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Article type : Letter to the Editor

**COVID-19 in Severe Asthma Network in Italy (SANI) patients: clinical features, impact of comorbidities and treatments**

Short title: COVID-19 and severe asthma in real-life

**To the Editor**

Since the end of February 2020 Italy, first non- Asian Country, has reported an ever increasing number of CoronaVirus Disease 19 (COVID-19) patients, which has reached over 200,000 confirmed Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infected subjects, resulting in more than 34000 deaths (data updated to June 19th, 2020 <sup>1</sup>).

Patients with asthma are potentially more severely affected by SARS-CoV-2 infection and respiratory viruses are known to be associated with severe adverse asthma outcomes, including increased risk of asthma exacerbation episodes <sup>2</sup>. Nonetheless, according to the epidemiological studies published so far, asthma is not amongst the most common clinical conditions in COVID-19 patients <sup>3</sup>

About 5-10% of asthmatics are severe <sup>4</sup> and one would expect increased vulnerability to SARS-CoV-2 infection, but no data is so fare available to confirm this hypothesis.

We investigated the incidence of COVID-19, describing its clinical course, in the population of the Severe Asthma Network in Italy (SANI), one of the largest registry for severe asthma worldwide <sup>5</sup>, and in an additional Center (Azienda Ospedaliero Univeristaria di Ferrara, Ferrara, Italy). All centers, have been contacted and inquired to report confirmed or highly suspect cases of COVID-19 (i.e. patients with

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symptoms, laboratory findings and lung imaging typical of COVID-19 but without access to nasopharyngeal or oropharyngeal swab specimens because of clinical contingencies/emergency) among their cohorts of severe asthma. Demographic and clinical have been obtained from the registry platform and collected from the additional Center. Additional data about COVID-19 symptoms, treatment and clinical course have been collected for all cases reported.

Ethical issues and statistical analysis are reported in the online supplementary material.

The entire severe asthmatics population accounted for 1504 patients, 65% of them were treated with biologicals (anti-IL5 or anti-IL5R agents: 52.9%, anti-IgE: 47.1%). Twenty-six (1.73%) patients had confirmed (11) or highly suspect COVID-19 (15); eighteen (69.2%) were females and mean age was  $56.2 \pm 10$  years. The geographical distribution of COVID-19 cases is presented in Figure 1.

Nine (34.6%) infected patients experienced worsening of asthma during the COVID-19 symptomatic period; four of them needed a short course of oral corticosteroids for controlling asthma exacerbation symptoms.

The most frequent COVID-19 symptoms were fever (100% of patients), malaise (84.6%), cough (80.8%), dyspnea (80.8%), headache (42.3%) and loss of smell (42.3%). Four patients (15.3%) have been hospitalized, one of which in intensive care unit; among hospitalized patients, two (7.7%) died for COVID-19 interstitial pneumonia (no deaths among the non-hospitalized patients).

Severe asthmatics affected by COVID-19, had a significantly higher prevalence of non-insulin-dependent diabetes mellitus (NIDDM) compared to non-infected severe asthma patients (15.4% vs 3.8%,  $p=0.002$ ; odds ratio: 4.7). No difference was found in other comorbidities, however patients with severe asthma and NIDDM had a not statistically significant trend of higher BMI (31.9 vs 26.9,  $p=0.09$ ), suggesting a possible interaction between obesity and NIDDM as risk factors for COVID-19 in severe asthmatics.

Twenty-one patients with COVID-19 were on biologicals: 15 (71%) on anti-IL-5 or anti-IL5R agents (Mepolizumab  $n=13$ ; Benralizumab  $n=2$  - counting for the 2.9% of all severe asthmatics treated with anti-IL5 in our study population) and 6 (29%) on anti IgE (Omalizumab - 1.3% of all severe asthmatics treated with omalizumab in our study population).

Table I describes the 26 COVID-19 patients.

In conclusion, in our large cohort of severe asthmatics, COVID-19 was infrequent, not supporting the concept of asthma as a particularly susceptible condition to SARS-CoV2 infection. This is in line with the under-reported asthma cases among patients with COVID-19 patients<sup>3</sup>. The COVID-19 related mortality

rate in our cohort of patients was 7.7%, lower than in the general population (14.5% in Italy <sup>1</sup>). These findings suggest that severe asthmatics are not at high risk of SARS-CoV-2 infection and of severe forms of COVID-19. There are potentially different reasons for this. Self-containment is the first, because of the awareness of viruses acting as a trigger for exacerbations, and therefore they could have acted with greater caution, scrupulously respecting social distancing, lockdown and hygiene rules of prevention, and being more careful in regularly taking asthma medications.

Another possible explanation stands in the intrinsic features of type-2 inflammation, that characterizes a great proportion of severe asthmatics. Respiratory allergies and allergen exposures are associated with significant reduction in angiotensin-converting enzyme 2 (ACE2) expression <sup>6</sup>, the cellular receptor for SARS-CoV-2. Interestingly, ACE2 and Transmembrane Serine Protease 2 (TMPRSS2) (another protein mediating SARS-CoV-2 cell entry) have been found highly expressed in asthmatics with concomitant NIDDM <sup>7</sup>, the only comorbidity that was more frequent reported in our COVID-19 severe asthmatics.

The third possible explanation refers to the possibility that inhaled corticosteroids (ICS) might prevent or mitigate the development of Coronaviruses infections. Severe asthmatics, treated with high doses of ICS <sup>4</sup>, may have been protected from SARS-CoV-2 infection.

Noteworthy, among our case-series of severe asthmatics with COVID-19, the proportion of those treated anti-IL5 biologics was higher (71%) compared to those treated with anti-IgE (29%). Although the number of cases is too small to draw any conclusion, it is tempting to speculate that different biological treatments can have specific and different impact on antiviral immune response, as suggested for anti-IgE as protective for other viral infections <sup>8</sup>. Moreover we may speculate of the consequence of blood eosinophils reduction induced by anti-IL5 agents, as more than 70% of infected patients were treated with them: eosinopenia has been reported in 52-90% of COVID-19 patients worldwide and it has been suggested as a risk factor for more severe COVID-19 <sup>9</sup>. So far, no other large series of severe asthmatics treated with biologics infected by COVID-19 has been published, so our speculations on the role of biologics in modulating the risk of COVID-19 need further evidence.

In conclusion, in our large cohort of severe asthmatics only a small minority experienced symptoms consistent with COVID-19, and these patients had peculiar clinical features including high prevalence of NIDDM as comorbidity. Further real-life registry-based studies are needed to confirm our findings and to extend the evidence that severe asthmatics are at low risk of developing COVID-19.

**TABLES:**

Table I – Demographic and clinical characteristics of severe asthmatics with COVID-19.

AD: atopic dermatitis; ALB: albuterol; AMC: amoxicillin/clavulanate; AR: allergic rhinitis; AZM: azithromycin; BENRA: benralizumab; BX: bronchiectasis; Cax: ceftriaxone; CIP: ciprofloxacin; CRSsNP: chronic rhinosinusitis without nasal polyps; CRSwNP: chronic rhinosinusitis with nasal polyps; CVD: cardiovascular diseases; GERD: gastroesophageal reflux disease; HCQ: hydroxychloroquine; HTN: hypertension; IBP: ibuprofen; ICS/LABA: Inhaled corticosteroids/Long-acting beta2-agonists; LAMA: long-acting muscarinic agents; LMWH: low molecular weight heparins; LPV/r: lopinavir/ritonavir; LTRA: leukotriene receptor antagonists; LVX: levofloxacin; MDD: major depressive disorder; MEPO: mepolizumab; MV: mechanical ventilation; NIDDM: non-insulin-dependent diabetes mellitus; NIV: non invasive ventilation; OCS: oral corticosteroids; OMA: omalizumab; PCM: paracetamol; ;TMP-SMX: trimethoprim/sulfamethoxazole; TOZ: tocilizumab

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	COVID-19 Therapy	COVID-19 clinical course
1	Emilia Romagna	Confirmed	48	F	34	Yes	No	GERD	Fever	No	ICS/LABA, LTRA, OMA	HCQ, AZM	Recovered
2	Emilia Romagna	Confirmed	67	M	33	Yes	No	NIDDM	Fever, Dyspnoea	No	ICS/LABA, OCS	HCQ, OCS	Recovered
3	Emilia	Confirmed	65	F	33	Yes	No	BX, CVD,	Fever, Cough,	No	ICS/LABA	HCQ,	Death

	Romagna							Anxiety, Osteoporosis	Dyspnoea			LVX, OCS, MV	
4	Emilia Romagna	Suspect	32	M	33	Yes	No	AR	Fever, Cough, Malaise, Anosmia, Ageusia, Sore throat, Dyspnoea, Wheezing, Diarrhea, Headache, Arthralgia, Myalgia	No	ICS/LABA, OMA	OCS, PCM	Resolved
5	Lombardia	Confirmed	45	F	20	Yes	Ex	CRSwNP, GERD,	Fever, Cough, Malaise, Anosmia, Ageusia	No	ICS/LABA, LTRA, OCS, MEPO	HCQ	Recovered
6	Lombardia	Confirmed	45	F	27	No	No	CRSwNP, GERD	Fever, Cough, Malaise, Anosmia, Ageusia, Dyspnoea,	No	ICS/LABA, LTRA, BENRA	HCQ, LVX, OCS	Recovered

									Chest tightness, Chest pain, Respiratory failure				
7	Lombardia	Confirmed	65	F	28	No	No	GERD, CVD, NIDDM, Osteoporosis	Fever, Cough, Dyspnoea, Respiratory failure	No	ICS/LABA, MEPO	OCS, LMWH, NIV	Death
8	Lombardia	Suspect	58	F	21	Yes	No	GERD	Fever, Cough, Malaise, Rhinitis, Dyspnoea	Yes	ICS/LABA, OMA	LVX	Resolved
9	Lombardia	Suspect	56	M	26	Yes	Former	AR, GERD, BX	Fever, Cough, Malaise, Rhinitis, Dyspnoea, Chest tightness, Wheezing, Arthralgia	Yes	ICS/LABA, MEPO	Non specified antibiotic	Resolved
10	Lombardia	Confirmed	62	M	33	Yes	No	AR, CRSsNP,	Fever, Cough,	No	ICS/LABA,	LPV/r,	Resolved

								GERD, BX, HTN	Malaise, Anosmia, Dyspnoea, Chest tightness, Respiratory failure, Nausea		LTRA, MEPO	HCQ, AZM, OCS, TOZ	
11	Lombardia	Confirmed	66	F	28	Yes	Yes	AR, CRSsNP, CVD, Glaucoma, Cataract, NIDDM	Fever, Cough, Malaise, Conjunctivitis, Dyspnoea, Chest tightness, Chest pain, Wheezing, Nausea, Headache	Yes	ICS/LABA, LTRA, MEPO	OCS	Resolved
12	Lombardia	Suspect	51	F	25	Yes	No	None	Fever, Malaise, Anosmia, Ageusia, Sore	No	ICS/LABA	AMC	Resolved

									throat, Dyspnoea, Chest tightness, Headache				
13	Lombardia	Suspect	37	F	19	No	No	CRSwNP, AD	Fever, Cough, Malaise, Rhinitis, Anosmia, Ageusia, Sore throat, Dyspnoea, Wheezing, Headache	Yes	ICS/LABA, LTRA, MEPO	LVX	Resolved
14	Piemonte	Suspect	66	F	23	Yes	No	AR, CRSwNP, GERD	Fever, Cough, Malaise, Rhinitis, Anosmia, Sore throat, Dyspnoea, Wheezing, Diarrhea,	Yes	ICS/LABA, LTRA, OMA	ALB, PCM, IBP	Resolved



									Headache				
15	Piemonte	Suspect	57	F	34	Yes	No	AR, GERD	Fever, Cough, Malaise, Dyspnoea, Chest tightness, Wheezing	Yes	ICS/LABA, LTRA	OCS, PCM	Resolved
16	Piemonte	Suspect	66	F	26	No	No	CRSwNP, MDD, Osteoporosis	Fever, Cough, Malaise, Rhinitis, Dyspnoea, Headache	No	ICS/LABA, LAMA, MEPO	CIP, PCM	Resolved
17	Piemonte	Suspect	59	F	21	Si	No	None	Fever, Cough, Malaise, Anosmia, Ageusia, Conjunctivitis, Dyspnoea, Chest tightness, Chest pain, Wheezing,	Yes	ICS/LABA, LAMA, BENRA	AMC, CIP, TMP- SMX, OCS	Resolved

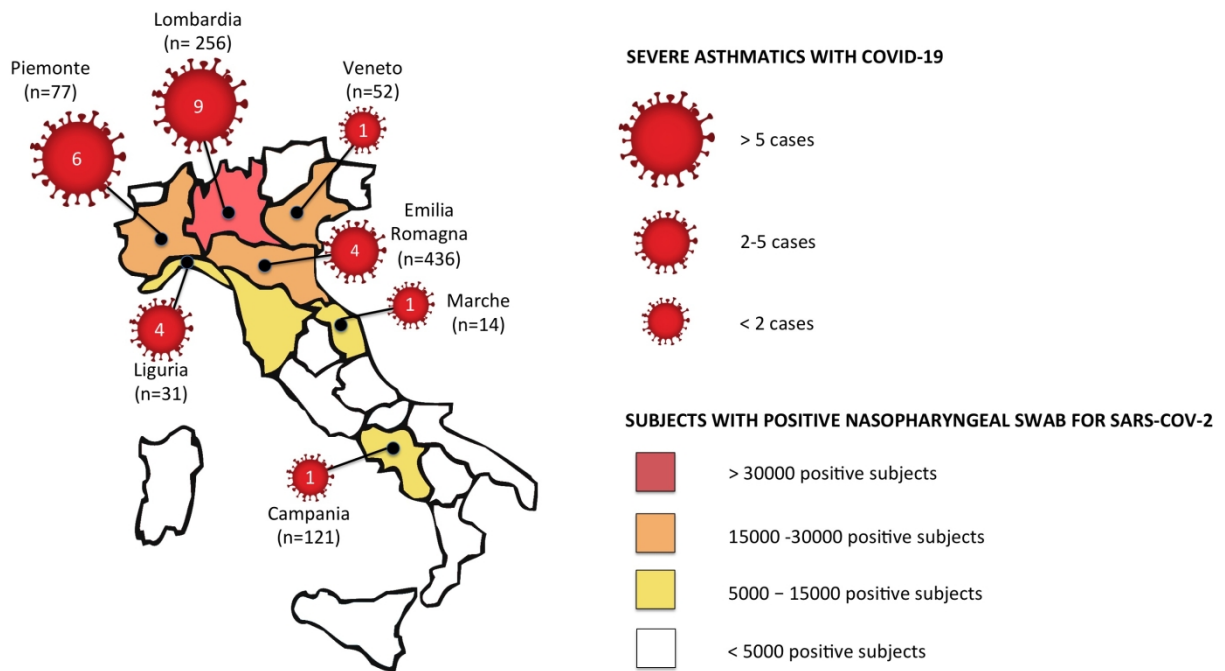
									Headache				
18	Piemonte	Suspect	61	M	25	No	No	CRSwNP	Fever, Malaise, Ageusia, Dyspnoea, Diarrhea, Headache	No	ICS/LABA, LAMA, MEPO	None	Resolved
19	Piemonte	Suspect	55	F	23	Yes	No	None	Fever, Cough, Malaise, Ageusia, Diarrhea	Yes	ICS/LABA, LAMA, OMA	LVX	Resolved
20	Veneto	Confirmed	53	F	23	No	No	None	Fever, Cough, Malaise, Anosmia	No	ICS/LABA, MEPO	PCM	Resolved
21	Liguria	Suspect	50	M	28	Yes	Yes	AR, CRSwNP	Fever, Cough, Malaise, Rhinitis, Dyspnoea	No	ICS/LABA, LTRA, MEPO	None	Resolved
22	Liguria	Suspect	46	F	27	Yes	Yes	None	Fever, Cough, Malaise, Rhinitis, Sore throat,	No	ICS/LABA, MEPO	AZM	Resolved

									Dyspnoea, Diarrhea				
23	Liguria	Suspect	70	M	25	No	Ex	CRSwNP, Osteoporosis	Fever, Cough, Malaise, Dyspnoea, Chest tightness	No	ICS/LABA, OMA	OCS	Resolved
24	Liguria	Suspect	60	F	20	No	No	CRSwNP, BX	Fever, Cough, Malaise, Dyspnoea, Headache	No	ICS/LABA, MEPO	AZM	Resolved
25	Campania	Confirmed	70	F	39	Yes	Ex	AR, GERD, CVD, NIDDM	Fever, Cough, Malaise, Dyspnoea, Chest tightness, Wheezing, Respiratory failure, Headache	Yes	ICS/LABA, LTRA, MEPO	AZM, Cax, OCS	Resolved
26	Marche	Confirmed	51	M	28	No	No	CRSwNP	Fever, Malaise,	No	ICS/LABA, MEPO	AMC, LMWH	Resolved

									Rhinitis, Anosmia, Headache, Arthralgia, Myalgia				
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**FIGURE LEGENDS:**

Figure 1 – Geographical distribution of severe asthmatics with COVID-19 (number of cases within the red circles) and subjects with positive nasopharyngeal swab positive for SARS-CoV-2 within the general population. The total number of patients with severe asthma for each single region is reported under the each region name.



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