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The risk for severe COVID 19 in patients with autoimmune and/or inflammatory diseases: First wave lessons

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Abstract

Data regarding the risk for severe COVID19 in patients with autoimmune or inflammatory diseases are scarce. To estimate the risk of those patients to develop a more severe COVID19 infection All active patients and those with dermatologic and/or rheumatologic autoimmune/inflammatory diseases were identified in a single tertiary center. The charts of those tested positive for COVID19 between 1 March 2020 and 31 May 2020 reviewed including demographics, co-morbidities, and medications. COVID19 outcome of those with dermatologic and/or rheumatologic autoimmune/inflammatory diseases were compared to COVID19 infected matched controls without an autoimmune/inflammatory background. Overall, 974 of 381 268 active patients were tested positive for COVID19, including 35 out of 13 225 with dermatologic and/or rheumatologic autoimmune/inflammatory diseases. No statistically significant difference in severity of COVID19 infection or mortality rate was found. The rate of asymptomatic, mild, moderate, severe/critical and fatal COVID19 infection was 11.4%, 37.1%, 22.8%, 11.4%, and 17.1%, respectively, for the patients with autoimmune diseases and 17.8%, 45.8%, 10.9%, 6.8%, and 18.4%, respectively for the controls . Patients with autoimmune/inflammatory diseases seem not to develop a more severe COVID19 infection than controls.

KEYWORDS
autoimmune, corona virus 19, COVID19, inflammatory disease

1 | INTRODUCTION

The COVID-19 pandemic, caused by the SARS CoV2 virus, is an ongoing worldwide medical challenge. The lack of specific treatment or vaccine has led to epidemiological research efforts in order to characterize patients at risk for developing severe infection.[1,2] So far, the established risk groups for higher severity and mortality rate of COVID-19 infection are elderly people and those with underlying medical co-morbidities such as hypertension and obesity.[3,4]

Patients with autoimmune and/or inflammatory diseases (AID) are a group of special interest regarding their risk for severe COVID19 as they are considered at a potential increased risk of infection because of their underlying disease coupled with the immunosuppressive therapy needed to control it.[5] On the other hand, some immunomodulatory drugs used to treat different autoimmune diseases are being studied as treatments for severe COVID19 infection[6] rendering patients on these therapies protected, in theory at least, from developing the "cytokine storm" associated with this virus. Thus, human CoV infections might have a dual influence: while they may trigger an immune response leading to viral clearance in the early stages of the infection, at later stage the secondary immune response may be exaggerated ("cytokine storm"), leading to pneumonitis, acute respiratory distress syndrome, organ failure, and potentially death.[7]

The current data regarding the risk of patients with AID to contract the SARS CoV2 virus and/or develop severe disease are insufficient and guidelines on treating patients with AID[8,9] are based on

limited experience from current and past pandemics alongside theoretical assumptions. Autoimmunity and/or immune-suppression has not, to date, been implicated as a risk factor for contracting SARS CoV2[10] or for severer COVID19 infection.[1] The largest series to date includes 600 patients from multiple countries with autoimmune rheumatic diseases[11] have shown that the majority of those patients recover from COVID-19. In this series older age, comorbidities and prednisone use ≥10 mg/day were associated with higher odds of hospitalization. On the other hand, anti-TNFα treatment was associated with reduced odds of hospitalization suggesting in fact that anti-cytokine therapy may have a protective role from severe COVID-19 infection.

In the current study, we describe a cohort of patients with AID from a single institution and compare those of them infected with SARS CoV2 to patients without AID, infected during the same period.

2 | MATERIALS AND METHODS

This was a single center study performed at the Sheba Medical Center—a 1400 bed tertiary hospital located in central Israel, where 381 268 patients were actively treated and/or followed up over the last 2 years. A subset of patients with a diagnosis of dermatologic and/or rheumatologic AID, commonly treated with immunosuppressive medications were defined. Their data collected from the computerized patients' files using MDClone, a data extraction and synthetization platform that provides patient level data around an index event (http://www.mdclone.com). All patients with a diagnosis of infection with SARS CoV2 between 1 March 2020 and 31 May 2020 (the first wave of pandemic period in Israel) were identified and data regarding age and comorbidities was extracted. The infected cases diagnosed in either the community or the hospital, whether in ambulatory, emergency room, or in ward settings. The computerized charts of patients with SARS CoV2 infection carrying a diagnosis of an AID were reviewed by the investigators and only cases with a verified AID who had at least one out- or inpatient visit, prior to the diagnosis of the SARS CoV2 infection, were included in the assessment. Data regarding age, sex, AID, immunosuppressive therapy prior to the SARS CoV2 infection and associated comorbidities as well as severity and outcome of COVID19 infection recorded. Those cases were matched to diagnosed control patients with COVID19 infection but no AID, by date of infection, age and gender. The computerized charts of the controls similarly were reviewed.

COVID19 infection diagnosed according to a positive PCR test by oral or nasal swab and scored as mild—lack of any mentioned below; moderate—presence of the pulmonary infiltrate; severe—breath rate over 30/minute or O_2 saturation < 93% or Pao_2/FIO_2 < 300 or pulmonary infiltrate progression to more than 50% of the lungs in 24-48 hours; critical—need for ventilation and/or vasopressors and/or ECMO support.

Institutional review board approval was obtained and patient consent was waived due to the non-interventional nature of the study.

Quantitative and parametric parameters were compared using a two-tailed *t* test and Fisher's exact test, respectively. To assess variables associated with severe COVID19, a multivariate Cox proportional hazards regression model was applied. An exploratory decision

TABLE 1 COVID19 infected patients' baseline characteristics by the presence of autoimmune/inflammatory diseases

Patients' baseline characteristics		Patients with AID n = 35	Patients without AID n = 146	*P*
Mean age	years	59	64	.1
Females	n (%)	17 (48%)	57 (39%)	.34
COVID severity n (%)	Asymptomatic	4 (11.5%)	26 (18%)	.45
	Mild	13 (37%)	67 (46%)	.44
	Moderate	8 (23%)	16 (11%)	.09
	Severe/critical	4 (11.5%)	27 (18%)	.48
	Death	6 (17%)	27 (18%)	1
Common comorbidities n (%)	Hypertension	17 (48.5%)	46 (31.5%)	.07
	Dyslipidemia	3 (8.5%)	44 (30.1%)	.009
	Diabetes	8 (23%)	37 (25%)	.83
	Malignancy	2 (5.7%)	21 (14.4%)	.25
	Ischemic heart disease	5 (14.3%)	19 (13%)	.78
	Arrhythmia	1 (2.8%)	18 (12.3%)	.12
	Obesity	7 (20%)	17 (11.6%)	.26
	Pulmonary disease	0	12 (8.2%)	.12
	Heart failure	0	10 (6.8%)	.21
	Smoking	1 (2.8%)	10 (6.8%)	.69
	CVA	0	9 (6.1%)	.2
	Renal failure	4 (11.43%)	6 (4.1%)	.1

TABLE 2 Characteristics of AID patients with COVID19

Case number	Gender	Age	Autoimmune disease	Low dose glucocorticoids	High dose glucocorticoids	DMARDs	Biological treatment	Comorbidities	COVID severity
1	Male	88	Bullous pemphigoid	yes				DM CABG AF IHD CA of BLADDER monocloncal gammopathy	Fatality
2	Male	77	RA		yes	PLQ		HTN DM	Fatality
3	Male	77	Gout					HTN CRF	Fatality
4	Male	73	Psoriasis					HTN OBESITY	Fatality
5	Male	62	SLE					CRF PVD HTN	Fatality
6	Female	51	Scleroderma			MTX		HTN	Fatality
7	Female	84	Gout					DM	Severe/ Critical
8	Male	78	Vasculitis					OBESITY DM HTN	Severe/ Critical
9	Male	71	Gout						Severe/ Critical
10	Female	62	RA			PLQ, SLZ		IHD	Severe/ Critical
11	Male	82	RA	yes		PLQ, MTX		HTN DM DYSLIPIDEMIA	Moderate
12	Male	68	Gout			Colchicine		OBESITY HTN DYSLIPIDEMIA IHD	Moderate
13	Male	68	Psoriasis					HTN DM DYSLIPIDEMIA	Moderate
14	Male	62	Myastenia gravis	yes				HTN	Moderate
15	Female	59	RA	yes		MTX			Moderate
16	Male	55	Psoriatic arthritis				Secukinumab		Moderate
17	Male	44	Fibromyalgia						Moderate
18	female	28	Autoimmune hepatitis					CONGENITAL HEART DISEASE	Moderate
19	Female	77	Unspecified arthritis					RHD CRF HTN	Mild
20	Female	75	Sarcoidosis					IHD OBESITY HTN DM HBV	Mild
21	Male	74	Gout						Mild
22	Male	70	SLE					OBESITY HTN	Mild
23	Female	60	RA						Mild
24	Male	56	Psoriasis					HTN SMOKER	Mild
25	Female	56	Hypersensitivity pneumonitis			Azathioprine			Mild
26	Female	49	RA					DM HTN OBESITY	Mild
27	Female	44	Scleritis		yes	MTX		HTN	Mild
28	Male	40	Pemphigus vulgaris	yes				OBESITY	Mild

(Continues)

TABLE 2 (Continued)

Case number	Gender	Age	Autoimmune disease	Low dose glucocorticoids	High dose glucocorticoids	DMARDs	Biological treatment	Comorbidities	COVID severity
29	Female	40	Multiple sclerosis			Fingolimod			Mild
30	Male	25	Atopic dermatitis					mild	Mild
31	Female	24	Vasculitis		yes	MTX	Tocilizumab	mild	Mild
32	Female	56	Unspecified arthritis						Asymptomatic
33	Female	52	SLE	yes		PLQ		APLA	Asymptomatic
34	Female	35	Sjorgen						Asymptomatic
35	Female	28	Atopic dermatitis					CRF s/p DIC d/t AMNIOTIC EMBOLISM	Asymptomatic

Note: Low dose glucocorticoids <10 mg prednisone. High dose glucocorticoids ≥10 mg prednisone.

Abbreviations: CABG, coronary artery bypass graft; DM, diabetes mellitus; PLQ, hydroxychloroquine; MTX, methotrexate; SLZ, sulfasalazine. Vascular disease: AF, atrial fibrillation; CA, carcinoma; CRF, chronic renal failure; DIC, disseminated intravascular coagulation; HBV, hepatitis B virus; HTN, hypertension; IHD, ischemic heart disease; PVD, peripheral; RA, rheumatoid arthritis; RHD, rheumatic heart disease; SLE, systemic lupus erythematosus.

tree analysis was used to assess the effect of different comorbidities, age and gender on the risk for severe COVID19 infection.[12]

3 | RESULTS

Of note, 13 225 of 381 268 (3.4%) active patients in the Sheba Medical Center database since 1 June 2018 had a diagnosis of rheumatologic and/or dermatologic AID, as detailed in Appendix, along the list of the immunomodulatory medications in the whole population cohort (6974 on DMARD's; 7974 on systemic steroids and/or 1752 on biologics/small molecules). Overall, 974 patients with a diagnosis of COVID19 infection were identified by our computerized database between 1 March 2020 and 31 May 2020, including 35 (3.6%) with an associated AID and were matched by age and gender to146 non-AID infected controls. According to our policy, at that time, the associated immunomodulatory medications were stopped or dose reduced (maximally possible) following COVID19 infection and started again 2 weeks after laboratory recovery.

As shown in Table 1, the comparison COVID19 infected groups included 35 AID patients (48% females) and 146 controls (39% females), with a mean age of 58.6 ± 17.8 and 63.6 ± 16.4, respectively (P = .1). There was no difference in the frequency of associated comorbidities in both groups except for dyslipidemia, more common among the controls (30.1 vs 8.5% for controls and study patients, respectively, P = .009). The majority of patients in both groups did not have severe disease. We did not find a statistically significant difference in the severity of COVID19 infection between the patients with AID and the control group, while the odds ratio for severe/critical or fatal COVID19 in AID patients was 1.17 (IQR 0.51-2.68). Table 2 shows the full clinical data of the patients with AID in our cohort who contracted SARS CoV2 including their age, diagnosis, immunomodulatory treatments and COVID19 severity. The most common infected AID was RA (six patients), followed by gout (five patients), psoriasis and SLE (three patients each). Of note, 6913, 1752, and 7974 of our general cohort patients, had a recent use of DMARD's, biologics/small molecules and systemic steroids, respectively. Among the COVID19 infected, three patients were on prednisone use ≥10 mg/day, one of them died while the other two had mild disease. Eleven patients were treated with DMARDs and two with biologics (tocilizumab and secukinumab). The number of patients treated with each medication was too low to reach statistical significance vs the control group.

Table 3 shows the odds ratio of each comorbid condition for severe/critical or fatal COVID19 in the univariate and multivariate analyses. Multivariate analysis using cox regression analysis in order to define the effect of age, gender and different comorbidities on the risk for severe/critical or fatal COVID19 infection found that only older age (OR 3.5, 1.12-11.41), an history of malignancy (OR 3.58, 1.13-11.76) or pulmonary disease (OR 5.59, 1.21-25.66) had a statistically significant effect on COVID19 severity. Autoimmune disease did not have a statistically significant effect on COVID19 severity (OR 1.95, 0.58-6.5).

Using a decision tree model we found that the variable contributing most for the prediction of severe/critical or fatal COVID19

TABLE 3 Odds ratios for severe, critical or fatal COVID19 according to risk factors

	Univariate analysis		Cox multivariate analysis	
Variable	**OR**	**95% CI**	**OR**	**95% CI**
Female gender	0.86	0.43-1.708	0.93	0.37-2.27
AID	1.17	0.51–2.68	1.95	0.58–6.5
Hypertension	0.92	0.46-1.84	0.57	0.18-1.67
Dyslipidemia	1.2	0.55-2.61	0.57	0.19-1.55
Diabetes	0.53	0.25-1.11	0.88	0.30-2.48
Malignancy[a,b]	3.83	1.55-9.43	3.58	1.13-11.76
IHD	0.53	0.21-1.31	0.68	0.17-2.48
Arrhythmia	0.73	0.26-2.05	0.54	0.11-2.25
Obesity	0.83	0.32-2.14	2.23	0.63-7.56
Pulmonary disease[b]	0.46	0.13-1.53	5.59	1.18-26.18
Heart failure	0.8	0.2-3.26	2.35	0.24-18.64
Smoking	1.62	0.33-7.78	0.49	0.05-3.03
CVA	2.92	0.35-23.99	0.36	0.01-3.12
Renal failure older age[a,b]	0.32	0.08-1.17	1.32 3.5	0.20-8.02 1.12-11.41

[a]Statistically significant in univariate analysis.
[b]Statistically significant in multivariate analysis.

infection was age, contributing almost 60% to the prediction in our cohort, followed by diabetes, malignancy and obesity, with other variables contributing less than 5% each. When using different subgroups created by the decision tree model to calculate the OR for severe/critical or fatal COVID19 according to the presence or absence of an AID, we did not find a statistically significant increased risk in patients with an AID.

4 | DISCUSSION

The established risk groups for higher severity and mortality rate of COVID-19 infection are elderly people and those with underlying medical co-morbidities.[3,4] Most rheumatologic and several cutaneous immune-mediated diseases, are treated with biologic and non-biologic immunosuppressive and immune-modulatory drugs increasing the risk for various infectious diseases.[5] Thus, at least theoretically, those patients are at higher risk of infection and/or worse course of the COVI19 disease. In addition, AID patients have a higher incidence of comorbidities, for example, metabolic syndrome and ischemic heart disease putting them at increased risk for severe infection.[13,14] Recommendations from dermatology and rheumatology societies so far[8,9,15-17] mostly suggested COVID-19 infected patients to discontinue or postpone immunosuppressive or biologic therapy, while the decision to stop or withhold treatment in the uninfected, was left to the treating physician judgment. Those recommendations based on limited experience from current and past pandemics, and mostly on intuition taking into account the mechanism of immune-modulatory therapy with a possible dual influence.[7]

Our study suggests that having an AID per se is not, by itself, a risk factor for acquiring COVID19 infection since only 35 of 13 225 (0.3%) active AID patients in our institution were diagnosed. It is true, that asymptomatic and mild cases might have been missed. However, the latter would have no clinical, but only epidemiological significance. It is also possible (though unlikely due to the local medical system structure) that a small number of our infected patients were diagnosed outside our center. Similarly, the AID patients could possibly be more precocious, compared to general population, thus having a lower chance to be infected and/or to acquire a smaller amount of COVID inoculum leading possibly to a milder disease. More importantly, those infected, do not develop more severe disease, whereas advanced age, previous pulmonary disease or malignancy are significant risk factors.

Of note, 6913, 1752 and 7974 of our cohort had a recent use of DMARD's, biologics/small molecules and systemic steroids, respectively. So far, little is known about the safety of different immunosuppressive treatments used for AIDs during the COVID19 pandemic. Based on our experience and until proven otherwise, we suggest that immunosuppressive treatment for AID should not be unanimously interrupted during the COVID19 pandemic as this may result in excess of disease flares potentially leading to more significant morbidity and mortality than the COVID infection by itself.

Our retrospective nested case control single center study based on a cohort of 381 268 patients including 13 225 with AID, provides reassuring data regarding the risk of a patient with an AID to develop severe COVID19 infection. The advantage of our study is its nested case control design, which enabled us to compare the patients with AID to controls who contracted COVID19 in the same geographic area during the same period. The main limitation (luckily) is the small number of patients with AIDs who were infected with COVID19, a problem which we addressed by the nested case-control design and the multi-variate statistical models. Other limitation included the

heterogeneous nature of AID group, both for the dermatologic and/or rheumatologic diseases, their various activity and severity levels and variability in immunosuppression level of the drugs used, including those suggested as potentially beneficial for COVID19. However, dissecting patients regarding their background diseases (and severity) and concomitant medications (and dosage), would lead to very small groups of those infected.

Further large-scale studies and meta-analyses are needed in order to clarify the risk of patients with AIDs and/or immune-modulatory therapy for severe COVID19.

CONFLICT OF INTEREST

None of the corresponding authors has any conflict of interest or funding sources related to this article.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and been involved in revising it critically and given final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

Data derived from public domain resources.

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APPENDIX

TABLE A1 The cohort patients with an autoimmune/inflammatory diseases and/or chronic immunomodulatory medications

Diagnosis	n	Medications		n
Psoriasis	2526	DMARD's	Methotrexate	1100
Atopic dermatitis	1148		Cyclosporine A/Tacrolimus	875
Bullous diseases[a]	351		Leflunomide	100
Scleroderma	275		Azathioprine	475
Raynaud's only	198		Mycophenolate mofetil	500
Lupus erythematosis	647		Sulfasalazine	275
Dermatomyositis	101		Hydroxychloroquine[d]	850
Rheumatoid arthritis	1275		Colchicine	2800
		Systemic steroids		7974
Gout	1325	Biologics and small molecules	Anti TNF's	775
Reactive arthritis	25		Ustekinumab	50
Ankylosing spondylitis	304		Anti IL17	50
Fibromyalgia	1571		Anti CTLA-4	25
Polymyositis	297		JAK inhibitors	125
MCTD[b] and unspecified	1574		IL-6 inhibitors	175
SICCA syndrome	322		IL-1 inhibitors	275
Behcet's	225		Apremilast	75
FMF[c]	1825		Dupilumab	51
			Omalizumab	100
Sarcoidosis	475		Belimumab	25
Arteritis/vasculitis	575		Rituximab	125

[a]Bullous diseases—pemphigus (n = 226) and bullous pemphigoid (n = 125).
[b]Mixed connective tissue disease.
[c]FMF—familial Mediterranean fever.
[d]Started prior to pandemic.