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

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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 and resulted in more than 34000 deaths (data updated to June 19th, 2020[1]).

Patients with asthma are potentially more severely affected by by SARS-CoV-2 infection [2] and it is well established that respiratory viral infections are associated with severe adverse outcomes in patients with asthma, including increased risk of asthma exacerbation episodes [3]. Nonetheless, according to the epidemiological studies published so far, chronic pulmonary diseases are not amongst the most common clinical conditions in COVID-19 patients[4]

About 5-10% of entire asthma population, are severe asthmatics[5] and one would expect increased vulnerability to SARS-CoV-2 infection, but no data is so fare available ti 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[6], and in an additional Center (Azienda Ospedaliero Univeristaria di Ferrara, Ferrara, Italy). All centers, have been

contacted and inquired to report confirmed (i.e. patients with positive test result for the virus SARS-CoV-2 from analysis of nasopharyngeal or oropharyngeal swab specimens) or highly suspect cases of COVID-19 (i.e. patients with 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 data of the entire cohort of severe asthmatics enrolled in the study and all reported cases of confirmed or suspect cases of COVID-19, 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.

Twenty-six (1.73%) out of 1504 severe asthmatics had confirmed (11 out of 26) or highly suspect COVID-19 (15 out 26); eighteen (69.2%) were females and mean age was 56.2 ± 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 reported 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 have been reported 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 (including rhinitis, chronic rhinosinusitis with or without nasal polyps, bronchiectasis, obesity, gastroesophageal reflux, arterial hypertension, cardiovascular diseases).

Twenty-one patients with COVID-19 were on biological treatments: 15 (71%) were 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%) were on anti IgE (Omalizumab - 1.3% of all severe asthmatics treated with omalizumab in our study population).

Table I summarizes demographic and clinical characteristics of 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 [2]. This is in line with the first published large epidemiological data on COVID-19 patients, in which asthma is under-reported as comorbidity[4]. The COVID-19 related mortality rate in our cohort of patients was 7.7%, lower than the COVID-19 mortality rate in the general population (14.5% in Italy [1]). These findings suggest that severe asthmatics are not at high risk of the 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 virus infections 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 controlled allergen exposures are associated with significant reduction in angiotensin-converting enzyme 2 (ACE2) expression [7], 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[8], 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. By definition, patients with severe asthma are treated

with high doses of ICS [5] and this may have had a protective effect for SARS-CoV-2 infection.

Noteworthy, among the patients of our case-series of severe asthmatics with COVID-19, the proportion of those treated anti-IL5 biologics was higher (71%) compared to the number of patients 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. In addition we may speculate of the consequence of blood eosinophils reduction: 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 [9].

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 rhinosinusits 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	C 1 T a
1	Emilia Romagna	Confirmed	48	F	34	Yes	No	GERD	Fever	No	ICS/LABA LTRA, OMA	A A
2	Emilia Romagna	Confirmed	67	M	33	Yes	No	NIDDM	Fever, Dyspnoea	No	ICS/LABA OCS	A C
3	Emilia Romagna	Confirmed	65	F	33	Yes	No	BX, CVD, Anxiety, Osteoporosis	Fever, Cough, Dyspnoea	No	ICS/LABA	A I C M

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
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	A F
5	Lombardia	Confirmed	45	F	20	Yes	Ex	CRSwNP, GERD,	Fever, Cough, Malaise, Anosmia, Ageusia	No	ICS/LABA LTRA, OCS, MEPO	A

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
6	Lombardia	Confirmed	45	F	27	No	No	CRSwNP, GERD	Fever, Cough, Malaise, Anosmia, Ageusia, Dyspnoea, Chest tightness, Chest pain, Respiratory failure	No	ICS/LABA LTRA, BENRA	I C
7	Lombardia	Confirmed	65	F	28	No	No	GERD, CVD, NIDDM, Osteoporosis	Fever, Cough, Dyspnoea, Respiratory failure	No	ICS/LABA MEPO	I N
8	Lombardia	Suspect	58	F	21	Yes	No	GERD	Fever, Cough, Malaise, Rhinitis, Dyspnoea	Yes	ICS/LABA OMA	I

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
9	Lombardia	Suspect	56	M	26	Yes	Former	AR, GERD, BX	Fever, Cough, Malaise, Rhinitis, Dyspnoea, Chest tightness, Wheezing, Arthralgia	Yes	ICS/LABA MEPO	A s i a
10	Lombardia	Confirmed	62	M	33	Yes	No	AR, CRSsNP, GERD, BX, HTN	Fever, Cough, Malaise, Anosmia, Dyspnoea, Chest tightness, Respiratory failure, Nausea	No	ICS/LABA LTRA, MEPO	A F A C T

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
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	A
12	Lombardia	Suspect	51	F	25	Yes	No	None	Fever, Malaise, Anosmia, Ageusia, Sore throat, Dyspnoea, Chest tightness, Headache	No	ICS/LABA	A

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
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	A
14	Piemonte	Suspect	66	F	23	Yes	No	AR, CRSwNP, GERD	Fever, Cough, Malaise, Rhinitis, Anosmia, Sore throat, Dyspnoea, Wheezing, Diarrhea, Headache	Yes	ICS/LABA LTRA, OMA	A I

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
15	Piemonte	Suspect	57	F	34	Yes	No	AR, GERD	Fever, Cough, Malaise, Dyspnoea, Chest tightness, Wheezing	Yes	ICS/LABA LTRA	A F
16	Piemonte	Suspect	66	F	26	No	No	CRSwNP, MDD, Osteoporosis	Fever, Cough, Malaise, Rhinitis, Dyspnoea, Headache	No	ICS/LABA LAMA, MEPO	A F
17	Piemonte	Suspect	59	F	21	Si	No	None	Fever, Cough, Malaise, Anosmia, Ageusia, Conjunctivitis, Dyspnoea, Chest tightness, Chest pain, Wheezing, Headache	Yes	ICS/LABA LAMA, BENRA	A C T S C

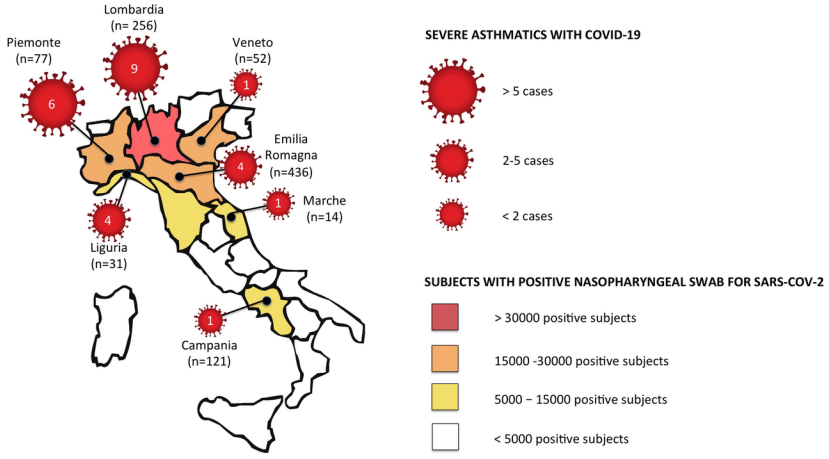
ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
18	Piemonte	Suspect	61	M	25	No	No	CRSwNP	Fever, Malaise, Ageusia, Dyspnoea, Diarrhea, Headache	No	ICS/LABA LAMA, MEPO	N
19	Piemonte	Suspect	55	F	23	Yes	No	None	Fever, Cough, Malaise, Ageusia, Diarrhea	Yes	ICS/LABA LAMA, OMA	N
20	Veneto	Confirmed	53	F	23	No	No	None	Fever, Cough, Malaise, Anosmia	No	ICS/LABA MEPO	N
21	Liguria	Suspect	50	M	28	Yes	Yes	AR, CRSwNP	Fever, Cough, Malaise, Rhinitis, Dyspnoea	No	ICS/LABA LTRA, MEPO	N
22	Liguria	Suspect	46	F	27	Yes	Yes	None	Fever, Cough, Malaise, Rhinitis, Sore throat, Dyspnoea, Diarrhea	No	ICS/LABA MEPO	N

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
23	Liguria	Suspect	70	M	25	No	Ex	CRSwNP, Osteoporosis	Fever, Cough, Malaise, Dyspnoea, Chest tightness	No	ICS/LABA OMA	A
24	Liguria	Suspect	60	F	20	No	No	CRSwNP, BX	Fever, Cough, Malaise, Dyspnoea, Headache	No	ICS/LABA MEPO	A
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	A C C

ID	Region	Suspector Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
26	Marche	Confirmed	51	M	28	No	No	CRSwNP	Fever, Malaise, Rhinitis, Anosmia, Headache, Arthralgia, Myalgia	No	ICS/LABA MEPO	A I

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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Conflict of interest statements:

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