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Short communication

COVID-19 infection in severe Alpha 1-antitrypsin deficiency: Looking for a rationale

I. Ferrarotti [a,*], S. Ottaviani [a], A.M. Balderacchi [a], V. Barzon [a], A. De Silvestri [b], D. Piloni [a], F. Mariani [a], A.G. Corsico [a]

[a] Centre for Diagnosis of Inherited Alpha-1 Antitrypsin Deficiency, Laboratory of Biochemistry and Genetics, Institute for Respiratory Disease, Department of Internal Medicine and Therapeutics, University of Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[b] Statistics Dept, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

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ABSTRACT

The clinical manifestations of COVID-19 are heterogeneous: 46.4% of patients admitted into hospital reported to have at least one comorbidity. Comorbidities such as COPD, diabetes, hypertension and malignancy predispose patients with Covid-19 to adverse clinical outcomes. Alpha 1-antitrypsin deficiency (AATD) is a genetic disorder caused by pathological mutation(s) in the SERPINA1 gene resulting in an imbalance in proteinase activity which may lead to premature emphysema and COPD.

Our aim was to investigate whether people with severe AAT deficiency (AATD) have an increased risk of (severe) COVID-19 infection.

We collected data on COVID-19 symptoms, laboratory-confirmed infection, hospitalization and treatment by means of a telephone survey, directly administered to Italian severe AATD subjects in May 2020. We then compared our findings with data collected by the Istituto Superiore di Sanità on the total population in Italy during the same period.

We found an higher frequency of SARS-CoV-2 infection in our cohort (3.8%) compared to national data regarding infection, thus giving severe AATD a relative risk of 8. 8 (95%CI 5.1-20,0; $p<0.0001$) for symptomatic SARS-CoV-2 infection. Moreover, the relative risk (RR) was higher in AATD patients with pre-existing lung diseases (RR 13.9; 95%CI 8.0-33.6; $p<0.001$), but with a similar death rate (1 in 8, 12.5%) compared to the general population (13.9%; RR 0.9).

These preliminary findings highlight the importance of close surveillance in the spread of COVID-19 in patients with severe AATD and underlines the need for further studies into the role of the antiprotease shield in preventing SARS-Cov-2 infection.

The spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) quickly took on pandemic proportions after March 2020, affecting over 100 countries in few weeks.

According to the literature, the clinical manifestations of COVID-19 are heterogeneous, with 46.4% of patients admitted into hospital reported as having at least one comorbidity [1].

Comorbidities such as COPD, diabetes, hypertension and malignancy predispose patients with Covid-19 to adverse clinical outcomes [2].

Alpha 1-antitrypsin (AAT) is the most abundant serum proteinase, whose deficiency caused by pathological mutation(s) in the SERPINA1 gene results in an imbalance in proteinase activity which may lead to proteolytic tissue damage and premature emphysema and COPD [3]. AAT also has a highly significant anti-inflammatory role with immunomodulatory properties [3]. Serine proteases, such as TMPRSS2 and TMPRSS4 enhance SARS-CoV-2 entry into enterocytes [4]. Moreover, a blunted AAT response to IL-16 has been observed in people with severe COVID-19 infections [5]. A recent paper looked into the potential role of AAT in COVID-19 infection [6]. Consequently, we investigated whether people with AAT deficiency (AATD) have an increased risk of (severe) COVID-19 infection.

With this aim, we collected data on COVID-19 symptoms, laboratory-confirmed infection, hospitalization and treatment by means of a telephone survey, directly administered to severe AATD subjects in May 2020, during Phase 2 of the lockdown in Italy. We compared our

* Corresponding author. V. le Golgi 19, 27100, Pavia, Italy.
E-mail address: ilaria.ferrarotti@unipv.it (I. Ferrarotti).

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Table 1
Demographic characteristics and clinical data of the full cohort and according to COVID-19 testing.

Variables	Total (n=209)	Not Tested (n = 191)	Tested, positive (n = 8)	Tested, negative (n = 10)	p-value
Males, n (%)	104 (49,8)	94 (49,2)	5 (62,5)	5 (50,0)	
Age (years), median (IQR)	57,0 (53,0–59,0)	57,0 (53,0–59,4)	54,5 (38,4–74,8)	46,0 (29,3–63,3)	
Smoke, n (%)					
Active smoker	27 (12,9)	25 (13,1)	–	2 (20,0)	
No smoker	100 (47,8)	92 (48,2)	3 (37,5)	5 (50.0)	
Former	82 (39,2)	74 (38,7)	5 (62,5)	3 (30,0)	
pack/years, median	5,1 (2,9–7,4)	5,2 (1,9–7,6)	12 (4,0–20,0)	18,7 (20,0–16,3)	
Genotype n (%)					
*PI*ZZ*	78 (37,3)	74 (38,8)	3 (37,5)	1 (10,0)	
*PI*SZ*	53 (25,4)	47 (24,6)	1 (12,5)	5 (50,0)	
Other genotypes	78 (37,3)	70 (36,6)	4 (50,0)	4 (40,0)	
AAT (mg/dL) median (IQR)	36,0 (31,0–45,0)	34,0 (30,0–40,0)	46,0 (22,0–70,0)	60,5 (44,4–78,9)	**0,04**
Lung diseases n (%), namely:	109 (52,1)	96 (50,3)	7 (87,5)	6 (60,0)	
Emphysema/COPD	77 (36,8)	72 (37.7)	4 (50,0)	1 (10,0)	
Asthma	22 (10,5)	17 (8,9)	2 (25,0)	3 (30,0)	
Bronchiectasis	7 (3,3)	5 (2,6)		2 (20,0)	
Other lung diseases	3 (1,4)	2 (1,0)	1 (12,5)	–	
Liver diseases	8 (3.8)	8 (4,2)	–	–	
Other Disease	8 (3.8)	8 (3.8)	–	–	
Healthy	80 (38,3)	75 (39,3)	1 (12,5)	4 (40,0)	
FEV1/FVC>70, n(%)	30 (14,3)	28 (14,7)	2 (25,0)	0	
Living in the most affected Italian Regions*, n (%)	122 (58,4)	110 (57,6)	7 (87.5)	6 (60,0)	
Living in Lombardy, n (%)	71 (34,0)	63 (33,0)	3 (37,5)	5 (50.0)	
Augmentation therapy n (%)	53 (25,4)	51 (26,7)	2 (25,0)	–	
Symptoms related to COVID-19, n (%)	29 (13,9)	20 (10,4)	8 (100)	1 (10,0)	
Hospital admission 3 (1,4) caused by COVID-19 n (%)		-	*3 (37,5)*	*0*	
Death n (%) 1 (0,5)		-	*1(12,5)*	-	

findings with data systematically collected by the Istituto Superiore di Sanità on the total population in Italy during the same period [7].

Inclusion criteria for the survey were age >18 years old and severely reduced serum AAT levels due to two inherited pathological alleles in the *SERPINA1* gene.

In total, we collected surveys from 209 subjects who answered to telephone calls out of 593 contacts (35%), derived from Italian Registry of Severe AATD. Prior to the pandemic, 113 (54.1%) of these subjects were suffering from lung diseases (emphysema, COPD, bronchiectasis, asthma) and 16 (7.7%) had other (mainly liver) diseases with no lung impairment. Eighty subjects (38.3%) were healthy and were likely detected because they were related to AATD patients or due to incidental diagnosis. Table 1 reports demographic and clinical data, AAT levels and SERPINA1 genotypes.

Interestingly, 122 subjects (58.4%) lived in regions with the highest levels of COVID-19 in Italy, 34% of whom in Lombardy, where the recorded rate of COVID-19 infections on 31st May 2020 [7] was the highest in Italy.

During the telephone survey, 29 subjects (13.9%) reported any symptoms that were most likely to be related to SARS-CoV-2 infection (discounting pre-existing symptoms), including fever, dry cough, sore throat, tiredness, diarrhoea, conjunctivitis, headache, loss of taste or smell and skin rash.

Eighteen subjects reported that they had had laboratory tests for SARS-CoV-2 on nasal swabs or blood samples (10 and 8 subjects, respectively). Of these, 8 turned out to be positive (6 nasal swabs and 2 blood tests), confirming a 3.8% SARS-CoV-2 incidence in our cohort. No specific risk factor for SARS-CoV-2 infection was found across categories, apart from AAT levels. On a regional level, 3 out of 71 (4.22%) subjects tested positive in Lombardy compared to 7 out of 122 (5.74%) in the most affected regions in Italy. These figures are higher than those reported in the general population (0.867% and 0.388% in Lombardy and Italy, respectively) [7].

Regarding the clinical impact of COVID-19 in AATD subjects, one patient, who was already long-term hospitalized because of severe lung impairment before COVID-19 infection, died. Seven out of 8 patients in the survey stated that their current health status was good, 3 of whom reported having been admitted into hospital for 3 days, 1 week and 2 months, respectively, with no need for intensive care. The other 4 subjects were treated at home with standard therapies.

The most intriguing data we gleaned from this survey is the higher frequency of SARS-CoV-2 infection in our cohort (3.8%) compared to national data regarding infection, thus giving severe AATD a relative risk of 8.8 (95%CI 5.1–20,0; $p < 0.0001$) for symptomatic SARS-CoV-2 infection. Moreover, the relative risk (RR) was higher in AATD patients with pre-existing lung diseases (5.4%) (RR 13.9; 95%CI 8.0–33.6; $p < 0.001$), but with a similar death rate (1 in 8, 12.5%) compared to the general population (13.9% [7]; RR 0.9). When we restricted the analysis to Lombardy, it emerged that patients with AATD had an approximate eight-fold risk of SARS-CoV-2 infection compared to the general population (RR 8.1; 95%CI 3.2–17.4; $p < 0.0001$) and an eleven-fold risk (RR 11.2; 95%CI 4.1–23.3; $p < 0.001$) if it was associated with pre-existing pulmonary diseases. We are aware that the findings could theoretically be subjected to selection bias, since the survey reached only 35% of the Italian cohort with Severe AATD. Anyway, if we assume that none of these two thirds not reached by the survey were positive, the incidence of SARS-Co-2 infection would have been higher (1,3%) than that of the general population.

Although the survey did not record individual behavior prior to the lockdown period, we might have justifiably expected hospital attendance to be a main risk factor for SARS-CoV-2 infection. However, only 2 out of 8 infected cases attended hospital on a weekly basis for augmentation therapy [3]. Moreover, we did not observe a statistically higher incidence of SARS-CoV-2 infection in patients treated with augmentation therapy in hospital (2/44; 4.5%) compared to other subjects (6/165; 3.6%).

Individuals with COPD have increased airway expression of ACE-2, which is the entry receptor for the COVID-19 virus [8]. The high frequency of emphysema and COPD in AATD patients could partially explain our data, since in our cohort only 29/113 patients (25.7%) reported lung obstruction and only one SARS-Cov-2 infected subject reported clinically-diagnosed COPD. A recent meta-analysis on

SARS-Cov-2 infection showed that individuals with pre-existing COPD have a fivefold increased risk of developing severe COVID-19 [9]. Our data is not able to indicate a worse prognosis of COVID-19 in AATD patients, since none of our infected subjects required intensive care.

A recent analysis identified a 3p21.31 gene cluster as a genetically susceptible locus in patients with Covid-19 and respiratory failure confirming the potential involvement of the ABO blood-group system [10]. The gene cluster 14p32.1 where SERPINA1 lies, didn't prove to be associated with COVID-19. Nevertheless, low frequency variants (such as those related to a rare disease like AATD) could contribute substantially to the missing heritability of a genetic trait and a possible association with specific clinical conditions can only be revealed in selected cohorts.

These preliminary findings highlight the importance of close surveillance in the spread of COVID-19 in patients with severe AATD and underlines the need for further studies into the role of the antiprotease shield in preventing SARS-Cov-2 infection.

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Ethics approval and consent to participate

This study is part of Italian Registry of Alpha 1-antitrypsin Deficiency (RIDA1), that received ethical approval by IRCCS Policlinico S. Matteo, Pavia (Italy) on 12th June 2019 (decreto n°0385). Informed consent from each patient has been obtained at the enrolment in the longitudinal study.

CRediT authorship contribution statement

I. Ferrarotti: Conceptualization, Methodology, Writing – original draft, preparation. **S. Ottaviani:** Methodology, Investigation, Writing – original draft, preparation. **A. Balderacchi:** Maria, Investigation, Formal analysis. **V. Barzon:** Investigation, Formal analysis. **A. De Silvestri:** Formal analysis, Writing – review & editing. **D. Piloni:** Formal analysis, Writing – original draft, preparation. **F. Mariani:** Formal analysis, Writing – review & editing. **A.G. Corsico:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, J. Am. Med. Assoc. 323 (2020) 1061–1069.

[2] W.J. Guan, W.H. Liang, Y. Zhao, H.R. Liang, Z.S. Chen, Y.M. Li, X.Q. Liu, R.C. Chen, C.L. Tang, T. Wang, C.Q. Ou, L. Li, P.Y. Chen, L. Sang, W. Wang, J.F. Li, C.C. Li, L. M. Ou, B. Cheng, S. Xiong, Z.Y. Ni, J. Xiang, Y. Hu, L. Liu, H. Shan, C.L. Lei, Y. X. Peng, L. Wei, Y. Liu, Y.H. Hu, P. Peng, J.M. Wang, J.Y. Liu, Z. Chen, G. Li, Z. J. Zheng, S.Q. Qiu, J. Luo, C.J. Ye, S.Y. Zhu, L.L. Cheng, F. Ye, S.Y. Li, J.P. Zheng, N.F. Zhang, N.S. Zhong, J.X. He, China Medical Treatment Expert Group for COVID-19Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis, Eur. Respir. J. 55 (2020) 2000547.

[3] C.M. Greene, S.J. Marciniak, J. Teckman, I. Ferrarotti, M.L. Brantly, D.A. Lomas, J. K. Stoller, N.G. McElvaney, Alpha 1-Antitrypsin deficiency, Nat. Rev. Dis. Primers 28 (2016) 16051, 2.

[4] R. Zang, M.F. Gomez Castro, B.T. McCune, Q. Zeng, P.W. Rothlauf, N.M. Sonnek, Z. Liu, K.F. Brulois, X. Wang, H.B. Greenberg, M.S. Diamond, M.A. Ciorba, S.P. J. Whelan, S. Ding, TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes, Sci. Immunol. 5 (2020), eabc3582.

[5] O.J. McElvaney, N.L. McEvoy, O.F. McElvaney, T.P. Carroll, M.P. Murphy, D. M. Dunlea, O. Ní Choileáin, J. Clarke, E. O'Connor, G. Hogan, D. Ryan, I. Sulaiman, C. Gunaratnam, P. Branagan, M.E. O'Brien, R.K. Morgan, R.W. Costello, K. Hurley, S. Walsh, E. de Barra, C. McNally, S. McConkey, F. Boland, S. Galvin, F. Kiernan, J. O'Rourke, R. Dwyer, M. Power, P. Geoghegan, C. Larkin, R.A. O'Leary, J. Freeman, A. Gaffney, B. Marsh, G.F. Curley, N.G. McElvaney, Characterization of the inflammatory response to severe COVID-19 illness, Am. J. Respir. Crit. Care Med. 202 (2020) 812–821.

[6] K.Y. Oguntuyo, C.S. Stevens, M.N. Siddiquey, R.M. Schilke, M.D. Woolard, H. Zhang, J.A. Acklin, S. Ikegame, C.T. Hung, J.K. Lim, R.W. Cross, T.W. Geisbert, S.S. Ivanov, J.P. Kamil, B. Lee, In plain sight: the role of alpha-1-antitrypsin in COVID-19 pathogenesis and therapeutics, bioRxiv 14 (2020) 248880, 08.

[7] Istituto Superiore di Sanitá, ISS, SARS-Cov-2. https://www.epicentro.iss.it/en/coronavirus/. (Accessed 31 May 2020). Date last accessed.

[8] J.M. Leung, C.X. Yang, A. Tam, T. Shaipanich, T.L. Hackett, G.K. Singhera, D. R. Dorscheid, Sin DD ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19, Eur. Respir. J. 55 (2020) 2000688.

[9] G. Lippi, B.M. Henry, Chronic obstructive pulmonary disease is associated with severe coronavirus disease 2019 (COVID-19), Respir. Med. 167 (2020) 105941.

[10] D. Ellinghaus, F. Degenhardt, L. Bujanda, M. Buti, A. Albillos, P. Invernizzi, J. Fernández, D. Prati, G. Baselli, R. Asselta, M.M. Grimsrud, C. Milani, F. Aziz, J. Kässens, S. May, M. Wendorff, L. Wienbrandt, F. Uellendahl-Werth, T. Zheng, X. Yi, R. de Pablo, A.G. Chercoles, A. Palom, A.E. Garcia-Fernandez, F. Rodriguez-Frias, A. Zanella, A. Bandera, A. Protti, A. Aghemo, A. Lleo, A. Biondi, A. Caballero-Garralda, A. Gori, A. Tanck, A. Carreras Nolla, A. Latiano, A.L. Fracanzani, A. Peschuck, A. Julià, A. Pesenti, A. Voza, D. Jiménez, B. Mateos, B. Nafria Jimenez, C. Quereda, C. Paccapelo, C. Gassner, C. Angelini, C. Cea, A. Solier, D. Pestaña, E. Muñiz-Diaz, E. Sandoval, E.M. Paraboschi, E. Navas, F. García Sánchez, F. Ceriotti, F. Martinelli-Boneschi, F. Peyvandi, F. Blasi, L. Téllez, A. Blanco-Grau, G. Hemmrich-Stanisak, G. Grasselli, G. Costantino, G. Cardamone, G. Foti, S. Aneli, H. Kurihara, H. ElAbd, I. My, I. Galván-Femenia, J. Martín, J. Erdmann, J. Ferrusquía-Acosta, K. Garcia-Etxebarria, L. Izquierdo-Sanchez, L. R. Bettini, L. Sumoy, L. Terranova, L. Moreira, L. Santoro, L. Scudeller, F. Mesonero, L. Roade, M.C. Rühlemann, M. Schaefer, M. Carrabba, M. Riveiro-Barciela, M.E. Figuera Basso, M.G. Valsecchi, M. Hernandez-Tejero, M. Acosta-Herrera, M. D'Angiò, M. Baldini, M. Cazzaniga, M. Schulzky, M. Cecconi, M. Wittig, M. Ciccarelli, M. Rodríguez-Gandía, M. Bocciolone, M. Miozzo, N. Montano, N. Braun, N. Sacchi, N. Martínez, O. Özer, O. Palmieri, P. Faverio, P. Preatoni, P. Bonfanti, P. Omodei, P. Tentorio, P. Castro, P.M. Rodrigues, A. Blandino Ortiz, R. de Cid, R. Ferrer, R. Gualtierotti, R. Nieto, S. Goerg, S. Badalamenti, S. Marsal, G. Matullo, S. Pelusi, S. Juzenas, S. Aliberti, V. Monzani, V. Moreno, T. Wesse, T.L. Lenz, T. Pumarola, V. Rimoldi, S. Bosari, W. Albrecht, W. Peter, M. Romero-Gómez, M. D'Amato, S. Duga, J.M. Banales, J.R. Hov, T. Folseraas, L. Valenti, A. Franke, T.H. Karlsen, Severe Covid-19 GWAS group. Genomewide association study of severe Covid-19 with respiratory failure, N. Engl. J. Med. 383 (2020) 1522–1534.