11, 3.4%). The IMIDs were in remission in 47.3% of the patients, and a total of 71.7% received medical treatment for the IMIDs, including biologic therapies (n = 51, 15.5%), methotrexate (n = 59, 18.0%), azathioprine (n = 17, 5.2%) and systemic steroids (n = 42, 12.8%) (Table 2).

3.3. COVID-19 symptomatology and disease course

Only 14 patients (4.3%) with laboratory-confirmed COVID-19 were asymptomatic. The most frequent symptoms included fever (n = 103, 31.4%), cough (n = 91, 27.7%) and dyspnea (n = 52, 15.9%). Furthermore, one-third of the patients with IMIDs and COVID-19 (n = 102, 31.1%) required a COVID-19-related hospitalization with an admission length of seven days (IQR 3–14). As shown in Table 3, both hospitalization rate and duration were significantly higher than observed in the background population without IMIDs (n = 1,997, 18.6%, length five days (IQR 2–10), p < 0.01).

Although only a small proportion of patients (n = 14, 4.3%) were admitted to an intensive care unit, one-in-ten patients (n = 32, 9.8%) died of COVID-19, a proportion significantly higher than that observed in the general population without IMIDs (n = 462, 4.3%, p < 0.01). Examining the various IMIDs, we found in the unadjusted model that

Table 1
Occurrence of COVID-19 among patients with and without immune-mediated inflammatory diseases.

	Overall N of patients	N tested	Proportion of patients tested (%)	N COVID-19	Frequency of COVID-19 (%)	p-value
Overall in the general population	2,734,422	604,301	22.10	11,120	1.84	
No IMIDs	2,662,689	583,788	21.92	10,792	1.85 (ref)	
Any IMID	71,733	20,513	28.60	328	1.60	<0.01
Any rheumatological IMID	36,060	10,418	24.41	184	2.05	0.54
Arthritis						
Rheumatoid arthritis	13,015	3367	25.87	79	2.35	0.03
Psoriatic arthritis	4160	1173	28.20	19	1.62	0.56
Reactive arthritis	2132	618	28.99	3	0.49	0.01
Ankylosing spondylitis	1986	511	25.73	11	2.15	0.61
Axial spondylopathies (unspecified)	1557	494	31.73	10	2.02	0.77
Connective tissue diseases						
Sarcoidosis	2894	1076	37.18	16	1.49	0.38
Sjogren's disease	1865	647	34.69	7	1.08	0.15
Systemic lupus erythematosus	1159	421	36.32	9	2.14	0.66
Systemic scleroderma	514	166	32.30	0	0.00	NA
Antiphospholipid syndrome	360	140	38.89	0	0.00	NA
Dermatomyositis	269	97	36.06	0	0.00	NA
Mixed connective tissue disease	170	45	26.47	1	2.22	0.85
Polymyositis	145	50	34.48	0	0.00	NA
Systemic vasculitis						
Polymyalgia rheumatica	4305	1163	27.02	28	2.41	0.16
Giant cell arteritis	938	255	27.19	4	1.57	0.74
ANCA-associated vasculitis						
Granulomatosis with polyangiitis	466	154	33.05	1	0.65	0.27
Microscopic polyangiitis	125	41	32.80	0	0.00	NA
Any dermatological IMID	16,676	4966	29.78	60	1.21	<0.01
Psoriasis	8784	2467	28.09	37	1.50	0.20
Atopic dermatitis	5305	1617	30.48	14	0.87	<0.01
Hidradenitis suppurativa	1776	631	35.53	6	0.95	0.09
Cutaneous lupus erythematosus	589	170	28.86	1	0.59	0.22
Pyoderma gangrenosum	222	81	36.49	2	2.47	0.68
Any gastrointestinal, hepatological or pancreatic IMID	19,717	5888	29.86	90	1.53	<0.01
Ulcerative colitis (UC)	11,882	3377	28.42	53	1.57	0.23
Crohn's disease (CD)	7165	2374	33.13	36	1.52	0.23
Autoimmune hepatitis	891	230	25.81	1	0.43	0.11
Autoimmune pancreatitis	51	14	27.45	0	0.00	NA
Autoimmune hepatitis with primary biliary cholangitis	77	17	22.08	0	0.00	NA
Autoimmune hepatitis with primary sclerosing cholangitis	62	27	43.55	0	0.00	NA
Multiple sclerosis	6775	1824	26.92	5	0.27	<0.01

Table 2
Demographics and clinical characteristics of the Danish COVID-IMID cohort.

		Overall	Rheumatological	p-value	Gastrointestinal	p-value	Dermatological	p-value	Multiple IMIDs	p-value
N	N (%)	328	184		90		60		17	
Age	median (IQR)	55 (41–74)	63 (50–78)		48 (37–60)		46 (26–63)	<0.01	55 (46–57)	
Duration of IMIDs	Median years (IQR)	7.6 (2.8–13.9)	6.8 (2.6–13.4)	0.90	12.8 (5.0–23.7)	0.12	4.4 (2.3–10.7)	0.76	13.0 (4.1–20.7)	0.52
Female	N (%)	188 (57.3)	113 (61.4)	0.09	39 (43.3)	<0.01	38 (63.3)	0.79	7 (41.2)	0.17
Body mass index	median (IQR)	25 (22.3–29.2)	24.6 (22.4–29.4)		22.0 (25.2–28.0)		26.5 (21.5–33.9)		27.2 (23.4–31.6)	
Active or former smoker	N (%)	154 (47.0)	97 (52.7)	0.02	34 (37.8)	0.04	25 (41.7)	0.11	6 (35.3)	0.32
Co-existing conditions	N (%)	166 (50.6)	112 (60.9)	<0.01	35 (38.9)	<0.01	21 (35.0)	<0.01	8 (47.1)	0.76
Hypertension	N (%)	59 (18.0)	41 (22.3)	0.02	11 (12.2)	0.09	7 (11.7)	0.14	1 (5.9)	0.18
Obesity	N (%)	58 (17.7)	33 (17.9)	0.89	13 (14.4)	0.34	14 (23.3)	0.28	4 (23.5)	0.52
Diabetes	N (%)	35 (10.7)	24 (13.0)	0.12	8 (8.9)	0.52	4 (6.7)	0.25	1 (5.9)	0.51
Cancer	N (%)	23 (7.0)	18 (9.8)	0.03	5 (5.6)	0.53	0	NA	0	NA
Congestive heart failure	N (%)	18 (5.5)	14 (7.6)	0.06	3 (3.3)	0.29	1 (1.7)	0.15	1 (5.9)	0.94
Chronic obstructive pulmonary disease	N (%)	17 (5.2)	14 (7.6)	0.03	1 (1.1)	0.04	2 (3.3)	0.47	0	NA
Psychiatric diseases	N (%)	17 (5.2)	12 (6.5)	0.22	3 (3.3)	0.35	2 (3.3)	0.47	1 (5.9)	0.89
History of stroke	N (%)	16 (4.9)	12 (6.5)	0.12	3 (3.3)	0.42	1 (1.7)	0.20	1 (5.9)	0.84
Chronic kidney disease	N (%)	11 (3.4)	8 (4.3)	0.26	1 (1.1)	0.17	2 (3.3)	0.98	0	NA
Coronary artery disease	N (%)	9 (2.7)	8 (4.3)	0.04	1 (0.01)	0.26	0	NA	0	NA
Disease activity										
Clinical remission	N (%)	155 (47.3)	79 (42.9)	0.08	58 (64.4)	<0.01	18 (30.0)	<0.01	6 (35.3)	0.31
C-reactive protein	median (IQR)	4.0 (2.5–14.8)	4.0 (2.9–19.0)		3.0 (2.1–7.4)		4.0 (1.8–7.8)		4.0 (2.0–10.0)	
Long-term medication										
Any medication for IMID	N (%)	235 (71.7)	133 (72.2)	0.77	62 (68.9)	0.50	46 (76.7)	NA	15 (88.2)	0.12
Duration of immunosuppressive therapies	Median months (IQR)	4.0 (1.8–7.5)	4.2 (1.9–8.2)	0.85	3.7 (2.1–6.8)	0.73	3.1 (1.8–6.7)	0.48	3.1 (2.8–8.4)	0.33
Corticosteroids										
Systemic steroids	N (%)	42 (12.8)	38 (20.7)	<0.01	3 (3.3)	<0.01	1 (1.7)	<0.01	3 (17.6)	0.54
Topical steroids	N (%)	49 (14.9)	15 (8.2)	<0.01	6 (6.7)	<0.01	33 (55.0)	<0.01	6 (35.3)	0.02
Intra-articular steroids	N (%)	1 (0.3)	1 (0.5)	NA	0	NA	0	NA	0	NA
Intra-muscular steroids	N (%)	0	0	NA	0	NA	0	NA	0	NA
Immunomodulators										
Methotrexate	N (%)	59 (18.0)	49 (26.6)	<0.01	3 (3.3)	0.01	11 (18.3)	0.95	5 (29.4)	0.21
Azathioprine	N (%)	17 (5.2)	4 (2.2)	<0.01	14 (15.6)	<0.01	0	NA	1 (5.9)	0.89
Hydroxychloroquine	N (%)	10 (3.0)	10 (5.4)	NA	0	NA	0	NA	2 (11.8)	0.03
Non-steroidal anti-inflammatory drugs	N (%)	7 (2.1)	7 (3.8)	NA	0	NA	0	NA	0	NA
Mercaptopurine	N (%)	1 (0.3)	0	NA	1 (1.1)	NA	0	NA	0	NA
Biologic therapies										
Any	N (%)	51 (15.5)	29 (15.8)	0.90	18 (20.0)	0.17	6 (10.0)	0.17	7 (41.2)	<0.01
Adalimumab	N (%)	14 (4.3)	8 (4.3)	0.94	6 (6.7)	0.19	2 (3.3)	0.68	3 (17.6)	<0.01
Abatacept	N (%)	1 (0.3)	1 (0.5)	NA	0	NA	0	NA	0	NA
Belimumab	N (%)	1 (0.3)	1 (0.5)	NA	0	NA	0	NA	0	NA
Etanercept	N (%)	7 (2.1)	6 (3.3)	0.11	1 (1.1)	0.43	0	NA	0	NA
Golimumab	N (%)	3 (0.9)	3 (1.6)	NA	0	NA	0	NA	0	NA
Infliximab	N (%)	11 (3.4)	6 (3.3)	0.92	6 (6.7)	0.04	0	NA	1 (5.9)	0.55
Natalizumab	N (%)	1 (0.3)	0	NA	1 (1.1)	NA	0	NA	1 (5.9)	NA
Ocrelizumab	N (%)	1 (0.3)	0	NA	0	NA	0	NA	0	NA
Rituximab	N (%)	1 (0.3)	1 (0.5)	NA	0	NA	0	NA	0	NA
Secukinumab	N (%)	2 (0.6)	0	NA	0	NA	2 (3.3)	NA	0	NA
Tocilizumab	N (%)	3 (0.9)	3 (1.6)	NA	0	NA	0	NA	2 (11.8)	NA
Ustekinumab	N (%)	2 (0.6)	0	NA	0	NA	2 (3.3)	NA	0	NA
Vedolizumab	N (%)	4 (1.2)	0	NA	4 (4.4)	NA	0	NA	0	NA
Small molecules										
Baricitinib		1 (0.3)	1 (0.5)	NA	0	NA	0	NA	0	NA

IMIDs, immune-mediated inflammatory diseases. The *p*-value indicates the difference between patients with the specific IMIDs and patients without those IMIDs. The “overall” groups includes the before mentioned rheumatological, gastrointestinal, hepatological, pancreatic and neurological IMIDs. Treatments that the cohort did not receive are not mentioned here, but all biological, small molecules and immunomodulators were assessed.

patients with rheumatological IMIDs more often required COVID-19-related hospitalization ($n = 77$, 41.8%, $p < 0.01$), and more often died of COVID-19 ($n = 25$, 13.6%, $p < 0.01$) than patients with different IMIDs. Furthermore, we found that patients with multiple IMIDs did not experience a COVID-19 disease course substantially different to that of patients with only one IMID (Table 3).

3.4. Risk factors for a more severe course of COVID-19

A summary of risk factors associated with a complicated COVID-19 disease course, in terms of hospitalization and mortality, is provided in Table 4. In the univariate analysis of the risk of COVID-19-related hospitalization, we found that being older than 65 at the time of diagnosis of COVID-19 (OR = 16.07 (95% CI 9.13–29.26), $p < 0.01$), being an active or a former smoker (OR = 4.04 (95% CI 2.45–6.78), $p < 0.01$),

Table 3
Outcomes of COVID-19 in the Danish COVID-IMID cohort.

		Overall	Rheumatological	p-value	Gastrointestinal	p-value	Dermatological	p-value	Multiple	p-value
COVID-19 symptoms		328	184		90		60 268		19	
No symptoms	N (%)	14 (4.3)	9 (4.9)	0.53	3 (3.3)	0.61	3 (5.0)	0.76	1 (5.9)	0.83
Fever	N (%)	103 (31.4)	57 (31.0)	0.85	31 (34.4)	0.47	15 (25.0)	0.24	2 (11.8)	0.04
Cough	N (%)	91 (27.7)	54 (29.3)	0.46	26 (28.9)	0.78	13 (21.7)	0.24	4 (23.5)	0.50
Shortness of breath	N (%)	52 (15.9)	37 (20.1)	0.02	11 (12.2)	0.27	5 (8.3)	0.08	2 (11.8)	0.51
Muscle pain or arthralgia	N (%)	48 (16.3)	29 (15.8)	0.51	16 (17.8)	0.32	6 (10.0)	0.26	3 (17.6)	0.88
Tiredness	N (%)	52 (15.9)	35 (19.0)	0.08	12 (13.3)	0.44	6 (10.0)	0.17	1 (5.9)	0.19
Headaches	N (%)	36 (11.0)	18 (9.8)	0.43	15 (16.7)	0.04	4 (6.7)	0.24	2 (11.8)	0.95
Vomiting	N (%)	7 (2.1)	3 (1.6)	0.48	1 (1.1)	0.43	3 (5.0)	0.09	0	NA
Sore throat	N (%)	31 (9.5)	19 (10.3)	0.54	9 (10.0)	0.83	4 (6.7)	0.41	2 (11.8)	0.87
Nausea	N (%)	17 (5.2)	9 (4.9)	0.79	5 (5.6)	0.85	3 (5.0)	0.94	0	NA
Diarrhea	N (%)	21 (6.4)	11 (6.0)	0.72	6 (6.7)	0.90	4 (6.7)	0.93	0	NA
Anosmia and/or ageusia	N (%)	11 (3.4)	8 (4.3)	0.26	4 (4.4)	0.50	1 (1.7)	0.42	3 (17.6)	< 0.01
Abdominal pain	N (%)	9 (2.7)	6 (3.3)	0.52	2 (2.2)	0.72	1 (1.7)	0.57	0	NA
Rhinorrhoea	N (%)	6 (1.8)	3 (1.6)	0.76	1 (1.1)	0.55	2 (3.3)	0.34	0	NA
Nasal congestion	N (%)	5 (1.5)	2 (1.1)	0.47	3 (3.3)	0.10	0	NA	0	NA
Shivers	N (%)	6 (1.8)	4 (2.2)	0.60	1 (1.1)	0.55	1 (1.7)	0.92	0	NA
Sneezing	N (%)	1 (0.3)	1 (0.5)	NA	0	NA	0	NA	0	NA
COVID-19 disease course										
Hospitalization	N (%)	102 (31.1)	77 (41.8)	< 0.01	15 (16.7)	< 0.01	11 (18.3)	0.02	3 (17.6)	0.14
Length	median days (IQR)	7 (3–14)	8 (3–14)		5 (3–8)		8 (2–14)		2 (2–6)	< 0.01
Use of supplementary oxygen	N (%)	54 (16.5)	42 (22.8)	< 0.01	10 (11.1)	0.11	3 (5.0)	< 0.01	1 (5.9)	0.17
Medical therapy	N (%)	52 (15.9)	41 (22.3)	< 0.01	7 (7.8)	0.01	4 (6.7)	0.03	0	NA
Piperacillin and tazobactam (combination)	N (%)	34 (10.4)	26 (14.1)	0.01	6 (6.7)	0.18	2 (3.3)	0.04	0	NA
Penicillins	N (%)	27 (8.2)	24 (13.0)	< 0.01	2 (2.2)	0.01	1 (1.7)	0.04	0	NA
Corticosteroids	N (%)	6 (1.8)	4 (2.2)	0.60	2 (2.2)	0.74	0	NA	0	NA
Remdesivir	N (%)	6 (1.8)	5 (2.7)	0.17	1 (1.1)	0.55	0	NA	0	NA
Hydroxychloroquine	N (%)	1 (0.3)	1 (0.5)	NA	0	NA	0	NA	0	NA
ICU level	N (%)	14 (4.3)	11 (6.0)	0.08	2 (2.2)	0.26	2 (3.3)	0.69	0	NA
Noninvasive ventilation	N (%)	27 (8.2)	19 (10.3)	0.12	5 (5.6)	0.28	4 (6.7)	0.63	1 (5.9)	0.63
Mechanical ventilation	N (%)	11 (3.4)	9 (4.9)	0.08	2 (2.2)	0.48	0	NA	0	NA
Deemed inappropriate to treat	N (%)	7 (2.1)	5 (2.7)	0.41	5 (5.6)	< 0.01	1 (1.7)	0.78	0	NA
COVID-19-related death	N (%)	32 (9.8)	25 (13.6)	< 0.01	5 (5.6)	0.11	3 (5.0)	0.17	1 (5.9)	0.50

IMIDs, immune-mediated inflammatory diseases. ICU, intensive care unit.
Bold p-values indicate statistical significance.

and several chronic cardiologic, nephrological, pulmonary and oncological comorbidities, to be associated with an increased risk of COVID-19-related hospitalization. In addition, the biochemical activity of IMIDs, in particular a CRP higher than 10 mg/L (OR = 7.08 (95% CI 3.85–13.40), $p < 0.01$), treatment with systemic steroids (OR = 3.56 (95% CI 1.83–7.10), $p < 0.01$), and suspension of immunosuppressive therapies (OR = 2.44 (95% CI 1.28–4.67), $p < 0.01$), was associated with an increased risk of COVID-19-related hospitalization. In contrast, treatment with biologic therapies (OR = 0.47 (95% CI 0.22–0.95), $p = 0.04$) was associated with a significantly reduced risk of needing hospitalization. In the multivariate analysis, we found that being older than 65, smoking, hypertension, as well as the suspension of immunosuppressive therapies, were independently associated with an increased risk of COVID-19-related hospitalization (Table 4).

The univariate analysis of COVID-19-related mortality is provided in Table 4. In multivariate analysis, we found that being older than 65 (OR = 4.82 (95% CI 1.22–24.22), $p = 0.03$), congestive heart failure (OR = 4.28 (95% CI 1.15–16.50), $p = 0.03$), a CRP higher than 10 mg/L (OR = 1.31 (OR = 1.63–3.70), $p < 0.01$), and systemic steroid treatment of IMIDs (OR = 1.31 (95%CI 1.04–9.94), $p = 0.04$), were independently associated with an increased risk of COVID-19-related mortality. Finally, we found no association between duration of IMIDs or

immunosuppressive therapies, combination therapy (of biologic therapy and either immunomodulators or systemic steroids) and a worsened COVID-19 disease course in terms of either hospitalization or mortality (Table 4).

4. Discussion

In this population-based cohort study of frequent rheumatological, dermatological, gastrointestinal and neurological IMIDs, we examined the disease course of COVID-19 and its relationship, if any, with immunosuppressive therapies. Although patients with IMIDs had no increased susceptibility to COVID-19 compared to the background population, those with IMIDs did have a greater risk of a severe COVID-19 disease course, with one-in-three requiring hospitalization and one-in-ten dying from the disease. These outcomes were associated with being older than 65, a smoking habit, and the presence of comorbidities. Multivariate analysis indicates that the use of systemic steroids for the treatment of IMIDs is associated with a significantly increased risk of COVID-19-related mortality. In contrast, biologic therapies were associated with a significantly reduced risk of COVID-19-related hospitalization according to a univariate analysis, but not in a multivariate analysis. We found that suspension of immunosuppressive therapies

Table 4
Regression analysis for primary and secondary outcomes from the Danish COVID-IMID cohort.

	Risk factors associated with COVID-19-related hospitalization				Risk factors associated with COVID-19-related mortality			
	univariate	p-value	multivariate	p-value	univariate	p-value	multivariate	p-value
Age >65	16.07 (9.13–29.26)	< 0.01	4.00 (1.51–10.92)	< 0.01	22.82 (7.84–97.07)	< 0.01	4.82 (1.22–24.22)	0.03
Female	0.92 (0.57–1.49)	0.73			1.33 (0.62–2.97)	0.47		
Body mass index >30	0.99 (0.53–1.82)	0.98			1.08 (0.39–2.59)	0.88		
Active or former smoker	4.04 (2.45–6.78)	< 0.01	7.37 (2.91–20.67)	< 0.01	4.51 (1.98–11.60)	< 0.01	1.31 (0.49–4.86)	0.49
Types of IMIDs								
Rheumatological IMIDs	3.45 (2.06–5.91)	< 0.01	7.37 (0.14–13.87)	0.73	3.17 (1.40–8.17)	< 0.01	0.11 (0.58–8.26)	0.49
Dermatological IMIDs	0.43 (0.20–0.84)	0.02	4.33 (0.12–17.18)	0.77	0.42 (0.10–1.24)	0.17		
Gastrointestinal IMIDs	0.35 (0.18–0.63)	< 0.01	2.21 (0.10–9.15)	0.97	0.45 (0.15–1.12)	0.11		
Multiple IMIDs	0.43 (0.10–1.36)	0.20			0.55 (0.03–2.84)	0.57		
Co-existing conditions	8.14 (4.65–14.90)	< 0.01	4.33 (1.58–12.44)	< 0.01	36.87 (7.76–660.70)	< 0.01	0.11 (0.01–1.77)	0.99
Hypertension	5.23 (2.88–9.72)	< 0.01	4.33 (1.11–17.34)	< 0.01	2.84 (1.24–6.20)	0.01	0.75 (0.22–2.37)	0.63
Diabetes	2.03 (1.0–4.17)	0.05			2.72 (1.01–6.61)	0.03	1.50 (0.39–5.29)	0.54
Congestive heart failure	42.6 (8.55–773.62)	< 0.01	NA		9.30 (3.28–25.86)	< 0.01	4.28 (1.15–16.50)	0.03
Coronary artery disease	7.81 (1.85–53.08)	0.01	2.89 (0.33–63.60)	0.38	1.13 (0.06–6.48)	0.91		
Chronic kidney disease	9.02 (2.21–60.53)	< 0.01	NA		3.63 (0.76–13.36)	0.07		
Chronic obstructive pulmonary disease	NA				5.83 (1.88–16.68)	< 0.01	3.96 (0.85–18.73)	0.08
Previous stroke	6.35 (2.11–23.38)	< 0.01	1.54 (0.77–510.20)	0.08	1.31 (0.20–4.99)	0.73		
Cancer	6.93 (2.78–19.77)	< 0.01	2.10 (0.68–7.06)	0.21	7.69 (2.93–19.55)	< 0.01	3.18 (0.80–12.78)	0.10
Psychiatric diseases	2.19 (0.78–6.13)	0.13			2.20 (0.48–7.31)	0.24		
Duration of IMIDs (>5 years vs. less)	1.40 (0.70–2.78)	0.20			1.63 (0.28–4.35)	0.84		
Disease activity of IMID								
Clinical activity	1.32 (0.82–2.14)	0.25			1.07 (0.51–2.25)	0.86		
C-reactive protein >10	7.08 (3.85–13.40)	< 0.01	2.21 (0.85–5.80)	0.10	9.42 (3.90–25.32)	< 0.01	1.31 (1.63–3.70)	< 0.01
Long-term medication								
Topical steroids	0.50 (0.23–1.02)	0.07			0.16 (0.01–0.78)	0.04	0.11 (1.63–6.28)	0.81
Salazopyrin	0.93 (0.25–2.93)	0.91			0.74 (0.04–3.98)	0.78		
Immunomodulators								
Any	0.91 (0.51–1.57)	0.73			0.89 (0.34–2.05)	0.80		
Methotrexate	1.24 (0.67–2.24)	0.48			1.31 (0.50–3.04)	0.56		
Azathioprine	0.29 (0.04–1.05)	0.10			NA			
Systemic steroids	3.56 (1.83–7.10)	< 0.01	1.16 (0.37–3.70)	0.80	6.38 (2.81–14.25)	< 0.01	1.31 (1.04–9.94)	0.04
Non-steroidal anti-inflammatory drugs	NA				NA			
Hydroxychloroquine	NA				NA			
Biologic therapies								
Any	0.47 (0.22–0.95)	0.04	0.55 (0.16–1.77)	0.32	NA			
Anti-TNFs	0.49 (0.19–1.10)	0.10			NA			
Adalimumab	0.83 (0.22–2.56)	0.76			NA			
Infliximab	0.52 (0.08–2.10)	0.41			NA			
Duration of any immunosuppressive therapy (>3 years vs. less)	0.80 (0.16–1.11)	0.14			0.91 (0.23–2.00)	0.82		
Combination treatment					NA			
Biologic therapy and immunomodulator	0.47 (0.11–1.49)	0.25			NA			
Biologic therapy and systemic steroid	NA				NA			
Suspension of IMID-related treatment	2.44 (1.28–4.67)	< 0.01	3.59 (1.31–10.78)	0.02	0.67 (0.19–1.92)	0.49		

Bold p-values indicate statistical significance.

more than tripled the risk of a subsequent COVID-19-related hospitalization.

Population-based data about the risk and disease course of COVID-19 among patients with IMIDs, stratified according to their treatment with immunosuppressive therapies, remain scarce, but are urgently needed to ensure evidence-based decision-making by physicians caring for patients with IMIDs and COVID-19 [19]. The possible detrimental effects

of immunosuppressive therapies have long been of concern [20], and conflicting data have indicated either no association [21] or increased rates of hospitalization when patients are exposed to glucocorticoids [12,22]. Based on multivariate analysis, we can confirm the detrimental effects of systemic steroids used to treat IMIDs, which we found to be associated with increased mortality. The mechanism for this remains unknown, but one hypothesis is that systemic steroids reduce viral

clearance [23].

A small number of studies have shown a beneficial role of immunosuppressive treatments in the occurrence and disease course of COVID-19; the latter was observed in our own univariate analysis, but not in our multivariate analysis [24]. It has been hypothesized that the efficacy of immunosuppressive treatments is in their inhibiting the cytokine storm commonly observed in patients with COVID-19 [25]. Furthermore, although not demonstrated in a clinical trial as of yet, animal studies of other influenza viruses indicate beneficial properties of anti-tumor necrosis factors [26]. Additional research is needed to confirm and elaborate a causal relationship between immunosuppressive therapies and COVID-19 before they can be recommended as treatments for COVID-19.

Our finding that suspending immunosuppressive therapies leads to a significant deterioration of the disease course of COVID-19 provides further evidence for the beneficial role of these therapies during COVID-19. This should be borne in mind by the rheumatologists, dermatologists, and gastroenterologists asked by their patients with IMIDs about the implications of COVID-19 for their immunosuppressive therapies. Also of note is that a worsening of IMID activity following withdrawal of immunosuppressive therapies might not manifest immediately due to the pharmacokinetics of the drugs [27]. As the current guidelines for use of immunosuppressive therapies during the COVID-19 pandemic are based on limited evidence [28–30], we suggest reconsidering withdrawing these therapies, despite the fact that the mechanism behind the observation has yet to be fully understood.

Our results suggest that there is no increased susceptibility to COVID-19 among patients with IMIDs and this is in agreement with the current literature [8,21]. Nonetheless, these results might to some extent reflect a heightened vigilance among our patients, who are categorized as high-risk by the Danish government and are advised to practice extreme caution through social distancing and personal hygiene in order to limit their risk of contracting COVID-19. Furthermore, and as in other countries, while Denmark has aimed to contain the spread of the coronavirus since January 15th, 2020, the Danish Health Authority initially recommended laboratory testing only of symptomatic patients. It is only since May 18th, 2020 that all Danish residents were offered free testing for COVID-19 without the need for a physician to order the test and regardless of a clinical suspicion of COVID-19. However, other factors such as a higher testing rate might be at play, which we observed among patients with IMIDs, which increases probability of detecting patients with COVID-19.

Despite no increased occurrence in our cohort, we observed higher rates of COVID-19-related hospitalization and mortality than in the background population, which is in line with the most extensive study to date, the COVID-19 Global Rheumatology Alliance (C19-GRA), of 600 patients with rheumatic IMIDs, which found rates of COVID-19-related hospitalization and mortality of 46% and 9%, respectively [31]. Furthermore, the largest registry of gastrointestinal IMIDs to date, Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD), found hospitalization and mortality rates of 31% and 3%, respectively, from 525 cases [22]. As current guidelines regarding COVID-19 hospitalization in Denmark do not support hospitalization of patients merely due to presence of IMIDs, the increased hospitalization rate is likely to represent severe COVID-19 cases [32]. However, the discrepancy between our observation of an increased mortality among patients with rheumatic IMIDs and fewer hospitalizations among patients with dermatological IMIDs compared to other studies might be due to differing study designs and reporting bias, as the C19-GRA and SECURE-IBD registries included patients from many countries, requiring a manual report, while our study is population-based. Furthermore, the increased mortality rate among patients with COVID-19 and IMIDs, especially those with rheumatological IMIDs, might be attributed to their age and comorbidities, as suggested by the regression analysis.

The present study has several strengths. First, this is the first large

population-based study of patients with IMIDs and COVID-19, all with RT-PCR-validated diagnoses of the latter. The inclusion of all patients tested for COVID-19 regardless of their test result, presence of IMIDs or treatment with immunosuppressive therapies, ensured the elimination of geographical and reporting bias, which was further reinforced through a high global test rate and a uniform registration of all COVID-19 tests in the same system. Secondly, there are currently no large-scale published reports of COVID-19 among patients with IMIDs and the role of immunosuppressive therapies; as such, this study works toward remedying that blind spot. Nevertheless, some limitations to the study must be borne in mind. A population-based study with a larger absolute number of patients undergoing immunosuppressive therapies is needed in order to clarify the role of specific immunosuppressants as predictive factors for COVID-19 outcomes, which also needs to be defined in a clinical trial. However, the guidelines for treating patients with COVID-19 in Denmark are centrally regulated by the Danish Health Authorities which ensures uniform clinical determination for COVID-19 related hospitalization. Furthermore, we were unable to adjust our results according to the viral loads, elimination half-time of immunosuppressants, socioeconomic and ethnical characteristics.

5. Conclusion

In conclusion, the epidemiological data presented here suggest that while the occurrence of COVID-19 is comparable among patients with IMIDs and in the general population, the former often experience a more severe disease course, leading to higher rates of hospitalization and death. In addition, our results show a detrimental effect of systemic steroids and the suspension of immunosuppressive therapies on patients with COVID-19 and IMIDs, yet also indicate that azathioprine and biologic therapies might have beneficial effects. Therefore, in applying our findings this study emphasizes the importance of a careful weighing of the risks and benefits when considering suspending immunosuppressive therapies other than systemic steroids.

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Authors' contributions

Guarantor of the article: JB.

MA and JB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

MA: study concept design, patient inclusion, data extraction, analysis and interpretation of data, and drafting of the manuscript.

OKF, MDW, LKVA, and MZS: data extraction and critical revision of the manuscript.

AE and NBV: contribution of valuable scientific content and critical revision of the manuscript.

JBS, FB, and JB: study concept design, contribution of valuable scientific content, supervision, and critical revision of the manuscript.

All authors approved the final version of the manuscript, including the authorship list. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Transparency declaration: The manuscript's guarantor (JB) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Author contributions using credit roles

Mohamed Attaubi: Conceptualization; Data curation; Formal

analysis; Investigation; Methodology; Project administration; Visualization; Roles/Writing - original draft; Jakob Benedict Seidelin: Conceptualization, Investigation; Methodology; Supervision; Writing - review & editing. Oluf Krautwald Felding: Data curation; Methodology; Writing - review & editing. Mads Damsgaard Wewer: Data curation; Methodology; Writing - review & editing. Laura Kirstine Vinther Arp: Data curation; Methodology; Writing - review & editing. Melek Zahra Sarikaya: Data curation; Methodology; Writing - review & editing. Alexander Egeberg: Methodology; Supervision; Writing - review & editing. Nora Vladimirova: Methodology; Supervision; Writing - review & editing. Flemming Bendtsen: Conceptualization, Investigation; Methodology; Supervision; Writing - review & editing. Johan Burisch: Conceptualization, Investigation; Methodology; Supervision; Validation; Writing - review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

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