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Research Article

Cumulative Incidence and Severity of COVID-19 in Patients with Immune-Mediated Diseases and the Impact of Social Distancing Measures

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ABSTRACT

Background: It is a matter of debate whether patients with Immune-Mediated Diseases (IMD) are at increased risk infection with SARS-Cov-2 and a severe course of disease. The aim of this study was to evaluate the cumulative incidence and severity of COVID-19 among patients with immune-mediated diseases and primary immunodeficiency, taking into account the adherence to social distancing measures.

Methods: A longitudinal cohort study of outpatients of the clinical immunology department of a tertiary medical Centre was conducted, with their household members as control population. Questionnaires regarding COVID-19, severity of disease and adherence to social distancing measures were systematically conducted by telephone. The cumulative incidence was calculated from the beginning of the pandemic until January 29, 2021.

Results: 552 patients (median age 52.4 years (range 18.2-89.0), 61.6% female) with auto-immune/auto-inflammatory diseases or an immunodeficiency and 486 household members (median age 49.8 (range 18.0-88.4) years, 41.8% female) were included. The cumulative incidence of COVID-19 was 8.2% in patients and 9.7% in household members. The hospitalization rate in patients was higher compared to household members (p=0.03). The cumulative incidence of COVID-19 was higher among patients than the general Dutch population (8.2% vs. 5.6%, p<0.001). Adherence to social distancing measures was not associated with lower rates of COVID-19.

Conclusion: The cumulative incidence of COVID-19 was higher among patients with IMD compared to the general population, but similar to their household members, although patients had a more severe course of disease. Adherence to social distancing measures did not appear to influence the cumulative incidence of COVID-19.

Keywords: COVID-19; Severe acute respiratory syndrome coronavirus 2; Autoimmune disease; Autoinflammatory disease; Immunodeficiency; Immunosuppression; Prevention; Incidence

INTRODUCTION

Severe Acute Respiratory Distress Syndrome Coronavirus-2 (COVID-19) has affected over one hundred million people worldwide since 2019 and continues to spread [1]. Next to respiratory and gastrointestinal symptoms directly related to viremia, COVID-19 can cause systemic hyper inflammation which has a high mortality rate [2,3]. Patients with severe COVID-19 are therefore often treated with immunosuppressant's such as dexamethasone, tocilizumab (anti-IL6) and JAK-inhibitors [4,5].

Patients with immune-mediated diseases (IMD) are theoretically at higher risk of a severe course of COVID-19. Firstly, patients who are immune compromised due to immunosuppressive

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therapy or a primary immunodeficiency are at higher risk of a severe course of infections in general [6,7]. Furthermore, COVID-19 could trigger a flare of existent auto-inflammatory diseases. On the other hand, the permanent use of immunosuppressant's in most patients with IMD could play a protective role in COVID-19 induced hyper inflammation [8]. Earlier studies on the incidence of COVID-19 in patients with IMD reported contradictory results. Whereas most studies showed no higher incidence of COVID-19 among patients with IMD [9,10], a recent meta-analysis showed that patients with auto-immune diseases have a slightly increased risk of COVID-19, primarily associated with the use of corticosteroids [11]. Interestingly, the use of immunosuppressive medication had a stronger influence on the risk of COVID-19 than other factors such as age, sex and comorbidities in some studies [11-13]. Regarding the severity of disease, recent reports indicated that patients with auto-immune disease were not more likely to be admitted to a hospital due to COVID-19 but did require transfer to the intensive care unit (ICU) and mechanical ventilation more often when admitted [14]. However, representative control populations were often lacking in previous studies. More importantly, it remains unclear whether a possible effect of preventive measures like social distancing confounded outcomes as this was not investigated. Preliminary results of a recent study show that patients with rheumatic diseases were almost twice as likely to adhere to strict isolation measures in comparison to a healthy control group [15]. Other research shows that patients with IMD showed greater risk-mitigating behavior, causing a lower risk of contracting SARS-CoV-2 and thus a lower risk of adverse outcomes due to COVID-19 [16]. Another factor that influences the risk of COVID-19 are regional differences in the prevalence of SARS-CoV-22 and socio-economic status [17]. Therefore, comparison with the general population could base in several ways, leading to an underestimation of the susceptibility to COVID-19. This stresses the importance of establishing an adequate control group when investigating the incidence of disease. We aimed to investigate the cumulative incidence and severity of COVID-19 in a real-world cohort of outpatients with a broad variety of IMD and compared this with their household members and the general Dutch population. Secondly, we wanted to explore the impact of adherence to social distancing measures on the risk of COVID-19.

METHODS

Study design and participants

This cohort study was performed at the department of internal medicine, division of allergy & clinical immunology at the Erasmus University Medical Centre which is a tertiary medical centre in The Netherlands. Adult patients who attended the department in the year 2020 and were analysed for or suffered from auto-immune disease, auto-inflammatory disease or primary immunodeficiency were eligible for inclusion. These conditions will be summarized by the term Immune-Mediated Diseases (IMD) in this article. The main outcome measure was confirmed SARS-CoV-2 infection. Secondary outcome measures were disease severity and adherence to social distancing measures.

Ethical considerations

This study was approved by the local medical ethical committee and conducted according to the latest Helsinki guidelines. All participants provided informed consent.

Data collection

In the period from 15th of October 2020 until 29th of January 2021, all eligible patients were contacted by phone. Next to demographic characteristics and relevant comorbidities, questionnaires regarding SARS-CoV-2 infection, symptoms, severity and social distancing measures were obtained. Comorbidities that were specifically asked were BMI>25 kg/m^2 cardiovascular disease, diabetes, malignancies, chronic pulmonary disease, liver disease, kidney disease, HIV-infection or transplantation [12,18-21]. See supplementary data for the questionnaires that were used. Questions regarding the quarantine measures were asked for three different periods, based on the restrictions that were advised by the government based on the number of infections in the Netherlands. These periods were: the first wave of the COVID-19 pandemic in the Netherlands (1st of March–1st of June), the summer period (1st of June–28th of September) and the remain of the study period (28th of September – date of interview). The same questions were asked for their household member's ≥ 18 years old.

Patients were asked to contact the research team if they tested positive after the interview date and were then contacted again. Data from the general Dutch population were obtained through the website of the RIVM and CBS on February 2nd, 2021 [22,23].

Statistics and data-analysis

The cumulative incidence of COVID-19 was calculated for each (sub) group, meaning the incidence of disease in the studied period. SPSS version 25 was used for most statistical analyses. Continuous variables were presented as median (range) and categorical variables as number (%). Continuous variables were compared using the Mann-Whitney U test. Differences in groups of unpaired categorical data were analysed using a Fisher's exact test.

For the analysis of the impact of social distancing, the exact Loglin Test package in R version 4.0.4 was used [24]. Prior to statistical analysis, the adherence to social distancing was categorised according to the number of visitors received (0-1 vs. ≥ 2), number of days going outside (0-1 vs. ≥ 2), type of participant (patient or household member), and COVID-19 (positive or negative). Tests were only performed for period 3 due to limited COVID-19 positive patients in period 1 and 2. Exact goodness-of-fit tests were performed with respect to seven hierarchical log-linear models. The level of significance was set to α=0.05.

RESULTS

Study population

Between October 15th 2020 and January 29th 2021, 660 patients from the clinical immunology department were contacted for participation in the study. In total, 552 patients and 486 adult household members were included (Figure 1). Reasons for declining participation were lack of time, lack of interest and inability to speak Dutch or English. The basic characteristics of all participants are summarized in Table 1. Patients were slightly older than household members, and more patients were female than household members (61% vs. 41% respectively, p<0.001). A minority of 4.1% of household members had immune mediated diseases including rheumatoid arthritis, sarcoidosis, Graves or Hashimoto's disease, psoriasis, vasculitis, multiple sclerosis, immunodeficiency and inflammatory bowel disease. The prevalence of comorbidities was lower in household members compared to patients (33% vs. 76.1%, respectively, p<0.01).

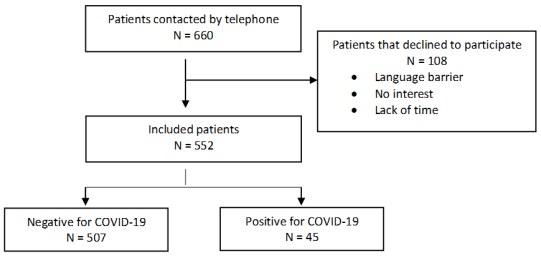

Figure 1: Flowchart of the inclusion process.

Characteristics	Patients n=552 (%)	Household n=486 (%)	p-value
Age (years), median (range)	52.4 (18.2-89.0)	49.8 (18.0-88.4)	0.003
Gender: Female	340(61.6)	203(41.8)	<0.001
Diagnosis	552(100)	20(4.1)	<0.001
Behçet's disease	123(22.3)	0(0)	
Primary immunodeficiency	84(15.2)	2(0.4)	
Sarcoidosis	65(11.8)	3(0.6)	
Vasculitis	53(9.6)	1(0.2)	
Sjögren's disease	47(8.5)	0(0)	
Uveitis	40(7.2)	0(0)	
SLE	28(5.1)	0(0)	
Systemic sclerosis	24(4.3)	0(0)	
Rheumatoid arthritis, polymyalgia rheumatica, SpA, MCTD, arthritis psoriatica	18(3.3)	8(1.6)	
Myositis/anti-synthetasis syndrome	15(2.7)	0(0)	
Lymphoproliferative diseases	14(2.5)	0(0)	
FMF	12(2.2)	0(0)	
Scleritis	5(0.9)	0(0)	
Amyloidosis	3(0.5)	0(0)	
Other auto-inflammatory syndromes	25(4.5)	0(0)	
Other medication related reactions	2(0.4)	0(0)	
Other auto-immune diseases	9(1.6)	7(1.4)	
No classified diagnosis	26(4.7)	0(0)	
Any comorbidities	420(76.1)	160(33.0)**	<0.001
Overweight (BMI>25 kg/m^2)	223(40.4)	18(3.7)	<0.001
Cardiovascular disease or hypertension	144(26.1)	73(15.1)	<0.001
Diabetes (type 1 or 2)	46(8.3)	19(3.9)	0.004
Malignancy	14(2.5)	11(2.3)	0.841
Kidney disease/ failure	16(2.9)	1(0.2)	<0.001
Chronic lung disease/ asthma/COPD	83(15.0)	26(5.4)	<0.001
Liver disease	16(2.9)	1(0.2)	<0.001

Transplantation	2(0.4)	1(0.2)	1
(Other) auto-immune disease treated elsewhere	35(6.3)	20(4.1)	NA
Other comorbidities	195(35.3)	36(7.4)	<0.001
Any immunosuppressant use	465(84.2)	23(4.7)**	<0.001
Topical steroids	130(23.6)		
Glucocorticoids	129(23.4)		
Conventional DMARDs	182(33.0)		
Rituximab	31(5.6)		
Anti-TNF	103(18.7)		
Interleukin antagonist	36(6.5)		
Targeted DMARDs and other biologicals	14(2.5)		
Immunoglobulins	63(11.4)		
Other	73(13.2)		

Abbreviations: IMD: Immune Mediated Disease; SLE: Systemic Lupus Erythematosus; SpA: Spondylo Arthritis; MCTD: Mixed Connective Tissue Disease; FMF: Familial Mediterranean Fever; COPD : Chronic Obstructive Pulmonary Disease; MCAS: Mast Cell Activation Syndrome; NA: Not Applicable

Note: *Data on comorbidities and immune modulating medication use were missing of 1 household member. Of note, some patients had multiple diagnoses, had multiple comorbidities and some patients used multiple immunosuppressant medication.

Table 1: Clinical characteristics of patients in the IMD cohort and their household members.

Vasculitis included eGPA/GPA/MPA, Giant cell arteritis, large and small vessel vasculitis, arteritis temporalis, IgA vasculitis, ANCA-associated vasculitis, urticarial vasculitis, cerebral vasculitis and polyarthritis nodosa. Uveitis includes Birdshot uveitis, APMPPE, AZOOR and chorioretinopathy. Lymphoproliferative diseases included Langerhanscell histiocytosis, IgG4 related diseases, Castleman disease, Clippers disease, Kimura syndrome and generalised lymphoproliferative disease. No classified diagnosis means patients have evidence of an underlying IMID disease but are not diagnosed yet. Other auto-immune diseases included less frequent diagnoses as auto-immune hepatitis, antiphospholipid syndrome, cicatricial pemphigoid, IgA dermatosis, carcinoma associated retinopathy and hyper eosinophilic syndrome. Other auto-inflammatory diseases included Sweet syndrome, relapsing polychondritis, cryopyrin-associated periodic syndrome, still's disease, complex regional pain syndrome, Schnitzler's syndrome, recurrent pericarditis/Dressler's syndrome and sarcoid inflammation after malignancy.

Cardiovascular diseases included heart failure, valve leaks, recent myocardial infarction, hypercholesterolemia, and hypertension. Pulmonary disease included interstitial lung disease, asthma, chronic obstructive pulmonary disease and obstructive sleep apnea. Liver diseases include hepatitis, portal hypertension, Budd-Chiari syndrome, liver cirrhosis or fibrosis, hepatoportal sclerosis and (non-alcoholic) steatosis. Transplantation included lung transplantation, kidney transplantation and (recent) stem cell transplantation. Other auto-immune diseases were auto-immune diseases for which the patient was not treated at the department of immunology in the Erasmus MC and included rheumatoid arthritis, spondylarthritis, sarcoidosis, inflammatory bowel disease, multiple sclerosis, coeliac disease, psoriasis, Hashimoto's disease and Graves' disease. Other comorbidities were (chronic) underlying medical conditions that were not covered by the aforementioned groups and not particularly increase the risk of a severe COVID-19 infection. The most common comorbidities in this group were eczema and thyroid dysfunction.

Glucocorticoids that were used included prednisone, hydrocortisone and dexamethasone. Conventional DMARDs include methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, hydroxychloroquine, thalidomide, tacrolimus and sulfasalazine. Anti-TNF medication that was used includes adalimumab, infliximab and golimumab. Interleukin antagonist medication that was used was anakinra, guselkumab, dupilumab, tocilizumab, canakinumab, secukinumab and ustekinumab. Targeted DMARDs and other biologicals included omalizumab, mepolizumab, belimumab, apremilast, tofacitinib, dimethyl fumarate and baricitinib. Other medication included dapson, colchicine, leniolisib and imatinib.

Incidence of COVID-19

As of January 29th, 2021, 45 patients had been tested positive for COVID-19. The incidence of COVID-19 between the start of the pandemic and the end of January 2020 was 8.2% among patients and 9.7% among household members, which was not different (p=0.44). Data from the general Dutch population indicated an incidence of 5.6% in the same time period [22,23]. The cumulative incidence of COVID-19 was thus higher in the cohort of IMD patients as well as their household members compared with the general population (p<0.001 for both groups).

Manifestation and outcomes of COVID-19 infection

Clinical characteristics and outcomes of COVID-19 positive patients and household members are displayed in Table 2. Of the 45 patients who had COVID-19 during the study period, 31

(68.9%) contracted SARS-CoV-2 in the third period studied (28 September – January 2021). Forty patients were tested positive by nasopharyngeal swab and 5 had detectable antibodies without being tested via nasopharyngeal swab due to scarcity of tests in the first months of the pandemic. Two patients were asymptomatic. One was tested positive by screening before attending hospital appointments, and in the other patient, a screening serological test performed for source investigation was positive.

Most frequently mentioned symptoms among patients were anosmia (77.8%), rhinitis (68.9%) and fever (62.2%), whereas among household members cough (63.8%), anosmia (59.6%) and fever (51.1%) were mentioned most frequently. There was no difference in disease duration between patients and household members; although a wide range in disease duration was reported. Patients more often required treatment for COVID-19 than their household members (20 versus 5 respectively, p<0.001). All patients that received treatment for COVID-19 were using immune modulating medication prior to infection. Nine of these patients temporarily discontinued immune modulating medication because of COVID-19.

Patients were more often hospitalised compared to household members (22.2% versus 6.4%, respectively) (p=0.04). No mortality was reported in both groups. Hospitalised patients were older (57.9(22.4-78.9)) compared to the non-hospitalised patients in the IMD cohort (39.7(18.3-71.7)), p=0.02. There was no difference between the use of immune modulating medication (p=0.42) or the presence of comorbidities (p=0.57) between hospitalised and non-hospitalised patients with COVID-19, possibly due to the small subgroup sizes. Eight out of ten hospitalised patients needed oxygen support. One patient was admitted to the ICU. This patient suffered from Behçet's disease but had an underlying malignancy as well. Of note, this case was also part of a previous, smaller case series [9]. Among household members, three hospital admissions were reported (6.4%), one of whom was already admitted to the hospital for other reasons and contracted SARS-CoV-2 there. None of the household members were admitted to the ICU.

	Patients (n=45) (%)	**Household (n=47)** (%)	**p-value**
Age (years), median (range)	46.8 (18.3-78.9)	43.9 (18.0-82.5)*	0.417
Gender: female	23(51.1)	24(51.1)	1
Diagnosis			
IMID	44(97.8)	3(6.4)	<0.001
No classified diagnosis	1(2.2)		
Any comorbidity	35(77.8)	13(27.7)	<0.001
Overweight (BMI>25 kg/m^2)	18(40.0)	3(6.4)	<0.001
Cardiovascular disease or hypertension	8(17.8)	2(4.3)	0.048
Diabetes	3(6.7)	2(4.3)	0.674
Malignancy	1(2.2)	0(0)	0.489
Kidney disease/ failure	1(2.2)	0(0)	0.489
Chronic lung disease/ asthma/COPD	4(8.9)	2(4.3)	0.43
Other comorbidities	13(28.9)	2(4.3)	0.002
Immunosuppressant use	40(88.9)	2(4.3)	<0.001
Topical steroids only	1(2.2)		
Glucocorticoids only	5(11.1)		
Glucocorticoids and one or more cDMARDs	4(8.9)		
Glucocorticoids and a targeted DMARD or biological	1(2.2)		
Glucocorticoids and a cDMARD and biological	1(2.2)		
One or more cDMARDs	10(22.2)		
Targeted DMARDs or biological	7(15.6)		
cDMARDs and biological	1(2.2)		
Immunoglobulins only	3(6.7)		
Immunoglobulins with (topical steroids) or biological	3(2.2)		

Other	4(8.9)		
COVID-19 infection			
Period 1	7(15.6)	6(12.8)	0.77
Period 2	7(15.6)	6(12.8)	0.77
Period 3	31(68.9)	35(74.5)	0.65
Symptoms			
No symptoms	1(2.2)	3(6.4)	0.617
1 symptom	3(6.7)	4(8.5)	1
2-5 symptoms	15(33.3)	27(57.4)	0.023
≥ 6 symptoms	26(57.8)	13(27.7)	0.006
Disease duration (days)	13.0 (0.0-261.0)	10.0 (0.0-260.0)**	0.224
Treatment of COVID	20(44.4)	5(10.6)	<0.001
Admission to hospital	10(22.2)	3(6.4)	0.038
Duration of hospital stay (days)	9.5 (3.0-24.0)	21.0 (12.0-31.0)	0.112
Admission to ICU	1(2.2)	0(0)	0.489
Duration of ICU stay (days)	1	NA	NA
Mortality	0	0	NA

Abbreviations: IMD : Immune Mediated Disease; cDMARDS : conventional DMARDs; ICU: Intensive Care Unit; NA: Not Applicable.

Note: *of 2 household members data about age were missing; **of 1 household member data about disease duration was unclear

Table 2: Clinical characteristics and outcomes of patients and their household members infected with COVID-19.

Adherence to social distancing measures

The statistical analysis on the impact of adherence to social distancing measures was only performed for the third period (28th of September 2020 until date of interview, maximum of 29th of January 2021) due to the limited number of patients that tested positive in the first and second period. Two social distancing measures were analysed: The number of days going outside per week and the number of visitors received at home. Both measures were categorized in 4 categories. For days outside, these were never, 1-2x/week, 3-6x/week and daily. For the number of visitors, these were none, <3, 3-6, >6 visitors per day. Frequently mentioned reasons to go outside were for running errands, work and taking a stroll.

When comparing patients with household members, patients stayed in more than their household members (53.1% went outside on a daily basis compared with 62.4% of the household members, p=0.012).

See Figure 2. Only few patients were very strict: Of the 552 patients, only 3.8% of patients and 2.1% of household members never went outside in the third period of the pandemic (p=0.778).

When comparing COVID positive versus COVID negative participants, there was no difference in the number of days going outside (p=0.993) nor the number of visitors received (p=0.682) in Table 3.

Patients without any household members did not get COVID less often than patients with household members (8.4% versus 8.1% respectively, p=0.861).

To better identify potential associations between the two different social adherence measures without creating multiple testing bias, log-linear analysis was also performed.
However, there was no association between the adherence to social distancing measures and the cumulative incidence of COVID-19 positivity.

		COVID-negative count	COVID-positive count
Number of visitors received in period 3	No visitors	247	23
	Less than 3	640	61
	3-6 people	55	8
Number of days outside in period 3	More than 6	3	0
	Never	28	3
	1-2 per week	148	15
	3-6 per week	226	21
	Daily	543	53

Table 3: Adherence to social distancing measures by COVID positive and negative patients.

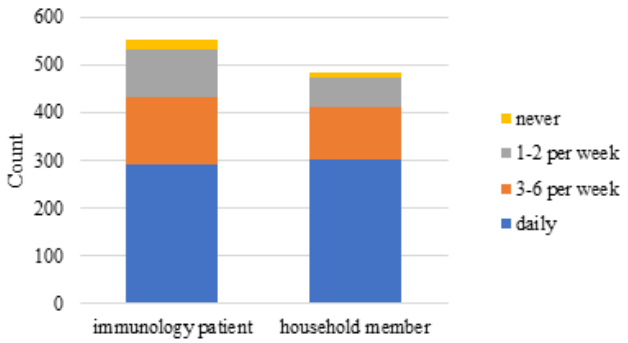

Figure 2: Average days going outside per week during pandemic (period 3).

Primary immunodeficiency

Separate analyses on the cumulative incidence and course of COVID-19 between PID patients and patients suffering from an autoimmune or auto-inflammatory disease were performed, because of the great pathophysiological differences between these two disease categories. Out of a total of 84 PID patients, eight (9.5%) had COVID-19 at some point in time, which was similar to the participants with autoimmune/auto-inflammatory diseases (cumulative incidence 7.9%, p=0.664). However, the cumulative incidence of COVID-19 among patients with a PID was higher compared with the general Dutch population (p<0.001). Among the eight PID patients that suffered from COVID-19, five were male and three were female. The median age was 50.8 years (range 19.5-80.6). Seven patients (87.5%) had other comorbidities. Four patients were treated with medication for COVID-19. Two patients were admitted to the hospital, one for 8 days and one for 17 days. No PID patients were admitted to the ICU. In the autoimmune and autoinflammatory group, 8 out of 37 COVID-19 positive patients were admitted to the hospital, which was not different compared with the PID group (p=0.588). Regarding social distancing measures, PID patients went outside more often in comparison to patients that suffer from autoimmune or autoinflammatory diseases (p=0.006). There were no differences in the number of visitors received between these groups.

DISCUSSION

In this comparative longitudinal cohort study, we investigated the cumulative incidence and severity of COVID-19 in patients with IMD. The incidence of COVID-19 was higher among patients with IMD compared to the general Dutch population. Although the cumulative incidence of COVID-19 was similar among patients compared to their household members, patients had a higher risk of severe course of disease and admittance to the hospital.

Since the cumulative incidence of COVID-19 between IMD patients and household members was similar, the increased cumulative incidence compared to the general population might have other reasons besides immunological vulnerability. Patients might be more pro-active in testing for SARS-CoV-2 than healthy persons. In addition, patients were often required to test before visiting the outpatient clinic. Although testing has become available for symptomatic persons since June 1st, 2020 and for asymptomatic persons since December 1st, 2020 in the Netherlands, underreporting in the general Dutch population could be an explanation for the relatively lower proportion of infections compared to the study cohort. Furthermore, patients might be more vigilant regarding COVID-19 symptoms and therefore have a lower threshold for testing.

Comparison of a specific group of patients to the general population induces a risk for several biases. Although never specifically studied, it is presumed that patients with IMD might be more poised to adhere to social distancing measures, putting themselves at lower risk for SARS-CoV-2 infection. Surprisingly, adherence to social distancing measures was not directly associated with the incidence of COVID-19 in the current study. A possible explanation could be that the questions used were not precise enough. It was questioned how many visitors patients received at once, however the duration of contact and the frequency was not part of this question. Another explanation could be that independent of the duration of exposure to COVID-19 some are more vulnerable than others to become infected with COVID-19. The presence of other factors than IMD, social distancing measures and relevant comorbidities could influence the risk of COVID-19 such as regional differences in SARS-Cov2 prevalence or socio-economic status [17]. Although our study did not include such data, household members were used as controls to minimize the influence of environmental or social factors.

Although the total amount of cases of COVID-19 was similar between patients and household members, patients experienced more symptoms, received treatment more often and were admitted to the hospital more often than household members. Surprisingly, there was no difference in the use of immunosuppressive medication between hospitalized and non-hospitalized patients with COVID-19. Other studies did not report an association between chronic use of immunosuppressive medication in general and clinical outcomes of COVID-19 infection either, although this appears to be differ between drug categories [25,26]. The use of biologicals prior to COVID-19 may have a protective effect of severe course of disease, whereas the use of DMARDS or multidrug therapy increased the risk of admission [27].

When further evaluating risk factors for a severe course of disease, it must be taken into account that the patients in our study differed from their household members regarding some relevant baseline characteristics: Patients were more often female and had more relevant comorbidities compared to their household members (76.1% vs. 33%, respectively). It is well-known that patients with auto-immune or auto-inflammatory diseases have a higher risk of cardiovascular disease, and weight gain is often caused by inactivity and corticosteroid use [28,29]. Other studies also reported increased rates of hospital admissions among patients with IMD and COVID-19 to be partly caused by a higher number of other comorbidities [30-32]. Furthermore, IMD patients had a higher risk of venous thromboembolism and renal failure [31]. It can be postulated that patients with IMD are at higher risk for a severe course of COVID-19 due to their immunological status, but other factors,

mainly comorbidities such as diabetes, cardiovascular disease and obesity, also play a major role in determining one's individual risk.

There are some relevant limitations to this study. Firstly, the questionnaire was obtained mostly retrospectively which could lead to recall bias. Secondly, the many individual characteristics that can all influence the course of COVID-19 are very difficult to identify and correct for in this comparative study. On the contrary, the relatively large cohort size and the comparison with household members were considered to minimize these intra-individual differences. Thirdly, we only considered patients positive for COVID-19 when it was confirmed by PCR test or antibody testing. Accordingly, patients that were asymptomatic during the first wave when testing availability was limited were not identified. However, this limitation also applies for household members, again stressing the importance of this control group to prevent possible biases [33].

CONCLUSION

In conclusion, the cumulative incidence of COVID-19 was similar among patients with IMD compared to their household members. However, both patients and controls showed a higher cumulative incidence of COVID-19 compared to the general population. Adherence to social distancing measures was not directly associated with the incidence of COVID-19. The course of disease was more severe in patients than in household members, and patients more often had relevant comorbidities such as cardiovascular disease and obesity than household members. The combination of the specific IMD and other comorbidities probably determines an individual's risk.

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