Correspondence
Riccardo Asero, Ambulatorio di Allergologia, Clinica San Carlo, Via Ospedale 21, 20037 Paderno Dugnano (MI), Italy.
Email: r.asero@libero.it

ORCID
Enrico Scala https://orcid.org/0000-0002-9391-9168
Riccardo Asero https://orcid.org/0000-0002-8277-1700

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733. [e-pub].
2. Soresina A, Moratto D, Chiarini M, et al. Favorable outcome of COVID19 in two patients with X-linked agammaglobulinemia. *Pediatric Allergy Immunol*. 2020. https://doi.org/10.1111/pai.13263
3. Wynn TA. Type 2 cytokines: mechanisms and therapeutic strategies. *Nat Rev Immunol*. 2015;15:271-282.
4. Berger A. Th1 and Th2 responses: what are they? *BMJ*. 2000;321(7258):424.
5. Callow KA, Tyrrell DA, Shaw RJ, Fitzharris P, Wardlaw AJ, Kay AB. Influence of atopy on the clinical manifestations of coronavirus infection in adult volunteers. *Clin Allergy*. 1988;18:119-129.
6. Jackson JJ, Busse WW, Bacarier LB, et al. Association of respiratory allergy, asthma and expression of the SARS-CoV-2 receptor, ACE2. *J Allergy Clin Immunol*. 2020;146(1):203. in press.
7. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061.
8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506.
9. Teijaro JR, Walsh KB, Rice S, Rosen H, Oldstone MB. Mapping the innate signalling cascade essential for cytokine storm during influenza virus infection. *Proc Natl Acad Sci USA*. 2014;111(10):3799-3804.
10. Carli G, Cecchi L, Stebbing J, Parronchi P, Farsi A. Is asthma protective against COVID-19? *Allergy*. 2021;76:866–936.
11. Heffler E, Detoraki A, Contoli M, et al. COVID-19 in severe asthma network in Italy (SANI) patients: clinical features, impact of comorbidities and treatments. *Allergy*. 2020. https://doi.org/10.1111/all.14532

SUPPORTING INFORMATION

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

DOI: 10.1111/all.14558

Severe asthma in adults does not significantly affect the outcome of COVID-19 disease: Results from the Italian Severe Asthma Registry

To the Editor,

Severe asthma is a chronic disease affecting around 3%-8% of adult asthma population in Europe, with the refractory form estimated to occur in 0.1% of the general population.[1,2] Severe asthma is characterized by increased use of healthcare resources (ie, emergency room/hospital admissions, access to intensive care units (ICU), and use of biologics) due to exacerbations compared with the less severe form. In the current SARS-CoV-2 pandemic, there is an ongoing debate on the role of asthma and use of immunomodulating drugs, like corticosteroids and biologics, on COVID-19 outcomes. According to available data on COVID-19 hospitalizations, asthma seems to play little role on the clinical severity or access to health resources, unlike other chronic conditions such as hypertension, obesity, and chronic obstructive pulmonary disease.[3] However, to date, no information is available on the burden of severe asthma on COVID-19 severity and hospitalization rates.

A questionnaire was submitted to clinicians of the Italian Registry of Severe Asthma (IRSA) network,[4] assessing the prevalence and clinical characteristics of patients with severe asthma who contracted COVID-19 during the outbreak in Italy (February 24, 2020 to May 18, 2020), and 41 out of 78 centers distributed evenly among different Italian regions participated to the survey, covering 65.6% of the total subjects of the IRSA registry (Figure 1).

Among the 558 subjects surveyed, 7 subjects contracted COVID-19 (1.25% of the national sample), 2 showing suggestive symptoms, 4 confirmed by positive reverse transcriptase-polymerase chain reaction and 1 with positive serology testing, with an average age of 54.5 years: 5 isolated at home/received home care (71.5%), while 2 subjects were admitted to the hospital (28.5%), none required accessed to ICU and no deaths were reported. All COVID-19 subjects with severe asthma came from 2 regions of Northern Italy (6 Lombardy, 1 Emilia-Romagna, 3.7% of the regional population), all showing one or more comorbidities and were treated with medium/high-dose inhaled corticosteroids plus long-acting beta-2 agonists (ICS-LABA) and biologics (Table 1).

We then compared our results with data provided by the Italian Department for Civil Protection in the same time period from the affected geographic areas,[5] and we observed that the frequency of COVID-19 among subjects referred to IRSA centers strongly correlated with the prevalence of SARS-CoV-2 infection in the corresponding province (r = .798, P = .025, Spearman rho test).

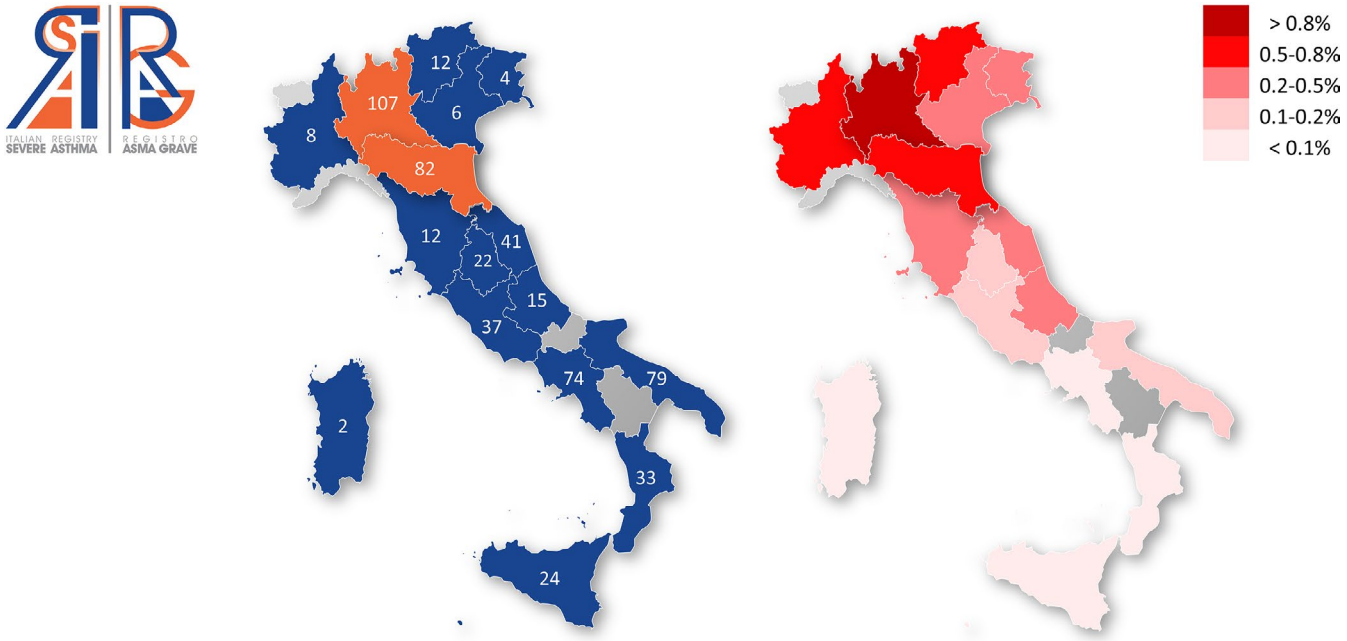

FIGURE 1 Distribution of IRSA Centers with number of surveyed subjects per region (left) and percent prevalence of COVID-19 cases per inhabitants per region (adapted from data of the Department of Civil Protection, 18/05/2020 report) (right)

Furthermore, the hospitalization rate in COVID-19+ subjects with severe asthma was not significantly different from the general population (24.1%, 23.6-24.6 95% CI; $P = .25$, Chi-squared test). Lastly, we could not observe a significantly increased COVID-19 frequency in subjects undergoing high-dose ICS-LABA and biologics (7/129, 5.43%) compared to subjects treated with ICS-LABA alone (0/60, 0%) coming from the same high-risk areas ($P = .09$, Fisher exact test).

These findings from the IRSA registry offer some insights on the susceptibility to SARS-CoV-2 infection, access to healthcare resources and mortality by severe asthma patients.

Given the low prevalence of severe asthma in Italy,[2] we expected less COVID-19 cases per region than what reported by the IRSA survey. However, we observed that the geographic location of COVID-19 patients with severe asthma mostly reflected the bimodal distribution of the COVID-19 outbreak in Italy, mainly clustered in Lombardy and neighboring regions, where the highest cumulative COVID-19 cases were recorded (>500/100 000 cases per inhabitants).[5] In these areas, the prevalence of positive cases by province also strongly correlated with the frequency of COVID-19+ asthma patients observed in each IRSA center, suggesting that patients with severe asthma most likely contract the infection when high circulation of the virus within the area of residence is present. The lack of positive cases reported in Southern regions further proves this hypothesis and demonstrates the efficacy of the lockdown measures adopted to contain the further spread of the virus.

Our results also suggest no increased risk of contracting COVID-19 in SA treated with biologics compared to ICS-LABA alone. Although there is currently no strong evidence that biologics used in asthma might affect the risk of contracting COVID-19, new evidence suggests a protective effect of inhaled corticosteroids against viral entry by ACE2 receptor downregulation, that are usually prescribed at a high dose in severe asthma,[6] thus a possible explanation to the lack of observed differences in our cohort.

Despite the severity of asthma and reported comorbidities, no ICU admissions were reported, and hospital admissions in COVID-19+ subjects with severe asthma did not differ from the median rate observed in the same geographic areas.[5] Furthermore, we could observe no difference in the median monthly hospitalization rate of severe asthma patients in 2019 compared with 2020 in Lombardy region where both hospital-admitted subjects reside (0.97% vs 0.9%, IRSA data).

Our result is consistent with recent literature, showing that asthma in Western countries was not associated with an increased hospitalization rate and ICU admissions due to COVID-19.[3,7] It is still debated if a protective effect of Th2-inflammation in a significant proportion of asthma sufferers,[8] or concomitant anti-inflammatory therapy could be the reasons for such outcomes.[6] However, if asthma patients with COVID-19 require intubation, the duration of hospitalization was shown to be longer than average.[7]

As for the role of biologics in COVID-19 disease progression, we could not observe an increase in hospital admissions in patients with severe asthma treated with biologics compared to the general population, with the majority isolating at home and requiring no additional treatment. Considering that, in areas with high prevalence of SARS-CoV-2 infection, 68.2% of severe asthma subjects were treated with either omalizumab (46.9%), mepolizumab (39.1%), or benralizumab (14%), our observations further suggest the safety of biologics during the COVID-19 pandemic.

TABLE 1 Clinical characteristics of subjects with severe asthma and COVID-19 (n = 7)

Demographic data							Comorbidities		
IRSA center id.	Region	Province	Pt. ID	Sex	Age	BMI	Smoking (active)	Hypertension	Nasal polyps
25	E-R	R. Emilia	1	F	48	32.1	No	No	No
40	Lombardy	Bergamo	2	F	65	24.5	No	Yes	No
46	Lombardy	Milan	3	F	40	29	No	No	Yes
102	Lombardy	Cremona	4	F	51	25.2	No	No	Yes
114	Lombardy	Brescia	5	F	57	22.3	No	Yes	Yes
114	Lombardy	Brescia	6	M	65	26.1	No	No	No
114	Lombardy	Brescia	7	F	56	17.9	No	No	Yes
Average	-	-	-	-	54.6	25.3	-	-	-
SD	-	-	-	-	8.4	4.2	-	-	-

(Continues)

Lastly, we did not observe any deaths in our cohort, but we speculate that this outcome is most likely due to the small sample size and younger average age. In fact, advanced age seems to be the most determining risk factor on mortality due to COVID-19 compared with other causes.[9]

Taken together, our results point at a neutral role of severe asthma in the COVID-19 disease course and hospital admissions. One major strength of our study is that, by using a fast and inexpensive tool, we could outline the salient features of severe asthma and COVID-19 at a national level, while the major weakness is the limited number of severe asthma subjects diagnosed with COVID-19 that could lead to sampling bias and low accuracy. Further confirmation of these results with an increased sample size is therefore warranted.

Despite the clinical burden of severe asthma is substantial, there is evidence of a neutral effect of severe asthma in the clinical progression and hospitalization due to COVID-19 in a cohort of Italian severe asthma patients. Treatment with biologics for severe asthma also seems to have no significant effect on the outcome of COVID-19.

ACKNOWLEDGMENTS

The authors wish to thank Centro Studi AIPO-ITS for its invaluable support in the generation of the data.

CONFLICT OF INTEREST

LA was an invited speaker by Novartis, GlaxoSmithKline, AstraZeneca, Sanofi Genzyme, Chiesi Group and Menarini. LR reports fees as invited speaker by Chiesi Group and GlaxoSmithKline. FB was an invited speaker by Chiesi Group, AstraZeneca, Novartis, Menarini, Roche and Boehringer Ingelheim. FDM declares fees as speaker/lecturer and Advisor Board by AstraZeneca and GlaxoSmithKline. AM declares Advisory Board fees from AstraZeneca, GlaxoSmithKline, Mylan, Sanofi Genzyme. CM was an invited speaker by Novartis, GlaxoSmithKline, AstraZeneca, Sanofi Genzyme, Chiesi Group, Menarini, Guidotti, Zambon, and Berlin Chemie. MBB declares receiving fees as invited speaker/lecturer by GlaxoSmithKline. CT, GM, AV, AS, and FM have no conflict of interest to disclose.

FUNDING INFORMATION

The Italian Registry for Severe Asthma (IRSA) is co-funded by the Italian Thoracic Society (ITS - AIPO) and the Italian Association of Territorial and Hospital Allergists and Immunologists (AAIITO).

DATA AVAILABILITY STATEMENT

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

KEYWORDS

asthma, asthma treatment, biologics, infections, virus

Leonardo Antonicelli[1]
Chiara Tontini[1]
Giuseppina Manzotti[2]
Luca Ronchi[3]
Adriano Vaghi[4,5]
Francesco Bini[4]
Alessandro Scartabellati[6]
Francesco Menzella[7]
Fausto De Michele[8]
Antonino Musarra[9]
Claudio Micheletto[10]
Maria Beatrice Bilò[11]

[1]*Allergy Unit, Department of Internal Medicine, Azienda Ospedaliero Universitaria Ospedali Riuniti Umberto I G M Lancisi G Salesi, Ancona, Italy*
[2]*Allergy Outpatient Clinic, Casa di Cura B. Palazzolo, Bergamo,*

TABLE 1 (Continued)

			Asthma treatment				
Bronchiectasis	GERD	Comorbidities (n.)	Treatment	ICS, daily dose (μg)	Add-on biologic drug	COVID-19 severity	ICU
No	No	1 (Obesity)	ICS + LABA	FP, 1000	Omalizumab	Home care	-
No	No	1	ICS + LABA + OCS	FP, 1000	Omalizumab	Hospitalized	No
Yes	No	2	ICS + LABA + LAMA	Bu, 960	Mepolizumab	Home care	-
Yes	No	2	ICS + LABA + LAMA	Be, 800	Omalizumab	Home care	-
Yes	No	3	ICS + LABA + LAMA	FF, 184	Mepolizumab	Hospitalized	No
No	Yes	1	ICS + LABA + LAMA	FF, 184	Mepolizumab	Home care	-
No	No	1	ICS + LABA	FF, 94	Mepolizumab	Home care	-
-	-	1.6	-	-	-	-	
-	-	0.7	-	-	-	-	

Abbreviations: Be, Beclomethasone; BMI, body mass index; Bu, Budesonide; E-R, Emilia-Romagna; FF, Fluticasone Furoate; FP, Fluticasone Propionate; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroids; ICU, intensive care unit; IRSA, Italian Registry of Severe Asthma; LABA, long-acting beta-2 agonists; LAMA, long-acting muscarinic antagonists; OCS, oral corticosteroids; SD, standard deviation.

Italy
[3]*Pneumology Unit, ASST Franciacorta, "Mellino Mellini" Hospital, Chiari, Italy*
[4]*Pneumology Unit, ASST Rhodense, Garbagnate Milanese Hospital, Garbagnate Milanese, Italy*
[5]*Former Pneumology Unit, ASST Rhodense, Garbagnate Milanese Hospital, Garbagnate Milanese, Italy*
[6]*Pneumology Unit, ASST Crema, Maggiore Hospital, Crema, Italy*
[7]*Pneumology Unit, Department of Medical Specialties, Arcispedale Santa Maria Nuova, Azienda USL di Reggio-Emilia IRCCS, Reggio Emilia, Italy*
[8]*Pneumology I and Respiratory Pathophysiology Unit, A. Cardarelli Hospital, Naples, Italy*
[9]*Allergology Department, Casa della Salute di Scilla, Scilla, Italy*
[10]*Respiratory Unit, Cardio-Thoracic Department, Integrated University Hospital of Verona, Verona, Italy*
[11]*Allergy Unit, Department of Clinical and Molecular Sciences, Polytechnic University of Marche, Ancona, Italy*

Correspondence
Chiara Tontini, Allergy Unit, Department of Internal Medicine, Azienda Ospedaliero Universitaria Ospedali Riuniti Umberto I G M Lancisi G Salesi, Ancona, Italy.
Email: c.tontini@live.com

ORCID

Leonardo Antonicelli https://orcid.org/0000-0002-7669-9116
Chiara Tontini https://orcid.org/0000-0002-8437-8697
Maria Beatrice Bilò https://orcid.org/0000-0002-9324-6039

REFERENCES

1. Hekking PP, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol*. 2015;135:896-902.
2. Vianello A, Caminati M, Andretta M, et al. Prevalence of severe asthma according to the drug regulatory agency perspective: an Italian experience. *World Allergy Organ J*. 2019;12:100032.
3. Chhiba KD, Patel GB, Vu THT, et al. Prevalence and characterization of asthma in hospitalized and non-hospitalized patients with COVID-19. *J Allergy Clin Immunol*. 2020;146(2):307-314.e4.
4. Micheletto C, Bilò MB, Antonicelli L, et al. and on behalf of IRSA. Severe asthma in adolescents and adults: a national, multicenter registry in real life. *Eur Ann Allergy Clin Immunol*. 2018;5:196-201.
5. Department of civil protection coronavirus task force, National and Subregional data repository available on GitHub. https://github.com/pcm-dpc/COVID-19. Accessed June 10, 2020.
6. Peters MC, Sajuthi S, Deford P, et al. COVID-19 related genes in sputum cells in asthma: relationship to demographic features and corticosteroids. *Am J Respir Crit Care Med*. 2020;202(1):83-90.
7. Mahdavinia M, Foster KJ, Jauregui E, et al. Asthma prolongs intubation in COVID-19. *J Allergy Clin Immunol Pract*. 2020;8(7):2388-2391.
8. Carli G, Cecchi L, Stebbing J, Parronchi P, Farsi A. Is asthma protective against COVID-19? *Allergy*. 2021;76:866–936.
9. Davies NG, Klepac P, Liu Y, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat Med*. 2020;26(8):1205-1211.