

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

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 34 000 deaths (data updated to June 19th, 2020¹).

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.² Nonetheless, according to the epidemiological studies published so far, asthma is not among the most common clinical conditions in COVID-19 patients.³

About 5%-10% of asthmatics are severe,⁴ and one would expect increased vulnerability to SARS-CoV-2 infection, but no data are so far 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,⁵ and in an additional Center (Azienda Ospedaliero Univeristaria di Ferrara, Ferrara, Italy). All centres have been contacted and inquired to report confirmed or highly suspect cases of COVID-19 (ie, 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 have been obtained from the

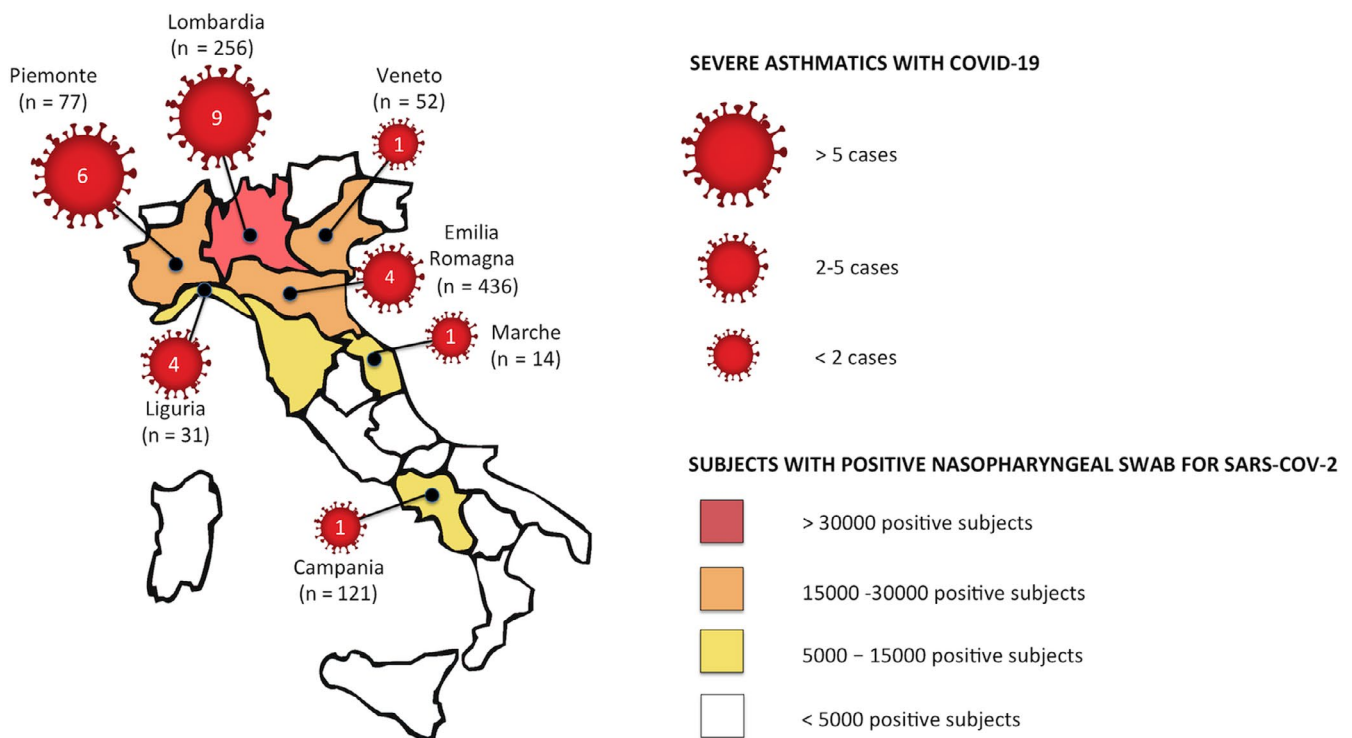


FIGURE 1 Geographical distribution of severe asthmatics with COVID-19 (number of cases within the red circles) and subjects with positive nasopharyngeal swab positive for SARS-CoV-2 within the general population. The total number of patients with severe asthma for each single region is reported under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

See SANI Working Group in Appendix 1

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TABLE 1 Demographic and clinical characteristics of severe asthmatics with COVID-19

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities
1	Emilia Romagna	Confirmed	48	F	34	Yes	No	GERD
2	Emilia Romagna	Confirmed	67	M	33	Yes	No	NIDDM
3	Emilia Romagna	Confirmed	65	F	33	Yes	No	BX, CVD, Anxiety, Osteoporosis
4	Emilia Romagna	Suspect	32	M	33	Yes	No	AR
5	Lombardia	Confirmed	45	F	20	Yes	Ex	CRSwNP, GERD,
6	Lombardia	Confirmed	45	F	27	No	No	CRSwNP, GERD
7	Lombardia	Confirmed	65	F	28	No	No	GERD, CVD, NIDDM, Osteoporosis
8	Lombardia	Suspect	58	F	21	Yes	No	GERD
9	Lombardia	Suspect	56	M	26	Yes	Former	AR, GERD, BX
10	Lombardia	Confirmed	62	M	33	Yes	No	AR, CRSsNP, GERD, BX, HTN
11	Lombardia	Confirmed	66	F	28	Yes	Yes	AR, CRSsNP, CVD, Glaucoma, Cataract, NIDDM
12	Lombardia	Suspect	51	F	25	Yes	No	None
13	Lombardia	Suspect	37	F	19	No	No	CRSwNP, AD
14	Piemonte	Suspect	66	F	23	Yes	No	AR, CRSwNP, GERD
15	Piemonte	Suspect	57	F	34	Yes	No	AR, GERD
16	Piemonte	Suspect	66	F	26	No	No	CRSwNP, MDD, Osteoporosis
17	Piemonte	Suspect	59	F	21	Si	No	None
18	Piemonte	Suspect	61	M	25	No	No	CRSwNP
19	Piemonte	Suspect	55	F	23	Yes	No	None
20	Veneto	Confirmed	53	F	23	No	No	None
21	Liguria	Suspect	50	M	28	Yes	Yes	AR, CRSwNP
22	Liguria	Suspect	46	F	27	Yes	Yes	None
23	Liguria	Suspect	70	M	25	No	Ex	CRSwNP, Osteoporosis
24	Liguria	Suspect	60	F	20	No	No	CRSwNP, BX
25	Campania	Confirmed	70	F	39	Yes	Ex	AR, GERD, CVD, NIDDM
26	Marche	Confirmed	51	M	28	No	No	CRSwNP

Abbreviations: 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, noninsulin-dependent diabetes mellitus; NIV, noninvasive ventilation; OCS, oral corticosteroids; OMA, omalizumab; PCM, paracetamol; TMP-SMX, trimethoprim/sulfamethoxazole; TOZ, tocilizumab.

COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	COVID-19 Therapy	COVID-19 clinical course
Fever	No	ICS/LABA, LTRA, OMA	HCQ, AZM	Recovered
Fever, Dyspnoea	No	ICS/LABA, OCS	HCQ, OCS	Recovered
Fever, Cough, Dyspnoea	No	ICS/LABA	HCQ, LVX, OCS, MV	Death
Fever, Cough, Malaise, Anosmia, Ageusia, Sore throat, Dyspnoea, Wheezing, Diarrhoea, Headache, Arthralgia, Myalgia	No	ICS/LABA, OMA	OCS, PCM	Resolved
Fever, Cough, Malaise, Anosmia, Ageusia	No	ICS/LABA, LTRA, OCS, MEPO	HCQ	Recovered
Fever, Cough, Malaise, Anosmia, Ageusia, Dyspnoea, Chest tightness, Chest pain, Respiratory failure	No	ICS/LABA, LTRA, BENRA	HCQ, LVX, OCS	Recovered
Fever, Cough, Dyspnoea, Respiratory failure	No	ICS/LABA, MEPO	OCS, LMWH, NIV	Death
Fever, Cough, Malaise, Rhinitis, Dyspnoea	Yes	ICS/LABA, OMA	LVX	Resolved
Fever, Cough, Malaise, Rhinitis, Dyspnoea, Chest tightness, Wheezing, Arthralgia	Yes	ICS/LABA, MEPO	Nonspecified antibiotic	Resolved
Fever, Cough, Malaise, Anosmia, Dyspnoea, Chest tightness, Respiratory failure, Nausea	No	ICS/LABA, LTRA, MEPO	LPV/r, HCQ, AZM, OCS, TOZ	Resolved
Fever, Cough, Malaise, Conjunctivitis, Dyspnoea, Chest tightness, Chest pain, Wheezing, Nausea, Headache	Yes	ICS/LABA, LTRA, MEPO	OCS	Resolved
Fever, Malaise, Anosmia, Ageusia, Sore throat, Dyspnoea, Chest tightness, Headache	No	ICS/LABA	AMC	Resolved
Fever, Cough, Malaise, Rhinitis, Anosmia, Ageusia, Sore throat, Dyspnoea, Wheezing, Headache	Yes	ICS/LABA, LTRA, MEPO	LVX	Resolved
Fever, Cough, Malaise, Rhinitis, Anosmia, Sore throat, Dyspnoea, Wheezing, Diarrhoea, Headache	Yes	ICS/LABA, LTRA, OMA	ALB, PCM, IBP	Resolved
Fever, Cough, Malaise, Dyspnoea, Chest tightness, Wheezing	Yes	ICS/LABA, LTRA	OCS, PCM	Resolved
Fever, Cough, Malaise, Rhinitis, Dyspnoea, Headache	No	ICS/LABA, LAMA, MEPO	CIP, PCM	Resolved
Fever, Cough, Malaise, Anosmia, Ageusia, Conjunctivitis, Dyspnoea, Chest tightness, Chest pain, Wheezing, Headache	Yes	ICS/LABA, LAMA, BENRA	AMC, CIP, TMP-SMX, OCS	Resolved
Fever, Malaise, Ageusia, Dyspnoea, Diarrhoea, Headache	No	ICS/LABA, LAMA, MEPO	None	Resolved
Fever, Cough, Malaise, Ageusia, Diarrhoea	Yes	ICS/LABA, LAMA, OMA	LVX	Resolved
Fever, Cough, Malaise, Anosmia	No	ICS/LABA, MEPO	PCM	Resolved
Fever, Cough, Malaise, Rhinitis, Dyspnoea	No	ICS/LABA, LTRA, MEPO	None	Resolved
Fever, Cough, Malaise, Rhinitis, Sore throat, Dyspnoea, Diarrhoea	No	ICS/LABA, MEPO	AZM	Resolved
Fever, Cough, Malaise, Dyspnoea, Chest tightness	No	ICS/LABA, OMA	OCS	Resolved
Fever, Cough, Malaise, Dyspnoea, Headache	No	ICS/LABA, MEPO	AZM	Resolved
Fever, Cough, Malaise, Dyspnoea, Chest tightness, Wheezing, Respiratory failure, Headache	Yes	ICS/LABA, LTRA, MEPO	AZM, Cax, OCS	Resolved
Fever, Malaise, Rhinitis, Anosmia, Headache, Arthralgia, Myalgia	No	ICS/LABA, MEPO	AMC, LMWH	Resolved

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 Appendix S1.

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 ± 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%), dyspnoea (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 nonhospitalized patients).

Severe asthmatics, affected by COVID-19, had a significantly higher prevalence of noninsulin-dependent diabetes mellitus (NIDDM) compared to noninfected severe asthma patients (15.4% vs 3.8%, $P = .002$; 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, $P = .09$), 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 1 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.³ The COVID-19 related mortality rate in our cohort of patients was 7.7%, lower than in the general population (14.5% in Italy¹). 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,⁶ 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,⁷ 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,⁴ 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.⁸ 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-19.⁹ So far, no other large series of severe asthmatics treated with biologicals infected by COVID-19 has been published, so our speculations on the role of biologicals 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.

ACKNOWLEDGMENTS

We are grateful to Silvia Rabotti, Concetta Sirena & the SANI staff for the invaluable work in managing the network.

CONFLICT OF INTEREST

Enrico Heffler reports participation to advisory boards and personal fees from AstraZeneca, Sanofi, GSK, Novartis, Circassia, Nestlè Purina, Boehringer Ingelheim, Valeas, outside the submitted work. Aikaterini Detoraki does not have any conflict of interest to report. Marco Contoli reports grants from Chiesi, University of Ferrara-Italy, personal fees from Chiesi, AstraZeneca, Boehringer Ingelheim, Alk-Abello, GlaxoSmithKline, Novartis, Zambon, outside the submitted work. Alberto Papi reports grants, personal fees and non-financial support from AstraZeneca, Menarini, grants, personal fees, nonfinancial support and other from Boehringer Ingelheim, Chiesi Farmaceutici, TEVA, personal fees, nonfinancial

support and other from GlaxoSmithKline, Mundipharma, Zambon, Novartis, Sanofi/Regeneron, personal fees from Roche, Edmondpharma, grants from Fondazione Maugeri, Fondazione Chiesi, outside the submitted work. Giovanni Paoletti does not have any conflict of interest to report. Giacomo Malipiero does not have any conflict of interest to report. Luisa Brussino does not have any conflict of interest to report. Claudia Crimi reports personal fees from Menarini. Daniela Morrone does not have any conflict of interest to report. Marianna Padovani does not have any conflict of interest to report. Giuseppe Guida does not have any conflict of interest to report. Alberto Giovanni Gerli does not have any conflict of interest to report. Stefano Centanni reports personal fees from GLAXOSMITHKLINE, NOVARTIS, MENARINI SPA, GUIDOTTI MALESCI, and grants and personal fees from CHIESI SPA, ASTRA ZENECA, VALEAS, BOEHRINGER INGELHEIM, outside the submitted work. Gianenrico Senna does not have any conflict of interest to report. Pierluigi Paggiaro reports grants and personal fees from AstraZeneca, Chiesi, Novartis and Sanofi, and personal fees from GlaxoSmithKline, Guidotti, Mundipharma, outside the submitted work. Francesco Blasi reports grants and personal fees from Astrazeneca, Chiesi, GSK, Pfizer and Insmmed, grants from Bayer, and personal fees from Guidotti, Grifols, Menarini, Mundipharma, Novartis and Zambon, outside the submitted work. Giorgio Walter Canonica reports grants as well as lecture or advisory board fees from: A. Menarini, Alk-Abello, Allergy Therapeutics, AstraZeneca, Boehringer-Ingelheim, Chiesi Farmaceutici, Genentech, Guidotti-Malesci, Glaxo Smith Kline, Hal Allergy, Mylan, Merck, Mundipharma, Novartis, Regeneron, Sanofi-Aventis, Sanofi-Genzyme, StallergenesGreer, UCB pharma, Uriach Pharma, Valeas, ViborPharma.

FUNDING INFORMATION

SANI is supported through unrestricted grants by AstraZeneca, Glaxo Smith Kline, Novartis & Sanofi Genzyme.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

APPENDIX 1

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