

REVIEW ARTICLE

Effect of immunosuppressive drugs in immune-mediated inflammatory disease during the coronavirus pandemic

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Abstract

The safety of immunosuppressive treatment in patients with Immune-Mediated Inflammatory Diseases (IMIDs) during the Coronavirus pandemic is questioned and it is utmost important for public health. We searched studies through MEDLINE/EMBASE database, including patient with IMID, undergoing immunosuppressive treatment with a positive diagnosis for SARS-CoV 2. We included 11 studies for the descriptive analysis and 10 studies for the pooled analysis, with a total population of 57 and 53 IMID-affected SARS-CoV-positive patients respectively. Overall no death was reported; 16 patients were hospitalized (30.2%) and only two cases were admitted to Intensive Care Unit (ICU) (3.8%). We found a significant association between the risk of hospitalization and older age (P .03), obesity (P .02), and presence of multi-comorbidity (P .03). No significant association was found between the risk of hospitalization and the use of biological or conventional DMARDs (respectively P .32 and .26), neither when they are used combined (P .85). We found consistent results in the sub-analysis of Psoriasis: 10 patients were hospitalized (31.3%) and only one case was admitted to Intensive Care Unit (ICU) (3.1%) Particular attention should be placed for patients with older age, obesity and multi-comorbidity that are at higher risk of hospitalization.

KEYWORDS

biologic, coronavirus, immune-mediate inflammatory disease, immunosuppressive drugs, psoriasis

1 | INTRODUCTION

Whether patients under biological treatment for dermatologic, rheumatologic, or gastroenterological immune mediated diseases (IMIDs) should stop or continue therapy during Coronavirus pandemic has been a matter of debate.¹ It has been advised that since the rate of respiratory infection during clinical trials with biologics for psoriasis was comparable with placebo and that these drugs should not be withheld.¹ In IBD patients, although, figures suggest that infection rate is low,² fear of a worst outcome in immunosuppressed patients has been put forward.³ Remarkably, in several IMID not undergoing immunosuppressive treatment was detected latent airway inflammation with the technique of fraction exhaled

nitric oxide (FeNO) that may contribute to increase COVID-19 vulnerability synergically with the dysimmunity typical of IMID.⁴⁻⁷ The use of some biological drug has been even suggested to ease the severity of lung disease following the infection.^{8,9} Pooled data on the clinical fate of SARS-CoV2 infected patients under biologicals were not available in literature to have any clue on this new pandemic. Data on the outcome of the same type of patients from first coronavirus pandemic with SARSCoV1 may help to understand how to manage these cases in the current pandemic. For this reason we performed a systematic review on patients with IMIDs treated with biologics or conventional DMARDs that become infected with SARS-CoV2 or SARS-CoV1 and analyzed their clinical outcome.

2 | METHODS/LITERATURE SEARCH

We searched studies from the database PubMed MEDLINE and OVID Embase, using the strategy shown in Table 1.

Two physicians independently (Federica Giuliani and Giulio Gualdi) proceeded to abstracts screening, according to inclusion and exclusion criteria, examined full-text articles to determine eligibility and discussed disagreements to reach consensus. We listed excluded studies and primary reasons for exclusion (Figure 1), then we extracted data from reports. We also check the references of the included studies.

TABLE 1 MEDLINE and EMBASE search strategy

#	Searches
1	Middle east respiratory syndrome coronavirus [mesh]
2	Severe acute respiratory syndrome [mesh]
3	SARS virus [mesh]
4	Betacoronavirus [mesh]
5	COVID-19 [word text]
6	or/1–5
7	Immunosuppressive agents [pharmacological action]
8	Immunosuppression [mesh]
9	Psoriasis [word text]
10	Psoriatic arthritis [word text]
11	Transplants/therapy [mesh]
12	Transplants/transplantation [mesh]
13	biologic [word text]
14	Infliximab/therapeutic use [mesh]
15	Adalimumab/therapeutic use [mesh]
16	Steroids/drug therapy [mesh] OR
17	Steroids/pharmacology [mesh]
18	Steroids/therapeutic use [mesh]
19	Ustekinumab [mesh]
20	guselkumab [supplementary concept]
21	risankizumab [supplementary concept]
22	anti-IL 23 [word text]
23	lxekizumab [supplementary concept]
24	Secukinumab [supplementary concept]
25	Brodalumab [supplementary concept]
26	Bimekizumab [supplementary concept]
27	or/7–26
28	animals/not humans/
29	27 not 28
30	and/6,29
31	limit 30 to (clinical conference or editorial)
32	30 not 31
33	remove duplicates from 32

Note: Database(s): NCBI PubMed Central (PMC) MEDLINE(R) U.S. National Institutes of Health's National Library Medicine; Embase Classic +Embase 1947 to May 14, 2020 Search Strategy run on May 14, 2020.

We included case report, case series, letter, review, register, prospective, and retrospective studies, in English language and Human. We excluded conference abstract.

We considered the outcomes “hospitalization,” “admission in Intensive Care Unit” and “death.”

We included adult and pediatric patients with a confirm diagnosis of Coronavirus infection made by naso/oro-pharyngeal swab for RT-PCR, affected by dermatologic, rheumatologic, and gastroenterological IMID, undergoing immunosuppressive therapy, including biologic and conventional DMARDs (as listed in Table 1). We excluded type of Psoriasis other than plaque psoriasis and psoriatic arthritis.

2.1 | Statistical analysis

Individual patient data were pooled from 10 reports.^{10–19} Categorical variables are described as absolute frequencies and percentages and continuous variables are presented as mean values \pm SD (SD). Fisher and *t*-test were used to compare variables between subjects with or without hospitalization. A two-sided *P* value $< .05$ was considered statistically significant. Statistical analyses were performed by SPSS version 20.0 (IBM Inc., Illinois).

2.2 | Missing data

We excluded the unique study²⁰ that contributed with one patient affected by SARS-CoV 1 infection, to avoid selection bias.

We excluded four patients from three reports^{14,15,17} for the comorbidity descriptive and pooled analysis because of unclear/missing data.

The study by Monti et al²¹ included only mean values of the four patients included, without individual data, and was thus accordingly excluded in the pooled analysis.

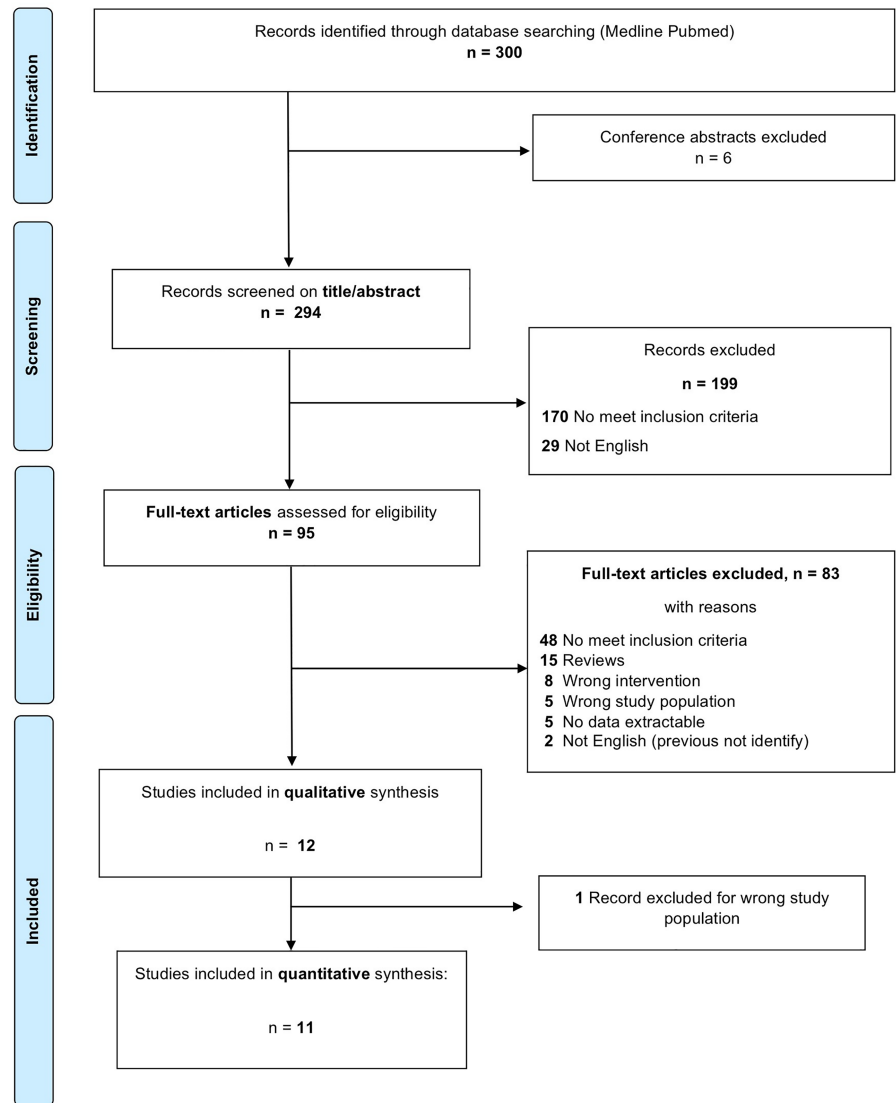
3 | RESULTS

3.1 | Search results

We identified through database searching 300 records: 6 have been excluded because duplicates or conference abstract; 294 records have been screened for titles and abstracts; then we excluded 199 records and we assessed 95 full text articles for eligibility. Of these, 83 full text articles were excluded and 12 records were included for qualitative synthesis. We extract data for a quantitative analysis of 11 complete records. For further descriptions see the study flow-diagram (Figure 1).

3.2 | Population characteristics of included studies

We included 11 reports^{10–19,21} for quantitative descriptive analysis, with a total population of 57 SARS-CoV 2 confirmed-infected

FIGURE 1 Flow-diagram chart of study selection and inclusion

patients, with an average age of 49.2 years (SD 17.6), and an equally gender distribution (29M, 50.8%; Table 2). Among IMIDs population, 32 had a Psoriasis diagnosis and 4 had also psoriatic arthritis; 20 patients suffered from Inflammatory Bowel Disease (IBD), with 12 Crohn's Diseases (CD), and 8 Ulcerative Colitis (UC). One patient has together Psoriasis and CD. Three patients had Rheumatoid Arthritis, one Ankylosing Spondylitis and one Sjögren Syndrome (SS).

From a total population of 53 patients (see Section 2.2), 13 had more than one comorbidity (24.5%). Comorbidities were: hypertension (26.4%), diabetes (9.4%), cardio-cerebrovascular disease (9.4%), obesity (11.3%), and other (26.4%).

3.3 | Intervention characteristics of included studies

On a total population of 57 patients, 50 patients were treated with a biologic therapy (87.7%) and 1 patient with a JAK inhibitor (Tofacitinib, 1.7%). Six patients used conventional DMARDs alone

(10.5%) and 10 patients were treated with combined biologic and conventional DMARDs (17.5%; see Table 2).

3.4 | Pooled analysis

We conducted a pooled analysis on 10 reports¹⁻¹⁰ regarding 53 patients (see Section 2.2 for population details) affected by SARS-CoV 2, with a previous diagnosis of IMIDs, treated with a biologic and/or conventional DMARDs, with the objective to assess how the drug-induced immunosuppressive status could impact the severity of the SARS-CoV infection clinical course. We also analyze the association between demographic patients characteristic and the outcomes "hospitalization" (Table 3).

No death was reported; 16 patients were hospitalized (30.2%, 95% CI 17.8-42.6%) and only 2 cases were admitted to Intensive Care Unit (ICU) (3.8%, 95% CI -1.3 to 8.9; see Table 2).

We found a significant association between the risk of hospitalization and older age (P .03), obesity (P .02), and the presence of

TABLE 2 Reports selected and included for data analysis and demographic characteristic of study population

Reports	Evidence levels	IMID	Duration of disease (years)	Patients	Age (mean/SD)	Sex	Comorbidity	Previous immunosuppressor	Immunosuppressive therapy before/during infection	Coronavirus infection	Symptoms/ diagnosis	Continued/ stopped immunosuppressor	Hospitalization	ICU	Death
Balestri, R (2020) <i>Dermatol Therapy</i>	5	Psoriasis	4	1	55	M	No	cDMARDs, Adalimumab	Ixekizumab	COVID-19	Asymptomatic	Continued	None	None	None
Benhadou, F (2020) <i>JEADV</i>	5	Psoriasis	20	1	40	F	Ehlers-Danlos Syndrome	CsA, MTX	Guselkumab	COVID-19	Fever (39.4°C), cough, myalgia, fatigue, shortness of breath	Continued	None	None	None
Conti, A (2020) <i>JEADV</i>	4	Psoriasis	–	2	64 (2.8)	M	hypertension, dyslipidemia, AMI, diabetes, IRC	–	Guselkumab Ustekinumab	COVID-19	ARDS, asthenia, anosmia ageusia	50% stopped	50%	50%	None
Damiani, G (2020) <i>JEADV</i>	4	PSO, PsA	>1	22	57.7 (12.5)	72.7% M	Hypertension, diabetes, obesity, CCD	–	Anti-IL12/23 31.8% Anti-IL17 31.8% Anti-TNF α (biosimilar) 22.7% Anti-TNF α 9%	COVID-19	Fever, anosmia, ageusia, astenia, cough	4.5% stopped	22.7%	None	None
Gisondi, P (2020) <i>BJD</i>	4	Psoriasis	–	4	61 (9.8)	50% M	Hypertension, diabetes, obesity	–	Ustekinumab 25% Adalimumab 25% Etanercept 25% Secukinumab 25%	COVID-19	75% interstitial pneumonia	–	75%	None	None
Messina, F (2020) <i>JEADV</i>	5	PSO, PsA	14	1	32	F	CD	cDMARDs, anti-TNF α , anti-IL17, anti-IL12/23	Guselkumab MTX	COVID-19	Fever (37.4°C), mild rhinorrhea	MTX stopped; Guselkumab postponed	None	None	None
Nasiri, S (2020) <i>J Dermatol Treat</i>	5	Psoriasis	–	1	73	M	–	–	CsA MTX	COVID-19	Fever, malaise, and dry cough	MTX stopped stopped & restarted CsA	Yes	None	None
Enmi, G (2020) <i>Autoimmun Rev</i>	5	Sjögren Syndrome	–	1	68	F	–	–	Prednisone + HCQ Tocilizumab (ICU)	COVID-19	Fever, dry cough, fatigue, dyspnea, interstitial pneumonia	cDMARDs increased doses Tocilizumab started in ICU	Yes	Yes	None
Monti, S (2020) <i>Ann Rheum Disease</i>	4	AR, SpA/PsA	–	4	58	4 F	Hypertension	–	Etanercept 50% Abatacept 25% Tofacitinib 25% + cDMARDs	COVID-19	Fever, fatigue, anosmia/dysgeusia, cough, rhinorrhea, myalgia, dyspnea	Stopped	25%	None	None
Allocca, M <i>Clin Gastroent Hepatol</i>	4	IBD	–	14	39.9 (10.4)	28.6% M	Renal transplantation, hypertension, obesity, arthritis, other	–	Infliximab 42.9% Ustekinumab 14.3% Adalimumab 14.3% cDMARDs 35.7% Vedolizumab 7.1%	COVID-19	–	–	35.7%	None	None
Turner, D (2020) <i>JPGN</i>	4	IBD	3.2	6	16.5 (2)	50% M	cardiovascular disease	cDMARDs infliximab	Infliximab 33.3% Vedolizumab 16.6% cDMARDs 66.6%	COVID-19	Fever, cough, fatigue, anosmia, ageusia, rhinitis, mild chest pain	Continued	None	None	None

Note: For evidence levels we used quality rating scheme for studies and other evidence modified from the Oxford Centre for evidence-based medicine; 4: case series with or without intervention; cross-sectional study, 5: opinion of respected authorities; case reports.
Abbreviations: bDMARDs, biologic disease-modifying anti-rheumatic drugs; CCD, cardio-cerebrovascular disease; CD, Crohn disease; cDMARDs, conventional disease-modifying anti-rheumatic drugs; CPP, chronic paranoid psychosis; HCQ, hydroxychloroquine; ICU, intensive care unit; IMID, immune-mediated inflammatory disease; PE, pulmonary embolism; PsA, psoriatic arthritis; PSO, psoriasis; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

TABLE 3 Clinical and therapeutic characteristics of hospitalized and not-hospitalized patients with IMID and SARS-CoV 2 infection

	Overall n = 53	Hospitalized n = 16 (30.2%)	Not-hospitalized n = 37 (69.8%)	P-value
Age (years), mean ± SD	49.2 ± 17.6	56.6 ± 7.9	44.9 ± 6.0	.03
Gender (M), n(%)	29 (50.9)	8 (50.0)	21 (56.8)	.65
Diabetes, n(%)	5 (10.2) ^a	3 (23.1) ^b	2 (5.6) ^c	.07
Hypertension, n(%)	13 (26.5) ^a	6 (46.2) ^b	7 (19.4) ^c	.06
Obesity, n(%)	6 (12.2) ^a	4 (30.8) ^b	2 (5.5) ^c	.02
Cardiocerebrovascular diseases, n(%)	6 (12.2) ^a	1 (7.7) ^b	5 (13.9) ^c	.55
Other, n(%)	10 (20.4) ^a	3 (23.1) ^b	7 (19.4) ^c	.78
>1 comorbidity, n(%)	12 (24.5) ^a	6 (46.2) ^b	6 (16.7) ^c	.03
bDMARDs ^d , n(%)	41 (77.4)	11 (68.8)	30 (81.1)	.32
Anti-IL23, n(%)	3 (5.7)	1 (6.3)	2 (5.4)	.90
Anti-IL12/23, n(%)	11 (20.8)	3 (18.8)	8 (21.6)	.81
Anti-TNF α , n(%)	18 (34.0)	4 (25.0)	14 (37.8)	.36
Anti-IL17, n(%)	9 (17.0)	3 (18.8)	6 (16.2)	.82
cDMARDs ^d , n(%)	6 (11.3)	3 (18.8)	3 (8.1)	.26
bDMARDs + cDMARDs, n(%)	6 (11.3)	2 (12.5)	4 (10.8)	.85

Note: Values are expressed as mean ± SD or n (%).

Abbreviations: bDMARDs, biologic disease-modifying antirheumatic drugs; cDMARDs, conventional disease-modifying antirheumatic drugs; M, male.

^aMissing data for comorbidity modify the total population analyzable on a total population of 49 patients.

^bMissing data for comorbidity modify the total population analyzable on a total population of 13 patients.

^cMissing data for comorbidity modify the total population analyzable on a total population of 36 patients.

^dNumbers indicates patients on bDMARDs or cDMARDs monotherapy.

TABLE 4 Clinical and therapeutic characteristics of hospitalized and not-hospitalized psoriatic patients with SARS-Cov2 infection

	Overall n = 32	Hospitalized n = 10 (31.3%)	Not-hospitalized n = 22 (68.7%)	P-value
Age (years), mean ± SD	57.6 ± 4.5	64.1 ± 6.5	54.6 ± 5.8	.04
Gender (M), n(%)	22 (68.8)	7 (70.0)	15 (68.2)	.91
Diabetes, n(%)	4 (13.7) ^a	3 (37.5) ^b	1 (4.8) ^c	.07
Hypertension, n(%)	12 (41.4) ^a	5 (62.5) ^b	7 (33.3) ^c	.15
Obesity, n(%)	3 (10.3) ^a	1 (12.5) ^b	2 (9.5) ^c	.28
Cardiocerebrovascular diseases, n(%)	4 (13.7) ^a	1 (12.5) ^b	3 (14.3) ^c	.90
Other, n(%)	4 (13.7) ^a	1 (12.5) ^b	3 (14.3) ^c	.90
>1 comorbidity, n(%)	11 (37.9) ^a	5 (62.5) ^b	6 (28.6) ^c	.09
bDMARDs ^d , n(%)	30 (93.8)	9 (90.0)	21 (95.4)	.55
Anti-IL23, n(%)	4 (12.5)	1 (10.0)	3 (13.6)	.77
Anti-IL12/23, n(%)	8 (25.0)	2 (20.0)	6 (27.3)	.66
Anti-TNF α , n(%)	9 (28.1)	2 (20.0)	7 (31.8)	.49
Anti-IL17, n(%)	9 (28.1)	3 (30.0)	6 (27.3)	.87
cDMARDs ^d , n(%)	1 (3.0)	1 (10.0)	0 (0)	.13
bDMARDs + cDMARDs, n(%)	1 (3.0)	0 (0)	1 (4.5)	.49

Note: Values are expressed as mean ± SD or n (%).

Abbreviations: bDMARDs, biologic disease-modifying antirheumatic drugs; cDMARDs, conventional disease-modifying antirheumatic drugs; M, male.

^aMissing data for comorbidity modify the total population analyzable on a total population of 29 patients.

^bMissing data for comorbidity modify the total population analyzable on a total population of 8 patients.

^cMissing data for comorbidity modify the total population analyzable on a total population of 21 patients.

^dNumbers indicates patients on bDMARDs or cDMARDs monotherapy.

multiple comorbidity ($P .03$). A positive trend for the outcome "hospitalization" was observed in diabetic ($P .07$), and hypertensive ($P .06$) patients. No significant association was found between the risk of hospitalization and the use of biological or conventional DMARDs (respectively, $P .32$ and $P .26$), neither when they are used combined ($P .85$; see Table 3).

We also conducted a pooled analysis on seven reports regarding 32 patients affected by COVID-19, with a previous diagnosis of Psoriasis, treated with a biologic and/or conventional DMARDs, with the objective to assess how the drug-induced immunosuppressive status could impact the severity of the SARS-CoV infection clinical course. We also analyze the association between demographic patients characteristic and the outcomes "hospitalization" (Table 4).

Also in this group no death was reported; 10 patients were hospitalized (31.3%, 95% CI 15.2-47.3%) and only one case was admitted to Intensive Care Unit (ICU) (3.1%, 95% CI -2.9 to 9.2%; see Table 1). We observed a significant association between the risk of hospitalization and older age ($P .04$). A positive trend for the outcome "hospitalization" was found for the variable diabetic ($P .07$). Even in the psoriatic population, no significant association was found between the risk of hospitalization and the use of biological or conventional DMARDs (respectively $P .55$ and $P .13$), neither when they are used combined ($P .49$; see Table 4).

4 | DISCUSSION

SARS Coronavirus (SARS-CoV1) caused an outbreak of severe acute respiratory syndrome in 2002. This SARS was characterized by an atypical acute, community-acquired pneumonia. The epidemic ended in July 2003, leaving a total of 8096 infected patients and 774 deaths (9.5%) in over 30 countries.²²⁻²⁴

In December 2019 a new coronavirus infection called SARS-CoV 2, causing a new diseases. Named COVID-19, was recognized in China and quickly spread to countries in and outside Asia becoming pandemic.

While in some individuals, the COVID-19 disease remains asymptomatic, albeit infective, other individuals present severe complications.²⁵ Around 15% of patients develop severe pneumonia and 5% progress to an acute respiratory distress syndrome, septic shock and/or a multiple organ failure, associated with high mortality.²⁶ Both innate and adaptive immune response were implicated in the severity differential of this disease.²⁷

A "cytokine storm" following hyper-activation of the immune system seems to be responsible for this progression.²⁸ Several cytokines such as IP-10, MCP-1 IL-2, IL-6, IL7, GM-CSF, and TNF alpha have been related not only to the severity of the disease but also with the probability of being admitted to the ICU.^{29,30}

In particular high TNF alpha and IL-6 levels have been described as biomarkers of worse outcome in particularly fragile cancer patients infected with SARSCoV2.³¹

Since immunosuppression across multiple cytokine axes has the potential to increase susceptibility, persistence, and reactivation of viral infections, the question for dermatology, rheumatology and

gastroenterology was whether to halt therapies for IMIDs patients during this pandemic. The discontinuation of immunosuppressants in IMIDs, however, may lead to disease flares, and severe psychological distress, that sometimes could be more harmful than stopping the therapy for the fear of getting the infection.³²

Moreover disease flare implies systemic inflammation and immunological disruption, two recognized factors responsible for increasing susceptibility to infection and severity of disease.³³

The choice of action is crucial since it can impact on the efficacy, safety of treatment, and quality of patient's life. The approach in the management of anti-interleukins anti-cytokines treated patients has been questioned among health care providers dealing with IMIDs in various areas of medicine.^{1,3,34,35}

We focused our review on the evaluation of immunosuppressants impact during COVID-19 outbreak in the understudied IMID population.

In our pooled analysis we found that 30.2% of SARS-CoV positive patients undergoing immunosuppressive or immunomodulatory therapy was hospitalized. When we analyzed the subgroup of psoriatic patients under therapy this figure remained stable at 31.3%. In Italy the hospitalization rate in the same period taken in consideration in our study was 16.9%,³⁶ but a direct comparison is not methodologically correct since the cases collected in our study come from different countries and they represent a selected population, not the totality of IMIDs patients undergoing immunosuppressive therapy. Instead as for the severity of the disease we found that 3.5% of the patients collected in our pooled analysis was admitted to ICU and this is very similar to the rate of ICU admission recorded in the Italian COVID-19 population.³⁶

We found that the features that may predict a worse prognosis for IMID treated patients were age, obesity and multi-comorbidity. Among the comorbidities usually described as being associated with a higher risk of infection and disease severity only diabetes and hypertension showed a tendency towards statistical significance in the patients collected.

This is in line with the literature that demonstrates that, among several clinical features and comorbidities that may predict the severity of the disease and thus the admission to ICU, age was the strongest of all.³⁷

As for the role of therapy, although the numbers are very small, our pooled analysis showed that nor classical DMARDs neither biological previous treatment, generates a higher risk of hospitalization in IMID patients and more specifically to psoriatic patients treated with these drugs. We think that this evidence may be helpful in guiding the management of these patients. Moreover this may be in line with the hypothesis that some level of immune modulation may be worthwhile to control the complication of COVID-19 infection.³⁸

Although there have been no cases of patients treated with Apremilast included in our review, the evidence is in support of a good safety profile with this drug³⁹ and probably this is the main reason for their absence. Indeed many authors reported that none of the patients treated with Apremilast developed COVID-19 related symptoms.⁴⁰

We combined the present evidences from this paper with the management suggestion already in place,^{41,42} and developed an

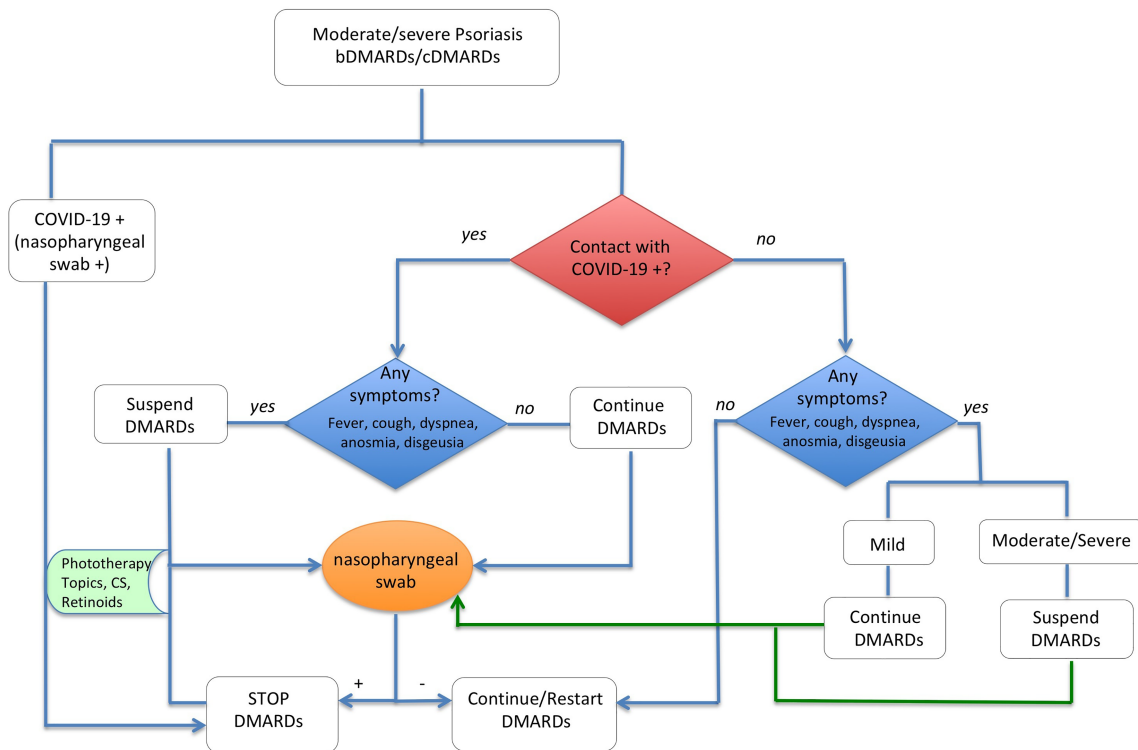


FIGURE 2 Algorithm proposal for psoriasis therapy management during COVID-19 era

algorithm for the management of patients treated with DMARDs during this pandemic (Figure 2). The main limitation of our pooled analysis is the small sample size, possibly not allowing adequate statistical power, even if representing an insightful description of the now available best knowledge about the topic.

5 | CONCLUSION

Our systematic review and pooled analysis on COVID-19 infected IMID patients treated with immunosuppressive and immunomodulatory drugs showed that there is no difference in the hospitalization rate for DMARDs users. Particular attention should be placed for patients with older age, obesity and multi-comorbidity in treatment with these drugs.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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