FÓRUM PRIMAVERA

DAS **COMISSÕES** DE **TRABALHO**

05 | 06 MAIO 2023
PORTO
TRYP Porto Expo Hotel

COMISSÃO DE TRABALHO DE FISIOPATOLOGIA RESPIRATÓRIA E DPOC

COMISSÃO DE TRABALHO DE TABAGISMO

COMISSÃO DE TRABALHO DE TUBERCULOSE

GRUPO DE ESTUDOS DE DÉFICE DE ALFA-1 ANTITRIPSINA

COMISSÃO DE TRABALHO DE DOENÇAS DO INTERSTÍCIO PULMONAR

COMISSÃO DE TRABALHO DE DOENTE CRÍTICO RESPIRATÓRIO

COMISSÃO DE TRABALHO DE PATOLOGIA RESPIRATÓRIA DO SONO

NÚCLEO DE CARDIOPNEUMOLOGISTAS

SPP SOCIEDADE PORTUGUESA DE PNEUMOLOGIA

Pulmonology Journal

volume 29 / number 3 / May/June 2023

PULMONOLOGY JOURNAL

Previously **Revista Portuguesa de Pneumologia**

volume 29 / number 3 / May/June 2023

Editorial

Commentary

Original articles

COPD

Covid-19

Respiratory sleep disorders

ISSN 2531-0437

www.journalpulmonology.org

SPP SOCIEDADE PORTUGUESA DE PNEUMOLOGIA

SPP SOCIEDADE PORTUGUESA DE PNEUMOLOGIA

www.sppneumologia.pt

Published every 2 months (6 issues per year).
www.journalpulmonology.org
Reprints information:
Clarissa Felix: c.felix@elsevier.com
Subscription of printed version available

One issue	30.00 € (VAT not included)
Anual	120.00 € (VAT not included)

(prices valid only for Portugal)
Subscriptions orders: geral@sppneumologia.pt

ELSEVIER
Av. Josep Tarradellas, 20-30, 1º
08029 Barcelona (Spain)
Phone: +34 932 000 711
Paseo de la Castellana, 163
28046 Madrid (Spain)
Phone: +34 914 021 212

Data protection: Elsevier España, S.L.U.. declares that it complies with that established by Organic Law 3/2018, of December 5, Protection of Personal Data and Guarantee of Digital Rights (LOPDGDD).
Indexed in: Science Citation Index Expanded (SCIE), Journal of Citation Reports (JCR), Index Medicus/MEDLINE, Scopus, EMBASE/Excerpt Medica
ISSN 2531-0437 (online)
Register 122.190 of Gabinete para os Meios de Comunicação Social
Printed in Spain
Printed in acid free paper
Legal deposit: B-20.760-2019

PULMONOLOGY

PULMONOLOGY

www.journalpulmonology.org

Volume 29. Number 3. May/June 2023

CONTENTS

Pulmonology 29 (2023) 179—183

PULMONOLOGY

www.journalpulmonology.org

EDITORIAL

Asthma hospitalizations: A call for a national strategy to fight health inequities

Health inequities are differences in the health status or the distribution of health resources between different population groups, arising from the social conditions in which people are born, grow, live, work and age.[1] Such inequities have high social and economic costs for individuals and societies worldwide.[1] Lower socioeconomic status is among the risk factors associated with worse health outcomes and leads to a higher rate of potentially preventable hospital admissions.[2] This may reflect regional differences in access to healthcare (e.g., delays in access to secondary care) and primary care quality, which have been significantly associated with avoidable emergency admissions.[3-5] This is especially important for chronic conditions in which proper management may avoid exacerbations,[6,7] as is the case of asthma.[8] There is evidence that people with asthma living in deprived areas may have impaired asthma outcomes across all stages of patient care, leading to a higher rate of hospitalizations and risk of asthma-related deaths.[9,10] As health inequities have remained insufficiently studied in Portugal, in particular regarding access to care,[11] we assessed whether such inequities may occur in Portugal as well, by studying the association between the region of residence and the frequency of asthma hospitalizations.

In mainland Portugal, between 2011 and 2015, there were 9161 asthma hospitalizations in adults, according to data from the national administrative database containing all hospitalizations in public hospitals from mainland Portugal (ICD-9-CM code 493.x). Therefore, there was an average of 92.6 hospital admissions per 100,000 inhabitants and 13.5 hospital admissions per 1000 inhabitants with asthma. Mainland Portugal is composed of 18 districts (Fig. 1A). The districts with the highest rates of asthma hospital admissions per 100,000 inhabitants were Coimbra (213.2 hospitalizations per 100,000 inhabitants), Castelo Branco (160.6/100,000), Viseu (155.4/100,000) and Guarda (140.9/100,000), all of which are in the center region of Portugal and are (except for Coimbra) inland districts. Taking into account the prevalence data from the most recent Portuguese epidemiological survey carried out in 2010[12] (Fig. 1B), the three districts with the most prevalence-adjusted asthma hospital admissions were Guarda (82.9 hospitalisations per 1000 inhabitants with asthma), Castelo Branco (32.8/1000), and Viseu (29.9/1000). All these three districts have a low urban coverage. Importantly, Coimbra, an urban district in coastal Portugal, is not among the districts with the highest rate of prevalence-adjusted hospital admissions, despite being among the districts displaying the highest crude hospitalization rate for asthma.

The inland regions of Portugal are, on average, less urbanized than its coastal regions,[13] and Guarda, Viseu and Castelo Branco are among the districts with the least purchasing power (according to data from the National Institute of Statistics[14] and defined according to its published definition[15]), so it is possible that such results could be partially explained by socioeconomic disadvantage. It is also known that the population in inland Portugal is, on average, older than its coastal counterpart. Guarda and Castelo Branco are in the top three districts with the highest aging index (proportion of inhabitants aged 65 years or older relative to those younger than 15 years older) in Portugal.[16] Several comorbidities are associated with asthma in the elderly, which may complicate asthma management in these patients.[17] Older age is also associated with lower literacy, which may hinder adherence to treatment in chronic diseases in elderly people.[18] As a result, differences in age distribution between districts in mainland Portugal may partially explain the differences in hospital admissions for asthma. Additionally, according to data from the Portuguese Medical Association, districts in inland Portugal, especially Guarda and Castelo Branco, are also among those with fewer registered physicians per 100,000 inhabitants.[19]

Nevertheless, even when adjusting for purchasing power, aging index and density of registered physicians in Portuguese districts, these three districts still showed the highest number of prevalence-adjusted asthma hospital admissions (Fig. 1D-F; Table 1). This suggests potential regional health inequities that are not solely explained by factors such as age and purchasing power and may reflect the ongoing asthma

https://doi.org/10.1016/j.pulmoe.2022.12.001

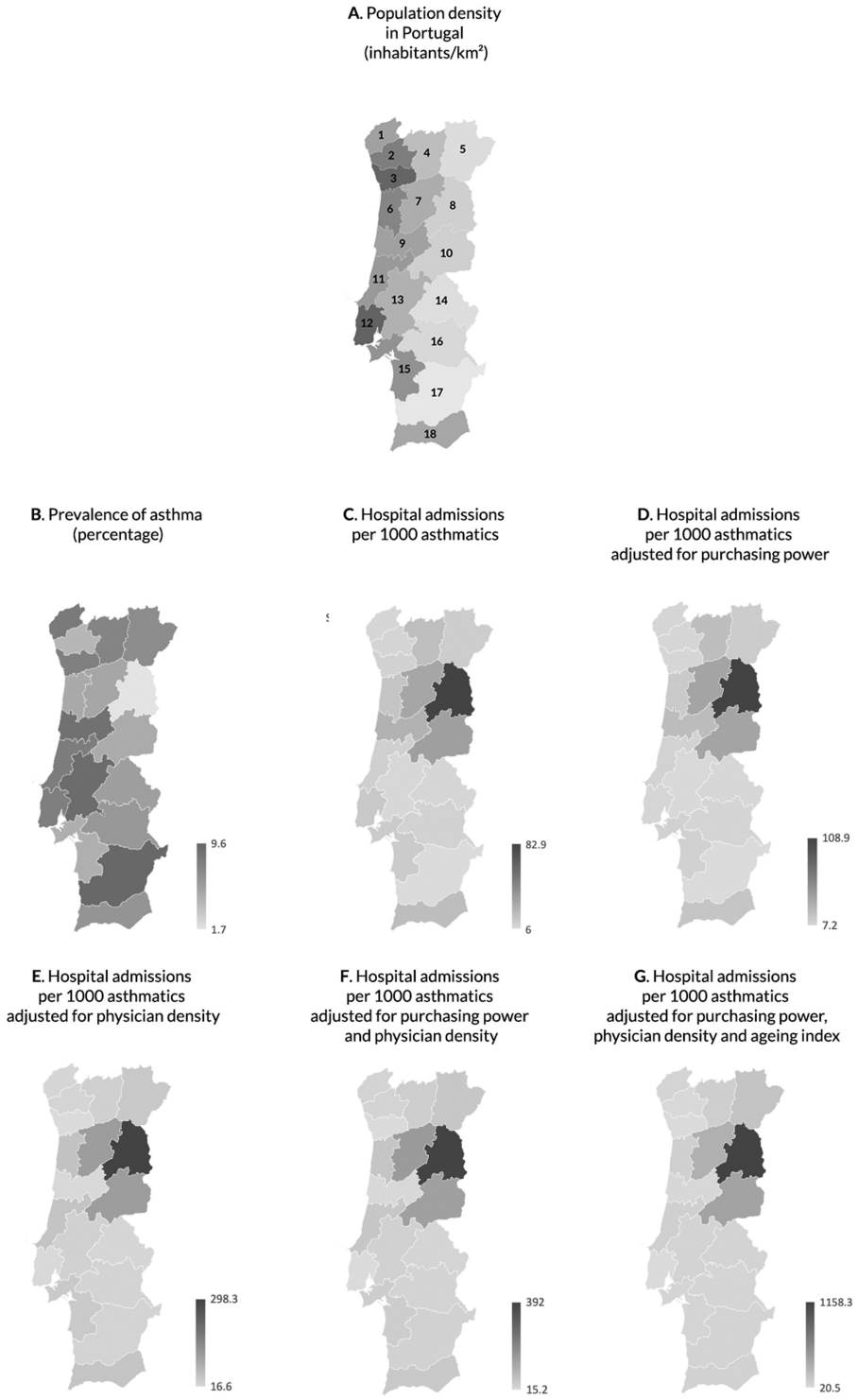

Fig. 1 Data on **(A)** population density per district in mainland Portugal (1 — Viana do Castelo, 2 — Braga, 3 — Porto, 4 — Vila Real, 5 — Bragança, 6 — Aveiro, 7 — Viseu, 8 — Guarda, 9 — Coimbra, 10 — Castelo Branco, 11 — Leiria, 12 — Lisboa, 13 — Santarém, 14 — Portalegre, 15 — Setúbal, 16 — Évora, 17 — Beja, 18 — Faro); **(B)** asthma prevalence in mainland Portugal (percentage), and on asthma hospital admissions in mainland Portugal **(C)** per 1000 patients with asthma; **(D)** per 1000 patients with asthma and adjusted for a purchasing power of 100% *per capita*; **(E)** per 1000 patients with asthma and adjusted for a standard population with 1000 physicians per 100,000 inhabitants; **(F)** per 1000 patients with asthma and adjusted for a purchasing power of 100% *per capita* and a standard population with 1000 physicians per 100,000 inhabitants; and **(G)** per 1000 patients with asthma and adjusted for a purchasing power of 100% *per capita* and a standard population with 1000 physicians per 100,000 inhabitants and an aging index of 100.

Table 1 Prevalence of asthma and hospital admissions for asthma per district of mainland Portugal.

	Prevalence of asthma,%	Hospital admissions, *n*	Hospital admissions per 100,000 inhabitants, *n*	Hospital admissions per 1000 asthmatics, *n*			
				Unadjusted	adjusted for purchasing power	adjusted for physician density	adjusted for purchasing power and physician density
Aveiro	5.0	552	78.3	15.7	17.5	55.8	62.3
Beja	9.6	86	58.0	6.0	7.2	28.3	34.0
Braga	4.2	413	36.7	8.7	10.2	26.2	30.7
Bragança	6.8	108	82.7	12.2	15.7	45.7	58.8
Castelo Branco	4.9	302	160.6	32.8	39.6	119.8	144.5
Coimbra	8.8	888	213.2	24.2	25.3	20.7	21.6
Évora	6.1	96	59.6	9.8	10.7	28.3	30.8
Faro	6.3	536	121.1	19.2	20.0	52.4	54.5
Guarda	1.7	216	140.9	82.9	108.9	298.3	392.0
Leiria	7.9	398	85.8	10.9	12.0	53.5	58.8
Lisboa	7.8	2423	108.2	13.9	10.4	20.3	15.2
Portalegre	5.6	52	46.0	8.2	9.6	24.6	28.9
Porto	7.7	1386	77.3	10.0	9.9	16.6	16.5
Santarém	9.2	302	68.0	7.4	8.3	33.1	37.2
Setúbal	4.6	501	58.8	12.8	12.8	45.0	45.0
Viana do Castelo	8.1	158	66.1	8.2	10.3	25.1	31.4
Vila Real	7.4	277	138.7	18.7	24.1	34.3	44.2
Viseu	5.2	571	155.4	29.9	39.2	121.0	158.6

management available/provided in different regions. This suggests that inequities in access to healthcare services may hinder asthma management in these inland districts. The results of this study may be a model to be implemented in other underserved populations in Europe and globally.

Early asthma diagnosis and vigilant control are crucial to prevent asthma exacerbations and reduce the healthcare burden. Initiatives in Finland, Poland and Brazil have shown that prioritizing asthma care and placing primary care at the center of asthma care reduce both asthma morbidity and mortality.[20,21] However, the Global Initiative for Asthma (GINA) guidelines have primarily been developed and tailored by tertiary care physicians and may be challenging to implement in primary care, particularly when physicians' density is low.[22-24] More easy-to-implement and patient-centered care pathways for asthma, including all health care professionals, are needed. Additionally, as medication adherence in asthma tends to be poor,[25] tailored, integrated and transdisciplinary approaches to raise asthma literacy in disfavored regions could increase adherence to medication by patients. Moreover, digital solutions may be of use to improve asthma care, especially for regions with suboptimal access to healthcare services. Telemedicine may facilitate access to asthma clinical reviews and allow for remote patient monitoring, thus preventing exacerbations.[26] Emerging technologies, such as monitoring devices and mobile apps, may further improve asthma care. The potential of mobile apps for patient-centered care has been previously shown for allergic rhinitis[27], and there are reasons to believe such may apply to asthma care as well.[28] Apps may therefore provide information on asthma-related triggers, such as pollen season and pollution, and feedback from mobile apps may be used by the patient and the physician to improve asthma management.[29]

In conclusion, our results suggest the existence of health inequities in asthma management in mainland Portugal and an urgent call for action from policy makers. This issue is surmounted as depopulation and aging are increasing in rural areas of Europe.[30] Complementary to the traditional Health Service approaches, in these regions, digitally-enabled, patient-centered care may contribute to reducing asthma burden and hospitalizations, as well as health inequities in this population.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

None.

References

1. World Health Organisation. Health inequities and their causes, https://www.who.int/news-room/facts-in-pictures/detail/health-inequities-and-their-causes; 2018 [accessed 30 November 2022].
2. McCartney G, Hart C, Watt G. How can socioeconomic inequalities in hospital admissions be explained? A cohort study. BMJ Open. 2013;3(8):e002433. https://doi.org/10.1136/bmjopen-2012-002433.
3. McCormick B, Hill PS, Redding S. Comparative morbidities and the share of emergencies in hospital admissions in deprived areas: a method and evidence from English administrative data. BMJ Open. 2018;8(8):e022573. https://doi.org/10.1136/bmjopen-2018-022573.
4. Parkinson B, Meacock R, Checkland K, Sutton M. How sensitive are avoidable emergency department attendances to primary care quality? Retrospective observational study. BMJ Qual Saf. 2021;30(11):884–92. https://doi.org/10.1136/bmjqs-2020-011651.
5. Prentice JC, Pizer SD. Waiting times and hospitalizations for ambulatory care sensitive conditions. Health Serv Outcomes Res Methodol. 2008;8(1):1–18. https://doi.org/10.1007/s10742-007-0024-5.
6. Crook ED, Peters M. Health disparities in chronic diseases: where the money is. Am J Med Sci. 2008;335(4):266–70. https://doi.org/10.1097/maj.0b013e31816902f1.
7. Van Loenen T, Faber MJ, Westert GP, Van den Berg MJ. The impact of primary care organization on avoidable hospital admissions for diabetes in 23 countries. Scand J Prim Health Care. 2016;34(1):5–12. https://doi.org/10.3109/02813432.2015.1132883.
8. Fleetcroft R, Noble M, Martin A, Coombes E, Ford J, Steel N. Emergency hospital admissions for asthma and access to primary care: cross-sectional analysis. Br J Gen Pract. 2016;66(650):e640–6. https://doi.org/10.3399/bjgp16X686089.
9. De La Cruz N, Hines JH, Shaw C, Appiah D. Geographic disparity in asthma hospitalizations: the role of race/ethnicity, socioeconomic status, and other factors. Cureus. 2021;13(11):e20015. https://doi.org/10.7759/cureus.20015.
10. Sallakh MAA, Rodgers SE, Lyons RA, Sheikh A, Davies GA. Socioeconomic deprivation and inequalities in asthma care in Wales. Lancet. 2017;390:S19. https://doi.org/10.1016/S0140-6736(17)32954-9.
11. Campos-Matos I, Russo G, Perelman J. Connecting the dots on health inequalities – a systematic review on the social determinants of health in Portugal. Int J Equity Health. 2016;15(1):26. https://doi.org/10.1186/s12939-016-0314-z.
12. Sa-Sousa A, Morais-Almeida M, Azevedo LF, et al. Prevalence of asthma in Portugal - the Portuguese National Asthma Survey. Clin Transl Allergy. 2012;2(1):15. https://doi.org/10.1186/2045-7022-2-15.
13. Ayres-Sampaio D, Teodoro AC, Sillero N, Santos C, Fonseca J, Freitas A. An investigation of the environmental determinants of asthma hospitalizations: an applied spatial approach. Appl Geogr. 2014;47:10–9. https://doi.org/10.1016/j.apgeog.2013.11.011.
14. PORDATA – Estatísticas sobre Portugal e Europa. Poder de compra per capita, https://www.pordata.pt/Municipios/Poder+de+compra+per+capita-118; 2022 [accessed 30 November 2022].
15. Instituto Nacional de Estatística. Estudo sobre o Poder de Compra Concelhio: 2015, htpps://www.ine.pt; 2017 [accessed 30 November 2022].
16. PORDATA – Estatísticas sobre Portugal e Europa. Indicadores de envelhecimento. https://www.pordata.pt/Portugal/Indicadores+de+envelhecimento-526; 2022 [accessed 30 November 2022].
17. Battaglia S, Benfante A, Spatafora M, Scichilone N. Asthma in the elderly: a different disease? Breathe. 2016;12(1):18. https://doi.org/10.1183/20734735.002816.
18. Barrett GF, Riddell WC. Ageing and skills: the case of literacy skills. Eur J Educ. 2019;54(1):60–71. https://doi.org/10.1111/ejed.12324.
19. Ordem dos Médicos. Estatísticas Nacionais, https://ordemdosmedicos.pt/estatisticas-nacionais/; 2022 [accessed 30 November 2022].
20. Haahtela T, Tuomisto LE, Pietinalho A, et al. A 10 year asthma programme in Finland: major change for the better. Thorax. 2006;61(8):663–70. https://doi.org/10.1136/thx.2005.055699.

21. Kupczyk M, Haahtela T, Cruz AA, Kuna P. Reduction of asthma burden is possible through National Asthma Plans. Allergy. 2010;65(4):415—9. https://doi.org/10.1111/j.1398-9995.2009.02265.x.
22. Gagné ME, Boulet LP. Implementation of asthma clinical practice guidelines in primary care: a cross-sectional study based on the Knowledge-to-Action Cycle. J Asthma. 2018;55(3):310—7. https://doi.org/10.1080/02770903.2017.1323919.
23. Global Initiative for Asthma. Global strategy for asthma management and prevention, www.ginasthma.org; 2022 [accessed 30 November 2022]
24. Price C, Agarwal G, Chan D, et al. Large care gaps in primary care management of asthma: a longitudinal practice audit. BMJ Open. 2019;9(1):e022506. https://doi.org/10.1136/bmjopen-2018-022506.
25. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MCJM, Verhamme KMC. Medication adherence and the risk of severe asthma exacerbations: a systematic review. Eur Respir J. 2015;45(2):396. https://doi.org/10.1183/09031936.00075614.
26. Chongmelaxme B, Lee S, Dhippayom T, Saokaew S, Chaiyakunapruk N, Dilokthornsakul P. The effects of telemedicine on asthma control and patients' quality of life in adults: a systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2019;7(1):199—216.e111. https://doi.org/10.1016/j.jaip.2018.07.015.
27. Antó A, Sousa-Pinto B, Czarlewski W, et al. Automatic market research of mobile health apps for the self-management of allergic rhinitis. Clin Exp Allergy. 2022;52(10):1195—207. https://doi.org/10.1111/cea.14135.
28. Bousquet J, Sousa-Pinto B, Anto J, et al. Identification by cluster analysis of patients with asthma and nasal symptoms using the MASK-air® mHealth app. Pulmonology. 2022. https://doi.org/10.1016/j.pulmoe.2022.10.005. Nov 22;S2531-0437(22)00252-5.
29. Kvedarienė V, Biliute G, Didziokaitė G, et al. Mobile health app for monitoring allergic rhinitis and asthma in real life in Lithuanian MASK-air users. Clin Transl Allergy. 2022;12(9):e12192. https://doi.org/10.1002/clt2.12192.
30. Camarero L, Oliva J. Thinking in rural gap: mobility and social inequalities. Palgrave Commun. 2019;5(1):1—7.

R.J. Vieira[a,b], B. Sousa-Pinto[a,b,*], A.M. Pereira[a,c], C.R. Cordeiro[d,e], C.C. Loureiro[d,e], F. Regateiro[f,g,h], L. Taborda-Barata[i,j,k], J. Bousquet[l,m,n,o], J. Fonseca[a,b,c]

[a] *Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine, University of Porto, Portugal*
[b] *Centre for Health Technology and Services Research, Health Research Network (CINTESIS@RISE), Faculty of Medicine of the University of Porto, Portugal*
[c] *Allergy Unit, CUF Porto Hospital & Institute, Portugal*
[d] *Department of Pulmonology, University Hospital of Coimbra, Portugal*
[e] *Faculty of Medicine, University of Coimbra, Portugal*
[f] *Allergy and Clinical Immunology Unit, Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal*
[g] *Institute of Immunology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal*
[h] *Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal*
[i] *UBIAir - Clinical & Experimental Lung Centre, University of Beira Interior, Covilhã, Portugal*
[j] *CICS-Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal*
[k] *Department of Immunoallergology, Cova da Beira University Hospital Centre, Covilhã, Portugal*
[l] *Institute for Allergology, Charité — Universitätsmedizin Berlin, Corporate, Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany*
[m] *Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany*
[n] *University Hospital, Montpellier, France*
[o] *ARIA, Montpellier, France*

[*] Corresponding author at: MEDCIDS — Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine, University of Porto, Rua Dr. Plácido da Costa s/n, 4200-450, Porto, Portugal.
E-mail address: bernardo@med.up.pt (B. Sousa-Pinto).
Received 22 August 2022; Accepted 1 December 2022
Available online 10 March 2023

Pulmonology 29 (2023) 184—187

PULMONOLOGY

www.journalpulmonology.org

COMMENT

Learning with the COVID-19 pandemic mistakes: Facing the progression of the first cases of Monkeypox in Brazil

M.N. Boschiero[a,1], C.V.C. Palamim[a,b,1], F.A.L. Marson[a,b,1,*]

[a] *Laboratory of Cell and Molecular Tumor Biology and Bioactive Compounds, São Francisco University, Bragança Paulista, SP, Brazil*
[b] *Laboratory of Human and Medical Genetics, São Francisco University, Bragança Paulista, SP, Brazil*

Received 18 August 2022; accepted 29 August 2022
Available online 9 September 2022

An ongoing outbreak of Monkeypox, a viral disease, was confirmed in May 2022, during the occurrence of the most important pandemic of the 21st century, namely, Coronavirus Disease (COVID)-19. According to the literature, Monkeypox does not have the potential to cause the same impact as COVID-19 in terms of the number of people infected and deaths.[1] However, the increase in the number of Monkeypox cases is a wakeup call to Health Authorities, and it is essential to take measures to control viral dissemination. Although Monkeypox is endemic and was first reported in Central and West Africa,[2] there was a deport of a previous outbreak outside Africa in 2003.[3] The United Kingdom, Singapore, and Israel also reported cases of Monkeypox among individuals returning from Nigeria.[4] This novel outbreak was also first described in the United Kingdom by a patient who came from Nigeria on May 07, 2022.[5,6]

In Brazil, the first case of Monkeypox was diagnosed on June 08, 2022. According to the last Pan American Health Organization, on August 17, 2022, the American continent accounted for nearly 48% of the total Monkeypox cases, the most affected countries being the United States of America (12,743 cases), Brazil (3,184 cases), Canada (1,091 cases), and Peru (867 cases), with nearly 96% of the total American confirmed cases.[7] Up to now, Brazil has accounted for approximately four thousand cases and only one death.

In this context, we performed the first Brazilian data collection of Monkeypox[8] and COVID-19[9] cases in Brazil from the Our World in Data Website. In our data search, we collected information on the number of Monkeypox and COVID-19 cases. We also summarized the number of deaths due to COVID-19. The Monkeypox cases were registered from June 08, 2022, to August 25, 2022; and the COVID-19 were registered from the same period (simultaneous disease progression) and from February 26, 2020, to May 14, 2020 (progression of both diseases after the first diagnostic case) (Fig. 1a to d; and Supplementary Fig. 1a to d). We also calculated the proportion of COVID-19 cases and deaths per Monkeypox cases (Fig. 1e and f).

In our data, we observed that the COVID-19 pandemic in Brazil presented a higher transmission rate (~50x after 79 days of the first case of both diseases, Fig. 1e) than the Monkeypox viral infection, indicating that the new emergent infection has a lower potential for dissemination compared to the COVID-19, at least in this early stage. Also, to date, the number of deaths due to COVID-19 was ~3x higher than the number of Monkeypox cases in Brazil (Fig. 1f). Although Brazil built several diverse molecular biology and sequencing laboratories that can perform real-time polymerase chain reaction (RT-PCR) to identify the Monkeypox virus, we should be careful not to make the same mistakes as in the COVID-19 pandemic where we observe intensive cross-infection, mainly associated with a high COVID-19 underdiagnosis in Brazil, thus harming public health measures.[10—12] Also, the

* Corresponding author at: São Francisco University; Post graduate Program in Health Science; Laboratory of Cell and Molecular Tumor Biology and Bioactive Compounds and Laboratory of Human and Medical Genetics. Avenida São Francisco de Assis, 218. Jardim São José, Bragança Paulista, São Paulo, 12916-900, Brazil.

E-mail addresses: fernando.marson@usf.edu.br, fernandolima marson@hotmail.com (F.A. Marson).

[1] These authors contributed equally to this study.

https://doi.org/10.1016/j.pulmoe.2022.08.007

onset of COVID-19 in Brazil was associated with a collapse in the Health System, causing high case fatality rates, as can be observed in the present study (Fig. 1d).

Although Monkeypox appears not to have the same pandemic potential as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, it already comprises more than 46,000 total cases on August 25, 2022, in several places where Monkeypox is not common, such as the United States of America, the United Kingdom, and several other European countries.[13] Curiously, on August 25, 2022, the United States of America accounted for more than 35% of the total cases worldwide (46,679 cases with 49.96 cases per million inhabitants). In contrast, Brazil accounts for nearly 8.5% (16,837 cases with 19.67 cases per million inhabitants) of total cases.[13] In addition, there have been 13 deaths due to Monkeypox in the world, one in Brazil as described above. The increase in Monkeypox cases might be explained by decreased population immunity against smallpox since that was eradicated and vaccinations stopped nearly 30 years ago; and due to new transmission patterns, which might increase the Monkeypox spread in the world.[5]

Although Monkeypox has been reported in several countries, its clinical presentation might differ. Perhaps one of the most significant differences may be related to skin lesions. The African skin lesions are more predictable than the American ones since the lesions have macule-papule-pustule evolution, which desquamates in 14 to 21 days, leaving a varioliform scarring;[14,15] in contrast, the American skin lesions vary their morphology from person to person, even among infected people from the same family,[15,16] in that the lesions have a papule-vesicle-pustule evolution, with erythematous flares, which are not reported in African cases.[15]

Even though the COVID-19 pandemic and the Monkeypox outbreak present some similar challenges, such as preconceptions against those who are most affected, the need for an efficient testing public policy, and the difficulty of clinical

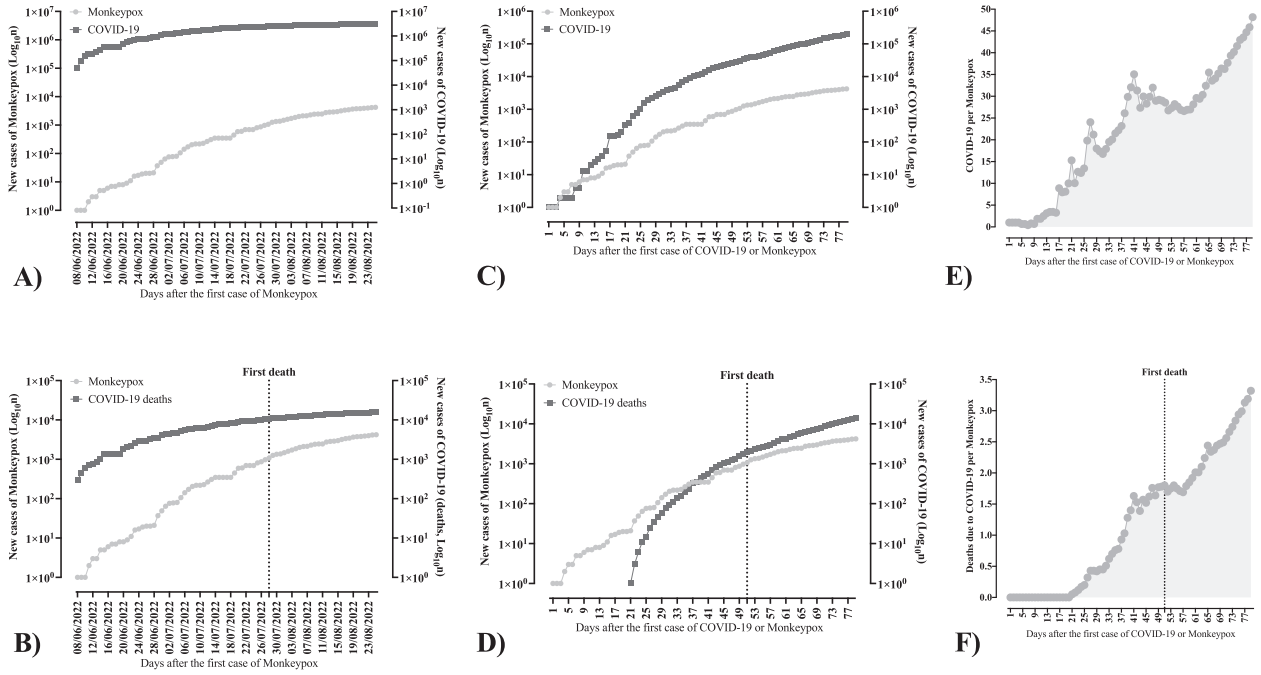

Fig. 1 Monkeypox and Coronavirus Disease (COVID)-19 disease progression in Brazil. We presented the cumulative number of new cases for both diseases (Monkeypox and COVID-19) per day and the cumulative number of new deaths due to COVID-19 per day. **A)** The cumulative number of new Monkeypox cases vs. the cumulative number of new cases of COVID-19 considering the period after the diagnosis of the first case of Monkeypox in Brazil. **B)** The cumulative number of new Monkeypox cases vs. the cumulative number of new deaths due to COVID-19 considering the period after the diagnosis of the first case of Monkeypox in Brazil. **C)** The cumulative number of new Monkeypox cases considering the period after the diagnosis of the first case of Monkeypox in Brazil vs. the cumulative number of new cases of COVID-19 considering the period after the diagnosis of the first case of COVID-19 in Brazil. **D)** The cumulative number of new Monkeypox cases considering the period after the diagnosis of the first case of Monkeypox in Brazil vs. the cumulative number of new deaths due to COVID-19 considering the period after the diagnosis of the first case of COVID-19 in Brazil. **E)** Proportion of new COVID-19 cases per new Monkeypox cases for the progression of both diseases after the diagnosis of the first case for both diseases — we calculated the proportion using the cumulative number of cases. **F)** Proportion of new deaths due to COVID-19 per new Monkeypox cases for the progression of both diseases after the diagnosis of the first case for both diseases — we calculated the proportion using the cumulative number of cases. We adjusted the y-axis (left — Monkeypox and right — COVID-19) using the Log_{10} scale to present our data in Fig. 1A to D with the units. We presented the x-axis as data for Fig. 1A and B, and as days after the first case for Fig. 1C to F. In Fig. 1C, D, and F, we marked the day where the first death due to Monkeypox in Brazil occurred. We retrieved the data from Our World in Data.[8,9] The Monkeypox cases were registered from June 08, 2022, to August 25, 2022; and the COVID-19 were registered from the same period (simultaneous disease progression) and from February 26, 2020, to May 14, 2020 (progression of both diseases after the first diagnostic case).

management of a little-known disease,[17] there might be some room for optimism, since there are treatments and vaccinations available, even though not fully available for countries in Latin America. In addition, the Smallpox vaccine appears to confer nearly 85% protection against Monkeypox.[18–20]

However, one fact needs to be called to attention; we observed a constant increase in the number of cases of Monkeypox while the number of new cases of COVID-19 is stagnating in Brazil. Furthermore, it is difficult to discuss the impact of the new Monkeypox in Brazil, even in more susceptible individuals, such as Indigenous peoples, Black/*Pardos* (multiracial background), and older individuals, when compared with COVID-19, which caused a significant impact in our country, since the disease onset was reported two years later.[21] Also, in a recent report, nearly 41% of the individuals with Monkeypox had Human Immunodeficiency Virus (HIV) infection, which could be a problem for Latin America, especially Brazil, since we have a high prevalence of people living with HIV.[22]

Curiously, after the COVID-19 pandemic, the Latin-American countries are better prepared to confront a new possible pandemic, such as the Monkeypox disease outbreak as described by Rodriguez-Morales and collaborators, as well as Cimerman and collaborators. They discussed the importance of optimizing genetic testing to identify the viral agent, which was improved during COVID-19, and also strengthening surveillance systems.[10,23] For example, the first case of the Monkeypox virus in Brazil was sequenced and published using shotgun metagenomic sequencing days after the clinical suspicion.[24] However, we should approach the Monkeypox threat carefully in developing countries, such as those in Latin America, since although experimental drugs, such as Cidofovir and Tecovirimat, have proven efficacy, and vaccines for contacts of positive cases have been implemented,[23] not only might the high prices of these inputs not be affordable for Latin America countries, but also they may not be available, which could enhance the Monkeypox threat.

Brazil is, fortunately, better prepared at least to diagnose Monkeypox compared to the COVID-19 diagnosis at the onset of the pandemic, mainly in the first wave, and it also has a strengthened surveillance system. Monkeypox does not have the same capacity to be a new pandemic compared with COVID-19, with low chances of infecting new individuals and causing deaths, as we present in our data (Fig. 1e and f).

However, we are in the early stages of this outbreak and have limited information about the Monkeypox disease progression in Brazil and the world. In addition, there is no evidence about the impact of the new viral infection among those with COVID-19 and susceptible individuals, which is alarming in Brazil, where several groups deserve special attention, such as the Indigenous peoples and those living with HIV. Countries around the world should learn from the Brazilian mistakes in the management of a pandemic, such as the COVID-19 ones.[25] Although Monkeypox appears not to have the same dissemination potential, public health policies should be adopted, such as a proper testing policy, implementation of vaccination, proper clinical management, self-isolation, when necessary, using only scientific data to guide public health policies, and even the investment in new antivirals to treat Monkeypox, in order to decrease the spread and lethality of Monkeypox, avoiding a new "COVID-19 crisis".

Funding

[MNB] Fundação de Amparo à Pesquisa do Estado de São Paulo (Foundation for Research Support of the State of São Paulo, Brazil; #2022/05810-7).

Ethics approval

The data used in our study were made publicly available, not containing consent-free personal data since it does not present risks to the research participants.

Consent to participate

Not required.

Consent for publication

The authors have approved the manuscript and agreed with the submission.

Data and material availability

We accessed the complete data in Our World in Data (https://ourworldindata.org/).

Code availability

Not required.

Authors' contributions

(FALM) made substantial contributions to the study conception and design; and performed the acquisition, analysis, and interpretation of data for the work. (MNB, CVCP, and FALM) drafted the work and revised it critically for important intellectual content. (MNB, CVCP, and FALM) gave the final approval for the version to be published.

Conflicts of interest

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2022.08.007.

References

1. Taseen S, Nasir F, Abbas M, Altaf M, Asghar MS, Tahir MJ Post-pandemic world at the mercy of Monkeypox virus outbreak: time to worry or not?*J Med Viro*l n.d.;**n/a**(n/a). https://doi.org/10.1002/jmv.27948.
2. McCollum AM, Damon IK. Human Monkeypox. Clin Infect Dis. 2014;58(2):260—7. https://doi.org/10.1093/cid/cit703.
3. Reed KD, Melski JW, Graham MB, Regnery RL, Sotir MJ, Wegner MV, et al. The detection of Monkeypox in humans in the Western Hemisphere. N Engl J Med. 2004;350(4):342—50. https://doi.org/10.1056/NEJMoa032299.
4. Sklenovská N, Van Ranst M. Emergence of Monkeypox as the Most Important Orthopoxvirus Infection in Humans. Front Public Health. 2018;6:241. https://doi.org/10.3389/fpubh.2018.00241.
5. Zhang Y, Zhang J-Y, Wang F-S. Monkeypox outbreak: a novel threat after COVID-19? Mil Med Res. 2022;9(1):29. https://doi.org/10.1186/s40779-022-00395-y.
6. Monkeypox Cases Confirmed in England — Latest Updates. GOV.UK. Available from: https://www.gov.uk/government/news/monkeypox-cases-confirmed-in-england-latest-updates [accessed August 25, 2022].
7. Weekly Situation Report on Monkeypox Multi-Country Outbreak Response - Region of the Americas. PAHO/WHO | Pan American Health Organization; 2022. 19 August. Available from: https://www.paho.org/en/documents/weekly-situation-report-monkeypox-multi-country-outbreak-response-region-americas-19 [accessed August 25, 2022].
8. Mathieu E, Spooner F, Dattani S, Ritchie H, Roser M. Monkeypox. Our World in Data; 2022.
9. Ritchie H, Mathieu E, Rodés-Guirao L, Appel C, Giattino C, Ortiz-Ospina E, et al. Coronavirus Pandemic (COVID-19). Our World in Data; 2020.
10. Cimerman S, Chebabo A, da Cunha CA, Barbosa AN, Rodríguez-Morales AJ. Human monkeypox preparedness in Latin America - are we ready for the next viral zoonotic disease outbreak after COVID-19? Braz J Infect Dis. 2022;26(3):102372. https://doi.org/10.1016/j.bjid.2022.102372.
11. Bastos SB, Cajueiro DO. Modeling and forecasting the early evolution of the Covid-19 pandemic in Brazil. Sci Rep. 2020;10(1):19457. https://doi.org/10.1038/s41598-020-76257-1.
12. Carvalho TA, Boschiero MN, Marson FAL. COVID-19 in Brazil: 150,000 deaths and the Brazilian underreporting. Diagn Microbiol Infect Dis. 2021;99(3):115258. https://doi.org/10.1016/j.diagmicrobio.2020.115258.
13. CDC. Monkeypox in the U.S. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html [accessed August 25, 2022].
14. Breman JG. Monkeypox: an Emerging Infection for Humans? *Emerging Infections*, 4. John Wiley & Sons, Ltd; 2000. p. 45—67.
15. Sale TA, Melski JW, Stratman EJ. Monkeypox: an epidemiologic and clinical comparison of African and US disease. J Am Acad Dermatol. 2006;55(3):478—81. https://doi.org/10.1016/j.jaad.2006.05.061.
16. Sejvar JJ, Chowdary Y, Schomogyi M, Stevens J, Patel J, Karem K, et al. Human monkeypox infection: a family cluster in the midwestern United States. J Infect Dis. 2004;190(10):1833—40. https://doi.org/10.1086/425039.
17. Bosworth A, Wakerley D, Houlihan CF, Atabani SF. Monkeypox: an old foe, with new challenges. Infect Prev Pract. 2022;4(3):100229. https://doi.org/10.1016/j.infpip.2022.100229.
18. Berhanu A, Prigge JT, Silvera PM, Honeychurch KM, Hruby DE, Grosenbach DW. Treatment with the smallpox antiviral tecovirimat (ST-246) alone or in combination with ACAM2000 vaccination is effective as a postsymptomatic therapy for monkeypox virus infection. Antimicrob Agents Chemother. 2015;59(7):4296—300. https://doi.org/10.1128/AAC.00208-15.
19. Monkeypox Vaccination Recommendations. GOV.UK. Available from: https://www.gov.uk/government/publications/monkeypox-vaccination [accessed August 25, 2022].
20. Petersen BW, Kabamba J, McCollum AM, Lushima RS, Wemakoy EO, Muyembe Tamfum J-J, et al. Vaccinating against Monkeypox in the Democratic Republic of the Congo. Antiviral Res. 2019;162:171—7. https://doi.org/10.1016/j.antiviral.2018.11.004.
21. Marson FAL, Ortega MM. COVID-19 in Brazil. Pulmonol. 2020;26(4):241—4. https://doi.org/10.1016/j.pulmoe.2020.04.008.
22. Thornhill JP, Barkati S, Walmsley S, Rockstroh J, Antinori A, Harrison LB, et al. Monkeypox virus infection in humans across 16 countries — April—June 2022. N Engl J Med. 2022;387(8):679—91. https://doi.org/10.1056/NEJMoa2207323.
23. Rodriguez-Morales AJ, Lopardo G, Verbanaz S, Orduna T, Lloveras S, Azeñas-Burgoa JM, et al. Latin America: situation and preparedness facing the multi-country human Monkeypox outbreak. Lancet Reg Health Am. 2022;13:100318. https://doi.org/10.1016/j.lana.2022.100318.
24. Claro IM, Romano CM, da Candido DS, de Lima EL, Lindoso JAL, Ramundo MS, et al. Shotgun metagenomic sequencing of the first case of Monkeypox virus in Brazil, 2022. Rev Inst Med Trop Sao Paulo. 2022;64:e48. https://doi.org/10.1590/S1678-9946202264048.
25. Boschiero MN, Palamim CVC, Ortega MM, Mauch RM, Marson FAL. One year of coronavirus disease 2019 (COVID-19) in Brazil: a political and social overview. Ann Glob Health. 2021;87(1):44. https://doi.org/10.5334/aogh.3182.

Pulmonology 29 (2023) 188–193

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Is group C really needed as a separate group from D in COPD? A single-center cross-sectional study

E.E. Yazar[a,*], B. Yiğitbaş[b], E.Y. Niksarlıoğlu[b], M. Bayraktaroğlu[a], S. Kul[c]

[a] *İstanbul Aydın University, Faculty of Medicine, Department of Chest Diseases, Küçükçekmece, Istanbul, 34295, Turkey*
[b] *Yedikule Chest Disease and Thorasic Surgery Training and Research Hospital, Zeytinburnu, Istanbul, TR 34100, Turkey*
[c] *Seval KUL, School of Medicine, University of Gaziantep, Gaziantep, TR 27310, Turkey*

Received 16 April 2020; accepted 10 June 2020
Available online 2 August 2020

KEYWORDS
COPD;
FEV_1;
GOLD 2017;
Group C;
ABCD classification;
GOLD 2019

Abstract
Introduction: GOLD 2017 report proposed that the combined COPD assessment should be done according only to symptom burden and exacerbation history in the previous year.
Objective: This study aims to investigate the change in the COPD groups after the GOLD 2017 revision and also to discuss the evaluation of group C and D as a single group after the GOLD 2019 report.
Method: The study was designed as a cross-sectional. 251 stable COPD patients admitted to our out-patient clinic; aged ≥40 years, at least one-year diagnosis of COPD and ≥10 pack-year smoking history were consecutively recruited for the study.
Results: In GOLD 2017, a significant difference was found between the distribution of all groups compared to GOLD 2011 (P = 0,001). 31 patients included in group C were reclassified into group A and 37 patients in group D were reclassified into group B. The FEV_1 values of group A and B patients were significantly low and group C and D patients had had exacerbations in more frequently the previous year in GOLD 2017 compared to GOLD 2011.
Conclusion: After the GOLD 2017 revision, the rate of group C patients decreased even more compared to GOLD 2011 and the group C and D may be considered as a single group in terms of the treatment recommendations with the GOLD 2019 revision. We think that future prospective studies are needed to support this suggestion.

* Corresponding author at: İstanbul Aydın University, Faculty of Medicine, Department of Chest Diseases, Küçükçekmece, İstanbul, TR 34295, Turkey.
E-mail address: esraertan76@yahoo.com (E.E. Yazar).

https://doi.org/10.1016/j.pulmoe.2020.06.012

Introduction

Global Initiative for Chronic Obstructive Lung Disease (GOLD) started its activities in 1998 to increase awareness of COPD all over the world and develop a common approach to the assessment and treatment of the disease. Their first report was published in 2001 with the title "Global Strategy for Diagnosis, Management, and Prevention of COPD''.[1] In the GOLD 2007 report, forced expiratory volume in 1 s (FEV_1) value was the most important determinant for the evaluation and treatment decision of COPD patients.[2] However, clinical studies have shown that there is a poor relationship between FEV_1, symptom status and quality of life and also FEV_1 is not sufficient alone to predict exacerbations and treatment response.[3,4] Thus, for the first time in the GOLD 2011 report, a combined assessment, including FEV_1 as well as a history of exacerbation and symptom status, was proposed for the assessment and treatment decision of the disease.[5] However, it was observed that this evaluation method was not useful in daily practice and that compliance with treatment recommendations according to GOLD 2011 was low worldwide.[6,7] On the other hand, combined evaluation could not be shown to be superior to spirometric staging, either as a predictor of mortality or other health outcomes.[8] The results of these studies required the 4th major revision in GOLD 2017 report.[9] It recommended that the combined COPD assessment should be done according only to symptom burden and exacerbation history in the previous year. However, the GOLD 2017 ABCD classification could not predict all-cause and respiratory mortality more accurately than the GOLD 2007 and 2011 classifications.[10] Finally, with the GOLD 2019 revision, very important changes were proposed for the pharmacological treatment in stable COPD. This study aims to investigate the change in the COPD groups after the GOLD 2017 revision and also to discuss whether groups C and D should be considered as a single group in terms of treatment after GOLD 2019 revision.[11]

Material method

The study was designed as single-center and cross-sectional. 251 stable COPD patients admitted to our out-patient clinic consecutively were recruited in the study. Inclusion criteria were as follows: aged $\geq$40 years, at least one-year diagnosis of COPD according to the GOLD classification with baseline post-bronchodilator FEV_1/forced vital capacity (FVC) ratio of less than 0.7, and at least 10 pack-year smoking history. Exclusion criteria were as follows: having COPD exacerbation within the past six weeks before enrollment, patient's with incompatible pulmonary function tests (PFTs) or those unable to complete the case report form were excluded from the study. The case report form which included patients demographic, clinical and laboratory details (age, gender, smoking history, comorbidities, COPD assessment test (CAT), modified Medical Research Council (mMRC), exacerbation history, PFTs) was completed for each patient. We evaluated the asthma-COPD overlap according to the existing clinical and laboratory data of the patients. The patients who fulfilled two major or one major and two minor criteria were diagnosed as ACO. The major criteria were as follows: a very positive bronchodilator response (>400 mL0 and >15% increase in forced expiratory volume in 1 s (FEV_1)), sputum eosinophilia or a previous diagnosis of asthma. Minor criteria were an increased total serum IgE, previous history of atopy or a positive bronchodilator test (>200 mL and >12% in FEV_1) on at least two occasions.[12]

The pulmonary function test was performed if the patient had not been tested within the previous 6 months or the test was not valid. Spirometry was performed using a Sensor Medics model 2400 (Yorba Linda, California, USA) in accordance with the GOLD guidelines, and COPD was classified by their FEV_1% predicted: stage1 (mild); FEV_1 $\geq$80%, stage 2 (moderate); 50%$\geq$ FEV_1<80%, stage 3 (severe); 30%$\geq$ FEV_1 <50% and stage 4 (very severe); FEV_1<30%.[2] All patients were divided into four risk/symptom categories according to both GOLD 2011 and 2017 reports: low risk, fewer symptoms (A); low risk, more symptoms (B); high risk, fewer symptoms (C); and high risk, more symptoms (D). Based on this categorization the cut-off points for risks; exacerbations in the previous year $\geq$ 2 or $\geq$1 leading to hospital admission and the cut-off points for symptoms; CAT scores $\geq$10 and/or mMRC $\geq$2 were chosen according to the GOLD 2017 classification (9). Unlike the 2017 report, the patients whose predicted FEV_1% was less than 50% were included in the high-risk group according to the GOLD 2011 classification.[5]

An informed consent was taken from each patient. The study protocol was approved by the Ethics Committee of Biruni University.

Statistical analysis

The normality of the distribution of continuous variables was tested by the Shapiro Wilk test. Mann–Whitney U test (for non-normal data) was used to compare two independent groups and the Chi-square test was used to assess the relationship between categorical variables. To compare non-normal data across more than 3 categories Kruskal Wallis and Dunn multiple comparison tests were applied. Statistical analysis was performed with SPSS for Windows version 22.0 and a p-value <0.05 was accepted as statistically significant.

Results

251 patients (average age of 64.4 $\pm$ 8.2 years and 88% male) were included in the study. 129 patients (51.4%) had at least one comorbidity. Hypertension (85 patients; 33.1%), coronary artery disease (37 patients; 14.7%), diabetes mellitus (31 patients; 12.7%) and gastroesophageal reflux (20 patients; 8%) were the most common comorbidities, respectively. Two hundred and fifteen patients were recorded with or without ACO. We accepted 36 patients as missing due to their non-classification as ACO or not with respect to their current clinical and laboratory data. Twenty-seven patients were evaluated as ACO in the study. The clinical and demographic characteristics of the patients are given in Table 1. When the proportions of the two groups were compared with McNemar–Bowker Test according to two sequential GOLD, 2011 and 2017, a significant difference was found between all groups (P = 0,001). 31 patients (31/47;66%) included in group C were reclassified into group A and 37 patients (37/129;28.7%) in group D were reclassified into group B according to GOLD 2017 because they had no

Table 1 Demographic and clinical features of the patients.

Demographic and clinical features of the patients	
Patients, n; %	251;100%
Male, n; %	223; 88%
GOLD grade I, n; %	11; 4.4%
GOLD grade II, n; %	92; 36.7%
GOLD grade III, n; %	95; 37.8%
GOLD grade IV, n; %	53; 21.1%
ACO, n; %*	27; 10.8%
The number of patients with at least one comorbidity, n; %	129; 51.4%
Age (year), mean ± std	64.4 ± 8.2
Smoking (pack-years), mean ± std	45.7 ± 25
COPD duration (year), mean ± std	7.8 ± 5
FVC % pred, mean ± std	60.2 ± 18
FEV1 % pred, mean ± std	46.6 ± 18
FEV1/FVC, mean ± std	55.7 ± 10.3
Blood eosinophil count (per μL), mean ± std	242.8 ± 178
The rate of blood eosinophil (%), mean ± std	2.7 ± 2.4
CAT score, mean ± std	12.1 ± 8.4
mMRC dyspnea score, mean ± std	1.63 ± 1.22
The number of exacerbations in previous year (moderate and severe), mean ± std	2 ± 3.6
GOLD 2011 % (A/B/C/D)	19.5/10.4/18.7/51.4
GOLD 2017 % (A/B/C/D)	31.9/25.1/6.4/36.7

Abbreviations: GOLD, global Initiative for chronic obstructive lung disease; COPD, chronic obstructive pulmonary disease; ACO, Asthma-COPD overlap; % pred, percent predicted; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; CAT, COPD assessment Test; mMRC, Modified Medical Research Council Scale.
Note: * data of 36 patients are missing.

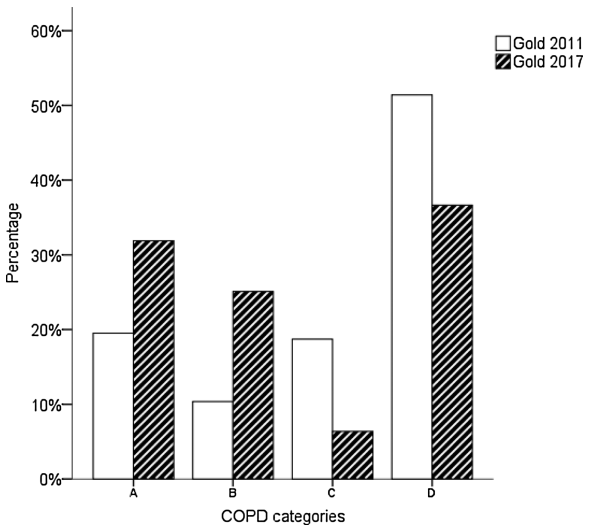

Figure 1 Distributions of groups A–D according to the GOLD 2011 and GOLD 2017 P = 0,001.

history of frequent exacerbations but only their predictive FEV_1 was below 50%. Therefore, while the rate of group C and D patients decreased, the rate of group A and B patients increased in all patients.

The distrubition of COPD categories according to GOLD 2017 is given in Fig. 1. It was observed that the group C ratio which is already lower than other groups, decreased more with the GOLD 2017 revision.

Pulmonary function values of GOLD 2017 group A and B patients were significantly lower than GOLD 2011 and also group A and B did not include patients with stages 3 and 4 in GOLD 2011. However, with the new classification (GOLD 2017), 31.3% of group A patients consisted of stage 3, 7.5% of them consisted of stage 4 patients, 42.9% of group B patients consisted of Stage 3 and 14.3% of them consisted of stage 4 patients. There was no difference in symptom scores (mMRC and CAT) and comorbidities between the groups according to the old and new classification. It was observed that GOLD 2017 group C and D patients had exacerbated more frequently in the previous year than GOLD 2011 group C and D patients. A comparison of demographic and clinical characteristics of the groups in GOLD 2011 and 2017 is given in Table 2.

Discussion

This study found that patients grouped as A and B according to GOLD 2011 were categorized in the same way in GOLD 2017, but 31 of 47 (66%) patients in group C were reclassified as group A and 37 of 129 (28.7%) patients in group D were reclassified as group B in GOLD 2017. Thus, patients in a high-risk group (68/176; 39% of high-risk patients) were reclassified as low-risk in GOLD 2017, since they did not have frequent attacks and only had FEV_1 values of below 50%. According to GOLD 2011, it is observed that the FEV_1 values of the low-risk group in GOLD 2017 are lower and the high-risk group had a higher average number of exacerbations in the previous year. In GOLD 2017, while the proportional dis-

Table 2 The distribution of COPD groups by GOLD 2011 and GOLD 2017 and comparison in demographic, clinical and laboratory features.

	Group A		Group B		Group C		Group D	
	2017	2011	2017	2011	2017	2011	2017	2011
Age (years), mean ± SD	64 ± 7.8	65 ± 7.5	65 ± 8	63.9 ± 8.2	65.8 ± 7.8	63.6 ± 8.2	64.1 ± 8.7	64.6 ± 8.5
Male, n (%)	76(95)	45(91.8)	51(81)	20(76.9)	12(75)	43(91.5)	84(91.3)	115(89.1)
Smoking index (pack-years)	45 ± 25.9	45.6 ± 28.7	45.6 ± 26.2	41.8 ± 16.9	36.9 ± 19.1	41.5 ± 20.4	48 ± 24.3	48 ± 26.3
COPD duration (year)	6.6 ± 5.3	6.7 ± 5.4	8.6 ± 5.2	7.1 ± 4.2	7.1 ± 4.3	6.7 ± 4.9	8.5 ± 4.8	8.8 ± 5.1
Post-bronchodilator FEV_1(L)	1.7 ± 0.5	**1.9 ± 0.5***	1.3 ± 0.6	**1.9 ± 0.4***	1.2 ± 0.3	1.2 ± 0.3	1 ± 0.4	1 ± 0.4
Post-bronchodilator FEV_1 % pred	55.9 ± 16.1	**65.9 ± 11.4***	48.1 ± 16.7	**65.4 ± 8.3***	45 ± 16.2	41.8 ± 11.1	37.2 ± 16.1	36.9 ± 14.3
Post-bronchodilator FVC (L)	2.6 ± 0.7	**2.8 ± 0.6***	2.1 ± 0.8	**2.6 ± 0.6***	2.1 ± 0.5	2.2 ± 0.5	2.5 ± 6.2	2.3 ± 5.3
Post-bronchodilator FVC % pred	67.7 ± 15.7	**76.4 ± 11.4***	61.4 ± 18.5	**74.7 ± 10.4***	61.2 ± 16.5	56.5 ± 13.5	52.7 ± 17.3	52.4 ± 17.2
Post-bronchodilator FEV1/FVC	59.9 ± 7.6	62.7 ± 5.4	57.1 ± 10.2	**64.5 ± 6.4***	53.4 ± 12.3	54.8 ± 9.9	51.5 ± 10.5	51.6 ± 10.1
Blood eosinophil count	268.4 ± 206.1	267.7 ± 214.1	240.5 ± 179	263.8 ± 215.1	262.5 ± 141.3	263.7 ± 177	221.7 ± 157	222.4 ± 154
The rate of blood eosinophils	2.9 ± 1.8	2.9 ± 1.8	3 ± 3.8	3 ± 2.2	2.9 ± 2.2	2.9 ± 1.9	2.4 ± 1.5	2.6 ± 2.8
CAT score	5.2 ± 2.5	4.8 ± 2.5	13.4 ± 5.4	12.2 ± 4.6	4.8 ± 2.7	5.6 ± 2.5	18.5 ± 8.6	17.3 ± 8.1
mMRC dyspnea score	0.6 ± 0.6	0.6 ± 0.6	1.9 ± 1	1,5 ± 1	0.8 ± 0.5	0.6 ± 0.5	2.5 ± 1	2.4 ± 1
The number of exacerbations (moderate and severe)	0.3 ± 0.5	0.2 ± 0.4	0.3 ± 0.6	0.4 ± 0.6	4.1 ± 3.4	**1.7 ± 2.8***	4.3 ± 4.7	**3.2 ± 4.3***
GOLD stage 1 n (%)	7 (8.8)	7 (14.3)	2 (3.2)	2 (7.4)	0 (0)	0 (0)	2 (2,2)	2 (1.6)
GOLD stage 2 n (%)	42 (52.5)	**42 (85.7)***	25 (39.7)	**25 (92.6)***	6 (37.5)	6 (12.8)	20 (21.7)	20 (15.6)
GOLD stage 3 n (%)	25 (31.3)	**0 (0)***	27 (42.9)	**0 (0)***	7 (43.8)	32 (68.1)	35 (38)	62 (48.4)
GOLD stage 4 n (%)	6 (7.5)	0 (0)	9 (14.3)	**0 (0)***	3 (18.8)	9 (19.1)	35 (38)	44 (34.4)
The number of patients with at least one comorbidity, n (%)	42 (57.5)	32 (65.3)	35 (55.6)	17 (65.4)	9 (56.3)	19 (40.4)	43 (46.7)	61 (47.3)
Hypertension	25 (31.3)	19 (38.8)	25 (39.7)	13 (50)	4 (25)	10 (21.3)	29 (31.5)	41 (31.8)
Coronary artery disease	13 (16.3)	10 (20.4)	10 (15.9)	6 (23.1)	2 (12.5)	5 (10.6)	12 (13)	16 (12.4)
Diabetes mellitus	7 (8.8)	5 (10.2)	9 (14.3)	5 (19.2)	2 (12.5)	4 (8.5)	14 (15.2)	18 (14)
Gastroesophageal reflux	6 (7.5)	5 (10.2)	5 (7.9)	1 (3.8)	0	1 (2.1)	9 (9.8)	13 (10.1)

Note: *Significant at 0.05 level.

Abbreviations: GOLD, global Initiative for chronic obstructive lung disease; COPD, chronic obstructive pulmonary disease; % pred, percent predicted; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; CAT, COPD assessment Test; mMRC, Modified Medical Research Council Scale.

tribution of the groups other than category C came close to each other and category C had the lowest number of patients, at 6.4%.

Taiwan Obstructive Lung Disease (TOLD) study showed that up to 67% of patients in GOLD 2011 group C and D were reclassified to GOLD 2017 group A and B.[13] A national cross-sectional survey in China indicated almost half of the old high-risk groups were regrouped to the new low-risk groups.[12] Another study from Sweden found that 2017 GOLD reclassifies half of COPD subjects to lower-risk groups.[15] According to the literature, almost half the patients formerly classified as ''C'' or ''D'', solely based on poor lung function, shifted from the high-risk groups to the low-risk groups in GOLD 2017.[13–18]

In many studies, it was observed that category C was lower than the other groups according to the GOLD 2011 combined assessment proposal and this rate was reduced even more with the major revision in GOLD 2017.[13,15,17,19,20] Furthermore, when using the assessment according to the GOLD 2017 report, publications are indicating that category C has dropped to 5% and below.[13,15–17,20] Some studies have shown that group C proportion is between 6–14% according to GOLD 2017, similar to our results.[14,18,21] These differences may be due to the country, center (tertiary hospital or primary health care, etc.) in which the study was conducted, or the methodology of the study (scales evaluating symptoms). Group C is expected to involve a small proportion of patients compared to other groups because a patient with frequent exacerbations is expected to have a high symptom score in clinical practice. However, some patients have poor dyspnea perception or restrict their physical activities to avoid dyspnea which may lead to their misclassification as group C instead of group D. This could explain why the acute exacerbation number of patients with Group C was similar to Group D despite having a low symptom score in our study. In the literature, researchers who were using only mMRC for symptom evaluation reported that as a limitation of their studies.[14,16,20,21] The use of only one or other of CAT or mMRC scores in clinical practice may also lead to an incorrect assessment of patients' symptom status. We used both mMRC and CAT scores to assess the symptom status in our study. According to a recent study, 2% of the participants from the general population and 3% of the patient population were classified as group C in GOLD 2017.[16] A similar result was shown in the population-based PLATINO study of the GOLD 2011 classification in which only 10 of 524 COPD patients (1,9%) were classified in group C.[20] Therefore some researchers argued that class C might be unnecessary.[8,16,20] We also questioned whether to evaluate Group C and D as two separate groups in terms of the treatment recomendations with the GOLD 2019 revision.

The same treatment options are proposed for frequent exacerbators with or without high symptoms at follow-up independent of the COPD categories with GOLD 2019 revision.[11] However different approaches are recommended as the initial treatment for Group C and D. Whereas some of the patients may be misclassified as group C because they perceive their symptoms incorrectly or are not evaluated in sufficient detail by their physician. It may be confusing in clinical practise that some options are presented in group D but are not recommended in group C. For instance, the blood eosinophil count or asthma history are not considered in the initial treatment of group C despite patients having frequent exacerbations. That is why we think that group C and D patients may be evaluated as a single group in terms of their treatment after GOLD 2019 revision.

The GOLD 2017 assessment led to changes in the distribution of patients' demography and clinical characteristics across categories used in previous studies. In GOLD 2017, patients of group C and D had a better pulmonary function but higher acute exacerbation rates, as well as a similar degree of dyspnea according to GOLD 2011. Group C and D had older patients and more patients with chronic bronchitis, coronary heart disease, and diabetes mellitus in GOLD 2017 than GOLD 2011. Pulmonary functions in the group A and B were worse in GOLD 2017.[14] Another study demonstrated that the GOLD 2017 reclassified more patients into group A and B those with significantly worse lung function and higher BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) index compared with the GOLD 2011. In the comprehensive assessment of the GOLD 2017, group B and D may have greater disease severity and the differences between groups A and C were small.[18] Similarly, the recent study indicated that group B has the same BODE index as group D, and both of them are significantly higher than groups A and C in the GOLD 2017 reclassification. The differences between groups (B versus D and A versus C) become smaller with this new approach thus decreasing the value of their separation.[21] We observed in the GOLD 2017 the patients with poor pulmonary function and without frequent exacerbation in the previous year were shifted to the low-risk groups, so pulmonary function in the group A and B were worse and also group C and D had more exacerbations in our study as in the literature. In addition, we did not detect any difference between the groups according to GOLD 2011 and GOLD 2017 in terms of comorbidities and symptom status.

There are two limitations to our study. First, this study is cross-sectional so the exacerbation history of the patients was obtained from the statements of patients and hospital records. Second, the results may not reflect the general population because the patients were only recruited from a tertiary hospital and single-center.

Conclusion

The question is growing as to whether that group C in which the number of patients decreased even more after the major revision of GOLD 2017 is really necessary as a separate group. Furthermore the same treatment options are proposed to frequent exacerbators with or without high symptoms at follow-up with GOLD 2019 revision. On the other hand different approaches are recommended as the initial treatment for group C and D in this report. Some of the patients may be misclassified as group C because they have a poor perception of their symptoms and/or are not evaluated in sufficient detail by their physician. It may cause confusion in clinical practise that some options are presented in group D but are not recommended in group C despite latter having frequent exacerbations. We think that group C and D patients may be reclassified as a single group in clinical practise and prospective studies are needed in this context.

Authors contributions

EY: Study design, prepared the article, statistics, BY: study design, data collection; EYN: data collection, study design; MB: study design and prepared the article; SK: statistics

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS, GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. Respir Care. 2001;46(8):798–825.
2. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176(6):532–55.
3. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) investigators. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res. 2010;11:122.
4. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363(12):1128–38.
5. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347–65.
6. Gunen H, Yilmaz M, Aktas O, Ergun P, Ortakoylu MG, Demir A, et al. Categorization of COPD patients in Turkey via GOLD 2013 strategy document: ALPHABET study. Int J Chron Obstruct Pulmon Dis. 2015;10:2485–94.
7. Corrado A, Rossi A. How far is real life from COPD therapy guidelines? An Italian observational study. Respir Med. 2012;106(July (7)):989–97.
8. Soriano JB, Lamprecht B, Ramírez AS, Martinez-Camblor P, Kaiser B, Alfageme I, et al. Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data. Lancet Respir Med. 2015;3:443–50.
9. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195(5):557–82.
10. Gedebjerg A, Szépligeti SK, Wackerhausen LH, Horváth-Puhó E, Dahl R, Hansen JG, et al. Prediction of mortality in patients with chronic obstructive pulmonary disease with the new Global Initiative for Chronic Obstructive Lung Disease 2017 classification: a cohort study. Lancet Respir Med. 2018;6(3):204–12.
11. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli B, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. Eur Respir J. 2019;53:1900164, http://dx.doi.org/10.1183/13993003.00164-2019.
12. Soler Cataluña JJ, Cosío B, Izquierdo JL, Luis López-Campos José, Marín José M, Agüero Ramón, et al. Consensus document on the overlap phenotype COPD-asthma in COPD. Arch Bronconeumol. 2012;48:331–7.
13. Hsieh MJ, Huang SY, Yang TM, Tao CW, Cheng SL, Lee CH, et al. The impact of 2011 and 2017 Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines on allocation and pharmacological management of patients with COPD in Taiwan: Taiwan Obstructive Lung Disease (TOLD) study. Int J Chron Obstruct Pulmon Dis. 2018;13:2949–59.
14. Sun L, Chen Y, Wu R, Lu M, Yao W. Changes in definition lead to changes in the clinical characteristics across COPD categories according to GOLD 2017: a national cross-sectional survey in China. Int J Chron Obstruct Pulmon Dis. 2017;12:3095–102.
15. Högman M, Sulku J, Ställberg B, Janson C, Bröms K, Hedenström H, et al. 2017 Global Initiative for Chronic Obstructive Lung Disease reclassifies half of COPD subjects to lower risk group. Int J Chron Obstruct Pulmon Dis. 2018;13:165–73.
16. Le LAK, Johannessen A, Hardie JA, Johansen OE, Gulsvik A, Vikse BE, et al. Prevalence and prognostic ability of the GOLD 2017 classification compared to the GOLD 2011 classification in a Norwegian COPD cohort. Int J Chron Obstruct Pulmon Dis. 2019;14:1639–55.
17. Tudoric N, Koblizek V, Miravitlles M, Valipour A, Milenkovic B, Barczyk A, et al. GOLD 2017 on the way to a phenotypic approach? Analysis from the phenotypes of COPD in central and eastern Europe (POPE) cohort. Eur Respir J. 2017;49(4):1602518.
18. Hu YH, Liang ZY, Xu LM, Xu WH, Liao H, Li R, et al. Comparison of the clinical characteristics and comprehensive assessments of the 2011 and 2017 GOLD classifications for patients with COPD in China. Int J Chron Obstruct Pulmon Dis. 2018;13:3011–9.
19. Han MZ, Hsiue TR, Tsai SH, Huang TH, Liao XM, Chen CZ. Validation of the GOLD 2017 and new 16 subgroups (1A-4D) classifications in predicting exacerbation and mortality in COPD patients. Int J Chron Obstruct Pulmon Dis. 2018;13:3425–33.
20. Menezes AM, Wehrmeister FC, Perez-Padilla R, Viana KP, Soares C, Müllerova H. The PLATINO study: description of the distribution, stability, and mortality according to the Global Initiative for Chronic Obstructive Lung Disease classification from 2007 to 2017. Int J Chron Obstruct Pulmon Dis. 2017;12:1491–501.
21. Cabrera López C, Casanova Macario C, Marín Trigo JM, de-Torres JP, Sicilia Torres R, González JM, et al. Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports. Impact on Grouping and Outcomes. Am J Respir Crit Care Med. 2018;197(4):463–9.

Pulmonology 29 (2023) 194—199

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

The COPD assessment test and the modified Medical Research Council scale are not equivalent when related to the maximal exercise capacity in COPD patients

R. Pisi, M. Aiello, L. Calzetta*, A. Frizzelli, P. Tzani, G. Bertorelli, A. Chetta

Department of Medicine and Surgery, Respiratory Disease and Lung Function Unit, University of Parma, Viale A. Gramsci, 14, 43126 Parma, Italy

Received 14 December 2020; accepted 5 June 2021
Available online 5 July 2021

KEYWORDS
CAT;
mMRC;
COPD;
Exercise capacity;
Health status

Abstract
Introduction: The management and treatment of Chronic Obstructive Pulmonary Disease (COPD) are based on a cutoff point either of $\geq$ 10 on the COPD Assessment Test (CAT) or of $\geq$ 2 of the Medical Research Council (mMRC). Up to now, no study has assessed the equivalence between CAT and mMRC, as related to exercise tolerance in COPD. The aim of this study was to investigate as primary outcome the relationship between CAT and mMRC and maximal exercise capacity in COPD patients. We also evaluated as secondary outcome the agreement between CAT ($\geq$ 10) and mMRC ($\geq$ 2) to categorize patients according to their exercise tolerance.
Material and methods: 118 consecutive COPD patients (39 females), aged between 47 and 85 years with a wide range of airflow obstruction and lung hyperinflation were studied. Maximal exercise capacity was assessed by cardiopulmonary exercise test.
Results: CAT and mMRC scores were significantly related to VO_2 peak ($p<0.01$). CAT ($\geq$ 10) and mMRC ($\geq$ 2) have a high likelihood to be associated to a value of VO_2 peak less than 15.7 and 15.6 mL/kg/min, respectively. The interrater agreement between CAT ($\geq$ 10) and mMRC ($\geq$ 2) was found to be fair ($\kappa = 0.20$) in all patients but slight when they were subdivided in those with VO_2 peak $<$ 15 mL/kg/min and in those with VO_2 peak $\geq$ 15 mL/kg/min ($\kappa = 0.10$ and $\kappa = 0.20$ respectively).
Conclusion: This study shows that CAT and mMRC are useful tools to predict exercise tolerance in COPD, but they cannot be considered as supplementary measures.

* Corresponding author.
E-mail address: luigino.calzetta@unipr.it (L. Calzetta).

https://doi.org/10.1016/j.pulmoe.2021.06.001

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an inflammatory disease of the lungs characterized by chronic, progressive and not fully reversible airflow limitation.[1] COPD is primarily a lung disease, but can induce systemic effects with a significant impairment in exercise tolerance, health status and patient quality of life[1] and is now considered as a heterogeneous disease with multiple phenotypes and endotypes.[2] Accordingly, COPD management and treatment imply not only spirometric evaluation, but also a multidimensional assessment of the functional status and patients' quality of life.[1] In this context, it is worth noting that more than half of COPD patients complain of fatigue which may have a substantial impact on physical activity, quality of life, hospitalization rate, morbidity and mortality.[3]

The COPD Assessment Test (CAT) is a self-administered questionnaire consisting of eight items, which evaluate the most burdensome symptoms and limitations of the patients.[4] The score for each item ranges from 0 to 5 and the total score (0—40) provides a simple and quantified measure of health-related quality of life, with higher scores indicating poorer health status.[4] There is a body of evidence concerning the reliability of CAT as predictor of diagnosis,[5,6] disease exacerbation,[6-8] and mortality.[9] On the other hand, a simple measure of dyspnea, such as the modified Medical Research Council (mMRC) scale is also considered appropriate for the assessment of the symptoms,[10] since it relates to health status,[11] and may predict mortality risk of COPD patients.[12] According to the Global Initiative for COPD (GOLD) document, symptom assessment and treatment of the patients are based on a cutoff point of $\geq$ 10 on the CAT, which is considered equivalent to that of $\geq$ 2 of the mMRC scale.[1]

Up to now there has been limited evidence specifically addressed to evaluate the relationship between CAT, mMRC and maximal exercise capacity in COPD patients.[13-15] Furthermore, so far no study has assessed the equivalence between CAT and mMRC, as related to exercise capacity in COPD. It is worth noting that both performance during standardized exercise tests and their related pathophysiological responses are recognized as important biomarkers of the multidimensional assessment of cardiac and pulmonary diseases.[16] In a small sample of COPD patients, CAT score together with the Forced Expiratory Volume at 1st second (FEV_1) value was found to predict oxygen uptake in COPD.[13] In COPD patients with airflow obstruction degree ranging from mild to severe, mMRC dyspnea scale score was weakly and negatively correlated with the peak oxygen uptake.[14] In addition, in COPD patients with the same severity of airflow obstruction, a high score of mMRC was related to a poor maximum exercise capacity.[15]

The aim of the present study was, therefore, as primary outcome to investigate in a large cohort of COPD patients, the relationship between CAT and mMRC and the maximal exercise capacity assessed by means of the cardiopulmonary exercise test (CPET). Furthermore, we evaluated as secondary outcome the agreement between CAT ($\geq$ 10) and mMRC ($\geq$ 2) in order to categorize COPD patients according to their maximal exercise capacity.

Material and methods

Subjects

Outpatients with COPD, diagnosed according to the GOLD criteria,[1] were consecutively enrolled in the study from December 2018 to January 2020. The inclusion criteria were: smoking history of $\geq$10 pack-years; post bronchodilator forced expiratory volume at 1st second (FEV_1)/forced vital capacity (FVC) $<$0.7; regular pharmacological treatment over the previous 6 months. The exclusion criteria were: a COPD exacerbation in the previous 2 months; patients with the coexistence of another chronic pulmonary disease; patients with severe comorbidities associated to COPD (i.e. unstable cardiovascular disease or cancer); patients unable to perform all the tests required.

Patients characteristics were recorded at baseline: anthropometric variables (age, sex and body mass index — BMI, in kg/m^2), smoking habit, CAT score (Italian version),[4] rate of COPD exacerbations and domiciliary medications. The Italian version of the five-point mMRC scale was used to assess the daily living activity-related dyspnea.[10]

Based on the GOLD document,[1] COPD patients are considered at increased risk, when their CAT and nMRC values are greater than 10 and 2, respectively. Accordingly, we subdivided the patients into two subgroups, by choosing the cut-off points of $\geq$ 10 for the CAT and of $\geq$ 2 for the mMRC scale.

The study protocol was approved by the local Ethics Committee (approval number n. 14,718). All patients gave their informed consent.

Pulmonary function tests

Pulmonary function tests were performed with a flow-sensing spirometer and a body plethysmograph (Vmax 22 and 6200; SensorMedics, Yorba Linda, CA, USA). FEV_1, and FVC were recorded and reported as absolute values (L) and percentage of predicted value (% pred); FEV_1/FVC were expressed as a ratio and taken as index of airway obstruction.

Body plethysmography was used to quantify the thoracic gas volume (TGV) and total lung capacity (TLC,% pred) was calculated by adding TGV to inspiratory capacity (IC). The residual Volume/TLC ratio was taken as an index of static hyperinflation.

Lung transfer factor for carbon monoxide (TLco,% pred) was assessed via the single breath method using a mixture of carbon monoxide and methane.

Patients were forbidden to use bronchodilators 12 h before baseline spirometry. The reversibility test was carried out by second spirometry 15 min after inhalation of salbutamol 400 μg.

CPET

A cycloergometer (Corival PB, Lode BV, Groningen, The Netherlands) was used to carried out CPET, in agreement with the current standardized procedure.[17] During the test patients were continuously monitored by a 12-lead electrocardiogram (ECG, CardioPerfect, Welch Allyn, Delft, The Netherlands) and a pulse oximeter (Pulse Oximeter 8600, Nonin Medical Inc, MPLS, Mn U.S.). The exercise protocol

included: 3 min of rest, a further 3 min of unloaded cycling, followed by a progressive increment of 5−15 W each minute, depending on the anthropometric characteristics of patients and individual functional impairment. The Wasserman's equation was used to calculate the work rate increment.[18] Blood pressure (mm Hg) was measured every 2 min. Stopping criteria included: unsustainable dyspnea, muscular fatigue, chest pain, significant ECG ST-segment depression, a drop in systolic blood pressure or arterial oxygen saturation <84%.

Breath-by-breath oxygen uptake (VO_2, L/min), carbon dioxide output (VCO_2, L/min), tidal volume (V_T, L), and minute ventilation (V_E, L/min) were recorded during the test (CPX/D; Med Graphics, St. Paul, MN, US). Peak work load and peak VO_2 were recorded during the last 20 s of the test. The Metabolic Equivalents of Task (METs) were also calculated. Changes in operational lung volumes were assessed every 2 min during exercise and at peak exercise. Both dyspnea and leg fatigue induced by CPET were measured at the end of the exercise by a 0−100 visual analogue scale (VAS).

Further details on CPET are reported in the supplementary file.

Statistical analysis

A Shapiro-Wilk test was used to assess the distribution of the variables. Data were reported as mean ± standard deviation (SD) for the variables with normal distribution and as median [25th − 75th percentile] for those with a non-normal distribution. Unpaired t-test, Mann-Whitney test, and Pearson's Chi square test were used for comparisons when appropriate. Relationships between variables were assessed by Pearson correlation coefficient (r) or by Spearman's rank correlation coefficient (rho), depending on distribution. Linear regression analysis was carried out for values reporting significant correlation. The receiver operating characteristic (ROC) curve was used to plot the true positive rate (sensitivity) in function of the false-positive rate (100-specificity) for a cutoff point of VO2 in mL/kg/min with respect to mMRC $\geq$ 2 and CAT $\geq$ 10 as threshold values.[19] To test the interrater agreement between CAT and mMRC Cohen's Kappa (κ) was calculated.[20] K< 0.00 indicates "poor", $0.00 \leq \kappa \leq 0.02$ "slight", $0.21 \leq \kappa \leq 0.40$ "fair", $0.41 \leq \kappa \leq 0.60$ "moderate", $0.61 \leq \kappa \leq 0.80$ "substantial" and $0.81 \leq \kappa \leq 1.00$ "perfect" agreement. K was calculated both in all patients and in two subgroups of patients, subdivided according to the median value of the VO_2peak.

A p value <0.05 was considered significant.

Results

We studied 118 consecutive COPD patients (39 females), aged between 47 and 85 years. Patient's characteristics are shown in Table 1. At study entrance, patients were treated with long-acting beta$_2$-agonists (87%), long-acting muscarinic antagonists (73%) and inhaled steroids (62%). All patients were ex-smokers (64%) or current smokers (36%).

In all patients, a wide range of airflow obstruction and lung hyperinflation was found (FEV_1/FVC from 26% to 70% and RV/TLC from 30% to 84%, respectively). CAT and mMRC values ranged respectively from 1 to 33 and from 0 to 4 (Table 1) and were positively related (*rho = 0.434, p = 0.001*). Moreover, CAT and mMRC showed a negative correlation with FEV_1/VC (*rho = - 0.223, p = 0.02*) and (*rho = - 0.327, p = 0.001*) and a positive correlation with RV/TLC values (*rho = 0.208, p = 0.035*) and (*rho = 0.270, p = 0.01*), respectively.

Table 1 Anthropometric, clinical and lung function characteristics of 118 COPD patients (39 females).

Age (years)	69 ± 8	(47−85)
BMI (kg/m^2)	27 ± 5	(17−41)
CAT (0−40)	11 [8−17]	(1−33)
mMRC (0−4)	1 [1−2]	(0−4)
TLC (% pred)	118 ± 19	(80−176)
FVC (% pred)	86 ± 20	(35−149)
FEV_1 (% pred)	53 ± 18	(17−106)
FEV_1/FVC (%)	47 ± 11	(27−70)
RV/TLC (%)	56 ± 10	(30−84)
TL_{CO} (% pred)	61 ± 21	(18−145)

Notes: Values are expressed as mean ± SD or median [25th − 75th percentile] and (range).

All patients underwent CPET without complications. Mean peak VO_2 values in absolute value and as percent of predicted were respectively 15.5 mL/kg/min ± 4.1 and 65% ± 20, while peak workload was 78 *W* ± 31 (Table 2). Table 3 lists the relationships between CAT scores and mMRC scale scores and exercise variables in all patients.

According to the ROC curve method, the plot of true-positive rate in function of false-positive rate for a cutoff point of VO_2 with respect to a CAT $\geq$ 10 as threshold value showed 0.703 area under curve value (*p = 0.001*). A cutoff point, which maximized sensitivity and specificity, was VO_2 < 15.7 mL/kg/min (0.64 sensitivity and 0.71 specificity) (Fig. 1). In addition, the plot of true-positive rate in function of false-positive rate for a cutoff point of VO_2 with respect to a mMRC $\geq$ 2 as threshold value showed 0.739 area under curve value (*p = 0.001*). A cutoff point, which maximized sensitivity and specificity, was VO_2 < 15.6 mL/kg/min (0.58 sensitivity and 0.81 specificity) (Fig. 2).

In all patients, the interrater agreement between CAT ($\geq$ 10) and mMRC ($\geq$ 2) was found to be fair (κ = 0.21). However, when patients where subdivided according to the median value of the VO_2peak (15 mL/kg/min) in those with VO_2 peak < 15 mL/kg/min (n. 58) and those with VO_2peak $\geq$ 15 mL/

Table 2 Exercise characteristics of 118 COPD patients (39 females).

Peak VO_2 (mL/kg/min)	15.5 ± 4.1	(8.1−27.6)
Peak VO_2 (% pred)	65 ± 20	(27−122)
METs	4.4 ± 1.2	(2.5−8.2)
Peak Workload (watts)	78 ± 31	(20−164)
V_E (L/min)	39.7 ± 10.9	(18.3−68.1)
IC rest (L)	1.93 ± 0.53	(1.07−3.85)
IC peak (L)	1.67 ± 0.50	(0.74−3.42)
$VAS/W_{dyspnea}$ (mm/watts)	1.16 ± 0.72	(0.25−4.74)
$VAS/W_{fatigue}$ (mm/watts)	0.98 ± 0.63	(0.15−4.21)

Notes: Values are expressed as mean ± SD and (range).

Table 3 Relationships between CAT score and mMRC scale score and exercise variables in 118 COPD patients.

	CAT		mMRC	
	rho	*p*	*rho*	*p*
VO_2 peak (mL/kg/min)	−0.279	0.002	−0.439	0.001
VO_2 peak (pred)	−0.268	0.003	−0.224	0.015
METs	−0.291	0.001	−0.446	0.001
Worload peak (watts)	−0.373	0.001	−0.490	0.001
V_E (L/min)	−0.328	0.001	−0.377	0.001
IC rest (L)	−0.329	0.001	−0.297	0.001
IC peak (L)	−0.384	0.001	−0.415	0.001
$VAS/W_{dyspnea}$ (mm/watts)	0.464	0.001	0.546	0.001
$VAS/W_{fatigue}$ (mm/watts)	0.241	0.001	0.253	0.001

kg/min (n. 62), the interrater agreement between CAT ($\geq$ 10) and mMRC ($\geq$ 2) was slight, $\kappa = 0.10$ and $\kappa = 0.20$ respectively.

Discussion

The main finding of the present study is that CAT and mMRC are strictly associated to the maximal exercise capacity in a large cohort of COPD patients with different degrees of severity. Higher scores of CAT or mMRC indicate poorer exercise tolerance. This study also confirmed that CAT and mMRC are related to baseline lung function of the patients, both in terms of airflow obstruction and lung hyperinflation.

The findings of the present study further support the value of CAT and mMRC in the integrated multidimensional management of COPD patients. However, our results show that the agreement between CAT ($\geq$ 10) and mMRC ($\geq$ 2) to categorize COPD patients according to the maximal exercise capacity was slight and, accordingly, this study does not support the use of the recommended cutoff points of $\geq$ 10 for CAT and $\geq$ 2 for mMRC as equivalents in the grading of exercise limitation of COPD patients.

The CAT was firstly created and developed to quantify COPD impact in routine practice and to aid patient's health status assessment and communication between patient and physician.[21] The CAT was then acknowledged as an accurate and reliable measure of health-related quality of life in COPD patients.[22,23] Dyspnea is the most frequent symptom reported by patients suffering from COPD,[24] and the mMRC scale is the most commonly used validated scale to assess dyspnea in daily living of these patients.[25,26] It is worth noting that the GOLD document recommends the use of both CAT and mMRC to assess symptoms and assign patients to treatment groups.[1]

Our main findings confirmed and extended the results from previous studies that investigated the relationship between CAT score,[13] or mMRC score,[14,15] and exercise capacity in COPD patients. In the present study, we provided the evidence that in COPD patients CAT and mMRC scores were inversely related with the maximal oxygen uptake both in terms of mL/kg/min and predicted value and of METs as well as with the maximal workload. Moreover, in our patients we found that a CAT score $\geq$ 10 and a mMRC score $\geq$ 2 are very likely to be associated to a value of VO_2 peak $<$ 15.7 mL/kg/min and $<$ 15.6 mL/kg/min, respectively. CAT and mMRC were also negatively related to IC at the peak of exercise, which is a measure of dynamic hyperinflation on exertion, and were positively related both to exertional dyspnea and to fatigue. Interestingly, a previous study showed that in COPD patients clinically relevant fatigue was associated with increasing total CAT score and CAT score $\geqslant$10, independently of age, airflow obstruction degree and concomitant heart disease or depression.[27] In addition, it has been previously reported that COPD patients who were more dyspneic in their daily living by mMRC scale, were found to complain of more dyspnea after CPET.[15]

In the present study, CAT score was positively related to mMRC and, interestingly, the cutoff points of CAT ($\geq$ 10) and mMRC ($\geq$ 2) have a high likelihood of being associated to a value of VO_2 peak approximately less than 15 mL/kg/min. Interestingly, the cutoff value of 15 mL/kg/min VO_2 peak has a potential to discriminate respiratory patients with different grading of functional status. In this study, patients with a VO_2 peak value less than 15 mL/kg/min had a significant poorer spirometry than patients with a VO_2 peak value greater than 15 mL/kg/min (data not shown). Moreover, it is well known that patients with lung cancer with 15 mL/kg/min VO_2 peak, being considered for resection surgery are considered as at increased risk of perioperative complications.[28,29]

It is worth noting that the interrater agreement between CAT ($\geq$ 10) and mMRC ($\geq$ 2) was found to be fair in all patients and even slight, when patients where subdivided into two subgroups, i.e. in patients with VO_2peak $<$ 15 mL/kg/min and in patients with VO_2peak $\geq$ 15 mL/kg/min. Our finding is

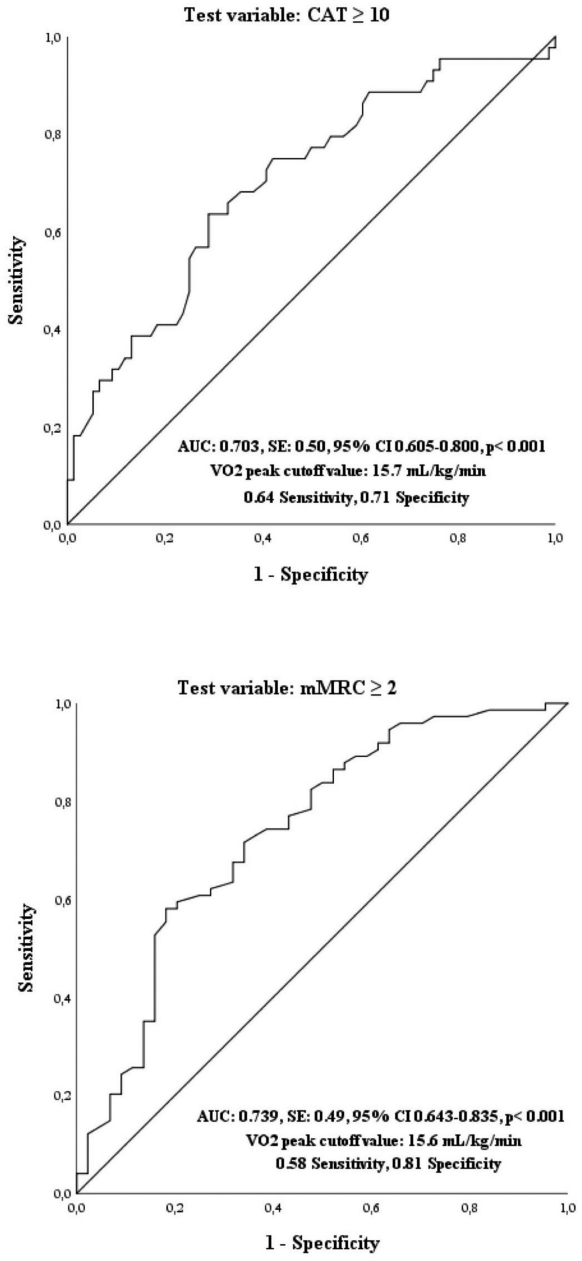

Figure 1 Receiver operating characteristic curve for VO_2 peak in mL/kg/min calculated with CAT $\geq$ 10 (*upper panel*) or mMRC $\geq$ 2 as test variable (*lower panel*).

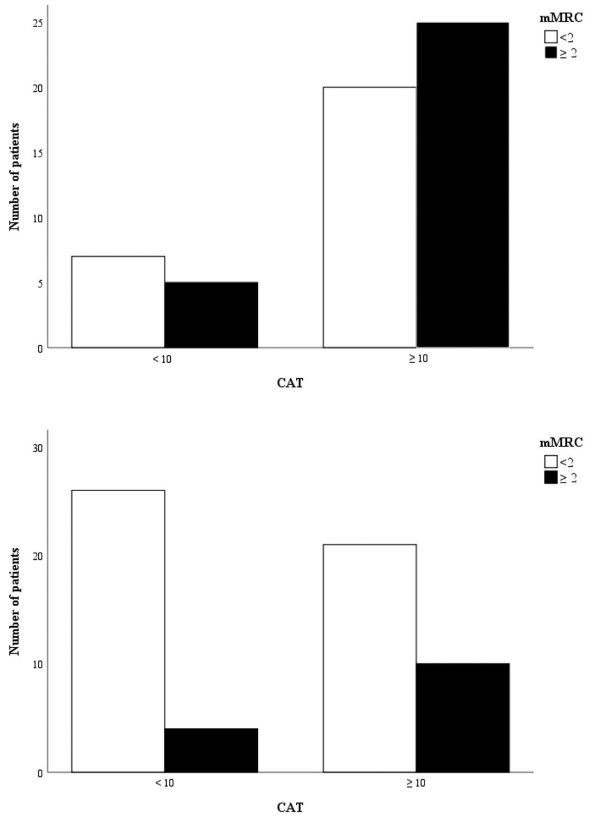

Figure 2 Bars represent the number of patients categorized according to CAT and mMRC and subdivided in two groups, i.e. patients with VO_2peak < 15 mL/kg/min (n. 58) (*upper panel*) and patients with VO_2peak $\geq$ 15 mL/kg/min (n. 62) (*lower panel*). The interrater agreement between CAT ($\geq$ 10) and mMRC ($\geq$ 2) was slight, κ = 0.10 (*upper panel*) and κ = 0.20 (*lower panel*).

the first evidence about the agreement between CAT and mMRC in relation to maximal exercise capacity. A previous systematic review and meta-analysis specifically addressed the evaluation of the agreement between patient's assignment into GOLD categories using CAT cut point $\geq$ 10) or mMRC cut point $\geq$ 2 showed a misclassification of 13% in all GOLD categories, agreement ranging between CAT and mMRC from poor to substantial (κ value 0.13 to 0.77).[23]

This study has some strengths: the large size of the patient's sample and the prospective and consecutive nature of the data collection. On the other hand, we acknowledge that this study also has some limitations. Firstly, our study is a cross-sectional study and our results may be of value in the assessment of the functional status of patients with COPD, but not in their prognostic evaluation. Thus, a further longitudinal study on exercise tolerance in COPD patients, who change their health-related quality of life over time, is needed. Secondly, in our study patients experienced maximal exercise capacity by using cycle ergometry, therefore, our results cannot be applicable to other forms of exercise, such as running on a treadmill, where the metabolic load is greater.

Conclusions

In conclusion, we demonstrated that CAT as well as mMRC are useful tools to predict exercise tolerance in COPD. Furthermore, in our patients CAT and mMRC were significantly related to dynamic hyperinflation on exertion and to exertional dyspnea and fatigue. However, we found that the agreement between the cutoff points of CAT ($\geq$ 10) and mMRC ($\geq$ 2) was poor, when related to maximal exercise capacity and, accordingly, they cannot be considered as supplementary measures.

Funding

This work was not supported by any financial source.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgment

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2021.06.001.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. Available from: http://goldcopd.org/.
2. Corlateanu A, Mendez Y, Wang Y, Garnica RJA, Botnaru V, Siafakas N. Chronic obstructive pulmonary disease and phenotypes: a state-of-the-art. Pulmonology. 2020 Mar-Apr;26(2):95—100. https://doi.org/10.1016/j.pulmoe.2019.10.006.
3. Paneroni M, Vitacca M, Venturelli M, Simonelli C, Bertacchini L, Scalvini S, et al. The impact of exercise training on fatigue in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Pulmonology. Sep-Oct 2020;26 (5):304—13. https://doi.org/10.1016/j.pulmoe.2020.02.004.
4. CAT Development Steering Group: COPD Assessment Test. Healthcare Professional User Guide. Available from: http://www.catestonline.org/. 2014.
5. Raghavan N, Lam Y-M, Webb KA, Guenette JA, Amornputtisathaporn N, et al. Components of the COPD Assessment Test (CAT) associated with a diagnosis of COPD in a random population sample. COPD: J Chronic Obstruct Pulm Dis. 2012;9(2):175—83.
6. Gupta N, Pinto L, Benedetti A, Zhi Li P, Tan WC, Aaron SD, et al. The COPD Assessment Test: can it discriminate across COPD subpopulations? Chest. 2016;150(5):1069—79.
7. Lee SD, Huang MS, Kang J, Lin CH, Park MJ, Oh YM, et al. The COPD assessment test (CAT) assists prediction of COPD exacerbations in high-risk patients. Respir Med. 2014;108(4):600—8.
8. Pothirat C, Chaiwong W, Limsukon A, Deesomchok A, Liwsrisakun C, Bumroongkit C, et al. Detection of acute deterioration in health status visit among COPD patients by monitoring COPD assessment test score. Int J Chron Obstruct Pulmon Dis. 2015;10:277—82.
9. Casanova C, Marin JM, Martinez-Gonzalez C, de Lucas-Ramos P, Mir-Viladrich I, Cosio B, et al. Differential effect of modified medical research council dyspnea, COPD assessment test, and clinical COPD questionnaire for symptoms evaluation within the new GOLD staging and mortality in COPD. Chest. 2015;148 (1):159—68.
10. Fletcher CM. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). BMJ. 1960;2:1662.
11. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54 (7):581—6.
12. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest. 2002;121(5):1434—40.
13. Carvalho-Jr LCS, Trimer R, Arêas GP, Caruso FC, Zangrando KT, Jürgensen SP, et al. COPD assessment test and FEV(1): do they predict oxygen uptake in COPD? Int J Chron Obstruct Pulmon Dis. 2018;13:3149—56.
14. Cote CG, Pinto-Plata V, Kasprzyk K, Dordelly LJ, Celli BR. The 6-min walk distance, peak oxygen uptake, and mortality in COPD. Chest. 2007;132(6):1778—85.
15. Crisafulli E, Aiello M, Tzani P, Ielpo A, Longo C, Alfieri V, et al. A high degree of dyspnea is associated with poor maximum exercise capacity in subjects with COPD with the same severity of air-flow obstruction. Respir Care. 2019;64(4):390—7.
16. Puente-Maestu L. Physiological rationale of commonly used clinical exercise tests. Pulmonology. 2020;26(3):159—65.
17. American Thoracic Society ACoCP. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211—77.
18. Wasserman K, Hansen JE, Sue DY, et al. Incremental exercise test to symptom limit maximum. In: Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ, eds. Principles of Exercise Testing & Interpretation, Philadelphia US: Lippincott Williams & Wilkins; 1994. p. 130.
19. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin Chem. 1993;39(4):561—77.
20. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159—74.
21. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648—54.
22. Gupta N, Pinto LM, Morogan A, Bourbeau J. The COPD assessment test: a systematic review. Eur Respir J. 2014;44 (4):873—84.
23. Karloh M, Fleig Mayer A, Maurici R, Pizzichini MMM, Jones PW, Pizzichini E. The COPD assessment test: what do we know so far?: a systematic review and meta-analysis about clinical outcomes prediction and classification of patients Into GOLD stages. Chest. 2016;149(2):413—25.
24. Miravitlles M, Worth H, Soler Cataluña JJ, Price D, De Benedetto F, Roche N, et al. Observational study to characterise 24-h COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. Respir Res. 2014;15 (1):122.
25. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest. 1988;93(3):580—6.
26. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Analysis of clinical methods used to evaluate dyspnea in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;158(4):1185—9.
27. Stridsman C, Svensson M, Johansson Strandkvist V, Hedman L, Backman H, Lindberg A. The COPD Assessment Test (CAT) can screen for fatigue among patients with COPD. Ther Adv Respir Dis. 2018;12:1753466618787380.
28. Beckles MA, Spiro SG, Colice GL, Rudd RM. The physiologic evaluation of patients with lung cancer being considered for resectional surgery. Chest. 2003 Jan;123(1 Suppl):105S—14S. https://doi.org/10.1378/chest.123.1_suppl.105s.
29. Bobbio A, Chetta A, Internullo E, Ampollini L, Carbognani P, Bettati S, Rusca M, Olivieri D. Exercise capacity assessment in patients undergoing lung resection. Eur J Cardiothorac Surg. 2009 Mar;35(3):419—22. https://doi.org/10.1016/j.ejcts.2008.11.004.

Pulmonology 29 (2023) 200—206

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Stratifying risk outcomes among adult COVID-19 inpatients with high flow oxygen: The R4 score

G.M. Aguirre-García[a,1], D. Ramonfaur[b,1], G. Torre-Amione[a], M.T. Ramírez-Elizondo[a], R. Lara-Medrano[a], J.F. Moreno-Hoyos[a], E.S. Velázquez-Ávila[c], C.A. Diaz-Garza[a], V.M. Sanchez-Nava[a], F. Castilleja-Leal[a], G.M. Rhoades[a], M.F. Martínez-Reséndez[a,c,*]

[a] *Instituto Tecnologico y de Estudios Superiores de Monterrey, School of Medicine and Health Sciences, Monterrey, Nuevo Leon, Mexico*
[b] *Harvard Medical School, Division of Postgraduate Medical Education, 25 Shattuck St, Boston, MA 02115, United States*
[c] *Hospital San Jose-Tec Salud, Epidemiological Surveillance Unit, Monterrey, Nuevo Leon, Mexico*

Received 19 August 2021; accepted 3 October 2021
Available online 12 October 2021

KEYWORDS
Coronavirus;
Risk;
Respiratory distress syndrome;
Oxygen inhalation therapy

Abstract
Background: High flow oxygen therapy (HFO) is a widely used intervention for pulmonary complications. Amid the coronavirus infectious disease 2019 (COVID-19) pandemic, HFO became a popular alternative to conventional oxygen supplementation therapies. Risk stratification tools have been repurposed —and new ones developed— to estimate outcome risks among COVID-19 patients. This study aims to provide a simple risk stratification system to predict invasive mechanical ventilation (IMV) or death among COVID-19 inpatients on HFO.
Methods: Among 529 adult inpatients with COVID-19 pneumonia, we selected unadjusted clinical risk factors for developing the composite endpoint of IMV or death. The risk for the primary outcome by each category was estimated using a Cox proportional hazards model. Bootstrapping was used to validate the results.
Results: Age above 62, eGFR under 60 ml/min, room air SpO2 $\leq$89 % upon admission, history of hypertension, history of diabetes, and any comorbidity (cancer, cardiovascular disease, COPD/asthma, hypothyroidism, or autoimmune disease) were considered for the score. Each of the six criteria scored 1 point. The score was further simplified into 4 categories: 1) 0 criteria, 2) 1 criterion, 3) 2-3 criteria, and 4) $\geq$4 criteria. Taking the first category as the reference, risk estimates

Abbreviations: HFO, High flow oxygen therapy; COVID-19, Coronavirus infectious disease 2019; IMV, invasive mechanical ventilation; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; COT, conventional oxygen therapy; NIV, non-invasive ventilation; RT-PCR, reverse transcriptase polymerase chain reaction; IV, intravenous; IL-6, interleukin-6; SOFA, Sequential Organ Failure Assessment; PSI, Pneumonia Severity Index; NEWS 2, National Early Warning Score 2; FiO_2, fraction of inspired oxygen; LDH, lactate dehydrogenase; CRP, C-reactive protein; BNP, brain natriuretic peptide; HS, highly sensitive; IQR, interquartile range; HR, hazard ratio; ROC, receiver operating characteristic; AUC, area under the curve; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease.

* Corresponding author at: Instituto Tecnologico y de Estudios Superiores de Monterrey, School of Medicine and Health Sciences, Monterrey, Nuevo Leon, Mexico. Av. Ignacio Morones Prieto 3000, Sertoma, 64710 Monterrey, N.L.
E-mail address: michel.martinez@tecsalud.mx (M.F. Martínez-Reséndez).
[1] These authors contributed equally.

https://doi.org/10.1016/j.pulmoe.2021.10.001

for the primary endpoint were HR; 2.94 [1.67 — 5.26], 4.08 [2.63 — 7.05], and 6.63 [3.74 — 11.77], respectively. In ROC analysis, the AUC for the model was 0.72.
Conclusions: Our score uses simple criteria to estimate the risk for IMV or death among COVID-19 inpatients with HFO. Higher category reflects consistent increases in risk for the endpoint.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the 2019 novel coronavirus disease (COVID-19) has overwhelmed entire health systems across the world.[1—3] An estimated 67% of patients with severe COVID-19 develop acute respiratory distress syndrome and almost 20% require ICU admission.[4,5] In Mexico, at the beginning of the surge, 46% of patients categorized as critically ill did not receive invasive mechanical ventilation (IMV). Similar estimates were seen in the United States, both because of a lack of ICU beds availability and mechanical ventilators.[3] High flow oxygen therapy (HFO) has become a safe[6] and effective[7] respiratory support alternative in patients with acute respiratory failure. However, its benefit in mortality is controversial.[8,9] In the setting of the current pandemic, HFO has been recommended over the use of non-invasive ventilation NIV,[10,11] despite limited evidence regarding its benefit in improving outcomes. Nonetheless, with a global shortage of mechanical ventilators and access to specialized care, HFO may be a useful alternative. Risk stratification for incident IMV or death among patients on HFO is unclear and may be population dependent. Traditional and novel scoring tools have been utilized to provide risk estimates among COVID-19 patients. While some of them have good prognostic value, others are non-specific or employ many variables. This study aims to provide new scoring criteria to estimate the risk for IMV or death on HFO among COVID-19 inpatients receiving HFO.

Methods

A retrospective analysis was conducted in a tertiary care hospital redesigned to treat COVID-19 patients (Hospital San José— TecSalud) in Monterrey, Mexico from April to October 2020. Demographics, clinical and laboratory information was collected in a deidentified database. Approval from the TecSalud Ethics Committee was obtained (P000353-COVID-19-TecSalud-CS001).

Study population

We included hospitalized patients over 18 years of age, with positive Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) for SARS-CoV-2 and oxygen requirements that demanded HFO. Criteria for initiation of HFO were oxygen saturation lower than 92% with conventional oxygen therapy (COT) (reservoir mask at 15 L/min), and tachypnea (> 30 breaths per minute) and/or self-reported rest dyspnea despite COT. All patients received a protocolized treatment which consisted of dexamethasone (6 mg IV, QD) plus baricitinib (4mg PO, QD) for 10 days and those with interleukin-6 (IL-6) higher than 80 pg/mL at third day of hospital stay and C-reactive protein higher than 7.5 mg/dL without respiratory improvement received tocilizumab (8mg/kg/dose IV, BID).

Variables and score implementation

We analyzed demographic characteristics that included: age, sex, body mass index (BMI), estimated glomerular filtration rate (eGFR), smoking status and comorbidities (type 2 diabetes, hypertension, chronic kidney disease and cardiac disease, COPD/Asthma, cancer, cardiovascular disease (CVD), and autoimmune conditions). eGFR was calculated using serum creatinine, with the CKD-EPI formula. All comorbidities were recorded by self-reported or by a proxy if patients were not able to provide their own history. Clinical characteristics included: number of days with symptoms prior to admission, oxygen saturation at room air upon admission, SAFI (saturation/fraction of inspired oxygen index), the CALL score, a COVID-19-specific score to predict disease progression that includes comorbidity, age, lymphocytes and lactate dehydrogenase (LDH),[12] severity scores such as Sequential Organ Failure Assessment (SOFA),[13] Pneumonia Severity Index (PSI),[14] CURB-65,[15] National Early Warning Score 2 (NEWS 2)[16,17]; days with HFO, length of hospital stay in days, ICU admission and length of stay in ICU, number of days since admission until HFO initiation. Respiratory parameters such as oxygen saturation, respiratory rate per minute, fraction of inspired oxygen (FiO_2) and the Respiratory rate and Oxygenation (ROX)[18] index were recorded upon admission, at the time of HFO, and 24 hours post HFO initiation. Superimposed bacterial infections were also documented at any time during hospitalization.

Admission laboratory tests that were analyzed included: complete blood count, LDH, C-reactive protein (CRP), procalcitonin, IL-6, D- dimer, brain natriuretic peptide (BNP), ferritin, and highly sensitive (HS) troponin.

Statistical analysis

Stata IC-16 was used to conduct statistical analyses. For categorical variables, frequencies and percentages are shown; for continuous variables, according to normal or non-normal distribution, mean and standard deviation or median and interquartile range (IQR), respectively, are shown. Chi-squared and t-test or U Mann-Whitney were used for comparisons between both groups. No imputation methods were utilized for data missingness. An alpha of 5% was set as threshold for statistical significance. The primary endpoint was IMV, or death while on HFO.

Demographic and clinical covariates associated with the endpoint were considered to construct the score. Cox proportional hazard models were employed to estimate the risk for the primary outcome by each category of the score. The

proportional hazards assumption was tested. Kaplan-Meier (KM) estimates were used to display cumulative incidence of the primary endpoint, where time zero is the day the patient was placed on HFO. Results from the models are expressed as hazard ratios (HR) and 95% confidence intervals (CI). Receiver operating characteristic (ROC) curves were utilized to assess the performance of our score compared to other utilized scores. Area under the curve (AUC) for different scores were compared using DeLong's test. A classic 1,000-replication bootstrapping method was used to validate the score. Normal-based CI are reported in our HR estimate.

Sensitivity analysis using IMV as one endpoint and using all-cause mortality as another endpoint was performed. A cox proportional hazards model was employed to assess the average increment in risk for each endpoint by each increasing category in the R4 score.

Results

A total of 1465 patients were hospitalized during the study period; 543 patients were started on HFO during their hospital stay. Fourteen had been intubated prior to the initiation of HFO and were excluded from the analysis (Supplement Fig. 1). The analysis includes 529 patients. Median follow-up time was 8 (3-11) days. The mean age was 55.8 $\pm$ 15 years, 25% were female. The median number of days of COVID-19 symptoms before admission was 7 (6-10). The median length of stay was 13.0 (9 $-$ 22) days and a total of 286 (54%) patients required intensive care. IMV was required in 200 (38%) of cases, and 13 (2.4%) died while on HFO. Causes for mortality among those on HFO were acute myocardial infarction (8/13), pancreatitis secondary to metastatic melanoma (1/13), respiratory insufficiency secondary to gastric carcinoma (DNR) (1/13), septic shock (1/13) and cerebrovascular complications (2/13). Nonetheless, no patients required cardiopulmonary resuscitation as a result of scarcity of ventilators. All-cause mortality was 126 (24%). A total of 213 (40%) participants met the primary endpoint. The complete description and comparison of the population is displayed in Table 1.

Development of the "Risk 4" (R4) score

Significant variables from Table 1 were imputed into a univariate model for predicting the primary endpoint. Due to low prevalence of comorbidities (CVD, COPD, cancer, autoimmune diseases, and hypothyroidism) were concatenated into one single variable. Clinical variables associated with the endpoint were selected to construct the score (Table 2). Bacterial infection was removed from the score because it is a consequence IMV. Six variables were included in the score. The score was optimized into 4 categories as follows: 0 criteria, 1 criterion, 2-3 criteria, and $\geq$4 criteria met. Event count and proportions per R4 score category are displayed in Supplement Table 1.

Primary endpoint by R4 category

Median follow-up time in patients who met the primary endpoint was 3 (1-9) days. Each category increase in the R4 score increased likelihood for meeting the endpoint (HR 1.45 [1.31$-$1.61], p$<$ 0.001). HR and CI by each category, as well as the bootstrapped sample CI are summarized in Table 3 and the KM estimate is displayed in Fig. 1. Sensitivity and specificity for each scoring component and for the R4 categories is summarized in Supplement Table 2. When breaking our primary endpoint into separate outcomes (VMI and death), the average HR for VMI and death by each increase in R4 category were 1.4 [1.26$-$1.56], p $<$0.001, and 1.62 [1.42$-$1.85] p$<$0.001, respectively.

Comparison against other scores

We compared the R4 score against other scoring methods described in the literature using receiver operating characteristic (ROC) curves for our primary endpoint. When comparing the R4 score against other scores, it performed better than CALL (AUC 0.64), SOFA (AUC 0.63) and NEWS2 (AUC 0.57) scores (p= 0.005 and 0.001, respectively). However, it did not perform significantly different than PSI (AUC 0.69), ROX-24 (AUC 0.71) and CURB65 (AUC 0.68) (p= 0.206, 0.647, and 0.113, respectively). When using the traditional cutoff of 4.88 for the ROX score at 24 hours of HFO, the AUC was 0.61 with a sensitivity and specificity of 46 and 78%, respectively. The ROC curves and AUC for each score is provided in Supplement Fig. 2.

Discussion

In our cohort, of 529 patients with COVID-19 pneumonia who required HFO, a high proportion (60%) avoided IMV and death. HFO could be an IMV-sparing therapy, improving survival, reducing hospital length of stay and lowering stress in health-care personnel.[19] We leveraged the high number of participants on HFO to construct a prognostic score. The reason some patients progress to severe complications is poorly understood, although, likely multifactorial.[5,20$-$22] Due to the myriad of factors that may influence the prognosis, developing highly reliable and widely generalizable scoring methods to predict clinical outcomes is challenging. While several authors have successfully designed tools to predict mortality,[23,24] some may have too many variables to incorporate which may hamper the ability of clinicians to complete these scores in some settings. The R4 score is a simple and easy to use tool that integrates clinical data to predict adverse outcomes among adult inpatients on HFO. In this study, the purpose of creating a scoring method has merely prognostic purposes, and its utility for guiding treatment remains unclear. Further studies evaluating its use as a decision making or triage tool must be conducted before attempting to give it such purpose.

The R4 score is composed of six variables, all of which were predictive of the endpoint in univariate analysis. When putting together the score, very few participants met 5 or 6 criteria (n= 17, and 2, respectively), these low frequencies limited the power to predict the endpoint. For this reason, we opted for consolidating into a single group any patient meeting more than 4 criteria. Moreover, participants meeting 2 or 3 criteria had a very similar risk (HR= 3.84 and 4.39, respectively) for meeting the primary endpoint. Additionally, the CI around those meeting 2 and 3 criteria completely

Table 1 Overall baseline characteristics and comparative between both outcome groups. LOS= Length of stay, BMI= Body mass index, CVD= Cardiovascular disease, eGFR= estimated glomerular filtration rate, IMV= invasive mechanical ventilation, IL-6= interleukin 6, HS= highly sensitive, BNP= brain natriuretic peptide, CRP= C-reactive protein.

	Overall	Composite endpoint met		
		No	Yes	
Variables	n=529	n=316	n=213	p-value
Age (years)	55.8 ± 15.1	52.7 ± 14.5	60.4 ± 14.8	< 0.001
Sex (female)	393 (74.3%)	70 (22.2%)	66 (31.0%)	0.02
LOS (days)	17.2 ± 12.8	12.2 ± 6.3	24.7 ± 16.0	< 0.001
Days of symptoms before admission	8.6 ± 4.8	8.9 ± 4.2	8.3 ± 5.4	0.16
BMI (kg/m^2)	31.4 ± 5.5	31.5 ± 5.6	31.2 ± 5.3	0.54
Hypertension	211 (39.9%)	101 (32.0%)	110 (51.6%)	< 0.001
Diabetes	153 (28.9%)	77 (24.4%)	76 (35.7%)	0.01
Current smoker	46 (8.7%)	28 (8.9%)	18 (8.5%)	0.80
CVD	32 (6.0 %)	13 (4.1 %)	19 (8.9 %)	0.02
Nephropathy	20 (3.8 %)	7 (2.2 %)	13 (6.1 %)	0.02
Hypothyroidism	31 (5.9 %)	12 (3.8 %)	19 (8.9 %)	0.01
COPD or Asthma	9 (1.7 %)	4 (1.3 %)	5 (2.3 %)	0.35
Active cancer	17 (3.2 %)	7 (2.2 %)	10 (4.7 %)	0.11
Autoimmune disease	6 (1.1 %)	2 (0.6 %)	4 (1.9 %)	0.18
Pregnancy	4 (0.8 %)	1 (0.3 %)	3 (1.4 %)	0.16
SpO2 at admission (%)	82.8 ± 11.9	84.7 ± 9.9	79.9 ± 13.9	< 0.001
ROX score at 24 hours	5.9 ± 2.2	6.4 ± 2.3	5.1 ± 1.9	< 0.001
SOFA	0.9 ± 1.4	0.7 ± 1.1	1.3 ± 1.6	< 0.001
PSI	65.4 ± 27.5	58.4 ± 22.4	76.2 ± 31.1	< 0.001
CURB-65	0.8 ± 0.9	0.6 ± 0.8	1.2 ± 1.0	< 0.001
CALL	9.8 ± 2.2	9.3 ± 2.1	10.5 ± 2.2	< 0.001
eGFR (mL/min)	0.9 ± 1.4	89.7 ± 23.5	76.6 ± 28.0	< 0.001
SpO2 before HFOT (%)	84.4 ± 26.2	89.9 ± 9.6	86.2 ± 13.2	< 0.001
Days on HFOT	5.7 ± 4.7	6.1 ± 4.0	5.1 ± 5.5	0.021
Days on IMV	14.1 ± 13.3	−	14.1 ± 13.3	−
Labs on admission				
Hemoglobin (mg/dL)	14.1 ± 1.9	14.2 ± 1.6	13.8 ± 2.2	0.01
Leucocytes (x 10^3/μL)	10.4 ± 5.3	10.4 ± 4.8	10.4 ± 6.0	1
Lymphocytes (x 10^3/μL)	1.0 ± 1.2	0.9 ± 1.0	1.0 ± 1.5	0.32
Platelets (x 10^3/μL)	241.6 ± 99.1	255.0 ± 97.3	221.8 ± 98.5	0.001
Potassium (mmol/L)	5.5 ± 21.8	4.1 ± 0.5	7.5 ± 34.3	0.08
IL-6 (pg/mL)	132.7 ± 302.5	91.8 ± 113.5	190.7 ± 444.6	0.001
Ferritin (μg/L)	2135.1 ± 2649.0	2130.6 ± 2664.5	2141.8 ± 2632.8	0.96
D-dimer (ng/mL)	1485.3 ± 5456.0	1344.8 ± 5647.5	1693.8 ± 5166.0	0.49
HS troponin (ng/mL)	34.5 ± 125.4	23.7 ± 90.9	50.1 ± 161.9	0.03
BNP (pg/mL)	87.1 ± 297.1	82.6 ± 359.6	93.3 ± 175.5	0.72
CRP (mg/dL)	18.0 ± 16.6	17.9 ± 19.2	18.1 ± 11.5	0.87
Procalcitonin (ng/mL)	0.6 ± 1.5	0.5 ± 1.4	0.7 ± 1.6	0.24
LDH (U/L)	508.0 ± 681.1	449.9 ± 317.0	592.6 ± 991.8	0.02
Admission to ICU	286 (54.1%)	88 (27.8%)	198 (93.0%)	< 0.001
Days on ICU	8.3 ± 12.8	1.5 ± 3.0	18.3 ± 14.9	< 0.001
Bacterial infection during hospitalization	161 (30.4%)	15 (4.7 %)	146 (68.5%)	< 0.001

overlapped, so creating a single category for patients meeting 2 or 3 criteria simplified the score.

Comparison with other standardized scores

Traditional scoring tools have been repurposed for use among COVID-19 inpatients.[25] In a cohort of 830 participants with COVID-19 pneumonia, the performance of qSOFA, NEWS2 and CURB-65 was evaluated. All tools lacked prognostic utility and underestimated the mortality rate in their population. The ROX score is a tool that predicts IVM among patients with HFO[18] and has been validated in the setting of COVID-19.[26,27] Moreover, a recent study demonstrated the value of the ROX in COVID-19 patients, and reiterates it's

Table 2 Components for the R4 score. Each criterion met sums 1 point.

R4 Score Components	
Age $\geq$ 63 years	
eGFR $\leq$ 60 ml/min	
ROX $\leq$ 5.2 at 24h of HFO	
History of Hypertension	
History of Diabetes	
Any of the following comorbidities:	CVD
	Autoimmune disease
	COPD
	Cancer
	Hypothyroidism

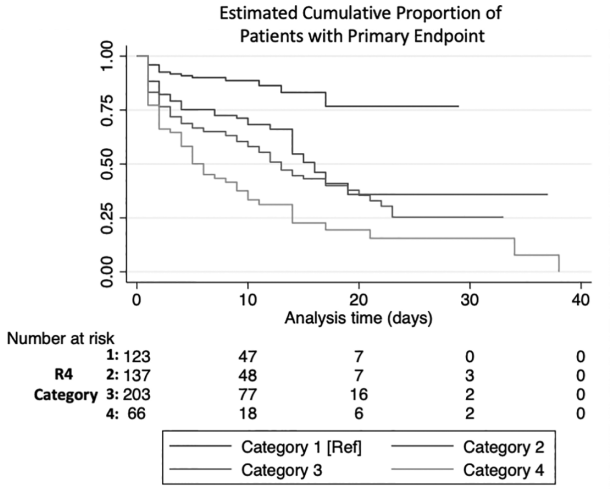

Figure 1

role in decision-making for clinicians to proceed to IMV.[27] This study also suggests that repurposing the ROX score for COVID-19 patients deemed a reevaluation of cutoff values, and found that ROX at 12 hours best predicted IMV when using a ROX cutoff of 5.99.[27] In agreement with this study, our data suggests using a higher cutoff value correctly classifies more patients to undergo IMV. Another cohort showed improved performance of the NEWS2 score,[16] with an AUC of 0.82 for predicting mortality. The SOFA score has also been repurposed by different groups but its value is inconsistent among different cohorts.[28,29] Evidence regarding the use of traditional scores to predict outcomes among COVID-19 inpatients is inconsistent, and likely sensitive to different populations and outcomes. Novel scores developed for COVID-19 disease like the CALL score[12] claim high sensitivity and specificity for disease progression. The R4 score proved to perform similarly to PSI, ROX and CURB-65 among our study cohort, while performing better than the SOFA, NEWS2, and CALL scores to predict our primary endpoint. Despite the latter being designed for COVID-19 patients and claiming an AUC of over 0.9 the results did not hold in our cohort, probably in part because we used it for a different endpoint, and we did not have data on HIV status to incorporate into the score. These positive results suggest the R4 score may be used in lieu of, or as a complement of other traditional and novel scores. However, it is important to note this score was evaluated only in the setting of a developmental cohort and reevaluated among our population using bootstrapping, which limits our ability to compare it with other scoring methods.

Our study is limited in that it is a retrospective analysis, thus a casual pathway cannot be determined. Initiation of IMV could have been altered by clinician judgement, as well as ventilator shortage, and ICU availability. Our study does not consider therapies that participants might have received before admission, which may introduce selection bias into our study. Our score was only assessed in a single cohort; it is unclear how it will perform in other cohorts. Comorbidities were assessed by self- or proxy report, which may raise concern for recall bias, exaggerating the effect size. Moreover, with the emergence of SARS-CoV-2 variants, and the implementation of vaccine programs, it is unclear whether the score will perform similarly in populations infected with other variants, and whether vaccines might influence the effect estimates. However, this limitation is present in any scoring tool, until further studies are conducted to evaluate the impact of variants and vaccines on risk tools. The R4 score was not significantly different to some scoring methods in predicting the primary endpoint, although, this may also be seen as a strength, as it may be used in lieu of other scores if information to impute in other tools is insufficient in the clinical setting. Other strengths in our cohort include a large sample size with relatively high event rates, powering our analysis to develop multiple risk stratification categories. Moreover, reliable clinical data collection was accomplished despite having missingness among inflammatory markers, variables used in the score did not suffer from missingness. Additionally, this study employs survival analysis within each R4 score categories to predict our primary endpoint, giving it additional analytical strength.

Inpatients with COVID-19 pneumonia are complex and their outcomes are hard to predict as much about COVID-19 must still be learned. Different tools exist that may be used with limited reliability in predicting outcomes among these

Table 3 Overall sample size, number of events, and hazard ratios for the primary endpoint by R4 category.

R4 Category (# of criteria)	n=	Events	HR	p-value	95 %CI	Bootstrap 95% CI
1 (0)	58	8 (14%)	–	–	–	–
2 (1)	173	53 (31%)	2.94	$<$ 0.001	1.67–5.19	1.65–5.26
3 (2–3)	215	96 (45%)	4.08	$<$ 0.001	2.41–6.93	2.36–7.05
4 ($\geq$4)	83	56 (67%)	6.63	$<$ 0.001	3.76–11.70	3.74–11.77

patients. The R4 score has proven to be a potentially useful tool that may be complementary to traditional tools to predict IMV or death among COVID-19 patients. It is imperative that this score be validated among another cohort to further understand the implications and utility of this tool. Therefore, we encourage other working groups to validate this tool among other cohorts to better understand the best ways to predict outcomes among COVID-19 patients with HFO.

Author contributions

(1) Conception and design of the study, or acquisition of data, or analysis and interpretation of data: GMA, DR, MTR, RL, JFM, ESV, CAD, AT, VMS, FC, GR MFM.

(2) Drafting the article or revising it critically for important intellectual content: GMA, DR, GTA, MFM.

(3) Final approval of the version to be submitted: GMA, DR, GTA, MTR, RL, JFM, ESV, CAD, AT, VMS, FC, GR MFM.

Conflicts of interest

None.

Funding

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2021.10.001.

References

1. Gebru AA, Birhanu T, Wendimu E, et al. Global burden of COVID-19: situational analyis and review. Hum Antibodies. 2021;29(2):139−48.
2. Miller IF, Becker AD, Grenfell BT, Metcalf CJE. Disease and healthcare burden of COVID-19 in the United States. Nat Med. 2020;26(8):1212−7.
3. Olivas-Martínez A, Cárdenas-Fragoso JL, Jiménez JV, et al. In-hospital mortality from severe COVID-19 in a tertiary care center in Mexico City; causes of death, risk factors and the impact of hospital saturation. PLOS ONE. 2021;16(2):e0245772.
4. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020;323(20):2052.
5. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk factors associated with In-Hospital mortality in a US national sample of patients with COVID-19. JAMA Netw Open. 2020;3(12):e2029058.
6. Westafer LM, Soares WE, Salvador D, Medarametla V, Schoenfeld EM. No evidence of increasing COVID-19 in health care workers after implementation of high flow nasal cannula: a safety evaluation. Am J Emerg Med. 2021;39:158−61.
7. Frat J-P, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185−96.
8. Lee CC, Mankodi D, Shaharyar S, et al. High flow nasal cannula versus conventional oxygen therapy and non-invasive ventilation in adults with acute hypoxemic respiratory failure: a systematic review. Respir Med. 2016;121:100−8.
9. Yasuda H, Okano H, Mayumi T, Nakane M, Shime N. Association of noninvasive respiratory support with mortality and intubation rates in acute respiratory failure: a systematic review and network meta-analysis. J Intensive Care. 2021;9(1):32.
10. Alhazzani W, Møller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). 2020;48(6):e440−69. https://doi.org/10.1097/CCM.0000000000004363.
11. Agarwal A, Basmaji J, Muttalib F, et al. High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. Can J Anesth Can Anesth. 2020;67(9):1217−48.
12. Ji D, Zhang D, Xu J, et al. Prediction for progression risk in patients with COVID-19 pneumonia: the CALL score. Clin Infect Dis. 2020;71(6):1393−9.
13. Vincent J-L, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22(7):707−10.
14. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336(4):243−50.
15. Lim WS. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58(5):377−82.
16. Myrstad M, Ihle-Hansen H, Tveita AA, et al. National Early Warning Score 2 (NEWS2) on admission predicts severe disease and in-hospital mortality from Covid-19 − a prospective cohort study. Scand J Trauma Resusc Emerg Med. 2020;28(1):66.
17. Smith GB, Redfern OC, Pimentel MA, et al. The National Early Warning Score 2 (NEWS2). Clin Med. 2019;19(3). 260−260.
18. Roca O, Caralt B, Messika J, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med. 2019;199(11):1368−76.
19. Teng X, Shen Y, Han M, Yang G, Zha L, Shi J. The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia. Eur J Clin Invest. 2021;51(3):e13435. https://onlinelibrary.wiley.com/doi/10.1111/eci.13435.
20. de Souza FSH, Hojo-Souza NS, Batista BD de O, da Silva CM, Guidoni DL. On the analysis of mortality risk factors for hospitalized COVID-19 patients: a data-driven study using the major Brazilian database. PLOS ONE. 2021;16(3):e0248580. https://doi.org/10.1371/journal.pone.0248580.
21. Dolan ME, Hill DP, Mukherjee G, McAndrews MS, Chesler EJ, Blake JA. Investigation of COVID-19 comorbidities reveals genes and pathways coincident with the SARS-CoV-2 viral disease. Sci Rep. 2020;10(1):20848. https://doi.org/10.1038/s41598-020-77632-8.
22. Yang L, Xie X, Tu Z, Fu J, Xu D, Zhou Y. The signal pathways and treatment of cytokine storm in COVID-19. Signal Transduct Target Ther. 2021;6(1):255.
23. Altschul DJ, Unda SR, Benton J, et al. A novel severity score to predict inpatient mortality in COVID-19 patients. Sci Rep. 2020;10(1):16726.
24. Gupta RK, Harrison EM, Ho A, et al. Development and validation of the ISARIC 4C Deterioration model for adults hospitalised with COVID-19: a prospective cohort study. Lancet Respir Med. 2021;9(4):349−59.
25. Bradley P, Frost F, Tharmaratnam K, Wootton DG. Utility of established prognostic scores in COVID-19 hospital admissions: multicentre prospective evaluation of CURB-65, NEWS2 and qSOFA. BMJ Open Respir Res. 2020;7(1):e000729.

26. Chandel A, Patolia S, Brown AW, et al. High-flow nasal cannula therapy in COVID-19: using the ROX index to predict success. Respir Care. 2021;66(6):909—19.
27. Vega ML, Dongilli R, Olaizola G, et al. COVID-19 Pneumonia and ROX index: time to set a new threshold for patients admitted outside the ICU. Pulmonology. 2021. S2531043721000921. https://doi.org/10.1016/j.pulmoe.2021.04.003 In press.
28. Liu S, Yao N, Qiu Y, He C. Predictive performance of SOFA and qSOFA for in-hospital mortality in severe novel coronavirus disease. Am J Emerg Med. 2020;38(10):2074—80.
29. Raschke RA, Agarwal S, Rangan P, Heise CW, Curry SC. Discriminant accuracy of the SOFA score for determining the probable mortality of patients with COVID-19 pneumonia requiring mechanical ventilation. JAMA. 2021;325(14):1469—70. https://doi.org/10.1001/jama.2021.1545.

Pulmonology 29 (2023) 207—213

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Obstructive sleep apnea: A categorical cluster analysis and visualization

D. Ferreira-Santos[a,b,*], P. Pereira Rodrigues[a,b]

[a] *MEDCIDS-FMUP - Community Medicine, Information and Decision Sciences, Faculty of Medicine of the University of Porto, Porto, Portugal*
[b] *CINTESIS - Center for Health Technology and Services Research, Porto, Portugal*

Received 16 March 2021; accepted 24 October 2021
Available online 17 November 2021

KEYWORDS
Clinical presentations;
Cluster visualization;
Data mining;
Obstructive sleep apnea

Abstract
Introduction and Objectives: Obstructive sleep apnea (OSA) is a prevalent sleep condition which is very heterogeneous although not formally characterized as such, resulting in missed or delayed diagnosis. Cluster analysis has been used in different clinical domains, particularly within sleep disorders. We aim to understand OSA heterogeneity and provide a variety of cluster visualizations to communicate the information clearly and efficiently.
Materials and Methods: We applied an extension of k-means to be used in categorical variables: k-modes, to identify OSA patients' groups, based on demographic, physical examination, clinical history, and comorbidities characterization variables ($n = 40$) obtained from a derivation and validation cohorts (211 and 53, respectively) from the northern region of Portugal. Missing values were imputed with k-nearest neighbours (k-NN) and a chi-square test was held for feature selection.
Results: Thirteen variables were inserted in phenotypes, resulting in the following three clusters: Cluster 1, middle-aged males reporting witnessed apneas and high alcohol consumption before sleep; Cluster 2, middle-aged women with increased neck circumference (NC), non-repairing sleep and morning headaches; and Cluster 3, obese elderly males with increased NC, witnessed apneas and alcohol consumption. Patients from the validation cohort assigned to different clusters showed similar proportions when compared with the derivation cohort, for mild (C1: 56 vs 75%, $P = 0.230$; C2: 61 vs 75%, $P = 0.128$; C3: 45 vs 48%, $P = 0.831$), moderate (C1: 24 vs 25%; C2: 20 vs 25%; C3: 25 vs 19%) and severe (C1: 20 vs 0%; C2: 18 vs 0%; C3: 29 vs 33%) levels. Therefore, the allocation supported the validation of the obtained clusters.
Conclusions: Our findings suggest different OSA patients' groups, creating the need to rethink these patients' stereotypical baseline characteristics.

* Corresponding author at: MEDCIDS - Departamento de Medicina da Comunidade, Informação e Decisão em Saúde, Faculdade de Medicina da Universidade do Porto (CIM - FMUP), Rua Dr. Plácido da Costa, s/n; 4200-450 Porto; Portugal.
E-mail address: danielasantos@med.up.pt (D. Ferreira-Santos).

https://doi.org/10.1016/j.pulmoe.2021.10.003

Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by recurrent episodes of collapse of the upper airway during sleep, which is estimated to occur in nearly 1 billion adults aged 30−69 years worldwide and in more than 5 million in Portugal.[1] Although commonly observed in clinical practice, OSA which is a heterogeneous condition with various predisposing factors, pathophysiological mechanisms, clinical manifestations and consequences of respiratory events; has not been formally characterized, posing critical challenges to its clinical recognition and resulting in missed or delayed diagnosis.[2] A diagnosis is established when a patient has an apnea-hypopnea index (AHI) $\geq$5 with associated symptoms or an AHI $\geq$15 regardless of associated symptoms.[3] Nevertheless, it has long been recognized that AHI alone does not capture OSA's patients' heterogeneity, that one-size does not fit all.[4] The review of Zinchuk et al., presents numerous studies that used analytic approaches to gain advantage of this heterogeneity.[4] In addition, Allan Pack studies discuss P4 medicine and how it might be applicable to OSA, specifically if OSA diagnosis or treatment were personalized, providing several examples of this personalized, predictive, preventative and participatory medicine.[5] Cluster analysis, a hypothesis-generating strategy (or unsupervised learning), is being used to identify subtypes of patients with unique characteristics, classifying patients with OSA into smaller and more homogeneous disorder phenotypes. This is a statistical approach that studies the relationships present among groups of participants or variables in a population, aiming at the benefit of allowing more specific diagnosis and treatment strategies. This is accomplished by assessing similarity (or dissimilarity) between subjects using metrics such as correlation or distance based on the features used to characterize each individual. Ideally, each cluster member is as similar as possible to each other and as different as possible from those in other clusters. One approach in cluster analysis is the *k*-modes algorithm.[6] This algorithm extends the *k*-means paradigm to cluster categorical data by using a simple matching dissimilarity measure for categorical objects, modes instead of means for clustering, and a frequency-based method to update modes in the *k*-means fashion clustering process.[7] The dissimilarity measure can be defined by the total mismatches of the two objects' corresponding variable categories: the smaller the number of mismatches, the more similar the two objects are. To better understand OSA heterogeneity, this study applies categorical cluster analysis to various observable and measurable OSA characteristics, such as signs, symptoms, demographics, and comorbidities. It also provides a variety of cluster visualizations to communicate this information clearly and efficiently.

Material and methods

A literature review was previously conducted to identify the most relevant OSA variables to be collected from the medical records and a total of 51 variables were noted, such as: demographic variables (e.g., gender); physical examination (e.g., body mass index (BMI)); clinical history (e.g., snoring); and comorbidities (e.g., stroke).

Derivation cohort

All patients who underwent polysomnography (PSG) at the Vila Nova de Gaia and Espinho Hospital Center Sleep Laboratory were included in the study. All administrative records were collected retrospectively between January and May 2015; patients included were aged above 18 years old and were suspected of having OSA. Patients already diagnosed with OSA or with severe lung diseases or neurological conditions and pregnant women were excluded. In the case of duplicate exams, the one with better sleep efficiency was selected.[8] This study was approved by the Ethics Commission of Vila Nova de Gaia and Espinho Hospital Center, in accordance with the Declaration of Helsinki.

Validation cohort

We have prospectively included adult patients suspected of having OSA referred to perform PSG at the Sleep Laboratory of São João University Hospital, between December 2019 and March 2020, following the previously mentioned inclusion and exclusion criteria. This study was approved by the Ethics Commission of São João University Hospital, in accordance with the Declaration of Helsinki.

Pre-processing phase

Although we had access to all the electronic medical records from the included patients, after screening all unstructured text reports, some predictive variables were not fully present or described, as physicians normally do not mention the absence of a disease, or it could only be noted in paper records (missing data proportions ranged from 0% for gender to 97% for bariatric surgery). Variables with more than 80% missing values were removed from the analysis (e.g., decreased libido). Also, daytime sleepiness exhibited contradictory results (higher percentage of patients in the normal group n = 77; 72%) with statistical significance. This was also described for the Epworth Sleepiness Scale (ESS), which presented a contradiction to the literature and the inherent meaning of the variables, and thus was not considered for statistical analysis. For more details, please refer to supplementary file (A). The outcome measure was OSA clinical diagnosis (AHI$\geq$5 plus excessive daytime sleepiness and at least two of the following three criteria: habitual loud snoring; witnessed apnea or gasping or choking; or diagnosed hypertension) obtained from PSG.[9]

We performed a pre-processing analysis, and continuous variables were categorized, plus *k*-nearest neighbours (*k*-NN) imputation was conducted to preserve all cases with missing data being replaced with a value obtained from related cases from the complete set of records.[10] After chi-square analysis, variables were selected if presenting a significant univariate association with the outcome (AHI), considering a 5% significance level. We used R software[11] to perform descriptive and associative analysis (packages gmodels[12] and epitools[13]), the *k*-modes categorical clustering

(package klaR[14]) and to create standard barplot (ggplot2[15]), heatmap (gplots[16]) and radar chart (fmsb[17]).

Results

Derivation cohort

In total, 211 patients were diagnosed with OSA (66%), of which 115 (55%) were categorized as mild, 50 (24%) as moderate and 46 (22%) as severe. Seventy percent were males with a mean age of 61 (53−68) years old and with OSA. The lower age category, 20−44 years old, had a lower percentage of patients with OSA, oppositely to categories 45−64 and 65−90 ($P<0.001$). Looking only at OSA patients, neck (NC) and abdominal circumference (AC) had a mean of 42 (39−44) cm and 107 (100- 113) cm, and a BMI median value of 30 (27−30) Kg/m^2 ($P = 0.008$). Several variables had no statistical significance but had a higher number of patients in the OSA group, namely craniofacial and upper airway abnormalities (CFA), snoring, nocturia, sleep fragmentation, insomnia, drivers, family history, myocardial infarction, arterial hypertension, pacemaker, stroke, renal failure, dyslipidaemia, and hypothyroidism. In contrast, a higher percentage of normal patients were seen in gasping/choking, behavioural changes, decreased libido, vehicle crashes, coffee, use of sedatives, respiratory alterations, and anxiety/depression.

A total of 13 variables were incorporated into the cluster analysis: gender, age, BMI, NC, modified Mallampati, witnessed apneas, nonrepairing sleep, morning headaches, driving sleepiness, alcohol consumption, congestive heart failure, arrhythmias, and pulmonary hypertension, resulting in three distinct clusters, presented in Table 1. Figure 1, 2 and 3 visually synthesizes the information obtained from Clusters 1 to 3.

Cluster 1 weighted the least and had non-increased neck circumference in middle-aged males. It had a higher percentage of driving sleepiness, and lower percentages in congestive heart failure, arrhythmias, pulmonary hypertension and modified Mallampati. In addition, it had the second higher percentage of witnessed apneas, nonrepairing sleep, morning headaches, and alcohol consumption. The mild severity level had a higher value. Cluster 2 was mainly middle-aged women with increased NC. It had the lowest percentage of witnessed apneas and alcohol consumption, and very low percentages of comorbidities. Finally, Cluster 3 presented older and obese men with increased NC. Witnessed apneas were reported in 75% of the patients, and alcohol consumption, congestive heart failure, and pulmonary hypertension had the highest percentages in all the clusters. In contrast, nonrepairing sleep, morning headaches, and driving sleepiness had the lowest rates. This cluster presented a lower value in the mild severity category and a higher value at the severe level.

Table 1 Clinical characteristics of the obstructive sleep apnea cohort by the defined clusters, % [95%CI].

	Cluster 1 (n = 112)	Cluster 2 (n = 44)	Cluster 3 (n = 55)	P value	P(C|F) (c_1, c_2, c_3)
Gender (male)	85 [77−91]	20 [10−36]	80 [67−89]	<**0.001**	(0.64, 0.06, 0.30)
Age (years)				<**0.001***	
20−44	6 [3−13]	11 [4−25]	11 [5−23]		(0.39, 0.28, 0.33)
45−64	65 [56−74]	57 [41−71]	27 [14−41]		(0.65, 0.22, 0.33)
65−90	29 [21−38]	32 [19−48]	62 [48−74]		(0.40, 0.18, 0.42)
Obesity	21 [14−29]	43 [29−59]	76 [63−86]	<**0.001**	(0.27, 0.23, 0.50)
Increased neck circumference	30 [22−40]	77 [62−88]	96 [86−99]	<**0.001**	(0.28, 0.28, 0.44)
Mallampati				<**0.001***	
Class I	22 [15−31]	11 [4−25]	36 [24−50]		(0.50, 0.10, 0.40)
Class II	48 [39−58]	61 [46−75]	5 [1−16]		(0.64, 0.32, 0.04)
Class III	26 [18−35]	23 [12−38]	47 [34−61]		(0.45, 0.15, 0.40)
Class IV	4 [1−9]	5 [1−17]	11 [5−23]		(0.33, 0.17, 0.50)
Witnessed apneas	64 [55−73]	30 [17−45]	75 [61−85]	<**0.001**	(0.57, 0.10, 0.33)
Nonrepairing sleep	46 [36−55]	70 [55−83]	29 [18−43]	<**0.001**	(0.52, 0.32, 0.16)
Morning headaches	45 [35−54]	84 [69−93]	18 [10−31]	<**0.001**	(0.52, 0.38, 0.10)
Driving sleepiness	13 [7−20]	5 [1−17]	2 [0−11]	**.05**	(0.82, 0.12, 0.06)
Alcohol consumption	85 [77−91]	20 [10−36]	91 [79−97]	<**0.001**	(0.62, 0.06, 0.32)
Congestive heart failure	10 [5−17]	14 [6−28]	18 [10−31]	.31	(0.41, 0.22, 0.37)
Arrhythmias	5 [2−12]	14 [6−28]	11 [5−23]	.15	(0.34, 0.33, 0.33)
Pulmonary hypertension	4 [1−9]	9 [3−23]	13 [6−25]	.07	(0.27, 0.27, 0.46)
Obstructive sleep apnea				.50	
Mild	56 [47−66]	61 [46−75]	45 [32−59]		
Moderate	24 [17−33]	20 [10−36]	25 [15−39]		
Severe	20 [13−28]	18 [9−33]	29 [18−43]		

* Fisher's exact test; $P<0.05$ are presented in bold; CI: confidence interval; P(C|F): probability of belonging to a cluster given the presence of a factor.

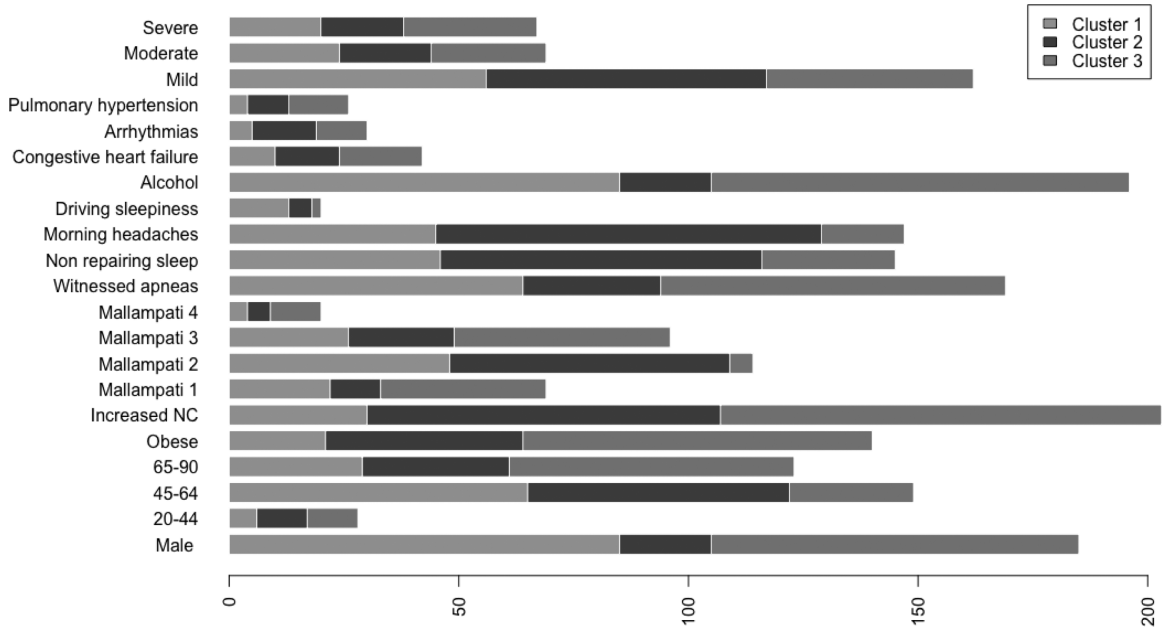

Fig. 1 Clinical characteristics of the obstructive sleep apnea cohort in Cluster 1, 2 and 3 visualized in a bar plot.

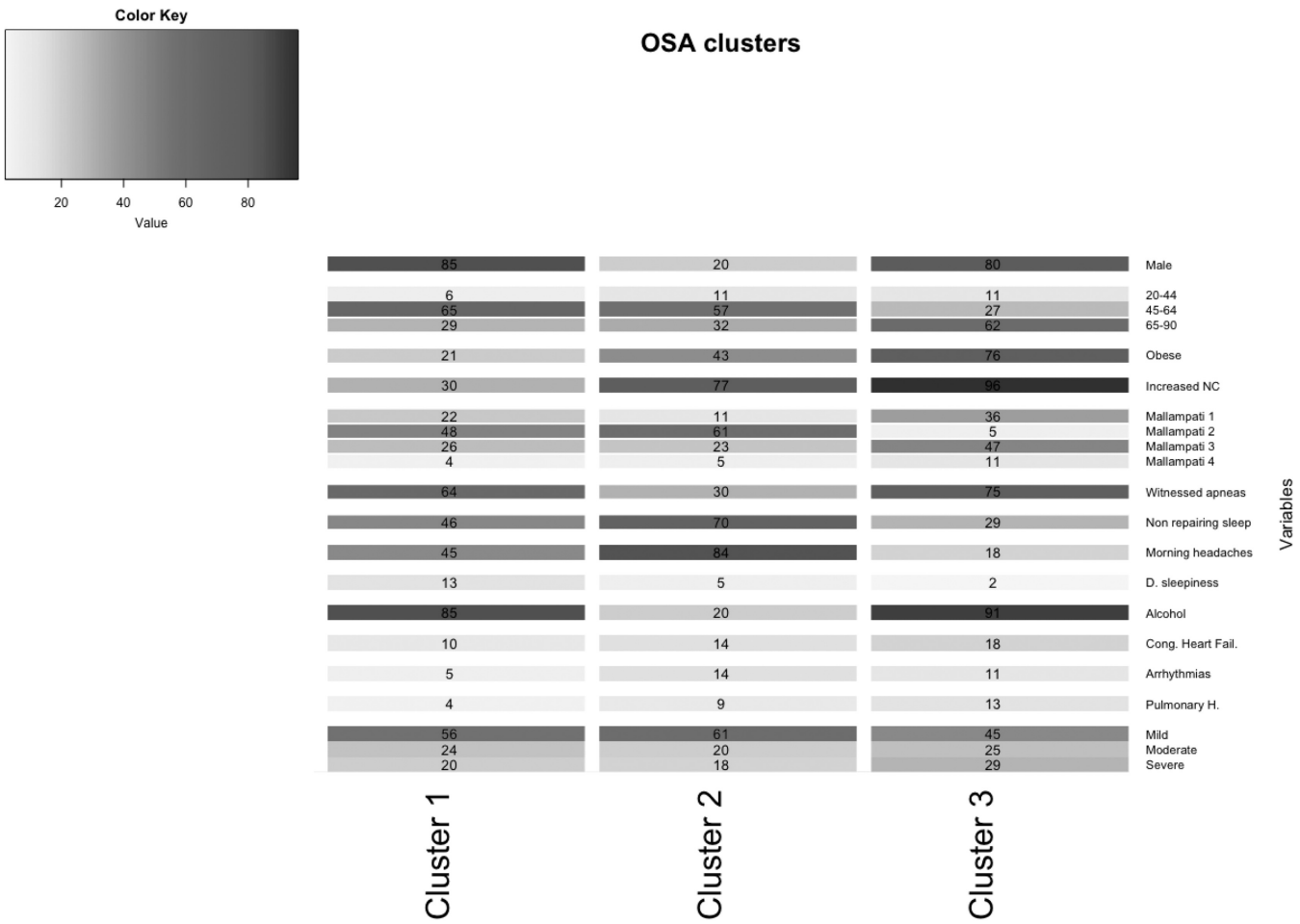

Fig. 2 Percentages of each clinical characteristics in obstructive sleep apnea patients' phenotypes visualized in a heatmap.

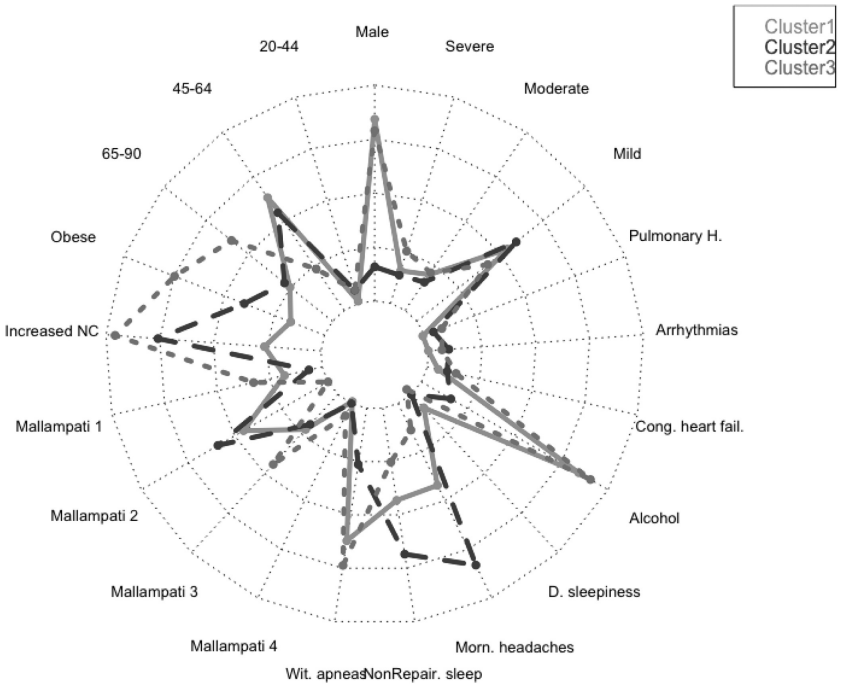

Fig. 3 Radar plot of obstructive sleep apnea patients' clinical characteristics distribution by cluster.

Validation cohort

Prospective data collection resulted in 53 OSA patients, 51% male. The median age was 59 (22—80) years old, with 8 (15%) in the 20—44 years old stratum, 30 (57%) in 45—64, and 15 (28%) in 65—90. Regarding NC and BMI, the median was 40 (31—48) cm and 31 (22—44) Kg/m^2, respectively. The highest proportion of patients (n = 35 (66%)) had been diagnosed with mild OSA, followed by moderate (11 (21%)), and severe (7 (13%)) levels. Concerning clinical history, witnessed apneas were reported in 64% of patients, followed by non-repairing sleep (26, 49%) and morning headaches (18, 34%). The most prevalent comorbidity was arrhythmias (4, 8%).

We calculated the dissimilarity between each new patient and the obtained clusters, based on the proposal of Huang,[6] as previously mentioned. Afterwards, we created a matrix and assigned the patients to their closest cluster (i.e., the cluster with the lowest dissimilarity), allocating 7 in Cluster 1, 17 in Cluster 2, and 18 in Cluster 3. Eleven patients had the same dissimilarity measure in two (n = 6) or three (5) clusters; we then assigned them randomly to any cluster, by generating 30 random assignments. This resulted in a mean (sd) allocation of 12 (1) in Cluster 1, 20 (1) in Cluster 2, and 21 (2) in Cluster 3. When comparing the proportion of patients in the derivation and validation cohorts in all clusters, we discovered no statistical differences for most variables (gender, age, witnessed apneas, non-repairing sleep, morning headaches, driving sleepiness, congestive heart failure, arrhythmias, pulmonary hypertension) and for the outcome, as showed in supplementary file (B). Regarding BMI and NC, statistical significance was found only in Cluster 1 (P = 0.001 and P = 0.024, respectively), while Mallampati and alcohol consumption was in Cluster 1 (P = 0.043 and P = 0.007) and 3 (P = 0.002 and $P<0.001$).

Discussion

In line with other studies, this research contributes to understanding OSA heterogeneity through exploring possible phenotypes by applying categorical cluster analysis (k-modes) in all severity levels. Our findings confirm that patients' phenotypes can be identified in the OSA population referred to the sleep laboratory (three in our case). Cluster 1 and 3 were middle-aged males or elderly, while Cluster 2 was middle-aged women. We verified that physical examination aspects, such as BMI and NC, were lower in Cluster 1 but extremely high in Cluster 3, especially NC. Regarding clinical history, the overall percentage of modified Mallampati was placed in the lower levels (Mallampati 1 and 2) and driving sleepiness percentages were low (higher value of 13% in Cluster 1). Alcohol consumption pre-sleep was widely described in Cluster 1 and 3. Reported witnessed apneas were higher in Cluster 3 and 1, while nonrepairing sleep and morning headaches in Cluster 2. All the chosen comorbidities (congestive heart failure, arrhythmias, and pulmonary hypertension) were low and without statistical significance in our analysis. The percentage of the outcome measure (AHI) was demonstrated in each cluster; Cluster 2 had 61% [46%—75%] of mild severity, followed by Cluster 1 (56% [47%—66%]) and Cluster 3, with a significantly smaller proportion (45% [32%—59%]), and high percentage in the severe level (29% [18%—43%]. When we observe the probability of belonging to a cluster given the presence of a factor, we can notice that factors such as male gender, lower levels of age

and modified Mallampati, witnessed apneas, nonrepairing sleep, morning headaches, driving sleepiness, alcohol consumption, congestive heart failure and arrhythmias put the patient in Cluster 1. On the other hand, elderly obese adults with increased NC, a level 4 modified Mallampati, and pulmonary hypertension, are allocated to Cluster 3. As a result, when applying our approach to the classification of a new case, physicians should choose the cluster with the greatest number of similar variables states, considering the ten statistically significant variables identified: gender, age, BMI, NC, modified Mallampati, witnessed apneas, nonrepairing sleep, morning headaches, driving sleepiness, and alcohol consumption. The validation cohort of OSA patients, confirmed the previous statistically significant variables as gender, age, witnessed apneas, nonrepairing sleep, morning headaches, and driving sleepiness. Additionally, BMI and NC can be considered in Cluster 2 ($P = 0.051$) and 3 ($P \geq 0.999$), while modified Mallampati and alcohol consumption only in Cluster 2 ($P = 0.417$ and $P = 0.085$), respectively.

Several authors have hypothesized the possible presence of OSA phenotypes, with the expected benefit of allowing a more precise diagnosis and treatment strategy, leading to improve patients outcomes, as described in the review of Zinchuk et al..[4] The referred studies were performed between 2012 and 2019 (a total of 17), with eight studies applying latent class analysis (LCA) as the clustering method, three applying hierarchical clustering (with multiple correspondences analysis for feature selection or principal component analysis (PCA)), one utilizing hierarchical clustering and *k*-means, two using *k*-means (with multiple correspondence for feature selection or PCA), one with *k*-means, one with time-series analysis and dynamic cluster analysis, and one exploiting *k*-modes (our previous work). Furthermore, the authors referred that these studies differ in terms of individuals included, sample size, patients features and outcomes, presented in the review. We also would like to point out that while our work chose PSG, as the standard diagnosis tool, other studies elected home studies or PSG mixed with home studies (seven studies). In the studies that selected PSG as the gold standard, different AHI cut-offs were applied, namely one study employed AHI ≥ 5[18] and two AHI ≥ 15,[19,20] while two other studies do not define the cut-off.[21,22] Analysing our results to the one that selected the same AHI cut-off, we noticed some differences. First, the study collected data from PSG, namely position, sleep state and arousals, while ours did not pre-select these variables as we focused our analysis only on pre-diagnostic data. Also, in our work we analysed the data as categorical while this study was numerical, reaching 6 clusters, all related to sleep position or sleep state. The only common aspect is that, like our study, it did not report outcomes. The two studies that reported a cut-off higher than 15 events per hour collected data from PSG in a supine position (not collected in our study) or symptoms and ESS. In this case, LCA was performed, and 4 clusters were found: 1) disturbed sleep; 2) minimally symptomatic; 3) excessively sleep, and 4) moderately sleepy. Although we could compare our results to this study, it is not our aim to assess the association with prevalent and incident cardiovascular disease. The main limitation of cluster analysis is that the phenotypes are always dependent on the number and the quality of the selected variables. Nevertheless, we believe that the process and the results are relevant. The inclusion of a comprehensive number of risk and diagnostic factors, as well as the observed robustness of the cluster-defined phenotypes in the validation cohort, enhances our understanding of OSA heterogeneity, emphasizing that the stereotypical OSA patient needs to be redefined.

Declarations of interest

None.

Acknowledgments

The work of DFS was supported by the Fundação para a Ciência e a Tecnologia (FCT) under Ph.D. grant number PD/BD/13553/2018 and the PhD Program in Clinical and Health Services Research (PD/00003/2013). We would like to acknowledge Pedro Amorim, for his valuable contribution regarding validation data collection.

Role of the funding source

The institutions who provided financial support had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report or in the decision to submit the article for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2021.10.003.

References

1. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med. 2019;7(8):687–98. https://doi.org/10.1016/S2213-2600(19)30198-5.
2. Ye L, Pien GW, Ratcliffe SJ, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. Eur Respir J. 2014;44(6):1600–7. https://doi.org/10.1183/09031936.00032314.
3. Flemons WW, Buysse D, Redline S, et al. Sleep-related breathing disorders in adults: rrecommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. Sleep. 1999;22(5):667–89. https://doi.org/10.1093/sleep/22.5.667.
4. Zinchuk A, Yaggi HK. Phenotypic subtypes of OSA: aa challenge and opportunity for precision medicine. Chest. 2020;157(2):403–20. https://doi.org/10.1016/j.chest.2019.09.002.
5. Pack AI. Application of personalized, predictive, preventative, and participatory (P4) medicine to obstructive sleep apnea: a roadmap for improving care? Ann Am Thorac Soc. 2016;13(9):1456–67. https://doi.org/10.1513/AnnalsATS.201604-235PS.
6. Huang Z. A fast clustering algorithm to cluster very large categorical data sets in data mining. In: DMKD; 1997. p. 1–8.

7. Kaufman L., Rousseeuw P.J. Finding Groups in Data: An Introduction to Cluster Analysis. (Kaufman L, Rousseeuw PJ, eds.). John Wiley & Sons, Inc.; 1990. doi:10.1002/9780470316801
8. Ferreira-Santos D, Rodrigues PP. Improving diagnosis in obstructive sleep apnea with clinical data: aa bayesian network approach. In: IEEE 30th International Symposium on Computer-Based Medical Systems, Institute of Electrical and Electronics Engineers Inc.; 2017:612—7. https://doi.org/10.1109/CBMS.2017.19.
9. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: aan American academy of sleep medicine clinical practice guideline. J Clin Sleep Med. 2017;13(3):479—504. https://doi.org/10.5664/jcsm.6506.
10. Ferreira-Santos D, Monteiro-Soares M, Rodrigues PP. Impact of imputing missing data in Bayesian network structure learning for obstructive sleep apnea diagnosis. Studies in Health Technology and Informatics. Vol 247. Zagreb, Croatia: IOS Press; 2018. p. 126—30. https://doi.org/10.3233/978-1-61499-852-5-126.
11. Team R.C. R: A Language and Environment for Statistical Computing, Vienna, Austria. Published online 2021.
12. R. GW, Bolker B., Lumley T., C. RJ. gmodels: Various R Programming Tools for Model Fitting, Bethesda, Maryland. Published online 2018.
13. T.J. Aragon. Epitools: Epidemiology Tools. Published online 2020.
14. Weihs C, Ligges U, Luebke K, Raabe N. KlaR Analyzing German Business Cycles. Dortmund, Germany: Springer-Verlag; 2005.
15. Wickham H. Ggplot2: Elegant Graphics for Data Analysis. New York: Springer-Verlag; 2016.
16. Warnes G.R., Bolker B., Bonebakker L., et al. gplots: Various R Programming Tools for Plotting Data. Published online 2020.
17. Nakazawa M. fmsb: Functions for Medical Statistics Book with some Demographic Data. Published online 2021.
18. Joosten SA, Hamza K, Sands S, Turton A, Berger P, Hamilton G. Phenotypes of patients with mild to moderate obstructive sleep apnoea as confirmed by cluster analysis. Respirology. 2012;17(1):99—107. https://doi.org/10.1111/j.1440-1843.2011.02037.x.
19. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. Am J Respir Crit Care Med. 2019;200(4):493—506. https://doi.org/10.1164/rccm.201808-1509OC.
20. Nakayama H, Kobayashi M, Tsuiki S, Yanagihara M, Inoue Y. Obstructive sleep apnea phenotypes in men based on characteristics of respiratory events during polysomnography. Sleep Breath. 2019;23(4):1087—94. https://doi.org/10.1007/s11325-019-01785-8.
21. Vavougios GD, George DG, Pastaka C, Zarogiannis SG, Gourgoulianis KI. Phenotypes of comorbidity in OSAS patients: combining categorical principal component analysis with cluster analysis. J Sleep Res. 2016;25(1):31—8. https://doi.org/10.1111/jsr.12344.
22. Zinchuk AV, Jeon S, Koo BB, et al. Polysomnographic phenotypes and their cardiovascular implications in obstructive sleep apnoea. Thorax. 2018;73(5):472—80. https://doi.org/10.1136/thoraxjnl-2017-210431.

Pulmonology 29 (2023) 214—220

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Frequency of alleles and genotypes associated with alpha-1 antitrypsin deficiency in clinical and general populations: Revelations about underdiagnosis

J.M. Hernández-Pérez[a], R. Ramos-Díaz[b], C. Vaquerizo-Pollino[c], J.A. Pérez[b,*]

[a] *Servicio de Neumología del Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Canary Islands, Spain*
[b] *Instituto Universitario de Enfermedades Tropicales y Salud Pública de Canarias, Universidad de La Laguna, Área de Genética. La Laguna, Tenerife, Spain*
[c] *Servicio de Pediatría del Hospital General de La Palma, La Palma, Canary Islands, Spain*

Received 1 September 2021; accepted 31 January 2022
Available online 26 March 2022

KEYWORDS
SERPINA1 gene;
Alpha-1 antitrypsin deficiency;
Screening;
Underdiagnosis;
Chronic obstructive pulmonary disease;
Bronchial asthma

Abstract
Background and objective: Alpha-1 antitrypsin deficiency (AATD) is an underdiagnosed hereditary condition that promotes the development of lung and liver diseases, and the most common potentially life-threatening genetic condition in Caucasian adults. In this study, the clinical and genetic profile of pulmonary patients from a single center in La Palma Island (Canary Islands, Spain) was assessed to predict how to increase AATD diagnosis.
Methods: AATD was tested in 1,493 pulmonary outpatients without regard to respiratory symptoms and 465 newborns. Variants of the *SERPINA1* gene were characterised by real-time PCR, DNA sequencing, molecular haplotyping and phenotyping (AAT isoelectric focusing). Different respiratory pathologies were diagnosed in patients and their levels of serum AAT were measured by nephelometry.
Results: The prevalence of pneumological patients with AATD alleles was 30.5%, including *PI*S*, *PI*Z* and 6 rare genetic variants. Certain deficiency genotypes were unevenly distributed among patients diagnosed with respiratory diseases: *PI*ZZ* (71.4%) and *PI*SS* (34.8%) genotypes were more represented in patients with chronic obstructive pulmonary disease (COPD), whereas *PI*MZ* (27.7%) and *PI*SZ* (34.5%) genotypes were more abundant in patients with bronchial asthma. The estimated frequency of *PI*S* and *PI*Z* alleles in the general population was 8.2% and 2.1%, respectively. A very significant enrichment ($p < 0.01$) of *PI*S* allele, independent of the *PI*Z* allele, was detected in the clinical population.

* Corresponding author.
E-mail address: joanpere@ull.edu.es (J.A. Pérez).

https://doi.org/10.1016/j.pulmoe.2022.01.017

Conclusions: AATD diagnosis would improve if both the COPD and the asthmatic patients were included to screening programs. The prevalence of *PI*ZZ* genotype in La Palma (1/2,162) was relatively high within Spain (average 1/3,344).

Introduction

Human alpha-1 antitrypsin (AAT) is a glycoprotein with antiprotease and immunomodulatory activity. It is synthesized mainly by hepatocytes and secreted into the bloodstream, where it reaches baseline concentrations of 0.9-1.75 g/L. AAT level in plasma can increase by up to 100% in response to inflammatory or infectious stimuli. The main function of AAT is to inhibit the excess of elastase 2 and proteinase 3 released by activated neutrophils, thus avoiding excessive proteolytic degradation of elastin and type IV collagen in the lungs.[1,2] Certain mutations in the *SERPINA1* gene (Serine Protease Inhibitor, group A, member 1) cause AAT deficiency (AATD), an inherited condition that predisposes to the development of different diseases, typically pulmonary emphysema and several liver pathologies. While liver disease is triggered by intracellular accumulation of AAT polymers, emphysema is caused by insufficient serum AAT concentration to protect connective lung tissue from the harmful effects of neutrophil proteases.[1,2]

Hundreds of variants of the *SERPINA1* gene have been identified by molecular analysis and about 70 of them have been associated with clinical manifestations.[3,4] Normal alleles are called *PI*M*, with the subtype *PI*M1-Val213* being the most common in Europe and North America (44-49%).[5] The most common deficient alleles in populations of European ancestry are *PI*S* and *PI*Z*, with frequencies of 5-10% and 1-3%, respectively. Nearly 100 percent of the clinical cases of AATD-associated pathologies involve the *PI*Z* allele, normally as *PI*ZZ* homozygous or less frequently as compound heterozygous.[1]

Despite being one of the most common genetic disorders among Caucasians, it is estimated that approximately 90% of individuals with severe AATD remain undiagnosed. In detected cases there has been an average delay of 6 years from the onset of symptoms, often when lung damage is irreversible. Delay in prescribing specific treatment leads to an increase in mortality.[6-9] The underdiagnosis can be ascribed to several causes: first, there is unawareness of AATD among physicians; second, the clinical symptoms caused by AATD are essentially indistinguishable from those of other common respiratory pathologies; and third, practitioners request the specific test for AATD diagnosis only if the patient closely matches the classic clinical description of AATD-associated lung disease.[2]

To analyse, in a local model, how actions on these causes could improve the AATD diagnosis, in the present study the variants of the *SERPINA1* gene were surveyed in pneumology outpatients and this information was used to predict what would have been the success of detection of AATD by applying different clinical criteria. In addition, we compare the frequencies of *PI*S* and *PI*Z* variants in clinical population with those in the general population to which they belong, to assess whether carriers of one of these deficiency alleles have higher probability of developing respiratory symptoms.

Methods

Study populations

Two subsets of subjects from La Palma Island (Canary Islands; Spain) were analysed in the context of AATD: one from a clinical population and one from the general population. For the first subset, pneumology outpatients were recruited during 54 consecutive months (January 2011 to June 2015), from the General Hospital of La Palma, regardless of the cause of the visit or of their respiratory symptomatology. Blood samples for the determination of AAT levels and phenotype or for *SERPINA1* gene genotyping were collected in non-anticoagulated tubes or dried blood spots (DBS), respectively. For the second subset, DBS cards were collected from all individuals born in 2014 in the Obstetrics Unit of the same hospital, taking advantage of blood sampling to rule out congenital metabolic diseases. This set of neonates was assumed to be a random and representative sample of the general population from La Palma, whose census in 2014 was 83,456 inhabitants (Spanish National Institute of Statistics).

The study was approved by the hospital's Ethics Committee with the number/date HGLaPalma_2010_7/ September 26, 2010 (patients) and HGLa Palma_2013_12/November 7, 2013 (newborns). Signed informed consent was collected from all patients and the parents of infants. Data on the genotype of newborns were incorporated into the corresponding clinical records and only communicated when requested by the parents. In these cases, and when appropriate, counselling about preventive health behaviours was offered.

Diagnosis of lung diseases

The respiratory pathologies diagnosed in the pneumology outpatients, following the criteria of specific guidelines, were bronchial asthma, chronic obstructive pulmonary disease (COPD), sleep apnea-hypopnea syndrome (SAHS), hypoventilation-obesity syndrome (HOS) and non-specific bronchial hyperreactivity (BHR).[10-13]

Genetic characterization of AATD variants

The approach followed for the genetic characterization of *SERPINA1* is summarized in Fig. 1. Genomic DNA extraction was performed in all subjects following an alkaline lysis method from peripheral blood samples deposited on filter paper (Whatman™ 903) and dried at room temperature.[14] From the nucleotide sequence of the *SERPINA1* gene

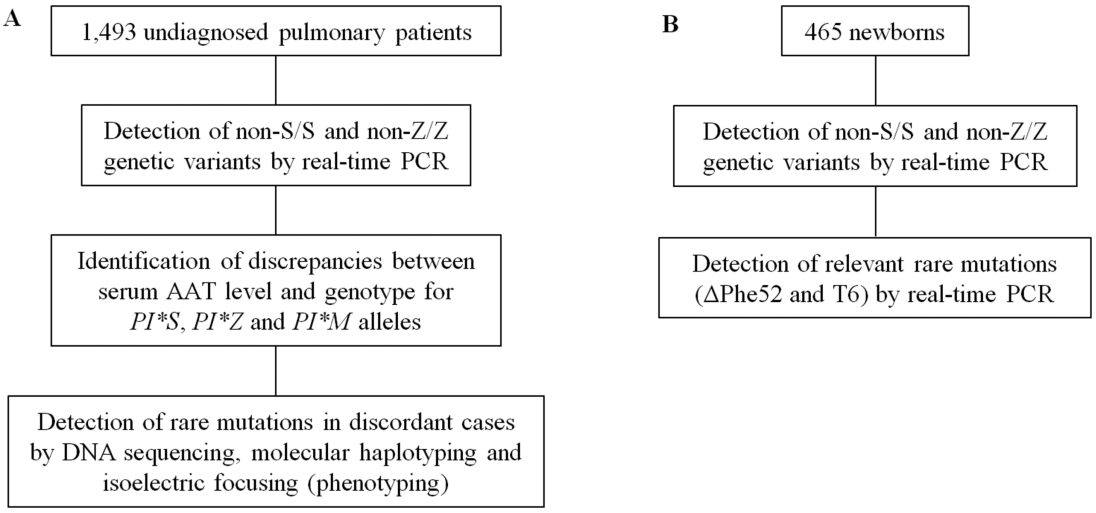

Fig. 1 Summary of the approaches used to genotype *SERPINA1* gene. In addition to non-S/S and non-Z/Z genetic variants, certain rare mutations previously detected in the patient cohort (A) were searched for in samples from newborns (B).

(NC_000014) amplification primers and HybProbe® fluorescent probes (Supplementary Table 1) were designed to detect, using the LightCycler 480 (Roche) platform, four different mutations: S (rs17580; c.863A>T; p.Glu264Val); Z (rs28929474; c.1096G>A; p.Glu342Lys); ΔPhe52 (rs775982338; c.226_228del; p.Phe52del); and T6 (rs763023697; c.1130insT; p.Leu353PhefsX24). These oligonucleotides were used for real-time PCR and melting analysis in the conditions described elsewhere,[15] with the exception of amplification primers for non-S/S and non-Z/Z variants that were used at an annealing temperature of 56°C. Genotyping assays were validated with a set of reference samples previously characterised by DNA sequencing, achieving a good resolution of alleles (Supplementary Figures 1 and 2).

For each patient, serum AAT concentration was determined by immunonephelometry and compared to the reference ranges (95% interval) described for the different combinations of the non-S/S and non-Z/Z genetic variants,[16] i.e. the *PI*MM*, *PI*MS*, *PI*MZ*, *PI*SS*, *PI*SZ*, and *PI*ZZ* genotypes (being *PI*M* = non-S, non-Z; *PI*S* = S, no-Z; *PI*Z* = no-S, Z). When the serum AAT level of a patient was less than the lower limit of the corresponding range, genotyping of the *SERPINA1* gene was expanded by sequencing the entire coding region and the exon/intron boundaries, using the primers and PCR conditions described elsewhere.[17] The nucleotide sequences obtained were compared to the *PI*M1-Val213* allele of the *SERPINA1* gene (NG_008290.1) to detect variants. In some cases, the complete genetic characterization also required molecular haplotyping by allele-specific PCR and sequencing of the resulting amplicons,[15,18,19] sometimes supplementing the diagnosis with data on the AAT phenotype determined by isoelectric focusing and immunodetection.[20]

Frequencies of alleles and genotypes, and statistical analysis

Relative allelic frequencies were determined by dividing the total number of alleles found of each type (*PI*M*, *PI*S*, and *PI*Z*) by the total alleles of the population, expressed as percent. The Chi-Square Test (χ^2) was used to determine the goodness of fit between the frequencies of genotypes observed in the general population of La Palma and the expected frequencies assuming Hardy-Weinberg equilibrium. The Hardy-Weinberg principle was applied to calculate the prevalence in the general population of genotypes carrying the defective alleles *PI*S* or *PI*Z*.[21] The χ^2 independence test was used to estimate the significance of the observed differences in the proportion of genotypes between the general population and the clinical population.

Results

Frequency of *PI*S* and *PI*Z* alleles and respiratory pathologies in the clinical population

Blood samples were collected from a total of 1,493 pneumology outpatients. The average age of subjects was 55 years, with a slight predominance of males (56%) and a high frequency of active smokers (20.5%) or ex-smokers (35.7%). The screening for *PI*S* and *PI*Z* alleles by real-time PCR in the set of 1,493 patients revealed that 29.7% of subjects were carriers of some of these deficiency allele (Table 1), most of them (87.5%) with *PI*MS* or *PI*MZ* genotype. The respiratory disease most frequently diagnosed in this cohort was bronchial asthma (32.5%), followed by COPD (26.9%), SAHS/HOS (11.9%) and BHR (6.4%).

The proportions of patients that were found in each of the groups defined by the variables "lung disease" or "genotype" are shown in Table 1. The group of patients diagnosed with SAHS/HOS presented the lowest incidence of deficiency genotypes (19.6%). The frequency of *PI*MS* patients was similar in the different respiratory disease groups (15.0-17.2%), but this was not the case for the other deficiency genotypes. *PI*ZZ* genotype showed the most skewed distribution, since it was exclusively detected in the COPD group, even with a frequency (1.2%) higher than the *PI*SZ* genotype (0.5%), although only 5 of 7 *PI*ZZ* subjects detected in the patient cohort (71.4%) have developed COPD. The frequency of *PI*MZ* and *PI*SZ* patients was higher in the bronchial asthma (6.3% and 1.9%) and BHR (5.1% and 2.1%) groups than in the

Table 1 Description of the clinical populations from La Palma Island in terms of diagnosed respiratory diseases and genotypes formed by combination of *PI*M*, *PI*S* and *PI*Z* alleles.

Genotype	Number of patients	Percentage of total	Percentage of genotypes within each respiratory disease group				Percentage of respiratory diseases within each genotype group			
			BA	COPD	SAHS/HOS	BHR	BA	COPD	SAHS/HOS	BHR
*PI*MM*	1050	70.3	75.8	76.5	80.4	73.6	35.0	29.3	13.6	6.7
*PI*MS*	278	18.6	15.0	15.2	16.3	17.2	26.2	22.0	10.4	5.9
*PI*MZ*	110	7.4	6.3	4.6	2.2	5.1	27.7	17.0	3.6	4.4
*PI*SS*	22	1.5	1.0	1.9	0.5	2.0	21.7	34.8	4.3	8.8
*PI*SZ*	26	1.7	1.9	0.5	0.6	2.1	34.5	7.7	3.8	7.7
*PI*ZZ*	7	0.5	0	1.2	0	0	0	71.4	0	0

BA: Bronchial asthma; COPD: chronic obstructive pulmonary disease; SAHS: sleep apnea-hypopnea syndrome; HOS: hypoventilation-obesity syndrome; BHR: non-specific bronchial hyperreactivity.

COPD group (4.6% and 0.5%). However, because of the differences in the relative frequency of the different lung diseases in the clinical population, the fractions of *PI*MZ* and *PI*SZ* subjects from the clinical population that were detected in the bronchial asthma group (27.7% and 34.5%) were much higher than in the BHR group (4.4 and 7.7%). Finally, the frequency of *PI*SS* patients was higher in the COPD (1.9%) and BHR (2.0%) groups than in the BA group (1.0%), although the fraction of all *PI*SS* patients that were detected in the COPD group (34.8%) was much higher than in the BHR group (8.8%).

Estimated prevalence of *PI*S* and *PI*Z* alleles in the general population

Blood samples were collected from a total of 465 newborns, which represented all municipalities of La Palma in proportion to their number of inhabitants. Table 2 shows their distribution among the six genotypic classes that can be made up of *PI*M*, *PI*S*, and *PI*Z* alleles, which were detected by real-time PCR. Subjects from the general population carrying deficiency alleles were 19.4%. From these data, the estimated frequencies of the *PI*S* and *PI*Z* alleles in the general population of La Palma were 8.2% (95% CI: 6.5-10.2) and 2.1% (95% CI: 1.3-3.4), respectively.

No significant differences were found between the number of individuals observed within each genotypic class (Table 2) and those expected under the Hardy-Weinberg law ($\chi^2 = 1.431$; $p > 0.69$). Assuming that general population from La Palma is in Hardy-Weinberg equilibrium, it can be predicted the prevalence of the different genotypes composed of the deficiency *PI*S* and *PI*Z* alleles, and the number of subjects within each genotypic class (Table 2).

Risk of respiratory disease and *PI*MZ* and *PI*MS* genotypes

If carrying only one *PI*S* or *PI*Z* allele represents a genetic risk factor for suffering some type of lung condition, the proportion of *PI*MM* vs. *PI*MS* or *PI*MM* vs. *PI*MZ* individuals would be expected to be significantly different between the clinical population and the general population from which the patients come. The $\chi 2$ independence test revealed that this difference was very significant in the case of the *PI*S* allele ($\chi^2 = 7.05$; $p < 0.01$) and highly significant for the *PI*Z* allele ($\chi^2 = 10.33$; $p < 0.0025$). Interestingly, like *PI*MM* homozygous, asthma was more frequent than COPD among *PI*MS* and *PI*MZ* heterozygous patients, whereas the opposite was observed in *PI*SS* and *PI*ZZ* homozygous (Table 1).

Spectrum of rare AATD variants

Patients whose serum AAT levels did not agree with their genotype for the non-S/S and non-Z/Z variants were analysed in more detail by DNA sequencing and, eventually, by molecular haplotyping. This allowed the detection of 6 rare AATD alleles (Table 3).[15,17,22-26] Most of them were found as compound heterozygous combined with a *PI*S* or *PI*Z* allele. This set of rare alleles accounted for 2.1% of the deficiency variants detected in the clinical population that, added to the *PI*S* and *PI*Z* alleles, cause the total prevalence of deficiency allele carriers in the clinical population to increase to

Table 2 Description of the general population from La Palma Island in terms of genotypes formed by combinations of *PI*M*, *PI*S* or *PI*Z* alleles.

Genotype	Observed number of individuals	Percentage of individuals	Estimated prevalence 1/X (CI 95%)	[a] Estimated number of individuals (CI 95%)
*PI*MM*	375	80.6	—	67,083 (63,882-69,871)
*PI*MS*	67	14.4	7 (5-9)	11.943 (9,312- 15,166)
*PI*MZ*	17	3.7	26 (16-42)	3.143 (1,931- 5,016)
*PI*SS*	3	0.6	150 (97-234)	544 (348-843)
*PI*SZ*	3	0.6	285 (146-565)	286 (144- 557)
*PI*ZZ*	0	0.0	2.162 (884-5,455)	38 (15-92)

CI: confidence interval
[a] Considering the current census of inhabitants.

30.5%. It is noteworthy that we used AAT levels without attending to the inflammatory status of pulmonary patients. This fact has not affected our results on prevalence of *PI*S* and *PI*Z* alleles in patient and newborn cohorts, because all subjects were genotyped for these alleles. However, it may have negatively affected the detection rate of rare mutations in the *SERPINA1* gene of the patients, although not significantly because of the uncommon nature of these AATD alleles.

The rare deficiency alleles of the *SERPINA1* gene most common in the clinical population from La Palma were the null allele *PI*Q0$_{ourém}$* and the *PI*I* allele, with 5 and 3 carrier patients from a total of 12 cases, respectively. Since there has been an important historical contribution of Portugal to the peopling of La Palma, a search for *PI*Q0$_{ourém}$* allele by real-time PCR (T_6 variant; supplementary Table 1) was carried out among the 465 neonates, but results were negative. The fact that ΔPhe52 variant were detected in three different genetic backgrounds in the clinical population (*PI*M$_{malton}$*, *PI*M$_{palermo}$* and *PI*Q0$_{la\ palma}$*; Table 3) led us to design a specific genotyping assay based on real-time PCR, but the screening of this mutation among the 465 neonates was unsuccessful.

Discussion

The high frequency of *PI*S* allele in the population of La Palma (8.2%) is slightly lower than those found in the Iberian Peninsula (11.4% in Portugal and 10.4% in Spain), but similar to those in southwestern France (7.5%) and higher than those found in other countries in the European continent.[21] The frequency of *PI*Z* allele in La Palma (2.1%) is comparable to that found in Portugal (2.1%) and slightly higher than that in Spain (1.7%). In Europe, it is only surpassed by those found in some northern countries as Latvia (4.5%) or Denmark (2.7%).[27] The prevalence of the *PI*ZZ* genotype in La Palma (1/2,162) is relatively high within the Spanish territory (average 1/3,344).[28] Therefore, it would be advisable to

Table 3 Rare alleles and genotypes of the SERPINA1gene, with their corresponding serum levels of alpha-1 antitrypsin, detected in the clinical population.

Deficiency allele	Mutation	Genetic background	Patient genotype	AAT level (mg/dL)
*PI*I*	c.187C>T; p.Arg39Cys	M4[25]	*PI*MI*	91.1
		M1-Val213[26]	*PI*SI*	73.9
		M2[a]	*PI*ZI*	56.8
*PI*M$_{malton}$*[22]	c.226_228delTTC; p.Phe52del	M2	*PI*ZM$_{malton}$*	15.1
*PI*M$_{palermo}$*[23]	c.226_228delTTC; p.Phe52del	M1-Val213	*PI*SM$_{palermo}$*	46.3
*PI*Q0$_{la\ palma}$*[18]	c.226_228delTTC; p.Phe52del c.863A>T; p.Glu264Val	M1-Val213	*PI*ZQ0$_{la\ palma}$*	8.5
*PI*Q0$_{ourém}$*[15,24]	c.1130insT; p.Leu353PhefsX24	M3	*PI*MQ0$_{ourém}$*	76.1[b]
			*PI*SQ0$_{ourém}$*	38.6
			*PI*ZQ0$_{ourém}$*	14.4
*PI*Z$_{la\ palma}$*[17]	c.321C>A; p.Asn83Lys	M1-Val213	*PI*MZ$_{la\ palma}$*	75.6

[a] Detected in this study.
[b] Average of 3 patients.

perform screening in this region aimed at identifying individuals at high risk of diseases associated with AATD.

Our data on *SERPINA1* genotypes and respiratory symptomatologies in a set of 1,493 pneumology outpatients could be analysed in search for causes of AATD underdiagnosis, keeping in mind the limitations of the local model represented by La Palma Island. If our genetic analysis of all pulmonary patients would have been focused exclusively on the COPD group, as recommended by some reference guides,[29,30] the fraction of subjects identified as carriers of *PI*S* and/or *PI*Z* alleles would have been reduced from 29.7% to 6.3%. Although the majority of *PI*ZZ* patients (71.4%) would be identified following this recommendation, only a small fraction of *PI*MZ* (17.0%) and *PI*SZ* (7.7%) patients could be detected, contributing to the underdiagnosis of AATD.[2,6,9,31] The inclusion of both asthmatic and COPD patients in our genetic analysis of the clinical population, as recommended by certain reference guides for AATD screening programs,[32-34] would significantly increase the success of detection of *PI*MZ* (44.7%) and *PI*SZ* (42.2%) patients. It should be taken into account that this observation may be related to local factors that determine the high prevalence of asthma in the Canary Islands.[35,36]

It is solidly demonstrated that *PI*ZZ* and, to a lesser extent, *PI*SZ* genotypes represent a risk factor for the development of dyspnea, cough, early onset pulmonary emphysema and air flow obstruction.[2] Our results indicate that the frequency of both *PI*MS* and *PI*MZ* genotypes is significantly higher in the pneumology outpatients population than in the reference general population. Although the number of evidence pointing to the *PI*MZ* genotype as a risk factor for lung conditions is increasing,[2,37] the clinical status of *PI*MS* individuals remains controversial.[38] It would be interesting to find out what additional risk factors contribute to the enrichment in *PI*MS* genotypes that we observed among pneumology outpatient and that was not detected in another similar study, probably because in this case the general population was compared to the results of screening aimed at the detection of AATD.[39]

Conclusions

According to our data, the inclusion of asthmatic patients in AATD screening programs would significantly increase success in detecting this inherited condition.

Declaration of Competing Interest

The authors state that they have no conflicts of interest.

Acknowledgments

We thank the health authorities of the island of La Palma for facilitating the realization of this research work, and Grifols S.A. for financial support. Jordi Bozzo and Eugenio Rosado (both from Grifols) are acknowledged for editorial support in the preparation of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2022.01.017.

References

1. de Serres F, Blanco I. Role of alpha-1 antitrypsin in human health and disease. J Intern Med. 2014;276:311—35. https://doi.org/10.1111/joim.12239.
2. Strnad P, McElvaney NG, Lomas DA. Alpha1-antitrypsin deficiency. N Engl J Med. 2020;382:1443—55. https://doi.org/10.1056/NEJMra1910234.
3. Silva D, Oliveira MJ, Guimarães M, Lima R, Gomes S, Seixas S. Alpha-1-antitrypsin (*SERPINA1*) mutation spectrum: three novel variants and haplotype characterization of rare deficiency alleles identified in Portugal. Respir Med. 2016;116:8—18. https://doi.org/10.1016/j.rmed.2016.05.002.
4. Kueppers F, Andrake MD, Xu Q, Dunbrack RL, Kim J, Sanders CL. Protein modeling to assess the pathogenicity of rare variants of *SERPINA1* in patients suspected of having alpha 1 antitrypsin deficiency. BMC Med Genet. 2019;20:125. https://doi.org/10.1186/s12881-019-0852-5.
5. Salahuddin P. Genetic variants of α1-antitrypsin. Curr Protein Pept Sci. 2010;11:101—17. https://doi.org/10.2174/138920310790848368.
6. Stoller JK, Brantly M. The challenge of detecting alpha-1 antitrypsin deficiency. COPD. 2013(Suppl 1):26—34. https://doi.org/10.3109/15412555.2013.763782.
7. Chapman KR, Chorostowska-Wynimko J, Koczulla AR, Ferrarotti I, McElvaney NG. Alpha 1 antitrypsin to treat lung disease in alpha 1 antitrypsin deficiency: recent developments and clinical implications. Int J Chron Obstruct Pulmon Dis. 2018;13:419—32. https://doi.org/10.2147/COPD.S149429.
8. Tejwani V, Nowacki AS, Fye E, Sanders C, Stoller JK. The impact of delayed diagnosis of alpha-1 antitrypsin deficiency: the association between diagnostic delay and worsened clinical status. Respir Care. 2019;64:915—22. https://doi.org/10.4187/respcare.06555.
9. Brantly M, Campos M, Davis AM, D'Armiento J, Goodman K, Hanna K, et al. Detection of alpha-1 antitrypsin deficiency: the past, present and future. Orphanet J Rare Dis. 2020;15:96. https://doi.org/10.1186/s13023-020-01352-5.
10. Plaza Moral V, Comité Ejecutivo de GEMA. GEMA (4.0). Guidelines for asthma management. Arch Bronconeumol. 2015;51:2—54. https://doi.org/10.1016/S0300-2896(15)32812-X.
11. Grupo de trabajo de GESEPOC. Moving towards a new focus on COPD. The Spanish COPD guidelines (GESEPOC). Arch Bronconeumol. 2011;47:379—81. https://doi.org/10.1016/j.arbres.2011.05.008.
12. Lloberes P, Durán-Cantolla J, Martínez-García MA, Marín JM, Ferrer A, Corral J, et al. Diagnosis and treatment of sleep apnea-hypopnea syndrome. Arch Bronconeumol. 2011;47:143—56. https://doi.org/10.1016/j.arbres.2011.01.001.
13. Perpiñá Tordera M, García Río F, Álvarez Gutierrez FJ, Cisneros Serrano C, Compte Torrero L, Entrenas Costa LM, et al. Guidelines for the study of nonspecific bronchial hyperresponsiveness in asthma. Spanish society of pulmonology and thoracic surgery (SEPAR). Arch Bronconeumol. 2013;49:432—46. https://doi.org/10.1016/j.arbres.2013.05.001.
14. Ramos-Díaz R, Gutiérrez-Nicolás F, Nazco-Casariego GJ, González Perea I, Pérez Pérez JA. Validation of a fast and low-cost alkaline lysis method for gDNA extraction in a pharmacogenetic context. Cancer Chemother Pharmacol. 2015;75:1095—8. https://doi.org/10.1007/s00280-015-2729-4.

15. Hernández Pérez JM, Ramos Díaz R, Fumero García S, Pérez Pérez JA. Description of alpha-1-antitrypsin deficiency associated with *PI*Q0ourém* allele in La Palma Island (Spain) and a genotyping assay for its detection. Arch Bronconeumol. 2015;51:e1—3. https://doi.org/10.1016/j.arbres.2014.01.011.
16. Ferrarotti I, Thun GA, Probst-Hensch NM, Luisetti M. α_1-Antitrypsin level and pheno/genotypes. Chest. 2013;144:1732—3. https://doi.org/10.1378/chest.13-1464.
17. Hernández Pérez JM, Ramos Díaz R, Pérez Pérez JA. Identification of a new defective *SERPINA1* allele (*PI*Zla palma*) encoding an alpha-1-antitrypsin with altered glycosylation pattern. Respir Med. 2017;131:114—7. https://doi.org/10.1016/j.rmed.2017.08.015.
18. Hernández Pérez JM, Ramos Díaz R, Fumero García S, Pérez Pérez JA. Molecular characterization of *PI*Q0la palma*, a new alpha-1-antitrypsin null allele that combines two defective genetic variants. Clin Genet. 2017;91:927—8. https://doi.org/10.1111/cge.12889.
19. Matamala N, Gomez-Mariano G, Perez JA, Baladrón B, Torres-Durán M, Michel FJ, et al. New cis-acting variants in *PI*S* background produce null phenotypes causing alpha-1 antitrypsin deficiency. Am J Respir Cell Mol Biol. 2020;63:444—51. https://doi.org/10.1165/rcmb.2020-0021OC.
20. Greene DN, Elliott-Jelf MC, Straseski JA, Grenache DG. Facilitating the laboratory diagnosis of α1-antitrypsin deficiency. Am J Clin Pathol. 2013;139:184—91. https://doi.org/10.1309/AJCP6XBK8ULZXWFP.
21. Blanco I, de Serres FJ, Fernandez-Bustillo E, Lara B, Miravitlles M. Estimated numbers and prevalence of *PI*S* and *PI*Z* alleles of alpha1-antitrypsin deficiency in European countries. Eur Respir J. 2006;27:77—84. https://doi.org/10.1183/09031936.06.00062305.
22. Fraizer GC, Harrold TR, Hofker MH, Cox DW. In-frame single codon deletion in the Mmalton deficiency allele of alpha 1-antitrypsin. Am J Hum Genet. 1989;44:894—902. PMC1715665.
23. Faber JP, Poller W, Weidinger S, Kirchgesser M, Schwaab R, Bidlingmaier F, et al. Identification and DNA sequence analysis of 15 new alpha1-antitrypsin variants, including two *PI*Q0* alleles and one deficient *PI*M* Allele. Am J Hum Genet. 1994;55:1113—21. PMC1918455.
24. Seixas S, Mendonça C, Costa F, Rocha J. Alpha1-antitrypsin null alleles: evidence for the recurrence of the L353fsX376 mutation and a novel G—>A transition in position +1 of intron IC affecting normal mRNA splicing. Clin Genet. 2002;62:175—80. https://doi.org/10.1034/j.1399-0004.2002.620212.x.
25. Graham A, Kalsheker NA, Newton CR, Bamforth FJ, Powell SJ, Markham AF. Molecular characterisation of three alpha-1-antitrypsin deficiency variants: proteinase inhibitor Pi*null cardiff (Asp256—-Val); PiMmalton (Phe51—-deletion) and PiI (Arg39—-Cys). Hum Genet. 1989;84:55—8. https://doi.org/10.1007/bf00210671.
26. Seri M, Magi B, Cellesi C, Olia PM, Renieri A, De Marchi M. Molecular characterization of the P and I variants of alpha 1-antitrypsin. Int J Clin Lab Res. 1992;22:119—21. https://doi.org/10.1007/BF02591409.
27. Blanco I, Bueno P, Diego I, Pérez-Holanda S, Casas-Maldonado F, Esquinas C, et al. Alpha-1 antitrypsin Pi*Z gene frequency and Pi*ZZ genotype numbers worldwide: an update. Int J Chron Obstruct Pulmon Dis. 2017;12:561—9. https://doi.org/10.2147/COPD.S125389.
28. Blanco I, Fernández-Bustillo E, de Serres FJ, Alkassam D, Rodríguez Menéndez C. Déficit de alfa-1-antitripsina en España (variantes deficientes *PI*S* y *PI*Z*): prevalencia estimada y número de sujetos calculados para cada fenotipo. Med Clin (Barc). 2004;123:761—5. https://doi.org/10.1016/S0025-7753(04)74661-8.
29. Stoller JK, Hupertz V, Aboussouan LS, et al. Alpha-1 antitrypsin deficiency. In: Adam MP, Ardinger HH, Pagon RA, eds. Gene Reviews, Seattle: 2006:1—24 https://www.ncbi.nlm.nih.gov/books/NBK1519/.
30. Casas F, Blanco I, Martínez MT, Bustamante A, Miravitlles M, Cadenas S, et al. Indications for active case searches and intravenous alpha-1 antitrypsin treatment for patients with alpha-1 antitrypsin deficiency chronic pulmonary obstructive disease: an update. Arch Bronconeumol. 2015;51:185—92. https://doi.org/10.1016/j.arbr.2014.12.006.
31. Stoller JK. Detecting alpha-1 antitrypsin deficiency. Ann Am Thorac Soc. 2016;4:S317—25. https://doi.org/10.1513/AnnalsATS.201506-349KV.
32. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168:818—900. https://doi.org/10.1164/rccm.168.7.818.
33. Miravitlles M, Dirksen A, Ferrarotti I, Koblizek V, Lange P, Mahadeva R, et al. European respiratory society statement: diagnosis and treatment of pulmonary disease in α 1-antitrypsin deficiency. Eur Respir J. 2017;50:1700610. https://doi.org/10.1183/13993003.00610-2017.
34. Lopes AP, Mineiro MA, Costa F, Gomes J, Santos C, Antunes C, et al. Portuguese consensus document for the management of alpha-1-antitrypsin deficiency. Pulmunol. 2018;24:1—21. https://doi.org/10.1016/j.pulmoe.2018.09.004.
35. Juliá-Serdá G, Cabrera-Navarro P, Acosta-Fernández O, Martín-Pérez P, Losada-Cabrera P, García-Bello MA, et al. High prevalence of asthma and atopy in the Canary Islands, Spain. Int J Tuberc Lung Dis. 2011;15:536—41. https://doi.org/10.5588/ijtld.10.0303.
36. López-Villarrubia E, Costa Estirado O, Íñiguez Hernández C, Ballester Díez F. Do Saharan dust days carry a risk of hospitalization from respiratory diseases for citizens of the Canary Islands (Spain)? Arch Bronconeumol. 2021;57:464—70. https://doi.org/10.1016/j.arbres.2020.03.009.
37. Foreman MG, Wilson C, DeMeo DL, Hersh CP, Beaty TH, Cho MH. Alpha-1 antitrypsin PiMZ genotype is associated with chronic obstructive pulmonary disease in two racial groups. Ann Am Thorac Soc. 2017;14:1280—7. https://doi.org/10.1513/AnnalsATS.201611-838OC.
38. Dahl M, Hersh CP, Ly NP, Berkey CS, Silverman EK, Nordestgaard BG. The protease inhibitor PI*S allele and COPD: a meta-analysis. Eur Respir J. 2005;26:67—76. https://doi.org/10.1183/09031936.05.00135704.
39. Carroll TP, O'Connor CA, Floyd O, McPartlin J, Kelleher DP, O'Brien G, et al. The prevalence of alpha-1 antitrypsin deficiency in Ireland. Respir Res. 2011;12:91. https://doi.org/10.1186/1465-9921-12-91.

Pulmonology 29 (2023) 221—229

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Differences in cerebral oxygenation during exercise in patients with idiopathic pulmonary fibrosis with and without exertional hypoxemia: does exercise intensity matter?

K. Dipla[a,*,1], A.K. Boutou[b,1], A. Markopoulou[b], S. Papadopoulos[a], S. Kritikou[a], G. Pitsiou[c], I. Stanopoulos[c], I. Kioumis[c], A. Zafeiridis[a]

[a] *Exercise Physiology & Biochemistry Laboratory, Dept. of Sport Sciences at Serres, Aristotle University of Thessaloniki, Ippokratous 22, Ag. Ioannis, Serres 621 22, Greece*
[b] *Department of Respiratory Medicine, G. Papanikolaou Hospital, Thessaloniki, Greece*
[c] *Department of Respiratory Failure, Aristotle University of Thessaloniki, Greece*

Received 20 January 2021; accepted 15 June 2021
Available online 15 July 2021

KEYWORDS
Idiopathic pulmonary fibrosis;
Cerebral oxygenation;
Exercise;
Exercise-desaturation;
Near-infrared-spectroscopy;
Dyspnea

Abstract
Introduction and Objectives: Patients with idiopathic pulmonary fibrosis (IPF) present respiratory derangements at rest and during exercise, accompanied by exercise intolerance. Some patients may develop profound exertional desaturation even without resting hypoxemia. Evidence suggests the involvement of reduced cerebral-oxygenation in exercise intolerance. We aimed to examine (i) differences in cerebral-oxygenation during exercise between IPF patients with and without isolated exertional desaturation, (ii) whether the impairments in cerebral-oxygenation are detected at similar exercise intensity, and (iii) correlations between cerebral-oxygenation indices, disease severity, and 6-min walk test (6MWT).
Materials and Methods: Patients with IPF (n = 24; 62.1 ± 9.3 years) without resting hypoxemia underwent cardiopulmonary exercise testing (CPET) with cerebral-oxygenation monitoring via near-infrared-spectroscopy (NIRS). Based on their pulse-oxymetry saturation (SpO_2) during CPET,

Abbreviations: CPET, Cardiopulmonary exercise testing; $DSpO_2$, Delta in saturation from pulse oxymetry (Nadir − Baseline value); EXE-DESAT, Patients with IPF and significant exertional desaturation; HHb, Deoxygenated hemoglobin; Hb_{Diff}, Difference in oxygenated − deoxygenated hemoglobin; IPF, Idiopathic pulmonary fibrosis; ILD, Interstitial lung disease; NIRS, Near-infrared-spectroscopy; Non-EXED, Patients with IPF and non-significant exertional desaturation; O_2HB, Oxygenated hemoglobin; PaO_2, Arterial oxygen tension; $PETCO_2$, Partial pressure of end-tidal carbon dioxide; sPAP, Systolic pulmonary artery pressure; SpO_2, Saturation from pulse oxymetry; tHB, Total hemoglobin; VE, Minute ventilation; $VE\text{-}VCO_2$, Minute ventilation—Carbon dioxide production relationship (ventilatory equivalent for CO_2); $VE\text{-}VO_2$, Minute ventilation—Oxygen uptake relationship; VO_{2peak}, Peak oxygen uptake; 6MWT, 6-minute walk test.

* Corresponding author.
E-mail address: kdipla@phed-sr.auth.gr (K. Dipla).
[1] KD and AKB contributed equally.

https://doi.org/10.1016/j.pulmoe.2021.06.006

patients were divided into the "exertional-desaturators" group ($SpO_{2nadir} \leq 89\%$ and $\geq 6\%$ drop in SpO_2) and the "non-exertional-desaturators" group ($SpO_{2nadir} \geq 90\%$ and $\leq 5\%$ drop).
Results: During CPET, the "exertional-desaturators" group exhibited lower oxygenated-hemoglobin (-0.67 $\pm$ 1.48 vs. 0.69 $\pm$ 1.75 μmol/l; $p < 0.05$) and higher deoxygenated-hemoglobin (1.67 $\pm$ 1.13 vs. 0.17 $\pm$ 0.62 μmol/l; $p < 0.001$) than the "non-exertional-desaturators" group. A different pattern ($p < 0.01$) in cerebral-oxygenation responses was observed in the two groups. In exertional-desaturators oxygenated-hemoglobin declined below baseline even at low/moderate-intensity exercise ($p < 0.05$), whereas, in non-exertional-desaturators cerebral-oxygenation declined ($p < 0.05$) at high-intensity exercise. Cerebral-NIRS indices correlated ($p < 0.05$) with CPET-duration, dyspnea, diffusion capacity, and 6MWT.
Conclusions: During incremental exercise, patients with IPF and exertional desaturation present a significant decline in cerebral-oxygenation even during low-intensity exercise. Our findings support the implementation of longer-duration rehabilitation programs in IPF so that lower intensity exercise can be applied at the initial stages. (NCT 03683082)

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a chronic progressive disorder characterized by aberrant accumulation of fibrotic tissue in the lungs, associated with poor prognosis.[1] In concert with alterations in the mechanical properties of the lungs and abnormalities in the lung vasculature in IPF, impairments in ventilation/perfusion occur, and the lung's diffusing capacity is progressively reduced.[2,3] The multiple derangements of the lung physiology in IPF, translate into significant reductions in exercise capacity and development of dyspnea.[4–6] Some patients may develop profound exercise-induced desaturation, even when oxygen saturation is acceptable when at rest.[2,6] Importantly, exertional desaturation and abnormal ventilatory responses during exercise are strong predictors of mortality in IPF.[7–9] Pathophysiologic mechanisms of exertional desaturation include ventilatory-perfusion mismatching, lung diffusion limitations, low mixed venous oxygen concentration, pulmonary vasculopathy, and high tissue oxygen extraction during exercise.[6,10–12] Exertional dyspnea, another cardinal feature of IPF,[13] also appears multifactorial, as abnormal pulmonary mechanics, hypoxemia, impaired cardiocirculatory responses, and peripheral muscle dysfunction contribute to its establishment.[9,14,15] Hypoxia and hyperventilation during exercise can reduce cerebral blood flow and also limit exercise tolerance,[16] however, studies examining the role of cerebral-oxygenation in exercise intolerance in IPF are limited.

In healthy individuals, cerebral-oxygenation during exercise increases from low to moderate/high intensities (25–75% of peak oxygen uptake, VO_{2peak}) and decreases at peak/exhaustive exercise.[17] Decrements in cerebral oxygenation can reduce cortical activation, contributing to the development of central fatigue, decreasing the muscles' force-generating capacity, and resulting in exercise termination.[18,19] A blunted cerebral-oxygenation during exercise has been reported in various chronic diseases,[20–22] and in patients with COPD it has been associated with exertional-dyspnea.[23] To the best of our knowledge, only two recent studies examined brain-oxygenation during exercise in patients with IPF/interstitial lung disease (ILD). Specifically, Marillier et al.[24] showed greater cerebral-desaturation during exercise in patients with ILD vs healthy controls; authors reported that cerebral responses varied substantially across patients. Patients with ILD were then divided based on the presence of cerebral-deoxygenation; an association of cerebral-deoxygenation with lower peak oxygen uptake (VO_{2peak}) and hypoxemia was observed.[24] The second study,[25] showed that oxygen-supplementation during steady-state exercise (at 65% of VO_{2peak}) improved brain/skeletal muscle-oxygenation, and prolonged exercise duration in patients with IPF. Although similarities in exercise-induced hypoxemia are documented in patients with ILDs of various aetiologies, there are differences in the pattern and gas exchange severity during exercise between IPF and other ILDs, attributable to specific underlying pathophysiological mechanisms.[11] Whether patients with IPF and isolated exertional desaturation, present lower cerebral-oxygenation during incremental exercise compared to patients without exertional desaturation and whether greater gas exchange abnormalities during exercise in the former group translate into the development of cerebral-deoxygenation at lower exercise intensity (lower VO_{2peak} percentage), have not been examined. This question is of importance for pulmonary rehabilitation professionals, in order to choose the appropriate exercise intensity for patients with IPF with and without exertional desaturation and avoid significant reductions in cerebral-oxygenation, possible negative effects on cognitive function/performance,[26] and premature exercise termination. Thus, the primary aims of this prospective, case-control study were to (i) examine whether patients with IPF and isolated exertional desaturation (as assessed by pulse oximetry, SpO_2) present lower cerebral-oxygenation during exercise vs those without exertional desaturation and (ii) identify whether decrements in cerebral-oxygenation occur at similar exercise intensity (%VO_{2peak}) in both groups. Secondary aims were to (i) explore the correlation of cerebral-indices during cardiopulmonary exercise (CPET) with exercise duration, dyspnea, lung diffusion capacity, and 6-min walk test (6MWT) in patients with IPF without resting hypoxemia.

Materials and methods

Participants

Patients with IPF (diagnosed based on current ATS/ERS guidelines[2]) were recruited from the ILD outpatient clinic, Papanikolaou Hospital (9/2018-2/2020). *Inclusion criteria:* (i) Patients stable on IPF medication, without hospitalization due to respiratory failure/infection during the past three months, (ii) resting arterial oxygen tension (PaO_2)≥60 mmHg and systolic pulmonary artery pressure (sPAP)<25mmHg. E*xclusion criteria:* (i) Patients with pulmonary hypertension or absolute contraindications for maximal CPET,[27] (ii) patients with SpO_2≤94 while sitting quietly in room air. Participants were divided into two groups: a) patients with exertional desaturation (EXE-DESAT), during CPET (defined as SpO_{2nadir}≤89% and a ≥6% drop in SpO_2 compared to resting levels), and b) patients without significant exertional desaturation (Non-EXED) during the CPET (SpO_{2nadir} ≥90% and ≤5% drop).[7,28] Prior to the study, patients underwent a thorough clinical examination, spirometry/lung volume assessment, carbon dioxide diffusion capacity (DL_{CO}) measurement, and a 6MWT (performed according to recommended guidelines[29]). This study was approved by the Scientific Review Board Committee of Papanikolaou Hospital (804/29.05.2018), registered with ClinicalTrials.gov (NCT 03683082), and conducted in accordance with the principles of the Declaration of Helsinki. This is a secondary analysis of a larger study evaluating the effects of oxygen supplementation in IPF.[25] All participants signed the informed consent form.

Experimental procedure and instrumentation

Patients underwent an incremental maximal/symptom-limited CPET on a cycle ergometer (Ergoselect, McKesson, USA; work-rate increments of 10 W/min, at 50 rpm), according to guidelines.[27] The protocol included a baseline/rest, a 2-min unloaded cycling, the incremental maximal test, and a 3-min recovery. A 12-lead electrocardiogram and SpO_2 (Nellcore N-180, California, USA) were continuously monitored. Respiratory gas exchange was recorded by a metabolic unit (Medgraphics, Ultima CPX™, MGC Diagnostics). Cerebral oxygenation was monitored via Near-Infrared-Spectroscopy (fNIRS, Oxymon, Artinis Medical Systems Elst, The Netherlands), by measuring relative changes (μmol/l) from pre-exercise values in oxygenated (O_2Hb), deoxygenated (HHb), and total (tHb) hemoglobin.[30] The O_2Hb and hemoglobin difference (Hb_{diff}) are used as indices of tissue-oxygenation, the HHb of oxygen extraction, and the tHb reflects regional changes in tissue-blood volume/local vasodilation.[31] The fNIRS-sensor was placed over the left prefrontal cortex.[31,32] Leg fatigue and dyspnea were assessed using the Borg CR10 (2010) scale.[33]

Based on previous results in cerebral-O_2Hb differences during exercise in hypoxemic-COPD vs non-hypoxemic-COPD,[31] we calculated (GPower software 3.1) that a sample size of 18 patients (9/group) is needed to achieve a power of 0.90 (α = 0.05, effect size=1.5). We contacted 24 patients, allowing for possible dropouts.

Statistical analyses

Variables are presented as mean±SD or median (interquartile range$_{25-75\%}$), depending on normality of distribution. For assessing between-group differences, independent t-tests were used for normally distributed data or Mann-Whitney U test for ordinal data. NIRS data were recorded and analyzed offline (Oxysoft, Artinis Medical Systems). The average O_2Hb-, HHb-, tHB-, and HB_{diff}-response during exercise per patient were calculated; differences between groups were compared using an independent *t*-test. NIRS data were also exported in 30s averages. The patient's cerebral responses at 0, 25, 50, 75, and 100% of VO_{2peak} were determined. The effects of exercise intensity on cerebral-NIRS responses in the two groups were analyzed using two-way repeated-measures ANOVA (Group × Time), followed by Tukey *Post-hoc* (Statistica 7.0, StatSoft, USA). Pearson(r) or Spearman(rho) correlation was used, depending on continuous/ordinal data, to examined possible associations between variables of interest.

Results

Participant characteristics

Twenty-four patients with IPF without resting hypoxemia were recruited. Thirteen patients exhibiting a significant desaturation comprised the "EXE-DESAT" group, and eleven patients comprised the "Non-EXED" group. One patient terminated the test early due to a hypertensive response to exercise and was not included in the analysis. There were no significant differences between groups in anthropometric characteristics and spirometry lung volumes (Table 1); however, the EXE-DESAT group had lower ($p < 0.05$) diffusion capacity (%predicted DL_{CO}).

Cardiopulmonary exercise testing

By study design, the EXE-DESAT group exhibited greater desaturation vs Non-EXED ($DSpO_2$: 12.2 ± 3.2% vs 3.6 ± 1.8%; $p < 0.001$) during CPET (Table 1). No statistically significant differences between groups were observed in $\dot{V}O_{2peak}$, peak minute ventilation (VE_{peak}), and ventilatory equivalent for CO_2 (VE/VCO_{2peak}), however, EXE-DESAT presented higher VE/VCO_2 at ventilatory threshold ($p < 0.05$). At exercise termination, groups reported no significant differences in leg fatigue (p = 0.56). The EXE-DESAT reported marginally higher dyspnea vs Non-EXED (p = 0.058)

Brain oxygenation

Accumulative data (all patients per group) of continuous NIRS-recordings during exercise are presented in Fig. 1. The EXE-DESAT exhibited a decline in O_2Hb and a progressive rise in HHb, from the initial minutes of the CPET-exercise. The average cerebral NIRS-oxygenation response during exercise in each patient is presented in Fig. 2. The EXE-DESAT group exhibited significantly lower ($p < 0.05$) O_2Hb and HB_{diff} than Non-EXED, and higher ($p < 0.001$) HHb, with no differences in tHb (p = 0.86).

Table 1 Participant Characteristics and cardiopulmonary exercise testing (CPET) results during the incremental (ramp) protocol to exhaustion in the group with significant exertional desaturation and non-exertional desaturation.

	Patients with exertional desaturation (n = 13) Mean ± SD	Patients with Non- exertional desaturation (n = 10) Mean ± SD
Anthropometrics		
Age (years)	62.9 ± 10.0	60.8 ± 8.6
Body mass index (kg/m2)	30.1 ± 4.5	28.3 ± 3.2
Resting pulmonary function variables		
FEV1 (%predicted)	80.3 ± 21.5	83.6 ± 18.5
FVC (%predicted)	79.9 ± 21.0	78.3 ± 17.8
TLC (%predicted)	59.2 ± 10.1	71.1 ± 20.5
DL_{CO} (%predicted)	41.7 ± 9.5	56.6 ± 16.0*
Medical treatment with antifibrosis-targeted agents		
Nintedanib	7	6
Pirfenidone	6	4
6-min walk test		
Distance (m)	451 ± 102	542 ± 56
SpO_{2start} (%)	94.5 ± 1.7	96.3 ± 1.7
SpO_{2nadir} (%)	82.6 ± 3.9	92.3 ± 2.8
Co-morbidities	5	4
Cardiac disease (n=)		
CPET Results		
Workload Peak (Watt)	92.5 ± 23.1	92.1 ± 31.3
Workload Peak (%Predicted)	68.3 ± 18.6	76.1 ± 20.9
SpO_2 Rest (%)	95.8 ± 1.2	96.4 ± 1.6
SpO_2 Nadir (%)	83.5 ± 3.4	92.8 ± 2.4 *
Heart rate Rest (bpm)	85.1 ± 13.3	85.6 ± 6.5
Heart rate Peak (bpm)	135.4 ± 12.7	137.3 ± 13.6
Respiratory Rate Rest (br/min)	24.3 ± 6.6	19.7 ± 6.6
Respiratory Rate Peak (br/min)	46.5 ± 9.6	42.9 ± 9.6
VE Peak (l/min)	73.7 ± 12.9	68.4 ± 15.0
VE Peak (%Predicted)	63.2 ± 15.8	62.5 ± 25.9
VO_{2peak} (ml/kg/min)	18.9 ± 2.8	18.3 ± 2.9
VO_{2peak} (%Predicted)	82.8 ± 19.0	82.3 ± 21.3
VO_2 at ventilatory threshold (%Predicted)	56.6 ± 13.1	52.9 ± 17.2
Respiratory Exchange Ratio Peak	1.12 ± 0.13	1.16 ± 0.12
VE-VCO_2 at ventilatory threshold	40.7 ± 5.7	35.8 ± 4.5*
VE-VCO_2 Peak	41.8 ± 7.9	38.1 ± 5.7
VE-VO_2 Peak	46.2 ± 8.2	43.0 ± 9.6
VO_{2peak}/Heart rate peak (%predicted)	95.4 ± 18.9	98.1 ± 26.6
$PETCO_2$ Rest (mmHg)	33.5 ± 4.4	36.3 ± 3.9
$PETCO_2$ Peak (mmHg)	33.5 ± 6.2	35.8 ± 6.3
Leg fatigue at exercise termination	7.3(0.5)	6.8(1.0)
Dyspnea at exercise termination	3.5(2.5)	2.3(2.0)

Data are presented as means±SD or median (interquartile range 25−75%;IQ_{25-75}); FEV1: forced expiratory volume in 1 s; FVC: forced expiratory volume; TLC: total lung capacity; DL_{CO}: lung diffusion capacity for carbon monoxide; SpO_2: Saturation from pulse oximetry; VO_2, oxygen consumption; VE: minute ventilation; VE-VCO_2: minute ventilation−carbon dioxide production relationship; VE-VO_2: minute ventilation−oxygen uptake relationship; $PETCO_2$: partial pressure of end-tidal carbon dioxide;
*$p < 0.05$ sign. vs the EXE-DESAT group.

Differences between groups in cerebral-oxygenation attained at various exercise intensities (% of VO_{2peak}) were examined (Fig. 3). Two-way ANOVAs revealed significant group differences in O_2Hb, HHb, and Hb_{diff}, and a different pattern ($p < 0.05$) of increase in HHB and Hb_{diff} in the two groups. Specifically, EXE-DESAT presented a trend towards an HHb increase at 25% of their VO_{2peak} ($p = 0.06$); then, HHb progressively increased at 50%, 75%, 100% of VO_{2peak} (vs the beginning of loaded exercise, 0% of VO_{2peak}; $p < 0.001$). In Non-EXED, significant increases in HHb were observed only at 75% and 100% ($p < 0.01$). In EXE-DESAT, Hb_{diff} significantly decreased at 50% VO_{2peak} ($p < 0.001$) and continued to decrease at 75% and 100%; whereas in Non-EXED, Hb_{diff} significantly decreased only at 100% VO_{2peak} ($p < 0.01$).

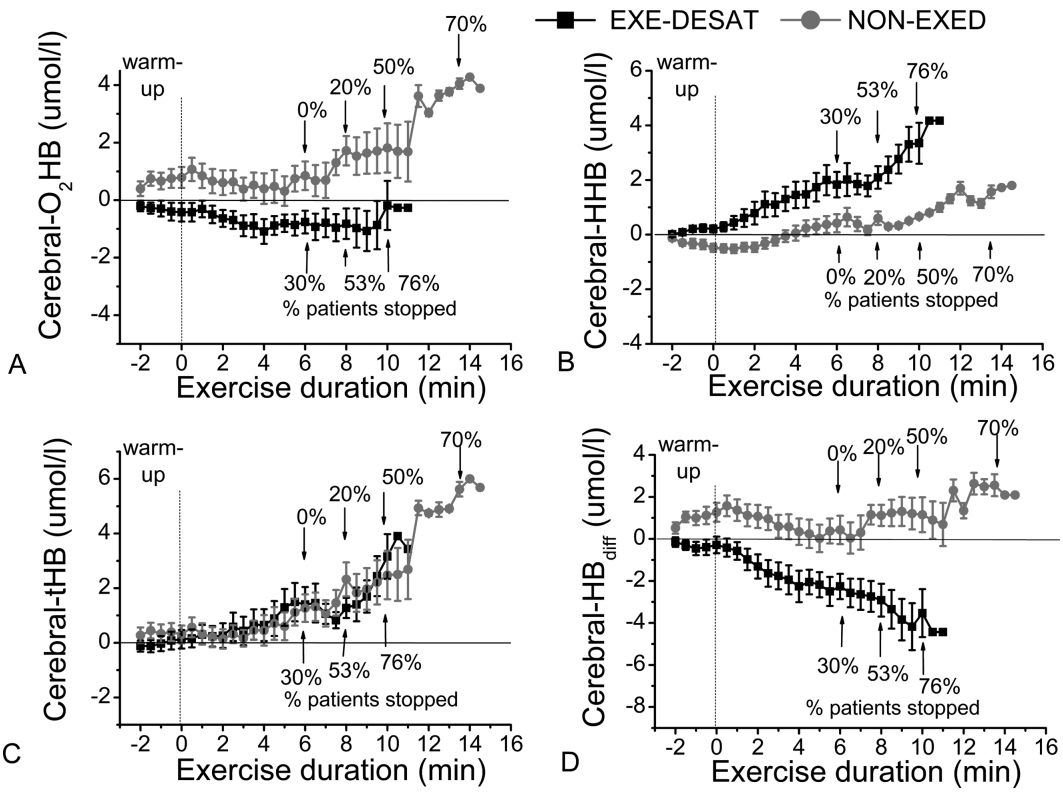

Fig. 1 Continuous near-infrared-spectroscopy recordings in cerebral prefrontal oxygenation. Accumulated data (mean±sd every 30 s) per group in (A) oxygenated hemoglobin (O_2Hb), (B) deoxygenated hemoglobin (HHb), (C) total hemoglobin (tHB), and (D) hemoglobin difference (Hb_{diff}) during the maximal test in the exertional desaturation (EXE-DESAT) and non-exertional desaturation (NON-EXED) groups. The arrows depict the percentage of patients that terminated the exercise at this time (at the 6th, 8th, 10th minute). CPET: Cardiopulmonary Exercise Testing.

Correlations

Cerebral-NIRS parameters during CPET were significantly correlated with lung diffusion capacity, 6MWT, and dyspnea (Appendix A-Fig.1S-4S). In detail, the average cerebral-O_2HB response was correlated (Fig. 1S) with dyspnea (rho = –0.71, $p < 0.05$), CPET-duration ($r = 0.42$, $p < 0.05$), %predicted DL_{CO} ($r = 0.53$, $p < 0.01$), and 6MWT-distance ($r = 0.58$, $p < 0.01$). The average-HHb (Fig. 2S) was correlated with dyspnea (rho=0.57, $p < 0.05$), %predicted DL_{CO} (r = -0.43, $p < 0.05$), and 6MWT-distance (r = –0.50, $p < 0.05$). The average-HB_{diff} (Fig. 3S) was correlated with dyspnea (rho=–0.66, $p < 0.05$), %predicted DL_{CO} ($r = 0.57$, $p < 0.01$), 6MWT-distance ($r = 0.60$, $p < 0.01$), and 6MWT-desaturation (r = -0.65, $p < 0.001$). Furthermore, the O_2Hb values obtained at 25% VO_{2peak}, were significantly correlated (Fig. 4S) with CPET-duration ($r = 0.49$, $p < 0.05$) and CPET-dyspnea (rho = –0.75, $p < 0.05$).

Discussion

Our primary outcomes were that patients with IPF and isolated exertional desaturation presented significantly lower cerebral-oxygenation and a differential pattern in this response during CPET-exercise compared with patients without exertional desaturation. That is, patients with exertional desaturation exhibited an inability to maintain cerebral-oxygenation from low exercise intensities (below 50% VO_{2peak}). In contrast, patients without exertional desaturation exhibited significant deoxygenation at high exercise intensity (above 75% of VO_{2peak}). Secondary outcomes were that cerebral-oxygenation/deoxygenation indices were significantly correlated with CPET-exercise duration and dyspnea, diffusion capacity, and 6MWT.

In healthy adults, the increase in O_2Hb and Hb_{diff}, coupled with a decrease in HHb during exercise has been suggested to reflect an enhanced cortical neuronal activity.[17–19] In contrast, O_2Hb reductions and significant HHb elevations have been described in cerebral ischemia.[34] Thus, in our study, the early decrease in cerebral-O_2HB and Hb_{diff} below baseline levels and the large increases in HHb from low exercise intensity reflect significant impairments in cerebral-oxygenation, as also evidenced in patients with COPD by Higashimoto et al.[31] In contrast, in patients without exertional desaturation, cerebral-Hb_{diff} was significantly reduced only at high exercise intensity (around 75% VO_{2peak}), above the critical power,[8] mimicking the pattern described in healthy individuals.[17–19,35,36] However, it should be noticed that despite the higher overall cerebral-O_2Hb and Hb_{Diff} responses in the non-desaturators group, the increase in O_2HB during exercise was still blunted, as indicated by the slightly higher than baseline values. This finding suggests limitations in cerebral-oxygenation during exercise, even without significant exertional desaturation in patients with IPF. The similar tHb-responses between groups suggest

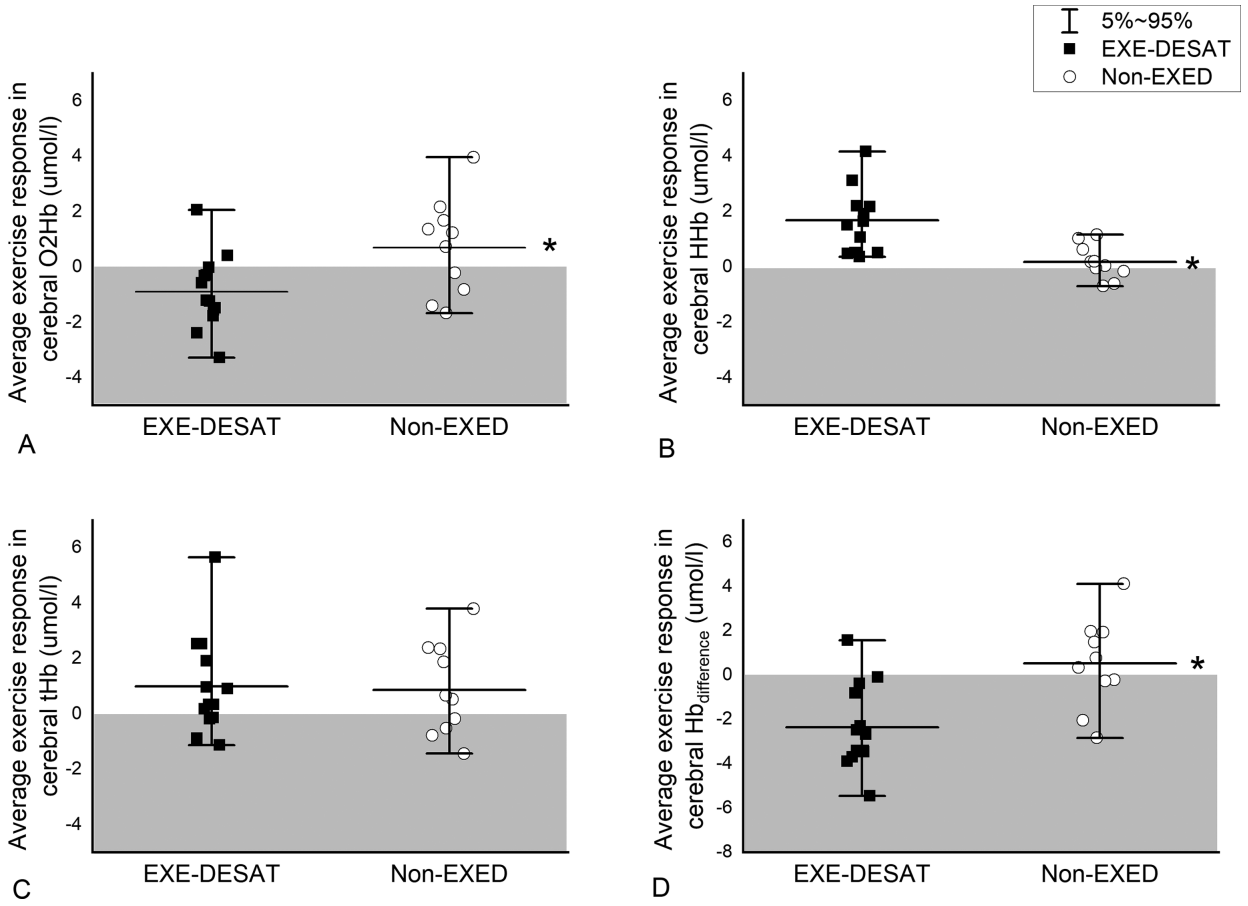

Fig. 2 Average cerebral-oxygenation responses during the maximal test. Scatter interval plots depicting the average response in (A) oxygenated hemoglobin (O_2Hb), (B) deoxygenated hemoglobin (HHb), (C) total hemoglobin (tHb), and (D) hemoglobin difference ($Hb_{difference}$) in patients with IPF and exertional desaturation (EXE-DESAT) and non-exertional desaturation (NON-EXED). The shaded area presents values below baseline. * $p < 0.01$ sign. EXE-DESAT vs NON-EXED group.

similar vasodilation/blood volume changes in the cerebral-microvasculature during exercise.[31]

An interesting finding in this study is the significant impact of cerebral-oxygenation on exercise duration and dyspnea. Patients that exhibited reduced cerebral-O_2Hb from low exercise intensity (25% of VO_{2peak}), had shorter exercise duration and presented greater dyspnea. Dyspnea, a subjective experience of breathing discomfort,[13] was marginally higher at exercise termination in EXE-DESAT compared with the Non-EXED group, even though VO_{2peak} did not differ between groups. In hypoxemic patients with COPD, exertional dyspnea was correlated with impaired cerebral-oxygenation and HHb-elevations during exercise, but not SpO_2 during CPET.[23,31] In our study, cerebral-NIRS variables were more strongly correlated with dyspnea than with the magnitude of desaturation during CPET. Although cerebral-deoxygenation was not significantly correlated with leg fatigue ratings, this does not suggest that skeletal muscles are not involved in exercise intolerance in patients with IPF. In fact, our patients rated higher their leg fatigue than dyspnea, which is expected during cycling, as previously discussed,[8] highlighting the importance of skeletal muscles in exercise limitations in these patients.

Importantly, the significant correlation between brain-oxygenation indices and DL_{CO}, suggests an association between cerebral-deoxygenation and diffusion limitations. Lung diffusion reduction is a known predictor of exercise-induced hypoxemia and disease outcomes/severity.[4,37] Both groups presented ventilatory inefficiency during exercise (as evidenced by high peak-VE/VCO_2 and VE/VCO_2 at ventilatory-threshold), however, the higher VE/VCO_2 at ventilatory threshold in the exertional-desaturators group, is suggestive of greater ventilation/perfusion mismatch in this group.[9,11] Groups did not exhibit signs of significant pulmonary hypertension during CPET, as peak oxygen-pulse (VO_2/HR) was $>95\%$ of predicted and VE/VCO_2 at ventilatory threshold was <45.[11,38]

This study has both strengths and limitations. Two strict criteria for defining exertional desaturation ($SpO_2<88\%$ and $\geq 6\%$ drop in SpO_2) were used, as the cycling test is less sensitive to diagnose desaturation than the 6MWT.[8] This allowed for a substantial difference in desaturation between groups. Groups with similar resting-SpO_2 were used because an exertional nadir of an absolute value of $SpO_2 \leq 89\%$ would have resulted in a different magnitude of SpO_2 decline in patients with various resting saturation levels.[39] Cerebral-oxygenation was assessed with NIRS, a noninvasive, reliable technique for measuring brain function/oxygenation, during exercise.[20,30] Cerebral-NIRS measurements were obtained from the left pre-frontal cortex, as activation in this area has been associated with exertional dyspnea in COPD.[23,40]

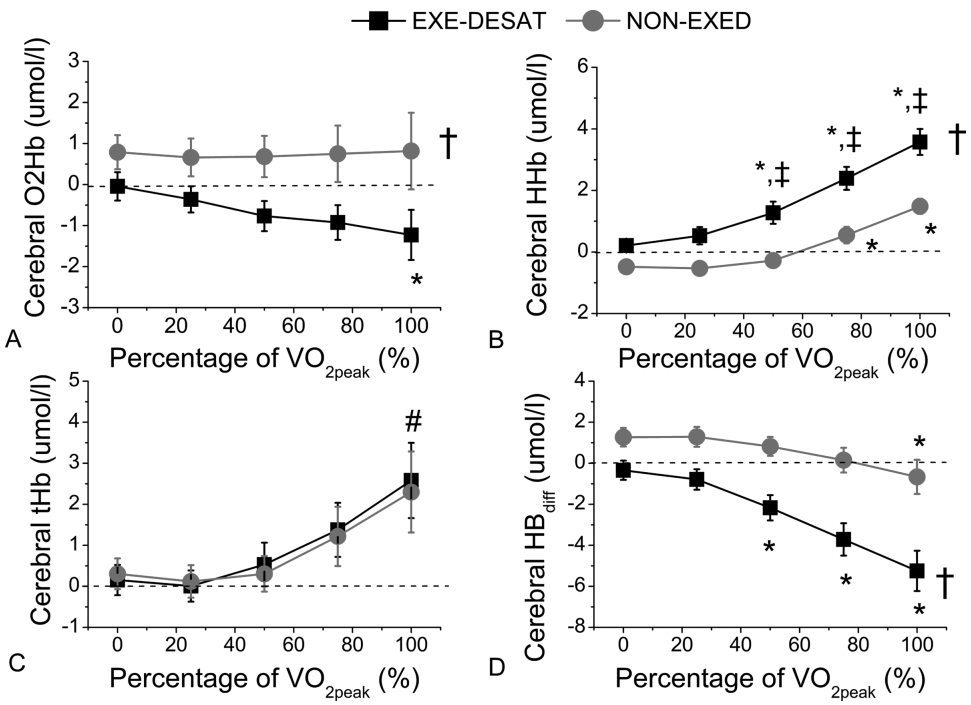

Fig. 3 Cerebral oxygenation at different exercise intensities. (A) Oxygenated hemoglobin (O_2Hb), (B) deoxygenated hemoglobin (HHb), (C) total hemoglobin (tHb), and (D) hemoglobin difference ($Hb_{difference}$) during the maximal test in patients with exertional desaturation (EXE-DESAT) and non-exertional desaturation (NON-EXED). †$p < 0.001$ sign. EXE-DESAT vs NON-EXED group; *$p < 0.05$ sign. vs the beginning of the test (0%) within the same group; ‡$p < 0.05$ sign. vs respective intensity in EXE-DESAT; #$p < 0.05$ sign. vs 25, 50, and 75% of VO_{2peak} within both groups; VO_{2peak}: peak oxygen uptake.

Other brain areas (premotor/motor regions) important in dyspnea perception,[17] were not examined. However, studies using multichannel-NIRS in COPD, showed that the pattern of cortical-deoxygenation during exercise was similar in prefrontal, premotor, and motor regions.[17] Finally, all participants were on anti-fibrotic medication; thus, results cannot be extrapolated to patients not using IPF-medication. Although ATS/ERS Guidelines on IPF treatment listed antifibrotic treatment as "conditional", most IPF-expert pulmonologists agree that antifibrotic treatment should be started as soon as the disease is diagnosed.[2,41]

Clinical application

Our data highlight the importance of selecting the appropriate exercise intensity in patients with IPF and exertional desaturation to maintain adequate brain oxygenation during exercise. Modifications in exercise intensity may be considered in IPF patients with exertional desaturation and low DL_{CO} (<50%), as brain ischemia might develop when exercising even at moderate intensity i.e. at 50−60% of VO_{2peak} which is often used in COPD patients. Alternatively, if higher exercise intensity is desired, oxygen supplementation[25] or intermittent exercise,[42] may be considered. However, the impact of different exercise modalities on cerebral-oxygenation requires further studies. Longer duration of exercise rehabilitation programs will allow slower progression of training. Beyond planned exercise, mild daily life physical activity might also cause cerebral hypoxia in patients with IPF. Brain oxygenation measurements could assist in identifying patients with significant exertional cerebral-deoxygenation.

Conclusions

Patients with IPF and isolated exertional desaturation exhibit significantly lower cerebral-oxygenation during incremental exercise than patients without exertional hypoxemia. Importantly, in patients with exertional desaturation inadequate cerebral-oxygenation develops at low/moderate exercise intensity (below 50% of VO_{2peak}), whereas in patients without exertional desaturation significant impairments in cerebral-oxygenation develop at high-intensity exercise. The significant associations of impaired cerebral-oxygenation with shorter exercise duration, higher dyspnea, and lower DL_{CO}, suggest a more severely compromised cerebral-oxygenation during exercise in patients with greater diffusion limitations. Our findings support the implementation of longer-duration rehabilitation programs so that lower intensity can be applied at the initial stages in these patients with IPF and highlight the need for personalized, IPF-specific exercise programs.

Authorship

Dipla K, Boutou AK, Zafeiridis A, and Markopoulou A conceived this study and supervised its implementation. Pitsiou G, Stanopoulos I, Kioumis I collaborated in the inception of the study and interpretation of data. Dipla K, Boutou AK, Zafeiridis A, Papadopoulos S, and Kritikou S collected the data and collaborated in the analysis. All the authors contributed to the interpretation of the results and revisions and approved the manuscript.

Conflicts of interest

The authors report no conflict of interest

Acknowledgements

The authors would like to thank Dr. A. Chloros and Dr. G. Kounti for their scientific advice, V. Pegklidou for her assistance with the 6-min walk tests, and P. Malli for English Proofreading.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2021.06.006.

References

1. Sgalla G, Iovene B, Calvello M, Ori M, Varone F, Richeldi L. Idiopathic pulmonary fibrosis: pathogenesis and management. Respir Res. 2018;19:32. https://doi.org/10.1186/s12931-018-0730-2.
2. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198:e44–68. https://doi.org/10.1164/rccm.201807-1255ST.
3. Wuyts WA, Wijsenbeek M, Bondue B, Bresser P, Bouros D, Robalo Cordeiro C, et al. Idiopathic pulmonary fibrosis: best practice in monitoring and managing a relentless fibrotic disease. Respiration. 2020;99:73–82. https://doi.org/10.1159/000504763.
4. Du Plessis JP, Fernandes S, Jamal R, Camp P, Johannson K, Schaeffer M, et al. Exertional hypoxemia is more severe in fibrotic interstitial lung disease than in COPD. Respirology. 2018;23:392–8. https://doi.org/10.1111/resp.13226.
5. Khor YH, Renzoni EA, Visca D, McDonald CF, Goh NSL. Oxygen therapy in COPD and interstitial lung disease: navigating the knowns and unknowns. ERJ Open Res. 2019;5. https://doi.org/10.1183/23120541.00118-2019.
6. Troy LK, Young IH, Lau EMT, Corte TJ. Exercise pathophysiology and the role of oxygen therapy in idiopathic interstitial pneumonia. Respirology. 2016;21:1005–14. https://doi.org/10.1111/resp.12650.
7. Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, et al. Prognostic value of desaturation during a 6 minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2003;168:1084–90. https://doi.org/10.1164/rccm.200302-219OC.
8. Puente-Maestu L. Physiological rationale of commonly used clinical exercise tests. Pulmonology. 2020;26:159–65. https://doi.org/10.1016/j.pulmoe.2019.10.004.
9. Vainshelboim B, Oliveira J, Fox BD, Kramer MR. The prognostic role of ventilatory inefficiency and exercise capacity in idiopathic pulmonary fibrosis. Respir Care. 2016;61:1100–9. https://doi.org/10.4187/respcare.04471.
10. Holland AE. Exercise limitation in interstitial lung disease - mechanisms, significance and therapeutic options. Chron Respir Dis. 2010;7:101–11. https://doi.org/10.1177/1479972309354689.
11. Bonini M, Fiorenzano G. Exertional dyspnoea in interstitial lung diseases: the clinical utility of cardiopulmonary exercise testing. Eur Respir Rev. 2017;26:1–11. https://doi.org/10.1183/16000617.0099-2016.
12. Cournoyer J, Ramos CF, Sturgill B, Tang F, DeLuca N, Mirsaeidi M, Jackson RM. Effects of 100% oxygen during exercise in patients with interstitial lung disease. Respir Physiol Neurobiol. 2020;274. https://doi.org/10.1016/j.resp.2019.103367.
13. Ambrosino N, Fracchia C. Strategies to relieve dyspnoea in patients with advanced chronic respiratory diseases. A narrative review. Pulmonology. 2019;25:289–98. https://doi.org/10.1016/j.pulmoe.2019.04.002.
14. Agustí AG, Roca J, Gea J, Wagner PD, Xaubet A, Rodriguez-Roisin R. Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. Am Rev Respir Dis. 1991;143:219–25. https://doi.org/10.1164/ajrccm/143.2.219.
15. Faisal A, Alghamdi BJ, Ciavaglia CE, lbehairy AF, Webb KA, Ora J, et al. Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. Am J Respir Crit Care Med. 2016;193:299–309. https://doi.org/10.1164/rccm.201504-0841OC.
16. Tosh W, Patteril M. Cerebral oximetry. BJA Educ. 2016;16:417–21. https://doi.org/10.1093/bjaed/mkw024.
17. Subudhi AW, Dimmen AC, Roach RC. Effects of acute hypoxia on cerebral and muscle oxygenation during incremental exercise. J Appl Physiol. 2007;103:177–83. https://doi.org/10.1152/japplphysiol.01460.2006.
18. Rasmussen P, Nielsen J, Overgaard M, Krogh-Madsen R, Gjedde A, Secher NH, Petersen NC. Reduced muscle activation during exercise related to brain oxygenation and metabolism in humans. J Physiol. 2010;588:1985–95. https://doi.org/10.1113/jphysiol.2009.186767.
19. Secher NH, Seifert T, Van Lieshout JJ. Cerebral blood flow and metabolism during exercise: Implications for fatigue. J Appl Physiol. 2008;104:306–14. https://doi.org/10.1152/japplphysiol.00853.2007.
20. Oliveira MF, Rodrigues MK, Treptow E, Cunha TM, Ferreira EM V, Neder JA. Effects of oxygen supplementation on cerebral oxygenation during exercise in chronic obstructive pulmonary disease patients not entitled to long-term oxygen therapy. Clin Physiol Funct Imaging. 2012;32:52–8. https://doi.org/10.1111/j.1475-097X.2011.01054.x.
21. Kintiraki E, Dipla K, Triantafyllou A, Koletsos N, Grigoriadou I, Poulakos P, et al. Blunted cerebral oxygenation during exercise in women with gestational diabetes mellitus: associations with macrovascular function and cardiovascular risk factors. Metabolism. 2018;83:25–30. https://doi.org/10.1016/j.metabol.2018.01.009.
22. Oliveira MF, Alencar MC, Arbex F, Souza A, Sperandio P, Medina L, et al. Effects of heart failure on cerebral blood flow in COPD: rest and exercise. Respir Physiol Neurobiol. 2016;221:41–8. https://doi.org/10.1016/j.resp.2015.10.005.
23. Higashimoto Y, Honda N, Yamagata T, Matsuoka T, Maeda K, Satoh R, et al. Activation of the prefrontal cortex is associated with exertional dyspnea in chronic obstructive pulmonary disease. Respiration. 2011;82:492–500. https://doi.org/10.1159/000324571.
24. Marillier M, Bernard A-C, Verges S, Moran-Mendoza O, O'Donnell DE, Neder JA. Influence of exertional hypoxemia on cerebral oxygenation in fibrotic interstitial lung disease. Respir Physiol Neurobiol. 2021;285:103601. https://doi.org/10.1016/j.resp.2020.103601.
25. Dipla K, Boutou AK, Markopoulou A, Pitsiou G, Papadopoulos S, Chatzikosti A, et al. Exertional desaturation in idiopathic pulmonary fibrosis: the role of oxygen supplementation in

modifying cerebral-skeletal muscle oxygenation and systemic hemodynamics. Respiration. 2021;30:1—13. https://doi.org/10.1159/000514320.
26. Lefferts WK, Babcock MC, Tiss MJ, Ives SJ, White CN, Brutsaert TD, Heffernan KS. Effect of hypoxia on cerebrovascular and cognitive function during moderate intensity exercise. Physiol Behav. 2016;165:108—18. https://doi.org/10.1016/j.physbeh.2016.07.003.
27. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167:211—77. https://doi.org/10.1164/rccm.167.2.211.
28. Jenkins S, Čečins N. Six-minute walk test: observed adverse events and oxygen desaturation in a large cohort of patients with chronic lung disease. Intern Med J. 2011;41:416—22. https://doi.org/10.1111/j.1445-5994.2010.02169.x.
29. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44:1428—46. https://doi.org/10.1183/09031936.00150314.
30. Huppert T, Diamond S, Franceschini M, Boas D. HomER: a review of time-series analysis methods for near-infrared spectroscopy of the brain. Appl Opt. 2009;48:D280—98. https://doi.org/10.1038/jid.2014.371.
31. Higashimoto Y, Honda N, Yamagata T, Sano A, Nishiyama O, Sano H, et al. Exertional dyspnoea and cortical oxygenation in patients with COPD. Eur Respir J. 2015;46:1615—24. https://doi.org/10.1183/13993003.00541-2015.
32. Vogiatzis I, Louvaris Z, Habazettl H, Andrianopoulos V, Wagner H, Roussos C, et al. Cerebral cortex oxygen delivery and exercise limitation in patients with COPD. Eur Respir J. 2013;41:295—301. https://doi.org/10.1183/09031936.00016312.
33. Borg G, Borg E. The Borg CR Scales® Folder. Åkersberga, Sweden:; 2010.
34. Chen S, Sakatani K, Lichty W, Ning P, Zhao S, Zuo H. Auditory-evoked cerebral oxygenation changes in hypoxic-ischemic encephalopathy of newborn infants monitored by near infrared spectroscopy. Early Hum Dev. 2002;67:113—21. https://doi.org/10.1016/s0378-3782(02)00004-x.
35. Rooks CR, Thom NJ, McCully KK, Dishman RK. Effects of incremental exercise on cerebral oxygenation measured by near-infrared spectroscopy: a systematic review. Prog Neurobiol. 2010;92:134—50. https://doi.org/10.1016/j.pneurobio.2010.06.002.
36. Mekari S, Fraser S, Bosquet L, Bonnéry C, Labelle V, Pouliot P, et al. The relationship between exercise intensity, cerebral oxygenation and cognitive performance in young adults. Eur J Appl Physiol. 2015;115:2189—97. https://doi.org/10.1007/s00421-015-3199-4.
37. Hyldgaard C, Møller J, Bendstrup E. Changes in management of idiopathic pulmonary fibrosis: impact on disease severity and mortality. Eur Clin Respir J. 2020;7:1807682. https://doi.org/10.1080/20018525.2020.1807682.
38. van der Plas MN, van Kan C, Blumenthal J, Jansen HM, Wells AU, Bresser P. Pulmonary vascular limitation to exercise and survival in idiopathic pulmonary fibrosis. Respirology. 2014;19:269—75. https://doi.org/10.1111/resp.12206.
39. Vainshelboim B, Kramer MR, Izhakian S, Lima RM, Oliveira J. Physical activity and exertional desaturation are associated with mortality in idiopathic pulmonary fibrosis. J Clin Med. 2016;5. https://doi.org/10.3390/jcm5080073.
40. Rasmussen P, Dawson EA, Nybo L, van Lieshout JJ, Secher NH, Gjedde A. Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. 2007;27:1082—93. https://doi.org/10.1038/sj.jcbfm.9600416.
41. Robalo-Cordeiro C, Morais A. Translating idiopathic pulmonary fibrosis guidelines into clinical practice. Pulmonology. 2021;27:7—13. https://doi.org/10.1016/j.pulmoe.2020.05.017.
42. Armstrong M, Vogiatzis I. Personalized exercise training in chronic lung diseases. Respirology. 2019;24:854—62. https://doi.org/10.1111/resp.13639.

Pulmonology 29 (2023) 230—239

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Clusters of individuals recovering from an exacerbation of chronic obstructive pulmonary disease and response to in-hospital pulmonary rehabilitation

M. Vitacca[a,*], A. Malovini[b], A. Spanevello[c,d], P. Ceriana[e], M. Paneroni[a], M. Maniscalco[f], B. Balbi[g], L. Rizzello[h], R. Murgia[i], R. Bellazzi[l,b], N. Ambrosino[i]

[a] *Respiratory Rehabilitation of the Institute of Lumezzane, Istituti Clinici Scientifici Maugeri IRCCS, Brescia, Italy*
[b] *Laboratory of Informatics and Systems Engineering for Clinical Research of the Institute of Pavia, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy*
[c] *Respiratory Rehabilitation of the Institute of Tradate, Istituti Clinici Scientifici Maugeri IRCCS, Varese, Italy*
[d] *Department of Medicine and Surgery, University of Insubria, Varese, Italy*
[e] *Respiratory Rehabilitation of the Institute of Pavia, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy*
[f] *Respiratory Rehabilitation of the Institute of Telese, Istituti Clinici Scientifici Maugeri IRCCS, Benevento, Italy*
[g] *Respiratory Rehabilitation of the Institute of Veruno, Istituti Clinici Scientifici Maugeri IRCCS, Novara, Italy*
[h] *Respiratory Rehabilitation of the Institute of Milano Istituti Clinici Scientifici Maugeri IRCCS, Milano, Italy*
[i] *Respiratory Rehabilitation of the Institute of Montescano, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy*
[l] *Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, Italy*

Received 28 September 2022; received in revised form 4 January 2023; accepted 7 January 2023
Available online 29 January 2023

KEYWORDS
COPD;
Dyspnoea;
Disease impact;
Exercise capacity;
Exercise training;
Rehabilitation

Abstract
Introduction and Objectives: Due to the present low availability of pulmonary rehabilitation (PR) for individuals recovering from a COPD exacerbation (ECOPD), we need admission priority criteria. We tested the hypothesis that these individuals might be clustered according to baseline characteristics to identify subpopulations with different responses to PR.
Methods: Multicentric retrospective analysis of individuals undergone in-hospital PR. Baseline characteristics and outcome measures (six-minute walking test - 6MWT, Medical Research Council scale for dyspnoea -MRC, COPD assessment test —CAT) were used for clustering analysis.
Results: Data analysis of 1159 individuals showed that after program, the proportion of individuals reaching the minimal clinically important difference (MCID) was 85.0%, 86.3%, and 65.6% for CAT, MRC, and 6MWT respectively. Three clusters were found (C1-severe: 10.9%; C2-intermediate: 74.4%; C3-mild: 14.7% of cases respectively). Cluster C1-severe showed the worst conditions with the largest post PR improvements in outcome measures; C3-mild showed the least severe baseline conditions, but the smallest improvements. The proportion of participants reaching the MCID in ALL three outcome measures was significantly different among clusters, with C1-severe

* Corresponding author at: Respiratory Rehabilitation Unit, Istituti Clinici Scientifici Maugeri IRCCS. Institute of Lumezzane, Via G. Mazzini 129, 25065, Lumezzane (Brescia), Italy.
E-mail address: michele.vitacca@icsmaugeri.it (M. Vitacca).

https://doi.org/10.1016/j.pulmoe.2023.01.002

having the highest proportion of full success (69.0%) as compared to C2-intermediate (48.3%) and C3-mild (37.4%). Participants in C2-intermediate and C1-severe had 1.7- and 4.6-fold increases in the probability to reach the MCID in all three outcomes as compared to those in C3-mild (OR = 1.72, 95% confidence interval [95% CI] = 1.2 − 2.49, p = 0.0035 and OR = 4.57, 95% CI = 2.68 − 7.91, p < 0.0001 respectively).

Conclusions: Clustering analysis can identify subpopulations of individuals recovering from ECOPD associated with different responses to PR. Our results may help in defining priority criteria based on the probability of success of PR.

Introduction

Pulmonary rehabilitation (PR) including exercise training is a recognized cornerstone of comprehensive management of chronic obstructive pulmonary disease (COPD). In different settings, this modality improves symptoms such as dyspnoea and fatigue, exercise capacity, and health-related quality of life (HRQL).[1,2] Therefore, guidelines recommend PR for individuals with persistent breathlessness and/or exercise limitation with reduced HRQL.[3] Furthermore early PR after an exacerbation (ECOPD) is associated with reduced prevalence of new ECOPD and longer survival and is cost-effective.[4,5] However, there are barriers to in-hospital programs, such as a high number of candidates, transportation, costs, and geographical obstacles.[6] To increase access to programs, governments should develop policies to increase resources, logistics, availability and expertise of healthcare providers, including tele-rehabilitation.[6,7] An additional approach might be to identify characteristics of individuals most likely to receive benefits from PR (responders) in order not to "waste" resources for candidates with scarce probabilities of success.

Clustering analyses are unsupervised multivariate methods helping to identify subpopulations or "clusters". By labelling observations according to the corresponding cluster, these techniques can help interpret the available data.[8] The aim of this multicentre, retrospective study was to test the hypothesis that individuals recovering from an ECOPD could be clustered according to their baseline characteristics, for early identification of subpopulations with different patterns of response to PR in accepted outcome measures.

Methods

This multicentre, retrospective study evaluated a database of hospital medical records of individuals recovering from ECOPD. The study was approved by the Istituti Clinici Scientifici (ICS) Maugeri Ethics Committee (2555 CE 8 June 2021). As a retrospective study, participants had not provided any specific written informed consent, however, at admission to ICS Maugeri hospitals, they had given − in- advance informed consent for the scientific use of their data. As a retrospective analysis, the study was not registered.

Participants

The study has been conducted on individuals consecutively admitted between July, 1th, 2018 to December, 31th, 2021 to hospitals of the ICS Maugeri network (Lumezzane, Pavia, Tradate, Veruno, Milano, Montescano, Telese, Italy), referral hospitals for PR, diagnosis, and care of chronic diseases. These hospitals share common indications to PR,[1] evaluation, diagnostic and management tools, and protocols. During the pandemic period of study (March 2020-December 2021), only participants with negative swab tests were admitted to the in-patient program.

Only data of individuals with lung function and paired prior and post PR results of outcome measures (exercise tolerance, disease impact, dyspnoea) were analyzed. Part of the data have been published or are in press elsewhere.

The inclusion criteria were:

1. Diagnosis of COPD and post-bronchodilator Forced Expiratory Volume at one second (FEV_1)/Forced Vital Capacity (FVC) ratio < 70%.[3]
2. Persistent breathlessness and/or exercise limitation after (within the previous 30 days) an ECOPD needing acute care hospital admission or after (within the previous 4 weeks) an ECOPD managed at the out-patient clinic.
3. Stable conditions as assessed by the absence of acute worsening in symptoms, i.e. no change in dyspnoea, cough, and/or sputum beyond the day-to-day variability, which would have required a change in management, as compared to the conditions reported at home or at discharge from the referring acute care hospital.
4. Availability of data on lung function and pre and post-assessment of outcome measures.

Exclusion criteria were: severe comorbidities: oncological, neurological disorders, heart failure or recent (less than 4 months) acute ischemic cardiovascular diseases with an instability status; inability or lack of willingness to perform or complete at least 12 sessions of the PR program.

Measurements

The following data had been recorded: demographics, anthropometrics (Body-mass index, BMI), history of ECOPD in the previous 12 months,[9] Comorbidity Index of the Cumulative Illness Rating Scale (CIRS),[10] BMI- airflow obstruction-dyspnoea, and exercise capacity (BODE) index,[11] provenience (hospital or home), length of ICS Maugeri hospitals stay (LoS), occurrence of chronic respiratory failure (CRF), distribution in Global Initiative for Obstructive Lung Disease (GOLD) stages, drug therapy.

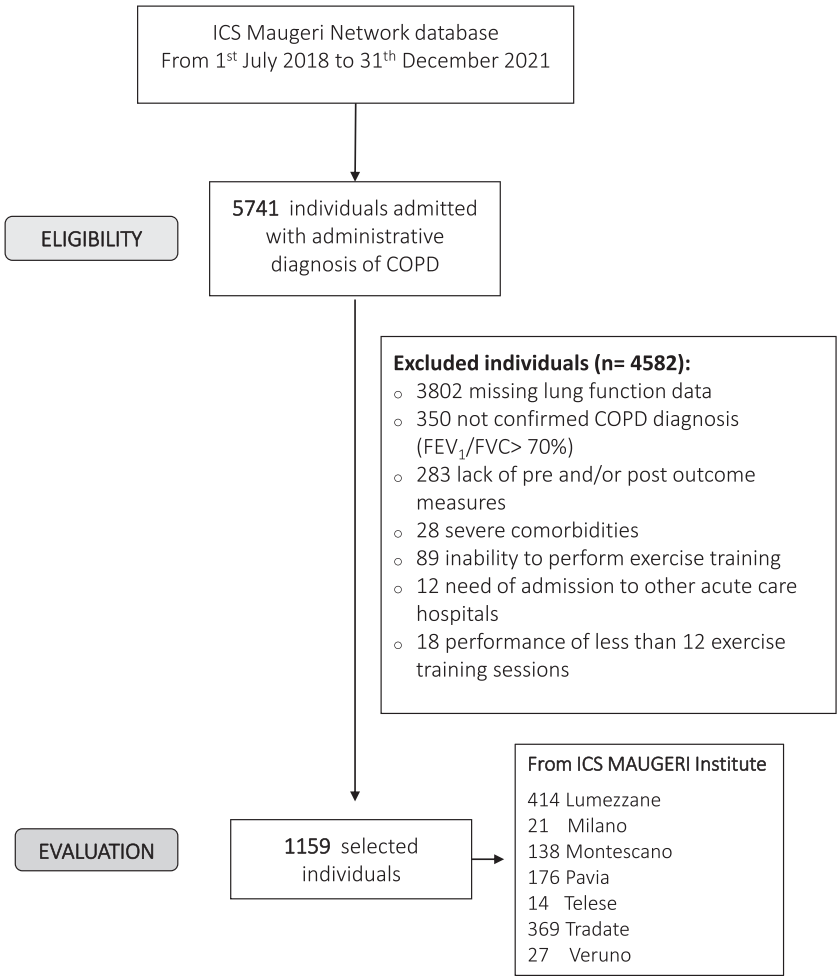

Fig. 1 Flow chart of the study.

Before the PR program the following assessments had been performed:

- Forced expiratory volumes (FEV_1, FVC and FEV_1/FVC, %) according to standards,[12] using the predicted values of Quanjer.[13]
- Dyspnoea by the Italian version of Barthel index Dyspnea (BiD).[14]
- Functional disability by the Barthel index.[15]

Before and after the program, the following outcome measures had been assessed:

- Exercise tolerance by the six-minute walking distance test (6MWT).[16] Data are shown as meters and percent of predicted values.[17] The minimal clinically important difference (MCID) in individuals with COPD has been reported as an improvement in the walked distance by at least 30 meters.[16]
- Dyspnoea by the Medical Research Council (MRC) scale.[18] A one-point reduction in score is considered equivalent to MCID.[19]
- Disease impact by the COPD assessment test (CAT).[20] A two-point reduction in score has been reported as the MCID.[21]

Pulmonary rehabilitation

The ICS Maugeri network hospitals, share a PR program supervised by a multidisciplinary team consisting of chest physicians, nurses, physical therapists, dieticians, and psychologists. The in-hospital multidisciplinary program includes optimization of drug therapy, education, nutritional programs, and psychosocial counseling when appropriate, abdominal, upper, and lower limb muscle activities lifting weights progressively. It includes also supervised cycle exercise training[22] according to Maltais et al[23] until performing 30 min continuous cycling at 50-70% of the maximal load calculated on the basis of the baseline 6MWT according to Luxton et al.[24] Pulse oximetry, arterial blood pressure, and heart rate are monitored during exercise. The total duration of daily activities is 2-3 hours.

During the pandemic period protective measures had been adopted, such as the use of personal protective equipment, increasing distance among individuals (not less than 2 meters during sessions), constant disinfection of tools such as bikes and instruments, frequent air changes, immediate execution of a swab at first harmful signs, and other commonly adopted measures.[25,26]

Statistical analysis

Statistical analyses have been performed by the R statistical software tool version 4.0.5 (www.r-project.org). Post PR changes were dichotomized based on MCID of outcome measures. Numeric variable distribution was described as median (25^{th}, 75^{th} percentiles) since most of them deviated from the normality assumptions based on visual inspection of histograms. Categorical nominal and ordinal variable distributions were described as absolute and relative (%) frequencies. No analysed variable suffered from missing values. The sign test was used to test the null hypothesis of no change (median change = 0) in numeric variable distribution between before and after PR. The Kruskal Wallis test was applied to compare numeric variables distributions among clusters while the Pearson chi-square test with 10,000 simulations was applied to test the null hypothesis of independence between categorical variables and clusters. Multivariate logistic regression was applied to test for association between clusters and the condition of reaching the MCID in all outcome measures including centre as covariate. The significance level was set at α = 0.05, the False Discovery Rate (FDR) correction was applied when appropriate, considering FDR values $<$ 0.10 as statistically significant.

Clustering of patients and machine learning analyses are described in the **Appendix A** section in **Supplementary Methods and Results**.

Results

Fig. 1 shows the flow chart of the study. Data from 1159 individuals were analyzed. The baseline characteristics of participants are shown in Table 1. More than half of the participants were males and included in the most severe GOLD stages.[3]

After the program, all assessed outcome measures improved significantly (Table 2). **Appendix A- Fig. A.1** shows the frequency distribution of outcome measures. The proportion of individuals reaching the MCID was 85.0%, 86.3%, and 65.6% for CAT, MRC, and 6MWT respectively.

The ability of different clustering strategies to identify distinct subpopulations of participants based on baseline characteristics was assessed (**Appendix A- Table A.1** and **Table A.2**). The selected approach allowed to identify three clusters (C) according to the baseline severity: C1-severe (n = 126, 10.9%), C2-intermediate (n = 862, 74.4%), and C3-mild (n = 171, 14.7%).

Table 3 shows the baseline characteristics and outcome measures according to clusters. Individuals in C1-severe were the oldest and the least likely to be treated at home for their ECOPD. These individuals shared also the most severe conditions such as inclusion in GOLD stage D in more than 91% of cases, airway obstruction, high prevalence of CRF, triple inhaler drug use, motor Barthel, BiD, and comorbidities. This subpopulation was characterized also by the worst baseline outcome measures. Individuals in C3-mild showed the least severe conditions, whereas those in C2-intermediate, the most prevalent, may represent an intermediate condition. As also shown in Table 3 among clusters there was a statistically significant difference in the proportion of individuals reaching the MCID of 6MWT ($p < 0.0001$), MRC (p = 0.0002) but not CAT (p = 0.8635).

The proportion of individuals reaching MCID in all three outcome measures was significantly different among clusters ($p < 0.0001$), C3-mild having a lower probability of full success (37.4% of participants) than C2-intermediate (48.3%) and C1-severe (69.0%). Multivariate logistic regression with

Table 1 Characteristics of participants.

Variable	Frequency or Median	Min:Max
Age, years	72 (65, 77)	34:93
Gender		
Females	392 (33.8%)	
Males	767 (66.2%)	
BMI, Kg/m^2	26.2 (22.8, 31)	11.7:64.5
BODE index, score	5 (4, 7)	0:10
LoS,days	25 (21, 32)	10:120
Provenience		
Home	851 (73.4%)	
Hospital	308 (26.6%)	
CRF		
No	770 (66.4%)	
Yes	389 (33.6%)	
Inhaler drugs		
Triple	690 (59.5%)	
No triple	469 (40.5%)	
CIRS, score	4 (2, 5)	0:12
Barthel, score	100 (90, 100)	0:100
BiD, score	25 (14, 39)	0:90
FEV_1, % prd	44 (34, 56)	12:86
FVC, % prd	70 (58, 81)	27:112
FEV_1/FVC, %	46 (42, 56)	21:69
GOLD airflow stages		
1	29 (2.5%)	
2	337 (29.1%)	
3	437 (37.7%)	
4	356 (30.7%)	
GOLD quadrant stages		
A	106 (9.2%)	
B	260 (22.4%)	
C	115 (9.9%)	
D	678 (58.5%)	
CAT, score	18 (12, 24)	0:37
MRC, score	3 (3, 3)	0:4
6MWT, metres	300 (200, 400)	0:635
6MWT % prd	64.1 (43.1, 83)	0:174.3

Legend: Variables distribution is described as absolute and relative frequency (%) or median (25^{th}, 75^{th} percentiles).
Min: max = minimum and maximum values of each numeric variable's distribution. LoS: Length of stay; CRF: Chronic respiratory failure; BMI: Body Mass Index; BiD: Barthel index Dyspnea; CAT: COPD assessment test; MRC: Medical research council; 6MWT: Six-minute walking distance test; FEV_1: Forced expiratory volume at one second; FVC: Forced vital capacity; prd: predicted; GOLD: Global Initiative for Obstructive Lung Disease; BODE: body-mass index, airflow obstruction, dyspnoea, and exercise capacity index; CIRS: Comorbidity Index of Cumulative Illness Rating Scale.

Table 2 Post to Pre-program changes in outcome measures.

Variable	Before	After	Change	p-value	
CAT, score	18 (12, 24)	11 (8, 16)	−5 (−9, −3)	< 0.0001	*
MRC, score	3 (3, 3)	2 (2, 2)	−1 (−2, −1)	< 0.0001	*
6MWT, metres	300 (200, 400)	351 (260, 440)	45 (18, 80)	< 0.0001	*

Legend: Variable = analyzed variable; Data as Median (25^{th}, 75^{th} percentiles).
CAT: COPD assessment test; MRC: Medical research council; 6MWT: Six-minute walking distance test.
* p-value < 0.05.

adjustment by centre showed that participants in C2-intermediate and C1-severe had 1.7- and 4.6-fold increase in the probability to reach the MCID in all three outcomes as compared to those in C3-mild (OR = 1.72, 95% confidence interval [95% CI] = 1.2 − 2.49, p = 0.0035 and OR = 4.57, 95% CI = 2.68 − 7.91, p < 0.0001 respectively).

Multivariate analyses showed that baseline 6MWT, BiD, inhaler drugs, GOLD stage as well as baseline CAT and MRC represented the subset of variables used for clusters definition with a major influence in discriminating among the three subpopulations (**Appendix A - Fig. A.2**).

The distribution of each outcome measure value was significantly different among clusters before, after PR, and in changes (FDR < 0.10) (Fig. 2).

Table 4 shows the distribution of participants and clusters by centres. C2-intermediate was the most prevalent in all centres, whereas almost 75% of C3-mild was observed in a single centre. **Appendix - Table A.3** reports the outcome variables distribution by cluster according to the participating centres.

Additional and preliminary analyses have been performed to identify decisional rules to classify participants into clusters using baseline variables (**Appendix A− Supplementary Methods and Results**). "Conditional inference trees" was selected as the most informative machine learning algorithm among those tested, reaching a mean classification accuracy (CA) from 10-fold cross validation of 82.49% (majority classifier CA = 74.40%) while mean sensitivity in discriminating between clusters ranging 41.5% - 92.37% (**Appendix A − Table A.4, Table A.5**). When learned on the whole dataset, the conditional inference trees model generated decisional rules to provide a rough distinction of participants into clusters (Fig. 3). According to these rules, an individual could be labelled as belonging to C1-severe if baseline 6MWT ≤ 159 meters AND BiD > 28 points; C2-indermediate if baseline 6MWT ≤ 159 m AND BiD ≤ 28 points or if baseline 6MWT > 159 meters AND GOLD quadrant stages = B, C or D; C3-mild if baseline 6MWT > 159 meters AND GOLD quadrant stage = A (Fig. 3 and **Appendix A − Table A.6**).

Discussion

By clustering analysis, our study distinguished different groups of individuals undergoing in-hospital PR after an ECOPD. These individuals could be characterized by three clusters with different prevalence, baseline characteristics, and responses to PR. Cluster C1-severe had the most severe baseline conditions with the largest improvement, C3-mild showed the best baseline conditions but the smallest change size, whereas C2-intermediate showed conditions and effect size intermediate between C1-severe and C3-mild.

While confirming evidence that individuals with a worse baseline status are good responders to PR,[27] our study also suggests a modality to analyze the characteristics of these individuals in order to define priority criteria for admission to PR of these individuals.

Multivariate analyses identified baseline 6MWT, BiD, inhaler drugs, GOLD stage as well as baseline CAT and MRC as the subset of variables used for clusters definition having a major influence in discriminating among the three subpopulations.

As an additional finding, we were also able to roughly assign participants to the corresponding cluster by conditional inference trees algorithm. Future studies will allow tuning and validating decisional rules on independent data, as well as evaluating the feasibility to implement more accurate models (10-fold cross validation: mean classification accuracy reached by Elastic net logistic regression = 94.41% [data not shown] vs. mean classification accuracy reached by conditional inference trees = 82.49%) into an interactive tool to be used in clinical practice for a more accurate classification.

This is a retrospective study investigating individuals with COPD as shown by lung function,[3] therefore, we excluded all cases without any available lung function data, and those with lung function not confirming COPD (e.g. FEV_1/FVC > 70%). We evaluated individuals admitted to in-hospital PR after an ECOPD. Despite a relevant improvement in COPD treatment, the natural course of ECOPD is unchanged highlighting the importance of prevention. It has been shown that early PR after an ECOPD is cost-effective and results in reduced prevalence of new exacerbations and longer survival.[4,5,28]

The outcome measures assessed in this study (dyspnoea, exercise capacity, disease impact) are widely accepted not only for PR, but are also suggested in an outcome set for clinical trials evaluating the management of ECOPD.[1,29] The present study confirms the benefits of PR including the proportion of responders.[1,2,30] Al Chikhanie et al[31] identified four clusters according to the response of 6MWT to PR. The cluster with the largest proportion of non-responders included older, more severe individuals.[31] However, exercise tolerance is only one of the benefits of PR. Also patient-centered outcomes such as symptoms and disease impact matter. Spruit et al[32] proposed a multidimensional response outcome. In our study, the proportion of individuals reaching the MCID in all three assessed outcome measures was significantly different among clusters.

The high proportion (66.2%) of individuals excluded from this retrospective study due to missing lung function data is not surprising. According to guidelines, lung function might have been not considered as an admission criterion to or an

Table 3 Characteristics and outcome measures according to clusters.

Variable	C1-severe (n = 126, 10.9%)	C2-intermediate (n = 862, 74.4%)	C3-mild (n = 171, 14.7%)	p-value	
Age, years #	74 (70, 79)	71 (65, 77)	71 (65, 76)	<0.0001	*
Gender #				0.0075	*
Females	57 (45.2%)	286 (33.2%)	49 (28.7%)		
Males	69 (54.8%)	576 (66.8%)	122 (71.3%)		
BMI, Kg/m^2 #	24.9 (21.5, 28.4)	26 (22.5, 30.7)	29 (25.3, 33.6)	<0.0001	*
Provenience #				<0.0001	*
Home	57 (45.2%)	630 (73.1%)	164 (95.9%)		
Hospital	69 (54.8%)	232 (26.9%)	7 (4.1%)		
CRF #				<0.0001	*
No	33 (26.2%)	567 (65.8%)	170 (99.4%)		
Yes	93 (73.8%)	295 (34.2%)	1 (0.6%)		
Inhaler drugs #				<0.0001	*
Triple	108 (85.7%)	572 (66.4%)	10 (5.8%)		
No triple	18 (14.3%)	290 (33.6%)	161 (94.2%)		
CIRS, score #	5 (5, 6)	4 (2, 5)	3 (2, 3)	<0.0001	*
Barthel, score #	80 (55, 94)	100 (90, 100)	100 (90, 100)	<0.0001	*
BiD, score #	45 (38, 61)	25 (17, 38)	11 (7, 16)	<0.0001	*
FEV_1/FVC, % #	45 (40, 48)	46 (40, 56)	55 (48, 60)	<0.0001	*
SpO_2, % #	95 (93, 96)	94 (92, 96)	95 (94, 96)	<0.0001	*
GOLD stages #				<0.0001	*
A	0 (0%)	34 (4%)	72 (42.1%)		
B	6 (4.7%)	189 (21.9%)	65 (38 %)		
C	5 (4%)	89 (10.3%)	21 (12.3%)		
D	115 (91.3%)	550 (63.8%)	13 (7.6%)		
CAT, score					
Before #	25 (23, 28)	18 (12, 23)	11 (8, 15)	<0.0001	*
After	16 (12, 23)	11 (8, 16)	6 (3, 9)	<0.0001	*
Change	−8 (−11, −4)	−5 (−10, −3)	−5 (−8, −2)	0.0002	*
Freq. Reach. MCID	109 (86.5%)	730 (84.7%)	146 (85.4%)	0.8635	
MRC, score					
Before #	4 (4, 4)	3 (3, 3)	3 (2, 3)	<0.0001	*
After	2 (2, 3)	2 (2, 2)	2 (1, 2)	<0.0001	*
Change	−2 (−2, −1)	−1 (−1, −1)	−1 (−1, −1)	<0.0001	*
Freq. Reach. MCID	118 (93.6%)	750 (87.0%)	132 (77.2%)	0.0002	*
6MWT, metres					
Before #	100 (45, 144)	299.5 (215.25, 380)	440 (389, 486.5)	<0.0001	*
After	180 (135, 234)	348 (270, 423)	476 (420, 525)	<0.0001	*
Change	87 (42, 141)	45 (16, 79)	30 (7, 60)	<0.0001	*
Freq. Reach. MCID	106 (84.1%)	563 (65.3%)	91 (53.2%)	<0.0001	*
6MWT% prd					
Before	20.8 (9.8, 30.2)	63.2 (47.0, 78.3)	94.5 (82.3, 102.8)	<0.0001	*
After	42.3 (30.3, 50.8)	74.2 (58.8, 86.9)	100.1 (90.3, 111.5)	<0.0001	*
Change	18.5 (10.2, 30.3)	9.3 (3.4, 16.7)	6.7 (1.3, 13.6)	<0.0001	*

Legend: Variables' distribution by clusters are described as absolute frequency (relative frequency, %) or median (25th, 75th percentiles).
* p-value < 0.05.
# Variable used for clustering.
C. Cluster; CRF: Chronic respiratory failure; SpO_2: pulsed oxygen saturation; BMI: Body Mass Index; BiD: Barthel index Dyspnea; CAT: COPD assessment test; MRC: Medical research council; 6MWT: Six-minute walking distance test; FEV_1: Forced expiratory volume at one second; FVC: Forced vital capacity; prd: predicted; GOLD: Global Initiative for Obstructive Lung Disease; Comorbidity Index of CIRS: Cumulative Illness Rating Scale; Freq. Reach. MCID: Frequency of patients reaching the Minimal Clinically Important Difference.

outcome measure for PR.[1] Of course a possible lack of inclusion in the database of results of performed lung function cannot be excluded. However, our study shows that the level of airway obstruction (**Appendix - Fig. A.2**) had a major influence in discriminating the clusters. Therefore, our study indicates that lung function should be incorporated into the core set of evaluations for admission to PR.

An original and not negligible result of our study is also that BiD[14] can be a reliable outcome measure of PR. Indeed, our study shows that the baseline level of dyspnoea as

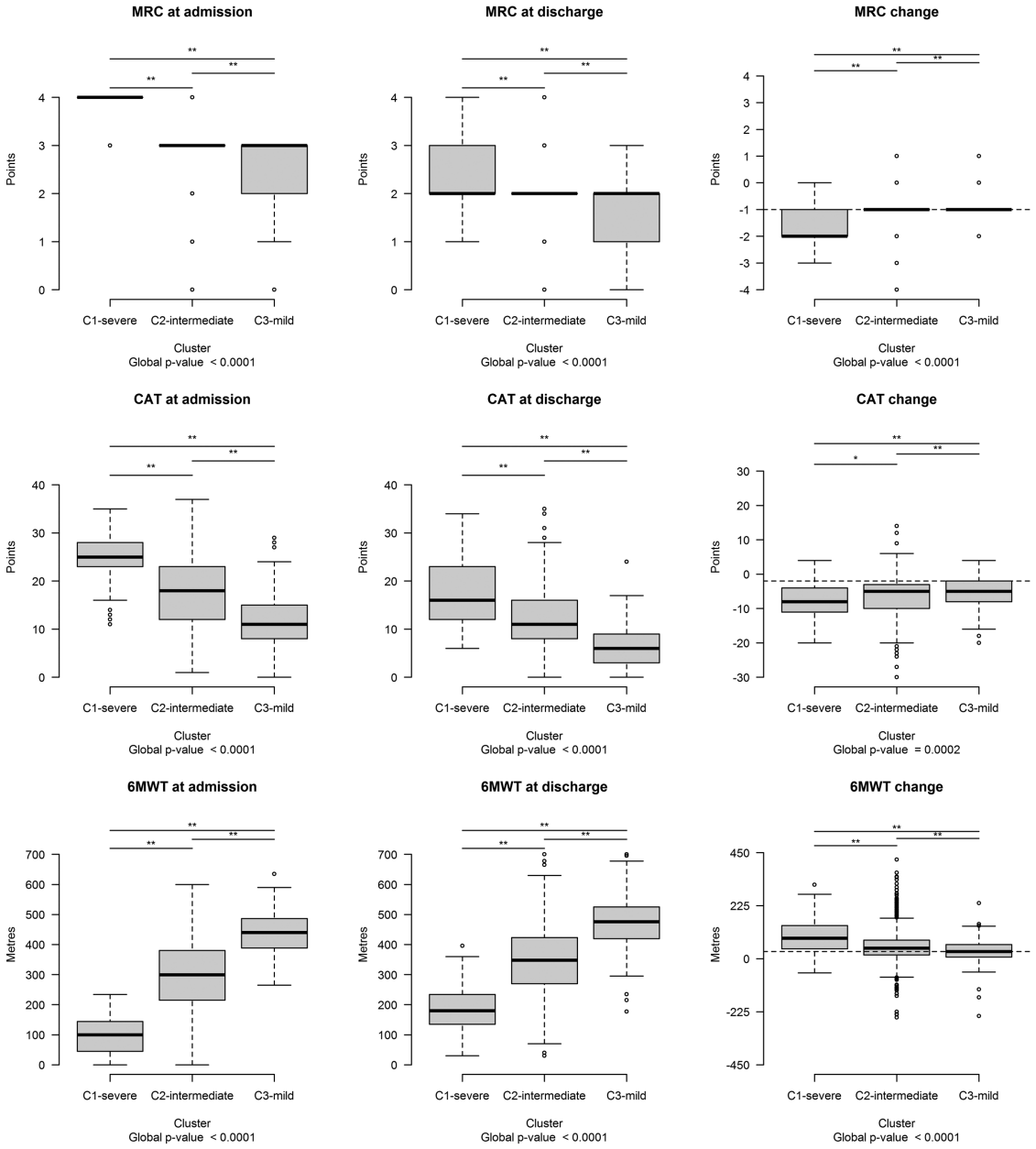

Fig. 2 Outcome measure distribution at admission, discharge, and post program changes. Each boxplot represents (from bottom to top): lowest non-outlier value, 25th, 50th (median value), 75th percentile and highest non-outlier value. Outliers with respect to each variable's distribution are reported as circles. The horizontal bar at the top of each plot indicates that the distribution differs significantly among clusters (** FDR $<$ 0.05; * 0.05 $\leq$ FDR $<$ 0.10). The horizontal dashed lines in black indicate the Minimal Clinically Important Difference of each outcome change. **Abbreviations** – CAT: COPD Assessment test; MRC: Medical Research Council; 6MWT: Six-minute walking distance test.

assessed by BiD was among the variables used for cluster definition with a major influence in discriminating the three subpopulations (Appendix - Fig. A.2) It has been shown that in-hospital PR results in clinically meaningful improvement in individuals recovering from ECOPD, independent of the severity of dyspnoea as assessed by BID. However, the levels of dyspnoea severity influenced the effect size.[27]

Limitations

This is a retrospective study, with the limitations of such type of studies. However, it represents a real-life condition and its results are supported by the large sample size in a time when also randomised controlled trials are questioned.[33]

Cluster analysis only applies to the cohort studied and replication is essential in a totally different environment or subsequent cohort.

There were differences in the prevalence of clusters among participating ICS Maugeri centres due to organizational and logistic conditions (**Appendix A - Table A.3**). Participants in C3-mild (about 14% of participants, mainly distributed in a single center- 34.7%) (Table 4) came from their home, were not prescribed inhaler triple therapy, showed better CAT, were included in GOLD A stage, and had a better lung function. The

Table 4 Clusters distribution in the whole sample and by centre.

Cluster	Whole sample (n = 1159, 100%)	Lumezzane (n = 414, 35.7%)	Tradate (n = 369, 31.8%)	Pavia (n = 176, 15.2%)	Montescano (n = 138, 11.9%)	Others (n = 62, 5.4%)
C1-severe	126 (10.9%)	48 (11.6%)	2 (0.5%)	48 (27.3%)	22 (15.9%)	6 (9.7%)
C2-intermediate	862 (74.4%)	325 (78.5%)	239 (64.8%)	128 (72.7%)	116 (84.1%)	54 (87.1%)
C3-mild	171 (14.7%)	41 (9.9%)	128 (34.7%)	0 (0%)	0 (0%)	2 (3.2%)

Legend: variables distribution is described as absolute and relative frequency (%) of patients belonging to the three clusters in the whole sample and by centre.

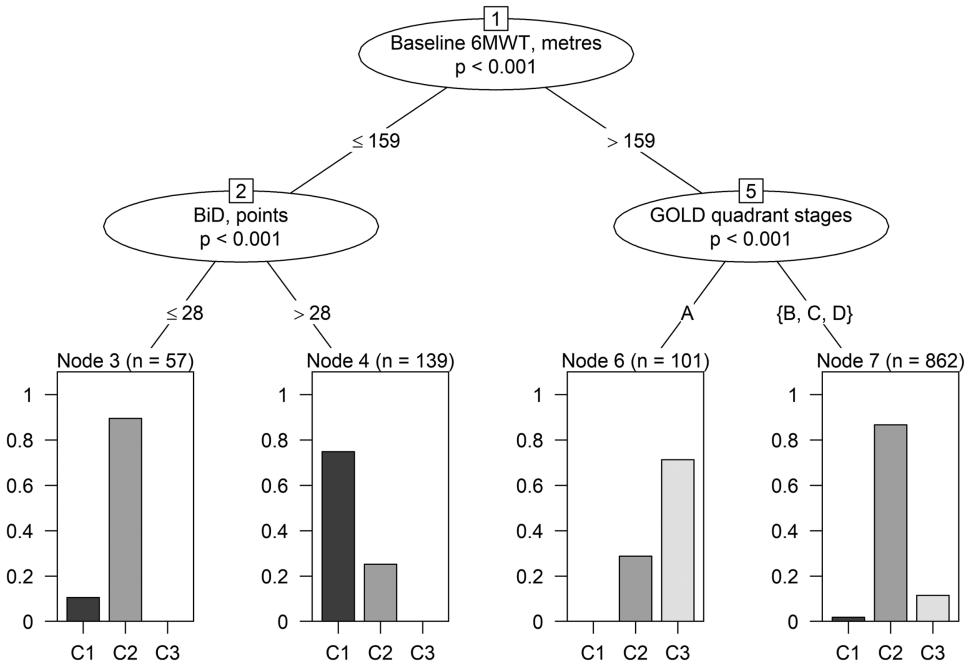

Fig. 3 Conditional inference tree structure. Branches correspond to informative splits in the data leading to the terminal node (leaves). Nodes describe the variable used to split data, branches indicate the splitting values; bar plots represent graphically the relative frequency of patients belonging to the three clusters by terminal node. As an example, approximately 90% of patients with baseline 6MWT values $\leq$ 159 meters and BiD $\leq$ 28 points belong to C2-intermediate cluster while about 10% to C1-severe and 0% to C3-mild. Patients within this terminal node are classified as belonging to C2-intermediate (the most frequent cluster within the terminal node). **Abbreviations** —6MWT: Six-minute walking distance test; BiD: Barthel index Dyspnea; GOLD: Global Initiative for Obstructive Lung Disease.

prescription of PR for these mild individuals might be questioned. However, participants were sent by other hospitals or by their GP and, given the retrospective design, we cannot exclude individual decisions by the accepting physicians according to criteria we cannot assess. Actually, all ICS Maugeri hospitals share the same admission criteria, evaluation, and rehabilitation protocols. Therefore, we are confident that these differences have not biased results.

Given the post-acute condition of participants, a control population not performing the program would have clarified whether any improvement in outcome would have been (also) time-dependent. However, given the recognized benefits of PR and the mission of our hospitals, not performing any program would have been unethical.

Conclusions

Our clustering analysis identified subpopulations of individuals recovering from ECOPD characterized by different PR success rates. These results may help in defining priority criteria based on the probability of success. Our results reflect the specific population of individuals with indications of PR, not comparable and extensible to other populations of individuals with COPD, and should be confirmed by prospective studies.

Authorship contributions

MV and NA conceived and designed the study. MV, AM, and NA contributed to the writing of the manuscript. AM and RB performed formal analysis and visualization. MV, AS, PC, MM, BB, LR, and RM were responsible for investigations. MV, AM, MP, and NA participated in the analysis and discussion of the data, All the authors revised the article critically and approved the final version.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

This work was supported by the "Ricerca Corrente" Funding scheme of the Ministry of Health, Italy.

Data availability statement

Data are available from the corresponding author upon reasonable request.

Conflicts of interest

Nicolino Ambrosino is the Chief Editor of Pulmonology. The authors declare they have no conflict of interest.

Acknowledgments

The authors thank the Maugeri Respiratory Network for data collection/evaluation and Adriana Olivares and Laura Comini for their technical assistance and editing.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2023.01.002.

References

1. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188:e13–64. https://doi.org/10.1164/rccm.201309-1634ST.
2. Paneroni M, Vitacca M, Venturelli M, et al. The impact of exercise training on fatigue in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Pulmonology. 2020;26:304–13. https://doi.org/10.1016/j.pulmoe.2020.02.004.
3. 2022 Global strategy for prevention, diagnosis and management of COPD. http://goldcopd.org/gold-reports/ Accessed September, 28th.
4. Lindenauer PK, Stefan MS, Pekow PS, et al. Association between initiation of pulmonary rehabilitation after hospitalization for COPD and 1-year survival among Medicare beneficiaries. JAMA. 2020;323:1813–23. https://doi.org/10.1001/jama.2020.4437.
5. Mosher CL, Nanna MG, Jawitz OK, et al. Cost-effectiveness of pulmonary rehabilitation among US adults with chronic obstructive pulmonary disease. JAMA Netw Open. 2022;5:e2218189. https://doi.org/10.1001/jamanetworkopen.2022.18189.
6. Vogiatzis I, Rochester CL, Spruit MA, et al. Increasing implementation and delivery of pulmonary rehabilitation: keymessages from the new ATS/ERS policy statement. Eur Respir J. 2016;47:1336–41. https://doi.org/10.1183/13993003.02151-2015.
7. Paneroni M, Vitacca M, Bernocchi P, Bertacchini L, Scalvini S. Feasibility of tele-rehabilitation in survivors of COVID-19 pneumonia. Pulmonology. 2022;28:152–4. https://doi.org/10.1016/j.pulmoe.2021.03.009.
8. Everitt BS, Landau S, Leese M, et al. Cluster analysis. 5th ed. 352. ISBN: 978-470-3Wiley Series in Probability and Statistics.
9. Kim V, Aaron SD. What is a COPD exacerbation? Current definitions, pitfalls, 8 challenges and opportunities for improvement. Eur Respir J. 2018;52:1801261. https://doi.org/10.1183/13993003.01261-2018.
10. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968;16:622–6.
11. Celli BR, Cote CG, Marin JM, Casanova C, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005–12. https://doi.org/10.1056/NEJMoa021322.
12. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319–38. https://doi.org/10.1183/09031936.05.00034805.
13. Quanjer PH, Stanojevic S, Cole TJ, et al. ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40:1324–43. https://doi.org/10.1183/09031936.00080312.
14. Vitacca M, Paneroni M, Baiardi P, et al. Development of a Barthel Index based on dyspnea for patients with respiratory diseases. Int J Chron Obstruct Pulmon Dis. 2016;11:1199–206. https://doi.org/10.2147/COPD.S104376.
15. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol. 1989;42:703–9. https://doi.org/10.1016/0895-4356(89)90065-6.
16. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44:1428–46. https://doi.org/10.1183/09031936.00150314.
17. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med. 1998;158:1384–7. https://doi.org/10.1164/ajrccm.158.5.9710086.
18. Fletcher CM. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the aetiology of chronic bronchitis (MRC breathlessness score). Br Med J. 1960;2:1665.
19. de Torres JP, Pinto-Plata V, Ingenito E, et al. Power of outcome measurements to detect clinically significant changes in pulmonary rehabilitation of patients with COPD. Chest. 2002;121:1092–8. https://doi.org/10.1378/chest.121.4.1092.
20. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34:648–54. https://doi.org/10.1183/09031936.00102509.
21. Kon SS, Canavan JL, Jones SE, et al. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. Lancet Respir Med. 2014;2:195–203. https://doi.org/10.1016/S2213-2600(14)70001-3.
22. Paneroni M, Simonelli C, Vitacca M, Ambrosino N. Aerobic exercise training in very severe chronic obstructive pulmonary disease: a systematic review and meta-analysis. Am J Phys Med Rehabil. 2017;96:541–8. https://doi.org/10.1097/PHM.0000000000000667.
23. Maltais F, LeBlanc P, Jobin J, et al. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;155:555–61. https://doi.org/10.1164/ajrccm.155.2.9032194.
24. Luxton N, Alison JA, Wu J, et al. Relationship between field walking tests and incremental cycle ergometry in COPD. Respirology. 2008;13:856–62. https://doi.org/10.1111/j.1440-1843.2008.01355.x.
25. Ippolito M, Vitale F, Accurso G, Iozzo P, Gregoretti C, Giarratano A, Cortegiani A. Medical masks and Respirators for the Protection of Healthcare Workers from SARS-CoV-2 and other viruses. Pulmonology. 2020;26:204–12. https://doi.org/10.1016/j.pulmoe.2020.04.009.
26. Vitacca M, Carone M, Clini EM, et al. Joint statement on the role of respiratory rehabilitation in the COVID-19 crisis: the Italian

position paper. Respiration. 2020;99:493—9. https://doi.org/10.1159/000508399.
27. Vitacca M, Ambrosino N, Belli S, et al. The severity of acute exacerbations of COPD and the effectiveness of pulmonary rehabilitation. Respir Med. 2021;184:106465. https://doi.org/10.1016/j.rmed.2021.106465.
28. Sánta B, Tomisa G, Horváth A, Balázs T, Németh L, Gálffy G. Severe exacerbations and mortality in COPD patients: a retrospective analysis of the database of the Hungarian National Health Insurance Fund. Pulmonology. 2022. https://doi.org/10.1016/j.pulmoe.2022.11.001. S2531-0437(22)00259-8Epub ahead of print.
29. Mathioudakis AG, Abroug F, Agusti A, et al. ERS statement: a core outcome set for clinical trials evaluating the management of COPD exacerbations. Eur Respir J. 2022;59:2102006. https://doi.org/10.1183/13993003.02006-2021.
30. Garrod R, Malerba M, Crisafulli E. Determinants of success. Eur Respir J. 2011;38:1215—8. https://doi.org/10.1183/09031936.00088611.
31. Al Chikhanie Y, Bailly S, Amroussa I, et al. Clustering of COPD patients and their response to pulmonary rehabilitation. Respir Med. 2022;198:106861. https://doi.org/10.1016/j.rmed.2022.106861.
32. Spruit MA, Augustin IM, Vanfleteren LE, et al. Differential response to pulmonary rehabilitation in COPD: multidimensional profiling. Eur Respir J. 2015;46:1625—35. https://doi.org/10.1183/13993003.00350-2015.
33. Duarte-de-Ara Jo AN, Teixeira P, Hespanhol V, Correia-de-Sousa J. COPD: how can evidence from randomised controlled trials apply to patients treated in everyday clinical practice? Pulmonology. 2022;28:431—9. https://doi.org/10.1016/j.pulmoe.2020.02.003.

Pulmonology 29 (2023) 240—243

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Outcome of patients receiving V-V ECMO for SARS-CoV-2 severe acute respiratory failure

Despite offering a potentially lifesaving intervention for severe acute respiratory failure (SARF), venovenous (V-V) ECMO is a highly invasive and costly resource that is itself associated with significant morbidity and mortality. Scoring systems such as the Murray[1] and RESP score[2] have been used to aid patient selection and prognostication during the COVID-19 pandemic.[3] However, these scoring systems may not accurately assess the multisystem nature of COVID-19. Thus, we set out to analyze the utility of these scores alongside other demographic, clinical, ventilatory and laboratory variables of potential prognostic importance, in a cohort of COVID-19 cases with SARF.

Prospectively collected data was retrospectively analyzed for all patients admitted to the Glenfield Adult Intensive Care Unit (GAICU; a large SARF and ECMO referral center in the UK) between October 2020 and March 2021 (inclusive) receiving V-V ECMO for a primary diagnosis of COVID-19 pneumonia. Demographic data alongside information provided at the time of referral in relation to ventilatory parameters and gas exchange were recorded (Table 1), and statistically compared between those who died and those who survived to ECMO decannulation and GAICU discharge (Table 2).

A total of 48 patients received V-V ECMO for COVID-19 pneumonia over the 6 months of the second UK wave, and 25 (52%) of them died. Patients had a median age of 42 years, body mass index (BMI) 34.0 and were more likely to be male (71%) than female. No significant differences in baseline demographics existed (Table 1) and similarly there was no difference in APACHE2 score at the time of GAICU admission, nor in Murray score or RESP score at time of referral.

Ventilation parameters were associated with prognostic outcome, with a higher positive end expiratory pressure (PEEP), peak and plateau pressure, usually reflecting more severe lung disease, paradoxically showing increased likelihood of survival. This did not correspond to a significant difference in static (plateau pressure − PEEP) or dynamic (peak pressure − PEEP) driving pressure. Biochemically a higher creatinine (lower eGFR) and urea, a relative metabolic acidosis (failure to compensate for respiratory acidosis) at time of referral, alongside a requirement for renal replacement therapy (RRT) during the ECMO run were significantly associated with mortality. Multivariable logistic regression showed that peri-cannulated bicarbonate (odds ratio per unit increase (OR) =0.80, p=0.003) and peak pressure (OR=0.75, p=0.004) remained significantly associated with mortality. There were no significant differences in the rates of co-infection or other complications between groups (Table 2).

From a treatment perspective, all patients received RECOVERY dexamethasone,[4] with no significant difference in timing of initiation relative to commencement of ECMO run, nor did there exist any differences in receipt of other COVID-19 specific therapies (tociluzimab, remdesivir etc). There was a trend towards increased survival in those receiving additional higher dose dexamethasone for treatment of ARDS, however this association may not be causally linked but rather reflect clinical opportunity, similar to that of the finding of increasing tracheostomy and spontaneous ventilation rates in the survivors.

Compared to the Murray (area under ROC curve (AUC) =0.58) and the RESP score (AUC=0.51), APACHE2 (AUC=0.65) was better able to discriminate survival from non-survival in patients undergoing V-V ECMO for COVID-19 SARF, though none of the scoring tools reached statistical significance (p value 0.577, 0.964 and 0.073 respectively).

From these data, acidemia pericannulation was associated with a poor prognosis. This failure to metabolically compensate for a respiratory acidosis (the degree of which was similar between groups) is predominantly attributable to renal failure with a small contribution from lactatemia. A requirement for RRT is well known to be associated with an increase in mortality in ICU[5] however in the SARF group further consideration is needed. Firstly timing of initiation of RRT and/or ECMO referral may be earlier (significant acidemia occurs sooner with concomitant respiratory-metabolic acidosis) and secondly institutional RRT practices may not facilitate adequate generation of physiological levels of bicarbonate that are frequently taken advantage of to facilitate a lung protective ventilator (LPV) strategy.

From a ventilation perspective however, there was no significant difference in severity of hypoxaemia (as assessed by PaO_2/FiO_2 ratio) at time of referral, and we can infer no significant difference in dead space ventilation ($PaCO_2$, adjusted tidal volume, respiratory rate, BMI and pulmonary embolism rates similar across groups). While both cohorts at referral generally had tidal volumes <8ml/kg/predicted

https://doi.org/10.1016/j.pulmoe.2023.01.001

Table 1 Baseline demographics, medical histories, baseline laboratory markers and COVID-19 treatment histories at referral and cannulation compared for survivors (n=23) and non-survivors (n=25). The differing n values reflect missing data points for these parameters. Normally-distributed data was expressed as a mean and standard deviation, whilst non-normally distributed data as a median and interquartile range. Continuous variables were compared using the Student t-test or Mann-Whitney test as appropriate, and categorical variables were compared using the Chi-squared test. Statistical analysis was performed in SAS 9.4 (SAS Institute Inc., Bucks., UK: https://www.sas.com/en_gb/contact.html).

	N	Survivor	N	Non-survivor	p-value
Demographics					
APACHE2: median (IQR)	23	13 (8—16)	25	14 (12—18)	0.073
Age: mean (SD)	23	40.9 (6.3)	25	42.5 (10.5)	0.518
BMI	23	33.5 (6.7)	25	34.5 (6.5)	0.591
Gender - male: n (%)	23	14 (61%)	25	20 (80%)	0.145
Ethnicity	23		25		0.472
White		4 (17%)		6 (24%)	
Asian		9 (39%)		9 (36%)	
Black		4 (17%)		1 (4%)	
mixed		6 (26%)		9 (36%)	
Medical history					
Comorbidities ≥1: n (%)	23	19 (83%)	25	23 (92%)	0.407
Diabetes	23	5 (22%)	25	7 (28%)	0.617
Hypertension	23	3 (13%)	25	9 (36%)	0.067
Lung disease	23	6 (26%)	25	3 (12%)	0.279
Other disease	23	1 (4%)	25	2 (8%)	0.999
Obesity	23	17 (74%)	25	21 (84%)	0.487
Status at referral					
P/F ratio: mean (SD)	18	9.3 (2.4)	15	9.3 (3.1)	0.999
$PaCO_2$ kPa	23	7.9 (1.8)	24	8.0 (2.6)	0.884
PEEP, cmH_2O	23	14.1 (6.5)	24	10.9 (3.6)	0.047
Tidal volume ml/kg PBW	23	6.6 (1.4)	24	7.3 (2.3)	0.207
Respiratory rate, min^{-1}	23	20.1 (5.6)	23	19.7 (6.0)	0.807
Peak pressure, cmH_2O	22	33.8 (4.5)	23	29.9 (5.0)	0.008
Plateau pressure, cmH_2O	23	30.1 (5.1)	21	26.2 (5.9)	0.023
Static driving pressure, cmH_2O	22	16.8 (5.8)	21	15.4 (4.9)	0.416
Dynamic driving pressure, cmH_2O	21	20.5 (5.7)	23	18.9 (4.8)	0.328
pH	23	7.3 (0.1)	24	7.3 (0.2)	0.416
Bicarbonate, mmol/L	22	26.6 (5.9)	23	24.2 (5.2)	0.148
Lactate, mmol/L: median (IQR)	20	1.7 (1.4—2.6)	24	1.4 (1.1—1.7)	0.059
Murray Score	21	3.5 (3.25—3.5)	17	3.25 (3—3.5)	0.577
RESP Score	18	5 (4—7)	20	5 (4—5.5)	0.964
Days ventilated pre ECMO	23	2 (0—5)	25	2 (1 — 3)	0.933
Peri-cannulation laboratory data					
PaO_2 kPa	23	13.8 (9.9)	25	10.9 (5.2)	0.221
pH	23	7.35 (0.12)	25	7.25 (0.15)	0.023
$PaCO_2$ kPa	23	7.3 (2.2)	25	7.6 (2.4)	0.725
Bicarbonate, mmol/L	23	27.7 (4.9)	25	22.8 (6.7)	0.006
Base Excess, mmol/L	22	3.0 (5.9)	25	−2.3 (8.2)	0.015
Lactate, mmol/L: median (IQR)	23	1.6 (1.3—2.1)	25	2.4 (1.7—5.7)	0.027
Haemoglobin, g/L: mean (SD)	23	113.6 (14.9)	25	109.5 (14.4)	0.344
Platelet count, $x10^9$/L	23	256.9 (103.5)	25	216.4 (125.9)	0.232
White cell count, $x10^9$/L	23	18.1 (10.3)	25	17.2 (10.7)	0.775
Neutrophil count, $x10^9$/L	23	16.4 (9.9)	25	15.0 (9.5)	0.619
Lymphocyte count, $x10^9$/L	23	0.9 (0.5)	25	1.0 (0.8)	0.621
Bilirubin, μmol/L	23	12.3 (7.8)	25	15.4 (10.0)	0.248
INR: median (IQR)	23	1.2 (1.1—1.2)	25	1.2 (1.1—1.4)	0.1
Fibrinogen, g/L	23	5.8 (3.6—6.8)	25	4.8 (2.9—7.1)	0.885
Urea, mmol/L: mean (SD)	23	9.7 (4.8)	25	14.8 (7.2)	0.007
Creatinine, μmol/L	23	91.3 (68.3)	25	150.2 (110.6)	0.031
eGFR, mL/min/1.73m^2: median (IQR)	23	101.8 (57.6—156.5)	25	50.7 (32.8—133.3)	0.027
CRP, mg/L	23	111 (54—176)	25	81 (53—201)	0.687
Troponin, ng/L	23	27 (6.8—60.7)	24	27 (8.9—153)	0.437
BNP, pg/mL	22	568 (198—746)	23	1069 (273—3819)	0.044
D-dimer, μg/mL	23	4.5 (2.0—14.4)	25	2.9 (1.8—8.6)	0.408
COVID therapies					
Recovery dexamethasone: n (%)	23	23 (100%)	25	25 (100%)	–
Started before ICU admission		3 (13%)		3 (12%)	0.999
Started after ICU admission		20 (87%)		22 (88%)	
Day relative to ECMO: mean (SD)	20	−4.5 (3.2)	22	−5.8 (4.3)	0.268
High dose dexamethasone: n (%)	23	15 (65%)	24	10 (42%)	0.106
Tociluzimab	23	13 (57%)	25	9 (36%)	0.154
Remdesivir	23	5 (22%)	25	9 (36%)	0.278
Convalescent plasma	23	1 (4%)	25	4 (16%)	0.35
Baricitinib	23	2 (9%)	25	1 (4%)	0.601

APACHE2=acute physiologic assessment and chronic health evaluation 2 score, N=number, SD=standard deviation, IQR=interquartile range, BMI=body mass index, P/F ratio=ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, pH=power of hydrogen, $PaCO_2$=arterial partial pressure of carbon dioxide, PaO_2=arterial partial pressure of oxygen, PEEP=positive end expiratory pressure, PBW=predicted body weight, INR=international normalized ratio, eGFR=estimated glomerular filtration rate, CRP=C-reactive protein, BNP=brain natriuretic peptide, ICU=intensive care unit.

Table 2 Differences in organ support, complications and outcomes between survivors (n=23) and non-survivors (n=25). Normally-distributed data was expressed as a mean and standard deviation, whilst non-normally distributed data as a median and interquartile range. Continuous variables were compared using the Student t-test or Mann-Whitney test as appropriate, and categorical variables were compared using the Chi-squared test. Statistical analysis was performed in SAS 9.4 (SAS Institute Inc., Bucks., UK: https://www.sas.com/en_gb/contact.html).

	N	Survivor	N	Non-survivor	p-value
Organ support during ECMO run					
Vasopressor and/or Inotropes: n (%)	23	7 (30%)	22	12 (55%)	0.102
Vasopressors	23	18 (78%)	25	22 (88%)	0.454
Left ventricular support	23	1 (4%)	25	1 (4%)	0.999
Right ventricular support	23	6 (26%)	25	10 (40%)	0.307
Liver support	23	0 (0%)	25	3 (12%)	0.235
Renal replacement therapy	23	2 (9%)	25	14 (56%)	0.001
Spontaneous ventilatory mode on ECMO:	23		24		0.008
<50% of the time		3 (13%)		10 (42%)	
50% of the time		0 (0%)		3 (13%)	
>50% of the time		20 (87%)		11 (46%)	
Tracheostomy status:	23		25		0.007
none		5 (22%)		16 (64%)	
peri ECMO		16 (70%)		8 (32%)	
post ECMO		2 (9%)		1 (4%)	
Disease and ECMO related complications					
Air Leak Syndrome: n (%)	23	4 (17%)	25	6 (24%)	0.727
Pneumothorax requiring drainage	23	2 (9%)	25	7 (28%)	0.14
Haemothorax/empyema requiring drainage	23	1 (4%)	25	4 (16%)	0.35
Significant pulmonary haemorrhage*	23	2 (9%)	25	5 (20%)	0.419
HITT	16	2 (13%)	11	3 (27%)	0.37
Pulmonary embolism	23	5 (22%)	24	8 (33%)	0.374
Respiratory bacterial coinfection	23	16 (70%)	24	14 (58%)	0.423
Invasive aspergillus coinfection	23	5 (22%)	24	6 (25%)	0.792
Other viral coinfection	23	2 (9%)	24	2 (8%)	0.999
Outcome					
Total days on ECMO: median (IQR)	23	15 (7—35)	25	19 (8—22)	0.679
GAICU length of stay	23	24 (14—58)	25	19 (12—26)	0.099

N=number, HITT=heparin induced thrombotic thrombocytopenia, ECMO=extracorporeal membrane oxygenation, GAICU=Glenfield adult intensive care unit, IQR=interquartile range.

* Significant pulmonary hemorrhage was defined as that requiring blood transfusion.

body weight in keeping with a LPV strategy, the survivors had a significantly higher PEEP, plateau and peak pressures compared to non-survivors.

One possible explanation for these seemingly disparate findings is that patients being subjected to more injurious ventilation (whether or not that represents a cohort with more severe respiratory disease) have more to gain from the lung rest facilitated by V-V ECMO. Another possible explanation is that as lung injury reversibility forms a key part of eligibility criteria at the time of assessment of candidacy for V-V ECMO, SARF severity per se may no longer then be significantly discriminatory and systemic sequelae of disease and ECMO-related complications play a greater role in determining outcome.

A recent systematic review and meta-analysis of ECMO for COVID-19 found that, mortality has increased as the pandemic progressed, a finding that has been echoed in our experience also.[6,7] This has been postulated to be due to multiple factors to include evolution in both the disease (increased virulence) and its therapeutic strategies (selecting out those with treatment failure), changes to patient selection more generally and resource availability. Recently Urner et al. used multinational data and statistical modelling to emulate a pragmatic randomized controlled trial, designed to estimate the effect of ECMO in severe respiratory failure from COVID-19. They found that ECMO was most effective in patients <65 years old, with $PaO_2/FiO_2 < 10.7$ kPa, driving pressures >15 cm.H_2O within the first 10 days of mechanical ventilation[8] — a cohort well represented in this study. Whilst mortality with ECMO in COVID-19 is high, a recent UK matched cohort study supports a survival benefit with ECMO in this population.[9] Outcomes from ECMO in COVID-19 patients are particularly sensitive to individual patient parameters at the time of presentation. As both disease and treatments evolve, broad comparisons of clinical outcomes may be less relevant to the decision to admit a COVID-19 for ECMO therapy than the pattern of illness they have at that time.

Conflicts of interest

None.

Acknowledgements

None.

References

1. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis. 1988;138(3):720—3. https://doi.org/10.1164/ajrccm/138.3.720.
2. Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure: the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Resp Crit Care. 2014;189(11):1374—82. https://doi.org/10.1164/rccm.201311-2023oc.
3. Camporota L, Meadows C, Ledot S, et al. Consensus on the referral and admission of patients with severe respiratory failure to the NHS ECMO service. Ann Thorac Surg. 2021;9:e16—7. https://doi.org/10.1016/j.athoracsur.2020.04.003. Correspondence.
4. Group TRC. Dexamethasone in hospitalized patients with Covid-19. New Engl J Med. 2021;384(8):693—704. https://doi.org/10.1056/nejmoa2021436.
5. Hoste EAJ, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intens Care Med. 2015;41(8):1411—23. https://doi.org/10.1007/s00134-015-3934-7.
6. Ling RR, Ramanathan K, Sim JJL, et al. Evolving outcomes of extracorporeal membrane oxygenation during the first 2 years of the COVID-19 pandemic: a systematic review and meta-analysis. Crit Care. 2022;26(1):147. https://doi.org/10.1186/s13054-022-04011-2.
7. Charlton M, Dashey S, Stubbs A, et al. Comparing SARS-CoV-2 and influenza A(H1N1)pdm09-infected patients requiring ECMO - a single-centre retrospective observational cohort experience. J Infect. 2021;82:107—9. Letter to the editor.
8. Urner M, Barnett AG, Bassi GL, et al. Venovenous extracorporeal membrane oxygenation in patients with acute covid-19 associated respiratory failure: comparative effectiveness study. BMJ. 2022;377:e068723. https://doi.org/10.1136/bmj-2021-068723.
9. Whebell S, Zhang J, Lewis R, et al. Survival benefit of extracorporeal membrane oxygenation in severe COVID-19: a multi-centre-matched cohort study. Intens Care Med. 2022;48(4):467—78. https://doi.org/10.1007/s00134-022-06645-w.

I.S. Morris[a,b,c], H. Taylor[d], D. Fleet[a,e], F. Y Lai[f], M. Charlton[a], J.W. Tang[g,h,*]

[a] *Glenfield Adult Intensive Care Unit, University Hospitals of Leicester NHS trust, UK*
[b] *Interdepartmental Division of Critical Care Medicine, University of Toronto. Toronto, Canada*
[c] *Department of Intensive Care Medicine, Nepean Hospital. New South Wales, Australia*
[d] *Kettering General Hospital NHS Foundation Trust, UK*
[e] *Adult Intensive Care Unit, Royal Derby Hospital, UK*
[f] *Cardiovascular Sciences, University of Leicester, Leicester, UK*
[g] *Clinical Microbiology, University Hospitals of Leicester NHS trust, UK*
[h] *Respiratory Sciences, University of Leicester, Leicester, UK*

[*] Corresponding author at: Clinical Microbiology, 5F Sandringham Building, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW, UK.
E-mail address: jwtang49@hotmail.com (J.W. Tang).
Received 12 November 2022; Accepted 5 January 2023
Available online 13 January 2023

Pulmonology 29 (2023) 244—246

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

COVID-19 effect on tuberculosis care in Sierra Leone: Are we in the recovery phase?

Dear Editor,

More than two years after the beginning of the COVID-19 pandemic, the direct clinical consequences of the global spread of SARS-CoV-2 and the indirect ones related to non-pharmacological interventions and public reactions are better recognized. On one hand, millions of people died or are suffering from long-term sequelae of the disease; on the other, social restrictions and "stay-at-home" mandates had a negative impact on the global economy and probably contributed to an important rise in mental health issues, particularly in young people. In addition, fears of catching SARS-Cov-2 infection in the healthcare settings, or the need of shifting resources from routine health services to COVID-19 emergency responses, had a negative impact on important screening or preventive programs, such as immunization campaigns[1,2] or detection of new cases of HIV or TB.[3]

In particular, TB is still the number-one infectious disease killer in the world with African countries having the highest rate of contagion. The importance of a well-conducted clinical surveillance for this pathology rests on the necessity of identifying people with the disease to offer access to treatment early, and to offer preventive therapy to those with latent infection and at higher risk to progress to TB (eg HIV infection or exposed children).[4] In our previous pilot study[5] available online already in 2020, we evaluated the impact of COVID-19 on active TB screening in the Community Health Post of Tombo, a village of Western Rural Area in Sierra Leone. We compared the number of patients tested with sputum smear and confirmed Acid Fast Bacilli (AFB)-positive during the first 4 months of the year 2020 (January, February, March, April) with the cases reported in 2018 and 2019. Although with the limitations of a retrospective study restricted to a small region, we showed a significant drop of confirmed TB cases in April 2020, the first month of lockdown in Sierra Leone; additionally, the number of TB suspected cases decreased in March and April 2020. This was the first description of a drop of new TB suspected or confirmed cases, which unfortunately was confirmed later by several international studies.[6-8] However, as restrictions have lifted with the beginning of vaccinations and public awareness on the transmission routes, our aim in the present study was to assess the potential change of this trend in the setting of Sierra Leone. Therefore, we continued collecting aggregated anonymized data about the number of patients tested for TB and those who tested positive in the Community Health Post of Tombo until April 2022. The study was approved by the authorities for the TB unit of the local health centre (J.S.B.). As shown in Fig. 1 the number of patients tested and diagnosed with TB in the first quarter period of 2021 compared to that of 2022 was similar to that recorded in the pre-Covid period. In particular, we tested 119 patients in the first 4 months of 2018 (50 resulted positive, 42%), 224 patients in the first four months of 2019 (58 resulted positive, 25,9%), 132 patients in the first four months of 2020 (40 resulted positive, 30,3%), 122 patients in the first four months of 2021, (65 resulted positive, 53,3%), 168 patients in the first four months of 2022 (60 resulted positive, 35,7%). This evidence, with the constraint of this small and retrospective study, suggests that local TB services in very resource-limited settings are returning to pre-pandemic activity standards and that patients are recovering trust in the health services and seeking medical advice when needed. This has important consequences because if true, we may contain the previously missed TB diagnoses that otherwise can lead to an additional increase of cases in the community and we may lose decades of progress in TB control programs. A similar trend of recovery of outpatient TB services has also been reported by Rodrigues and colleagues in Portugal,[9] which reported that TB diagnosis, treatment, and prevention services were only affected during the 1st State of Emergency. However, as Covid-19 cases still keep rising across the globe, given the possible interactions of TB and Covid-19 (reactivation or worsening of TB during SARS-CoV-2 infection, use of steroids during Covid-19),[10] it is of primary importance to further reinforce TB preventive programs globally.

However, despite the positivity of this trend which gives us hope, there is still the need to be vigilant aboutthe problem of facing the need to maintain effective health surveillance and management of TB programs. Considering what is observed, it is essential to promote and facilitate access to primary care to allow a broader and more accurate screening for TB.

https://doi.org/10.1016/j.pulmoe.2022.10.008

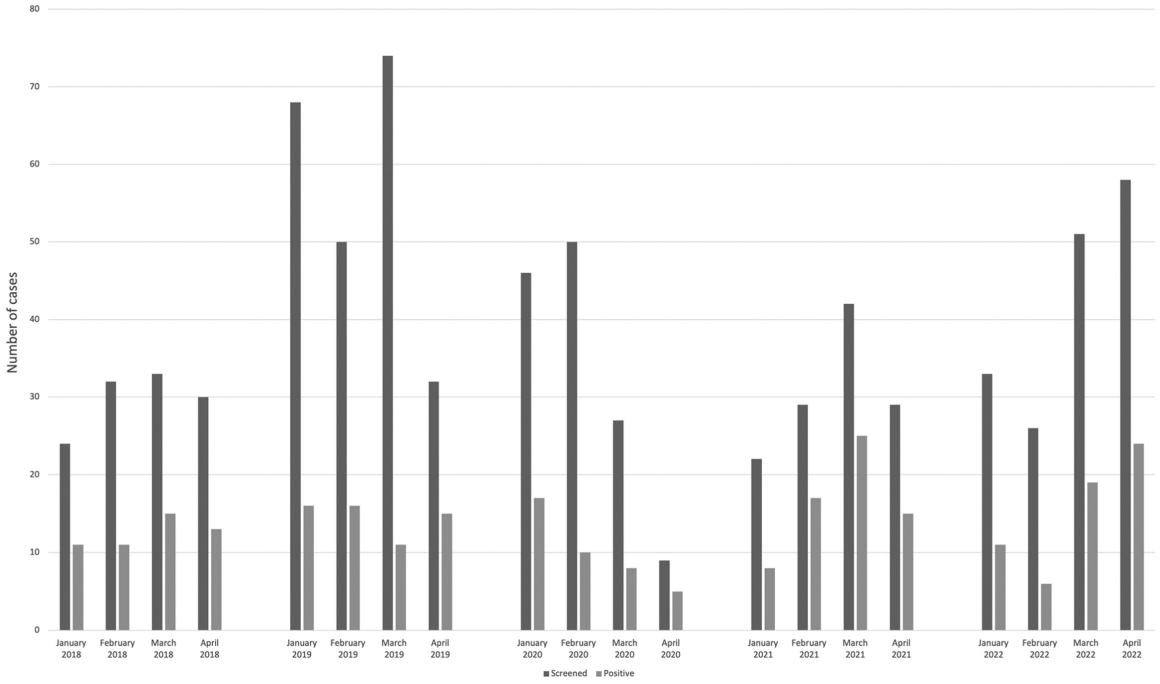

Figure 1 The number of presumptive TB and confirmed TB cases in Tombo Health Centre, Sierra Leone, in the first months of 2018, 2019, 2020, 2021 and 2022. April 2020, the month of the beginning of the first lockdown in Sierra Leone, was the month with the lowest number of people tested and tested-positive while it is possible to observe a positive trend in the number of the following two years.

Funding

The study was partially supported by the Italian Ministry of Health, Linea di Ricerca Corrente four.

Conflicts of interest

Nothing to declare.

References

1. Mariani F, Valentini P, Yamba M, Turay AS, Bulubisi H, Moscato U, Raffaelli F, et al. Changes in childhood immunizations and intermittent preventive malaria treatment in a peripheral, referral immunization center during the first 12 months of COVID-19 pandemic in Sierra Leone, Western Africa. Front Pediatr. 2022;10:774281. https://doi.org/10.3389/fped.2022.774281.
2. Buonsenso D, Cinicola B, Kallon MN, Iodice F. Child healthcare and immunizations in Sub-Saharan Africa during the COVID-19 pandemic. Front Pediatr. 2020;8:517. https://doi.org/10.3389/fped.2020.00517.
3. Ong CWM, Migliori GB, Raviglione M, MacGregor-Skinner G, Sotgiu G, Alffenaar JW, et al. Epidemic and pandemic viral infections: impact on tuberculosis and the lung: a consensus by the World Association for Infectious Diseases and Immunological Disorders (WAidid), Global Tuberculosis Network (GTN), and members of the European Society of Clinical Microbiology and Infectious Diseases Study Group for Mycobacterial Infections (ESGMYC). Eur Respir J. 2020;56(4):2001727. https://doi.org/10.1183/13993003.01727-2020.
4. Goletti D, Delogu G, Matteelli A, Migliori GB. The role of IGRA in the diagnosis of tuberculosis infection, differentiating from active tuberculosis, and decision making for initiating treatment or preventive therapy of tuberculosis infection. Int J Infect Dis. 2022. https://doi.org/10.1016/j.ijid.2022.02.047. S1201-9712(22)00126-6.
5. Buonsenso D, Iodice F, Sorba Biala J, Goletti D. COVID-19 effects on tuberculosis care in Sierra Leone. Pulmonology. 2021;27(1):67—9. https://doi.org/10.1016/j.pulmoe.2020.05.013.
6. Migliori GB, Thong PM, Akkerman O, Alffenaar JW, Álvarez-Navascués F, Assao-Neino MM, et al. Worldwide effects of coronavirus disease pandemic on tuberculosis services, January-April 2020. Emerg Infect Dis. 2020;26(11):2709—12. https://doi.org/10.3201/eid2611.203163.
7. Migliori GB, Thong PM, Alffenaar JW, Denholm J, Tadolini M, Alyaquobi F, et al. Gauging the impact of the COVID-19 pandemic on tuberculosis services: a global study. Eur Respir J. 2021;58(5):2101786. https://doi.org/10.1183/13993003.01786-2021.
8. Migliori GB, Thong PM, Alffenaar JW, Denholm J, Tadolini M, Alyaquobi F, et al. Country-specific lockdown measures in response to the COVID-19 pandemic and its impact on tuberculosis control: a global study. J Bras Pneumol. 2022;48(2):e20220087. https://doi.org/10.36416/1806-3756/e20220087.
9. Rodrigues I, Aguiar A, Migliori GB, Duarte R. Impact of the COVID-19 pandemic on tuberculosis services. Pulmonology. 2022;28(3):210—9. https://doi.org/10.1016/j.pulmoe.2022.01.015.
10. Visca D, Ong CWM, Tiberi S, Centis R, D'Ambrosio L, Chen B, Mueller J, Mueller P, Duarte R, Dalcolmo M, Sotgiu G, Migliori GB, Goletti D. Tuberculosis and COVID-19 interaction: a review of biological, clinical and public health effects. Pulmonology. 2021;27(2):151—65. https://doi.org/10.1016/j.pulmoe.2020.12.012.

D. Buonsenso[a,b,*], F. Mariani[c], J.S. Biala[d], D. Goletti[e]

[a] *Department of Woman and Child Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy*
[b] *Centro di Salute Globale, Università Cattolica del Sacro Cuore, Roma, Italia*
[c] *Pediatric Resident, Università Cattolica del Sacro Cuore, Rome, Italy*
[d] *Tuberculosis Unit, Tombo Community Health Centre, Western Rural Area, Sierra Leone*
[e] *Translational Research Unit, Department of Epidemiology and Preclinical Research, National Institute for Infectious Diseases-IRCCS L. Spallanzani, Rome, Italy*

[*] Corresponding author at:
E-mail address: danilobuonsenso@gmail.com
(D. Buonsenso).
Received 2 July 2022; Accepted 18 October 2022
Available online 31 October 2022

Pulmonology 29 (2023) 247—249

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Prevalence of asthma and COPD in a cohort of patients at the follow up after COVID-19 pneumonia

To the Editor,

A relevant (but still unpredictable) proportion of patients after COVID-19, particularly those hospitalized with severe acute disease, may present persistent symptoms (i.e. long-COVID syndrome),[1] even clustering in specific clinical presentation (i.e. more dyspnea, fatigue, or anxiety/depression, etc).[2] Patients suffering from asthma and COPD have been considered less exposed to infection,[3] however, there is a lack of data on their prevalence in the long-COVID populations. We hypothesized that individuals with existing chronic airway disease could experience more long term symptoms and/or have respiratory functional impairment 6 months after discharge. Thus we aimed at: i) determining the prevalence of asthma and COPD at the follow-up in a cohort of patients recovering from COVID-19 pneumonia; ii) investigating their dyspnea grade, pulmonary function, and exercise tolerance.

A post-COVID service was established at the Respiratory Outpatient Clinic (University Hospital of Modena Policlinico) for all patients previously hospitalized and cases of SARS-CoV-2 infection not requiring admission for in-person follow up 3-6 months after discharge or recovery from viral infection. Out of 911 patients followed up between July 2020 and February 2022, 780 were hospitalized (85.6%). From the cohort of individuals previously hospitalized, we selected patients with existing diagnosis of asthma or COPD at hospital admission and newly diagnosed at the follow up according to the international guidelines.[4,5] Other individuals with asthma or COPD but not hospitalized for COVID-19, patients with confirmed interstitial lung disease, concomitant neuromuscular diseases, cognitive impairment or severe psychiatric disorders, and patients not able to perform follow up assessment were excluded.

This study summarises the clinical-functional assessment of 82 patients (10.5%) reviewed following hospital discharge. The mean time from discharge to follow up was 4 ±1.1 months. Out of 82 individuals, 41 were asthmatic patients and 41 COPD. The prevalence of asthma in the study cohort was 5.2%, and the same for COPD.

The characteristics of the participants and a summary of their COVID-19 admission are reported in **Table 1a**; patients with asthma and COPD were similar except for age and smoking history, as expected. Out of 41 patients with asthma, 3 (7.3%) were newly diagnosed, whereas 18 (44%) COPD patients had new diagnosis at the follow up. In patients with asthma, 18 (47%) were allergic, 19 (48%) obese, and 2 (5%) had bronchiectasis. The 23 patients with confirmed COPD were predominantly in GOLD 1-2 grades (87%). The newly diagnosed COPD patients were predominantly male (83%), all former or current smokers, and with similar grade of the disease.

Modified Medical Research Council (mMRC) dyspnea grade,[6] spirometry and lung diffusing capacity (DL_{CO})[7] parameters, and six-minute walk distance (6MWT)[8,9] were collected at the follow up as outcomes (**Table 1b**). Persisting oxygen desaturation during exercise was observed in 9.7% of cases: 6 COPD patients with 3 newly diagnosed and 2 asthmatic patients with confirmed diagnosis.

According to the study purpose, we were able to show interesting findings.

First, data collection helped quantify the proportion of patients with diagnosis of asthma and COPD in a large cohort of people at the follow up after COVID-19 pneumonia. The prevalence of asthmatic patients is in line with that observed in the general population in Italy,[10] but it seems larger than previously reported data in COVID-19 patients.[11,12] On the other hand, COPD patients in our study cohort are less prevalent than in the general population,[13] which may support a different epidemiology within COVID-19 patients.[3] Notwithstanding, the follow-up service provided a new diagnosis of chronic respiratory disease, particularly COPD. This provided patients with an opportunity for an appropriate disease identification and care plan.

Second, a clinically meaningful post-COVID mMRC dyspnea score observed in 41.5% of the COPD patients, who were in mild GOLD grade of severity, confirms the findings of Huang *et al* in a large population of patients discharged in Wuhan and assessed six months later.[14] This emphasises that older age is not the only responsible factor for long-term residual dyspnea in COPD survivors.

Abbreviations: 6MWT, 6-Minute Walk Test; BMI, Body Mass Index; COT_1, Conventional Oxygen Therapy; DL_{CO}, Diffusing Lung Capacity for Carbon Monoxide; FEV_1, Forced Expiratory Volume in 1 Second; FVC, Forced Vital Capacity; HFNC, High Flow Nasal Cannula; LOS, Length of Stay; LTOT, Long Term Oxygen Therapy; mMRC, modified Medical Research Council; MV, Mechanical Ventilation; NIV, Non-invasive Ventilation; O_2, Oxygen; TLC, Total Lung Capacity.

https://doi.org/10.1016/j.pulmoe.2022.05.005

Table 1a Characteristics of the study population on hospital admission.

	All patients N = 82	Asthma N = 41	COPD N = 41	p-value
Age[&], years	66 [34-88]	58 [34-83]	74 [58-88]	<0.0001
Male gender[&&]	53 [64.6]	23 [56.1]	30 [73.2]	0.17
Ethnicity, Caucasian	82 [100]	-	-	
Smoking history[&&]	5 [6.1]	1 [2.4]	4 [9.7]	<0.0001
Current smoker				
Former smoker	54 [66]	17 [41.5]	37 [90.2]	
Non-smoker	23 [28]	23 [56.1]	0 [0]	
BMI (pre-admission)[&]	28.6 [20-44]	29 [20-44]	28 [21-41]	0.31
BMI[&&] ≥ 30	30 [36.6]	18 [43.9]	12 [29.3]	0.25
Length of hospital stay[&] (days)	14 [1-94]	14 [1-94]	14 [2-45]	0.85
COT only[&&]	70 [85.3]	34 [83]	36 [88]	0.76
HFNC[&&]	5 [6.1]	3 [7.3]	2 [4.9]	1.00
NIV[&&]	7 [8.5]	4 [9.7]	3 [7.3]	1.00
Intubation/MV[&&]	4 [5]	3 [7.3]	1 [2.4]	0.62
O_2 at discharge[&&]	5 [6.2]	2 [4.9]	3 [7.3]	0.048
**** COPD patients on pre-admission LTOT were excluded (n=5)***				

Key: Data reported as mean and range or number and % as appropriate.
MV, mechanical ventilation
[&] Analysis by Student-t test
[&&] Fisher's Exact test

Table 1b Follow-up assessment in the study population.

	All patients N = 82	Asthma N = 41	COPD N = 41	p-value
mMRC[&]	0.5 [0-3]	0.2 [0-2]	0.7 [0-3]	0.02
mMRC ≥ 1 point[&&]	22 [26.8]	5 [12.2]	17 [41.5]	0.005
FEV_1/FVC[&]	69.2 [35.6-86.4]	75.8 [59-86.4]	62.7 [35.6-70.5]	<0.0001
FEV_1[&] (%pred)	88.2 [27-145]	97.4 [42-138]	79 [27-145]	0.0002
TLC[&] (%pred)	111 [75-150]	109 [75-150]	112 [77-148]	0.36
TLC[&&] (<90%pred)	5 [6.1]	3 [7.3]	2 [4.9]	1.00
DL_{CO}[&] (%pred)	73.6 [25-128]	85 [37-128]	61 [25-119]	<0.0001
DL_{CO}[&&] (<80%pred)	47 [57.3]	16 [39]	31 [75.6]	0.002
6MWT[&] (meters)	425 [220-610]	452 [300-610]	399 [220-530]	0.003
6MWT[&] (%pred)	77 [46-98]	79 [56-97]	77 [46-98]	0.023
6MWT[&&], desaturation	10 [12.2]	2 [4.9]	8 [19.5]	0.048

Key: Data reported as mean and range or number and % as appropriate.
[&] Analysis by Student-t test
[&&] Fisher's Exact test

Third, the reduction in DL_{CO} (mean 73.6% pred with <80%pred in 57.3% of cases) as a marker of residual lung damage following interstitial pneumonia was similar to that observed in unselected patients treated with respiratory support therapies (HFNC, NIV, intubation),[14-16] even though more frequent in COPD (75.6%) than in patients with asthma in our cohort.

Finally, the great proportion of people with asthma and obesity (43.9%), confirmed that this comorbidity makes asthma difficult to treat[17] and may also impact negatively on the patient's perception of good health in individuals recovering from COVID-19.

Considering major limitations (i.e. the single-center analysis and the lack of *pre-to-post* comparison of pulmonary function test in patients with existing diagnosis of asthma and COPD), the study results are informative. Indeed, the patients with asthma and COPD is a representative real-word disease-group, and the follow up assessment can be useful for unknown diagnoses of chronic respiratory disease. Therefore, the findings highlight the importance of a tight respiratory follow-up assessment in individuals recovering from COVID-19 pneumonia who should be investigated for long-term symptoms including dyspnea, especially those underdiagnosed for having asthma or COPD.

Funding

EC have received research grant support from Chiesi Italia S. p.A. (letter of intent signed on 09/04/2021).

Consent for data publication

The consent for data publication was given by the Ethics Committee (CE 453/2020-OSS/AOUMO and CE EM453/2020-OSS/AOUMO).

Conflicts of interest

There are no conflicts of interest.

Acknowledgments

None.

References

1. COVID-19 rapid guideline: managing the long-term effects of COVID-19. National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) and Royal College of General Practitioners (RCGP). NICE guideline; 2021. [NG188] Published: 18 December 2020 Last updated: 11 November https://www.nice.org.uk/guidance/ng188.
2. Carfi A, Bernabei R, Landi F. for the Gemelli against COVID-19 Post-acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA. 2020;324(6):603—5.
3. Eger K, Bel EH. Asthma and COVID-19: do we finally have answers? Eur Respir J. 2021;57(3):2004451.
4. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347—65.
5. Global Initiative for Asthma. Global strategy for Asthma management and prevention, 2019. Available from www.ginasthma.org.
6. Fletcher CM. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). Br Med J. 1960;2:1662.
7. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardization of spirometry. Eur Respir J. 2005;26 (2):319—38.
8. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111—7.
9. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med. 1998;158 (1):1384—7.
10. de Marco R, Cappa V, Accordini S, Rava M, Antonicelli L, Bortolami O, et al. Trends in the prevalence of asthma and allergic rhinitis in Italy between 1991 and 2010. Eur Respir J. 2012;39(4):883—92.
11. Caminati M, Vultaggio A, Matucci A, Senna G, Almerigogna F, Bagnasco D, et al. Asthma in a large COVID-19 cohort: prevalence, features, and determinants of COVID-19 disease severity. Respir Med. 2021;176:106261.
12. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis. 2020. 30136—3S1201—9712.
13. Viegi G, Maio S, Fasola S, Baldacci S. Global burden of chronic respiratory diseases. J Aerosol Med Pulm Drug Deliv. 2020;33(4):171—7.
14. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220—32.
15. Fabbri L, Moss S, Khan FA, Chi W, Xia J, Robinson K, et al. Parenchymal lung abnormalities following hospitalisation for COVID-19 and viral pneumonitis: a systematic review and meta-analysis. Thorax. 2022. https://doi.org/10.1136/thoraxjnl-2021-218275.
16. Torres-Castro R, Vasconcello-Castillo L, Alsina-Restoy X, Solis-Navarro L, Burgos F, Puppo H, et al. Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis. Pulmonology. 2021;27(4):328—37. Jul-Aug.
17. Moitra S, Carsin A, Abramson MJ, Accordini S, Amaral AFS, Anto J, et al. Long-term effect of asthma on the development of obesity among adults: an international cohort study, ECRHS. Thorax. 2022. https://doi.org/10.1136/thoraxjnl-2021-217867. Online ahead of print.

A. Verduri[a], J. Hewitt[b], B. Carter[c], R. Tonelli[d], E. Clini[a,*], B. Beghè[a]

[a] *Department of Surgical and Medical Sciences (SMECHIMAI), University of Modena and Reggio Emilia, and Respiratory Unit, University Hospital of Modena Policlinico, Modena, I*
[b] *Division of Population Medicine, Cardiff University, Wales, UK*
[c] *Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, England, UK*
[d] *Clinical and Experimental Medicine PhD School, University of Modena and Reggio, Modena, I*

[*] Corresponding author at: University of Modena and Reggio Emilia, Modena (I), Department of Surgical and Medical Sciences, Respiratory Unit, University Hospital of Modena Policlinico

E-mail address: enrico.clini@unimore.it (E. Clini).
Received 21 May 2022; Accepted 30 May 2022
Available online 10 June 2022

Pulmonology 29 (2023) 250—252

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Tuberculosis and risk of Parkinson's disease: A nationwide cohort study

As neuroinflammation is increasingly recognized to be associated with neurodegenerative diseases, accumulating evidence suggests viral or bacterial infections are potential causes of Parkinson's disease (PD). Tuberculosis (TB) infection is associated with various diseases linked by chronic infections and inflammation. However, there are few studies which evaluated an association between TB and incident PD. In this context, we estimated PD incidence among TB survivors compared to that of the general population.

We performed a population-based retrospective cohort study using the Korean Nationwide Health Insurance System (NHIS) database. We included 67,475 TB survivors who underwent health screening within two years before TB diagnosis between 2010 and 2017, and 67,475 age- and sex-matched controls. The cohort were followed up for incident PD from one year after TB diagnosis to the date of PD event, date of death, or until the last follow-up date (December 31, 2018), whichever came first.

The mean follow-up duration was 3.6 and 3.7 years for TB survivors and matched controls, respectively. In total, 0.5% of TB survivors (363/67,475) and 0.3% of matched-control subjects (228/67,475) developed PD, with incidence rates of 1.5 and 0.9 per 1,000 person-years, respectively **(**Table 1**)**. TB survivors had a higher risk of PD (adjusted hazard ratio 1.45, 95% confidence interval=1.22—1.73) compared with matched control. Fig. 1 shows the results from stratified analyses regarding the risk of PD among TB survivors with the matched control group as the reference after adjusting for potential confounding variables in all subgroups. TB survivors continued to have higher PD incidence in all subgroups compared with matched controls (*P* for interaction >0.05 for all).

Although the role of TB infection in PD is far from being confirmed, both diseases share some inflammation mechanisms via interleukin-6, tumor necrosis factor, interleukin-1β, and matrix metalloproteinase.[1] When an infectious bacterial agent is inhaled, swallowed, or enters the eyes, it induces abnormally enhanced cytokine production, so-called cytokine storm.[2] Circulating dysregulated cytokines travel through the circulatory system to the brain, inducing fenestration in the blood brain barrier.[2] In the brain, cytokines induce activation of resident microglia and astrocytes that induce neuronal damage.[2] Dopaminergic neurons aggregate α-synuclein into Lewy Bodies and oxidative-stress-induced cellular damage.[2] Conversely, in a mouse model, vaccination with neuronal antigens in complete Freund's adjuvant, which contains heat-inactivated *M. tuberculosis* or the TB vaccine strain Bacilli Calmette-Guerin partially protected against PD-associated neuronal death.[3] Together, these data suggest that immune response to TB may trigger or exacerbate neuroinflammation.

Additionally, several genes confer susceptibility to both TB infection and PD.[4] Leucine Rich Repeat Kinase 2 (LRRK2) mutation, the most common genetic cause of PD, might result in dysregulation of peripheral immune responses to pathogens and inflammation, which can have long-term consequences such as loss of dopaminergic neurons.[5] Parkin RBR E3 ubiquitin protein ligase (PARK2) mutation is also a well-known genetic risk factor for PD. Polymorphisms in the regulatory region of PARK2 result in reduced expression of the parkin protein.[6] The parkin protein is an ubiquitin ligase in mitophagy, which is a key innate defense mechanism against invading microbes.[7] Therefore, mutations in LRRK2 or PARK2, which imply an impaired innate defense mechanism against TB infection may also lead to increased PD susceptibility.

We also noted that TB survivors were associated with increased PD risk even after various stratifications. These findings may highlight the causal relationship between TB and PD development. Interestingly, TB survivors who engaged in regular physical activity had no increased PD risk compared with healthy controls. Although the clinical significance of this finding is unclear due to the small difference, this study supports evidence that physical activity has a preventive impact on PD, even in high-risk groups like TB survivors

One major strength of our study was the reliability of the data obtained from the TB control system of Korea. In 2000, the Tuberculosis Notification Information System was established, and since 2001 all patients with TB have been required to register their cases electronically. Other strengths are that the NHIS database includes data from the entire Korean population, which results in almost complete

https://doi.org/10.1016/j.pulmoe.2022.10.002

Table 1 Hazard ratios and 95% confidence intervals for the incidence of Parkinson's disease in tuberculosis survivors compared to the matched control group.

	Subjects (N)	Events (n)	Follow-up duration (person-years)	IR	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Matched control	67,475	228	250,066.4	0.9	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
TB survivors	67,475	363	242,378.0	1.5	1.64 (1.39−1.94)	1.70 (1.43−2.01)	1.49 (1.25−1.78)	1.45 (1.22−1.73)

IR, incidence rate per 1,000 person-years; HR, hazard ratio; CI, confidence interval; TB, tuberculosis.
Model 1: crude model.
Model 2: adjusted for age, sex, socioeconomic position (income level and place of residence), smoking, alcohol consumption, regular physical activity, and body mass index.
Model 3: Model 2 + adjusted for Charlson comorbidity index.
Model 4: Model 3 + adjusted for competing risk for mortality.

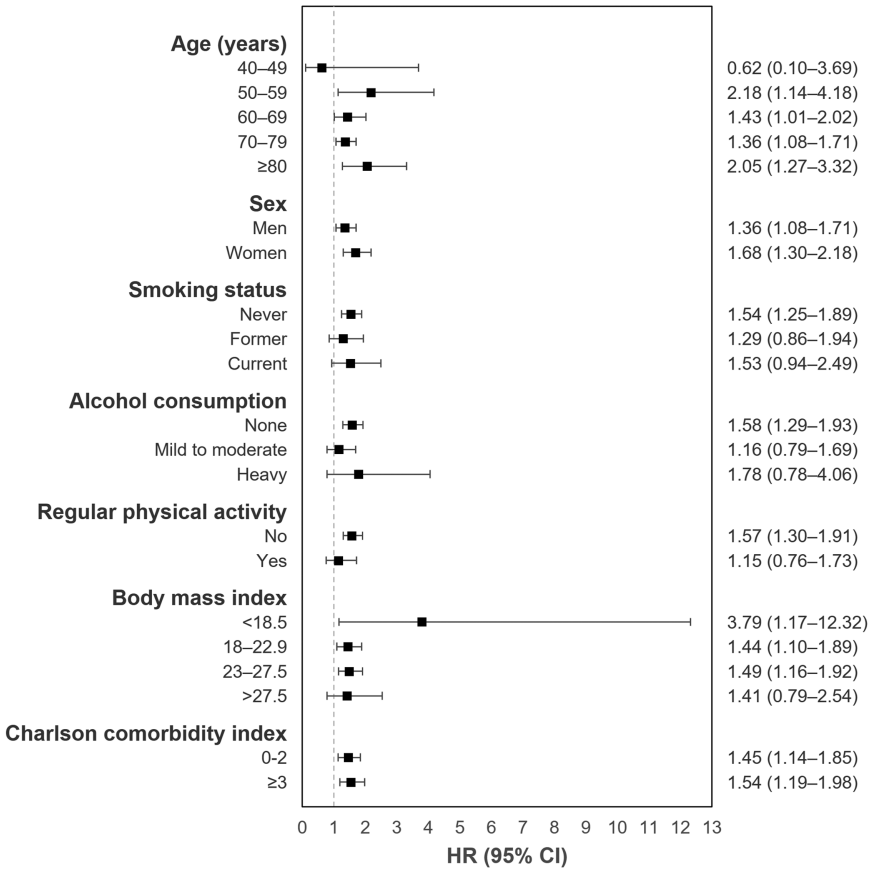

Fig. 1 Subgroup analysis for Parkinson's disease incidence in tuberculosis survivors compared with the matched control group, HR, hazard ratio; CI, confidence interval, Adjusted for age, sex, socioeconomic position (income level and place of residence), smoking, alcohol consumption, regular physical activity, body mass index, Charlson comorbidity index, and competing risk for mortality.

follow-up. Our study also had some limitations. First, because this study is based on data that were not originally designed for studying the association between TB and PD, we were not able to control acute or chronic infections other than TB. Further studies are needed to verify the association between TB and PD. Second, because we used claims data, it is possible that PD was undetected, overestimated, or misdiagnosed. However, we also used a special registration code for PD, so that our definition of PD would have high accuracy.

In conclusion, we demonstrated that TB survivors exhibited a higher risk of PD compared to the general population, indicating that TB is an important infectious factor associated with increased incidence of PD.

Funding

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Ministry of Science, Information and Communications Technologies (MSIT) (NRF-2020R1F1A1070468 and 2021M3E5D1A01015176).

Conflicts of interest

None.

Acknowledgement

This study was performed using the database from the National Health Insurance System, and the results do not represent the opinion of the National Health Insurance Corporation.

References

1. Qin XY, Zhang SP, Cao C, Loh YP, Cheng Y. Aberrations in peripheral inflammatory cytokine levels in Parkinson disease: a systematic review and meta-analysis. JAMA Neurol. 2016;73: 1316–24.
2. Smeyne RJ, Noyce AJ, Byrne M, Savica R, Marras C. Infection and risk of Parkinson's disease. J Parkinsons Dis. 2021;11:31–43.
3. Yong J, Lacan G, Dang H, Hsieh T, Middleton B, Wasserfall C, Tian J, Melega WP, Kaufman DL. BCG vaccine-induced neuroprotection in a mouse model of Parkinson's disease. PLoS One. 2011;6: e16610.
4. Patrick KL, Bell SL, Weindel CG, Watson RO. Exploring the "multiple-hit hypothesis" of neurodegenerative disease: bacterial infection comes up to bat. Front Cell Infect Microbiol. 2019; 9:138.
5. Herbst S, Gutierrez MG. LRRK2 in infection: friend or foe? ACS Infect Dis. 2019;5:809–15.
6. Klein C, Westenberger A. Genetics of Parkinson's disease. Cold Spring Harb Perspect Med. 2012;2. a008888.
7. Manzanillo PS, Ayres JS, Watson RO, Collins AC, Souza G, Rae CS, Schneider DS, Nakamura K, Shiloh MU, Cox JS. The ubiquitin ligase parkin mediates resistance to intracellular pathogens. Nature. 2013;501:512–6.

J.E. Yoo[a], H. Choi[b], K. Han[c], S.H. Park[d], J. Park[e], H. Lee[f,1,*], D.W. Shin[g,h,**,1]

[a] *Department of Family Medicine, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, Republic of Korea*
[b] *Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Hallym University of College of Medicine, Seoul, Republic of Korea*
[c] *Department of Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea*
[d] *Department of Medical Statistics, The Catholic University of Korea, Seoul, Republic of Korea*
[e] *Department of Neurology, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan, Republic of Korea*
[f] *Division of Pulmonary Medicine and Allergy, Department of Internal Medicine, Hanyang Medical Center, Hanyang University College of Medicine, Seoul, Republic of Korea*
[g] *Supportive Care Center/Department of Family Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[h] *Department of Clinical Research Design & Evaluation, Samsung Advanced Institute for Health Science & Technology (SAIHST), Sungkyunkwan University, Seoul, Republic of Korea*

[*] Corresponding author at: Division of Pulmonary Medicine and Allergy, Department of Internal Medicine, Hanyang Medical Center, Hanyang University College of Medicine, Seoul, Republic of Korea 222-1 Wangsimni-ro, Seongdong-gu, Seoul 04763, Republic of Korea

[**] Corresponding author at: Department of Family Medicine/ Supportive Care Center, Samsung Medical Center, Sungkyunkwan University School of Medicine Department of Clinical Research Design & Evaluation/ Department of Digital Health, Samsung Advanced Institute for Health Science & Technology (SAIHST), Sungkyunkwan University, 81 Irwon-Ro, Gangnam-gu, Seoul 06351, Republic of Korea.
E-mail addresses: namuhanayeyo@naver.com (H. Lee), dwshin@skku.edu (D.W. Shin).
Received 22 July 2022; Accepted 5 October 2022
Available online 5 December 2022

[1] These authors contributed equally as co-corresponding authors.

Pulmonology 29 (2023) 253—256

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

The benefit of macrolide therapy in patients with pneumococcal pneumonia is only present in patients with bacteremia

Dear Editor

Community acquired pneumonia (CAP) remains the deadliest infectious disease worldwide, especially at the extremes of life and *Streptococcus pneumoniae* continues to be its most important pathogen.[1] The role of combination antibiotic therapy with a macrolide in patients with *Streptococcus pneumoniae* severe pneumonia, admitted to hospital, although commonly recommended, is still controversial. Identification of patients who might benefit from this strategy is crucial to maximize its benefit whilst reducing antimicrobial overuse, bacterial resistance pressure and toxicity. Positive effects have been previously reported in patients with invasive mechanical ventilation,[2] severe CAP[3] and with bacteremia,[4] although these studies have been carried out in the intensive care unit (ICU) population and the same benefit may not apply to the general population. Moreover, as the population admitted to the hospital is also changing (patients are commonly older and often present comorbidities), this deserves further clarification.

We performed a multicenter study addressing the outcomes of patients admitted with *Streptococcus pneumoniae* CAP. The study protocol was approved by the Hospital Vila Franca de Xira Ethical Committee at their 25-1-2019 meeting. Informed consent was waived due to the retrospective, observational only, nature of the study. All Ethical Committee of participating centers approved the submitted protocol.

We included 797 adult patients (53.4% male, mean age 72.4±16.5 years, 92.5% with at least one comorbidity) admitted to one of the 4 participating centers, between 2015 and 2018, with microbiological documented *Streptococcus pneumoniae* (either bacteremia or urinary antigen) CAP. Bacteremia was defined as a clinical and radiological syndrome consistent with pneumonia and ≥1 blood culture(s) positive for *Streptococcus pneumoniae*.

ICU admission was recorded in 18.8%. Demographic and clinical data, along with antimicrobial therapy, were collected. Outcome data included length of hospital stay, 30-day and 1-year all-cause mortality. Patients were split according to the presence of pneumococcal bacteremia (N=240, 30.1%). Their characteristics are presented in Table 1.

Cox proportional Hazards (HR), along with the 95% CI, was used for assessment of combination antimicrobial therapy with a macrolide, for patients with and without bacteremia.

Mean hospital length of stay was 11.7±9.8 days. The overall 30-day all-cause mortality was 19.2% (32.2% at 1-year follow-up). Patients with bacteremia had higher 30-day all-cause mortality (26.2% vs. 16.3%, age adjusted Hazards Ratio [aHR] 1.84; 95% CI 1.33-2.53) and 1-year all-cause mortality (38.5% vs. 30.4%, aHR 1.43; 95% CI 1.05-1.96). Combination of a ß-lactam plus a macrolide was given to 459 patients (57.6%), 57.1% of those with bacteremia and 57.8% of those without (p=0.88). This proved to be beneficial but only for patients with bacteremia (30-day all-cause mortality 18.8% vs. 36.1%, aHR 0.49 95% CI 0.30-0.80, p=0.004) - Fig. 1. After 1-year of follow up, patients with bacteremia, who received combination antimicrobial therapy with a macrolide, still had lower all-cause mortality, 31.3% vs. 48.1%, p=0.009.

The benefit of combination antimicrobial therapy with a macrolide in patients with bacteremia was also found in a large 2007 retrospective study,[5] even in patients who received only 24h of a macrolide.[5] However, this study failed to provide a control group. The same benefit, improved survival of patients with pneumococcal bacteremia with combination antimicrobial therapy, was noted in another small study, but only in the most severe group. However, the population included was younger and healthier than ours, with an all-cause mortality rate of only 16.9%.[4]

The reasons for the benefit of macrolides may be related to its non-antibiotic properties, namely a potential "immunomodulatory" effect, although this needs further clarification.[6] Persistent inflammation probably plays a contributing role in a worst short- and long-term prognosis in patients with CAP,[7] especially related with an increased incidence of cardiovascular diseases. In our cohort 18.3% of patients discharged alive from the hospital died during the 1-year of follow-up, slightly higher than previously reported.[8] It should be noted that our population was older (71±16.8 vs. 63 years old) and age is a well-known risk factor for long term mortality.

Our study has some limitations. It is retrospective and included all hospitalized patients diagnosed with

https://doi.org/10.1016/j.pulmoe.2022.08.003

Table 1 Characteristics of subjects with or without bacteremia.

	Bacteriemia	No	Odds Ratio (95% CI)	P Value
Age (years)	71.3±15.8	72.9±16.8		0.195*
Time of symptoms before admission (days)	2 [1-4.3]	3 [1-5]		0.037‡
CRP max (mg/dL)	29.3±12.3	21.5±11.8		<0.001*
Diabetes	28.2	26.5	1.09 [0.78-1.53]	0.667†
Hypertension	44.4	48.8	0.84 [0.62-1.14]	0.283†
Smoking	17.5	18.5	0.93 [0.63-1.38]	0.766†
COPD	15.5	18.1	0.83 [0.55-1.24]	0.418†
Atrial Fibrillation	24.2	17.6	1.50 [1.04-2.16]	0.034†
Cachexia	4.8	5.9	0.80 [0.41-1.60]	0.616†
Malignant Neoplasm	9.1	7.6	1.23 [0.72-2.1]	0.483†
ICU admission	27.0	15.3	2.04 [1.42-2.95]	<0.001†
IMV	9.1	15.7	1.67 [0.95-2.93]	0.093†
NIMV	15.1	10.6	1.50 [0.96-2.33]	0.078†
RRT	13.5	12.1	1.13 [0.72-1.76]	0.644†
Multilobar involvement	39.0	38.3	1.03 [0.76-1.41]	0.875†
Sepsis	45.8	50.4	0.832 [0.62-1.13]	0.248†
Hospital length of stay (days)	13.8±11.9	10.8±8.5		<0.001*
Hospital mortality	26.6	14.0	2.23 [1.54-3.23]	<0.001†
30-day mortality	26.2	16.3	1.83 [1.27-2.63]	0.001†
1-Year mortality	38.5	30.4	1.43 [1.05-1.96]	0.028†

Data presented as %, unless otherwise stated; Continuous variables are presented as mean ± standard deviation or median [interquartile range] according to data distribution; CRP - C reactive protein; COPD – Chronic obstructive pulmonary disease; IMV – Invasive mechanical ventilation; NIMV – Non invasive mechanical ventilation; RRT – Renal Replacement therapy.

* Student' T Test.

† Chi-Square Test.

‡ Mann Whitney U test.

Streptococcus pneumoniae CAP. However, there was no systematic patient assessment on admission, and a significant number may have been missed. Moreover, although collection of blood cultures is common practice in patients with CAP who require hospital admission, previous use of antimicrobials or failure to collect blood while still in the emergency department may have contributed to a misclassification. Also, our database included only patients admitted to the hospital between 2015 and 2018, before the SARS-CoV2 pandemic. However, we believe that no significant changes have been made to the approach to patients with pneumococcal CAP.[9] Finally, we did not collect all patient' clinical and laboratory data on hospital admission and severity imbalances between groups may have occurred.

In conclusion we presented a large cohort of patients with pneumococcal CAP. Isolation of *Streptococcus pneumoniae* bacteremia was associated with high 30-day and 1-year all-cause mortality. On the other hand, patients with bacteremia who received combination antimicrobial therapy with a macrolide had lower 30-day mortality, but this benefit was not found in those with negative blood cultures.

Financial support

This work was supported by a research grant from Merck Sharp & Dohme Corp., a division of Merck & Co., Inc., Kenilworth, NJ, USA [IIS# 60150] under the Investigator Studies Program.

The content of this publication reflects only the views of the authors. The sponsor had no role in the analyses or interpretation of the data.

Authors contributions

João Gonçalves Pereira acts as guarantor of the integrity and accuracy of the data.

JGP, DL, PM, FF designed the study; AS, PVR, LC, RA, IS, MC, PM acquired the data and performed literature search; JGP, AG check the data for missing or implausible values; JGP, PM, IS, DL, AG analyse and interpret the data; JGP, PM, FF drafted the manuscript; JGP, AS, AG, PM, FF, DL revised the manuscript for important intelectual content; JGP, AG provided the statistical expertise. All authors review and approved the final manuscript.

Conflicts of interest

JGP reported he had received an unrestricted grant from Merck Sharp and Dohme; Consulting fees from Pfizer pharmaceuticals, Biomerieux and AOP pharmaceuticals; Honoraria for lectures from Abionic and Pfizer pharmaceuticals; and honoraria for participating in an advisory board from

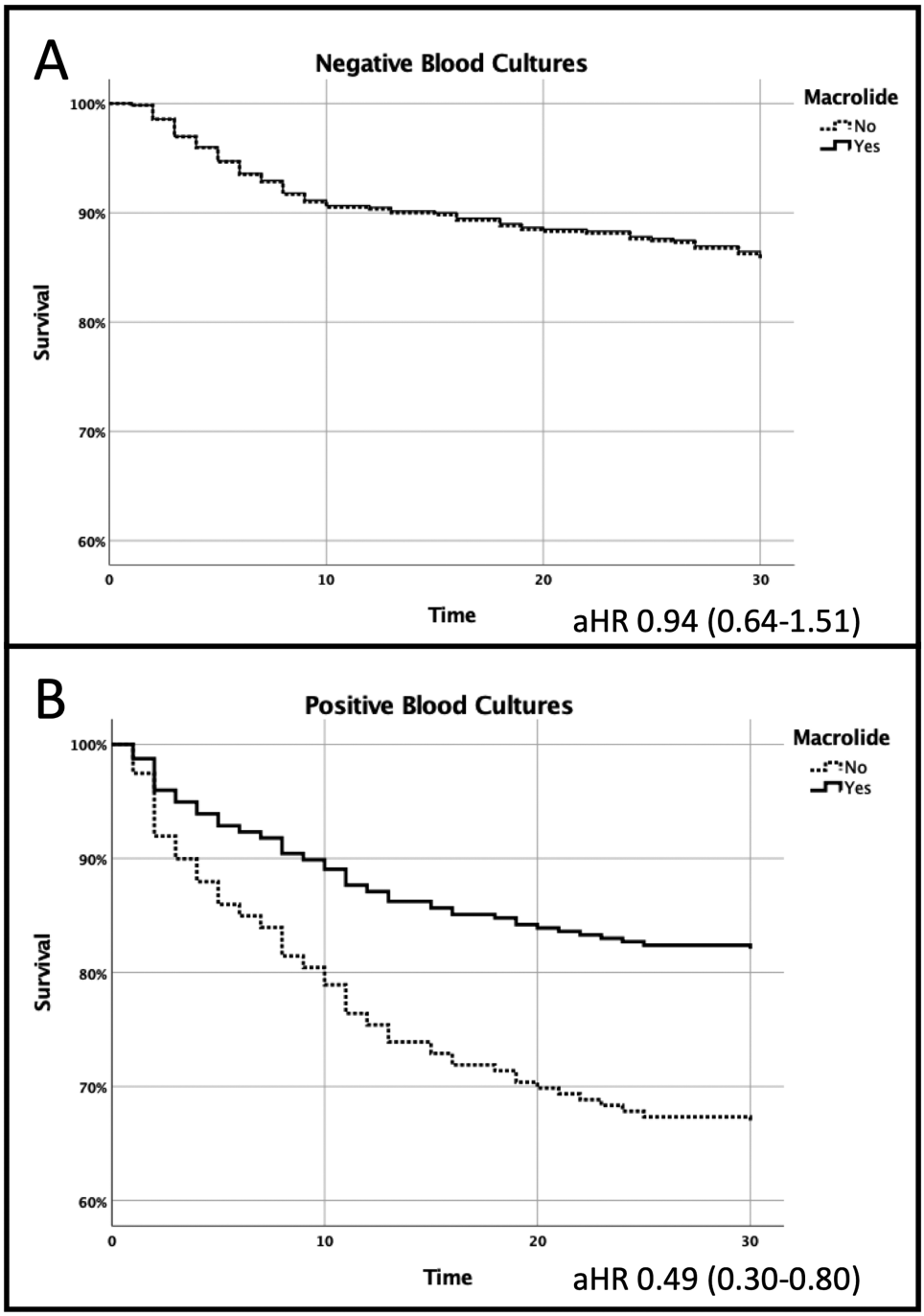

Fig. 1 A 30-day Mortality benefit was found in patients who received combination antimicrobial therapy with a macrolide but only in those with pneumococcal bacteremia (panel A); No differences were found in those without bacteremia (panel B): Age adjusted hazards ratio 0.49; 95% CI 0.30-0.80 and 0.94; 95% CI 0.64-1.51, respectively.

Pfizer Pharmaceutical. He is currently the president of "Grupo de Investigação e Desenvolvimento em Sépsis". FF reported he had received honoraria for lectures from Merck Sharp and Dohme, Pfizer pharmaceuticals and Sanofi; support for attending meetings from Merck Sharp and Dohme, Pfizer pharmaceuticals and Sanofi; and honoraria for participating in advisory boards from Merck Sharp and Dohme, Pfizer pharmaceuticals and Sanofi. PM reported he had received unrestricted grant from Merck Sharp and Dohme and Astra Zeneca; Consulting fees from Glaxo, Smith, Kline pharmaceuticals, Biomerieux, Astra Zeneca, Merck Sharp and Dohme and Shinogi; Honoraria for lectures from Cepheid, Glaxo Smith Kline, Merck Sharp and Dohme, Octapharma and Pfizer pharmaceuticals; support for attending meetings from Merck Sharp and Dohme. He is currently the president of the Portuguese National Society of Intensive Care. The other authors have nothing to disclose.

References

1. Feldman C, Anderson R. The role of streptococcus pneumoniae in community-acquired pneumonia. Semin Respir Crit Care Med. 2020;41:455—69. https://doi.org/10.1055/s-0040-1702193.
2. Martin-Loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. Intensive Care Med. 2010;36:612—20. https://doi.org/10.1007/s00134-009-1730-y.
3. Pereira JM, Gonçalves-Pereira J, Ribeiro O, Baptista JP, Froes F, Paiva JA. Impact of antibiotic therapy in severe community-acquired pneumonia: data from the Infauci study. J Crit Care. 2018;43:183—9. https://doi.org/10.1016/j.jcrc.2017.08.048.
4. Baddour LM, Yu VL, Klugman KP, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med. 2004;170:440—4. https://doi.org/10.1164/rccm.200311-1578OC.
5. Metersky ML, Ma A, Houck PM, Bratzler DW. Antibiotics for bacteremic pneumonia: improved outcomes with macrolides but not fluoroquinolones. Chest. 2007;131:466—73. https://doi.org/10.1378/chest.06-1426.
6. Reijnders TDY, Saris A, Schultz MJ, van der Poll T. Immunomodulation by macrolides: therapeutic potential for critical care. Lancet Respir Med. 2020;8:619—30. https://doi.org/10.1016/S2213-2600(20)30080-1.
7. Steel HC, Cockeran R, Anderson R, Feldman C. Overview of community-acquired pneumonia and the role of inflammatory mechanisms in the immunopathogenesis of severe pneumococcal disease. Mediators Inflamm. 2013. https://doi.org/10.1155/2013/490346. 2013.
8. Sandvall B, Rueda AM, Musher DM. Long-term survival following pneumococcal pneumonia. Clin Infect Dis. 2013;56:1145—6. https://doi.org/10.1093/cid/cis1207.
9. Garber B. Pneumonia update for emergency clinicians. Curr Emerg Hosp Med Rep. 2022;10:36—44. https://doi.org/10.1007/s40138-022-00246-z.

J. Gonçalves-Pereira[a,b,c,*], L. Costa[d], I. Silva[e], A. Simões[a], F. Froes[f,g], P. Mergulhão[c,h,i], P. Varela Ramos[a], D. Leal[d], R. Alves[d], M. Custódio[e], A. Gomes[c,e,i]

[a] *Intensive Care Department, Hospital Vila Franca de Xira; Vila Franca de Xira, Portugal*
[b] *Nova Medical School, Universidade Nova de Lisboa, Lisbon, Portugal*
[c] *Grupo de Infeção e Desenvolvimento em Sépsis, Oporto, Portugal*
[d] *Intensive Care Department, Hospital Braga; Braga, Portugal*
[e] *Internal Medicine Department, Hospital Cascais; Cascais, Portugal*
[f] *Intensive Care Department, Centro Hospitalar S. João, Oporto, Portugal*
[g] *Chest Department, Hospital Pulido Valente, Centro Hospitalar Lisboa Norte, Lisbon, Portugal*
[h] *Intensive Care Unit, Hospital Lusíadas, Oporto, Portugal*
[i] *Faculdade de Medicina, Universidade do Porto, Oporto, Portugal*

[*] Corresponding author at: Intensive Care Unit, Hospital Vila Franca de Xira, Estrada Carlos Lima Costa, N2, 2600-009 Vila Franca de Xira, Portugal.
E-mail address: joao.goncalvespereira@hvfx.min-saude.pt (J. Gonçalves-Pereira).

Received 25 July 2022; Accepted 5 August 2022
Available online 1 November 2022

Pulmonology 29 (2023) 257—260

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Preclinical interstitial lung disease in relatives of familial pulmonary fibrosis patients

Interstitial lung disease (ILD) is a group of disorders characterised by chronic lung inflammation and/or fibrosis. Idiopathic pulmonary fibrosis (IPF) is one of the most common and devastating forms of ILD and is frequently diagnosed at an advanced stage, when patients have a life-expectancy of 2-3 years. There is growing evidence that genetic factors involved in IPF also contribute to a broader range of ILDs and interstitial lung abnormalities (ILA).[1] ILA is defined as incidental findings of specific computed tomography features that affect more than 5% of any lung zone and are potentially compatible with ILD (i.e. ground glass or reticular abnormalities, traction bronchiectasis, honeycombing and non-emphysematous cysts).[2] A growing number of studies have reported evidence of ILAs in clinically unaffected relatives of IPF patients and suggest that screening first-degree relatives is a worthwhile approach to improve detection of ILD in its early stages.[3-5] Indeed, the recent Fleischner Society's position paper recommends that the identification of ILA in familial ILD should not be considered incidental and suggests use of the term "preclinical ILD",[2] and this terminology has been adopted here. We have established a clinically-annotated familial ILD genetic resource aiming to

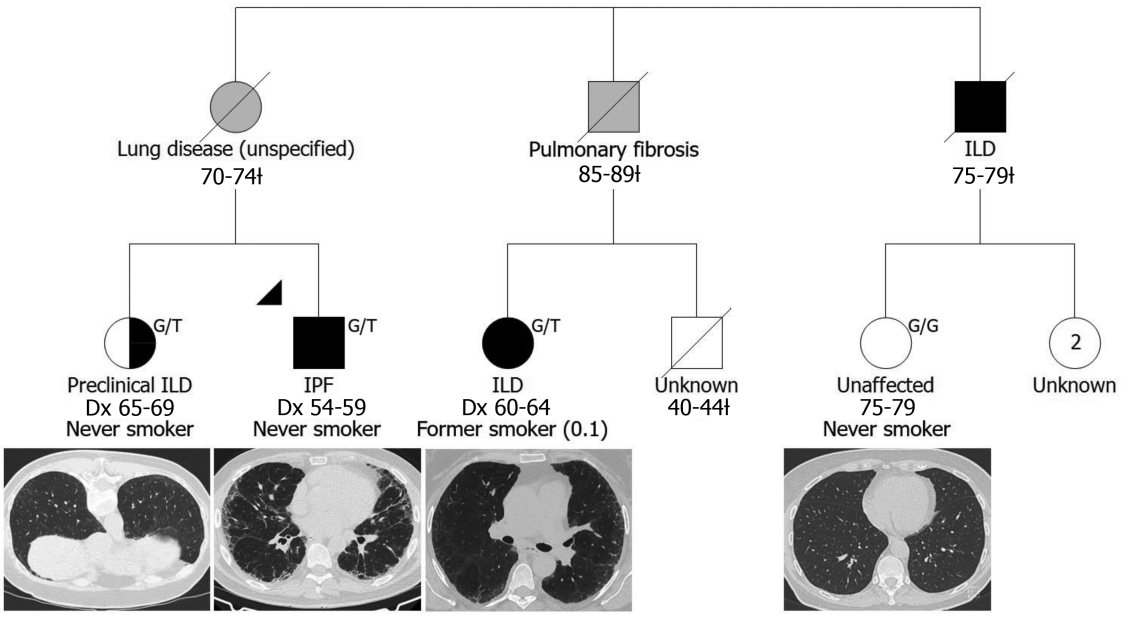

Fig. 1 A simplified pedigree depicting a family in which two relatives were screened: one was diagnosed with preclinical ILD while the other was unaffected at the time of examination. Males and females are depicted by squares and circles (respectively); the proband is indicated by the black triangle; deceased individuals are indicated by a diagonal slash and the age range at death is indicated below followed by a †; grey shading indicates that the clinical diagnosis was reported by the living generation; black shading indicates participants confirmed to have IPF/ILD and participants diagnosed with preclinical ILD are indicated by half black shading; age range at examination for the unaffected relative is indicated below unshaded symbol; 'Dx' indicates age range at diagnosis; two living, unscreened female relatives are currently 64-69 years of age; self-reported smoking status is indicated and pack years is presented in brackets; *MUC5B* rs35705950 genotype is presented at the top right, G/T indicates a heterozygous carrier and G/G indicates homozygous wildtype; representative chest HRCT images are presented below study participants.

https://doi.org/10.1016/j.pulmoe.2022.09.002

Table 1 Clinical characteristics of participants at the time of recruitment

	Patients (n=22)	Relatives with preclinical ILD (n=7)	Unaffected relatives (n=8)
Age	69.0 (49.0-83.0)	71.6 (56.0-88.0)	60.8 (47.0-75.0)
Female Sex, n (%)	10 (45.5)	5 (71.4)	4 (50.0)
BMI	28.4 (19.7-40.4)	25.3 (22.2-29.6)	30.1 (27.0-37.7); n=7
Ever Smoker, n (%)	12 (54.5)	2 (28.6)	4 (50.0)
Pack years	11.3 (0.0-58.0)	1.6 (0-9)	7.5 (0.0-24.8)
Sibling of a patient, n (%)	-	7 (100)	5 (62.5)
Clinical Diagnosis			
IPF	16	1	0
HP	2	0	0
CTD-ILD	1	0	0
ILA	3	6	0
Self-reported medical history, n (%)			
Asthma	4 (19.0); n=21	2 (25.0)	2 (25.0)
Ischemic heart disease	3 (14.3); n=21	0	0
Diabetes	1 (4.8); n=21	1 (14.3)	0
Lung cancer	0; n=21	0	0
Hypertension	7 (33.3); n=21	1 (14.3)	3 (37.5)
COPD	3 (14.3); n=21	0	0
Connective tissue disease	2 (9.5); n=21	0	0
Self-reported symptoms, n (%)			
Breathlessness	16 (80.0); n=20	1 (14.3)	2 (25.0)
Cough	16 (80.0); n=20	1 (14.3)	4 (50.0)
Wheeze	8 (40.0); n=20	1 (14.3)	3 (37.5)
Sputum	10 (50.0); n=20	0	2 (25.0)
Haemoptysis	1 (5.0); n=20	0	1 (12.5)
Specific examination features, n (%)			
Crackles on examination	15 (83.3); n=18	2 (28.6)	0
Wheezes on auscultation	0; n=18	0	1 (12.5)
Clubbing	2 (11.1); n=18	0	0
Specific HRCT findings, n (%)*			
Honeycombing	11 (50.0)	1 (14.2)	0
Ground-glass opacities	9 (40.9)	4 (57.1))	0
Interlobular reticular opacities	21 (95.5)	6 (85.7)	0
Lung distortion	18 (81.8)	3 (42.9)	0
Traction bronchiectasis	17 (77.3)	3 (42.9)	0
Traction bronchiolectasis	18 (81.8)	3 (42.9)	0
Any bilateral findings	22 (100.0)	6 (85.7)	0
Pulmonary function measures			
FVC % predicted	78.8 (34.2-121.8)	101.5 (84.3-115.6)	98.1 (77.6-120.2); n=7
FEV1 % predicted	81.7 (43.3-124.8)	100.3 (83.3-127.7)	92.9 (65.7-115.5); n=7
DLCO % predicted	56.2 (19.6-114.1)	88.2(68.4-117.9); n=6	102.2 (79.8-119.9); n=7
SGRQ scores			
SGRQ symptoms	48.8 (0.0-83.8)	10.0 (0.0-29.49)	17.0 (0.0-39.0)
SGRQ activity	52.2 (0.0-92.5)	20.4 (0.0-48.5)	13.2 (0.0-35.6)
SGRQ impacts	30.9 (0.0-81.4)	5.7 (0.0-25.9)	3.6 (0.0-21.4)
SGRQ total score	41.4 (6.2-85.2)	12.1 (0.0-25.8)	9.7 (0.0-28.7)
***MUC5B* rs35705950 genotype**, n (%)**			
GG	5 (23.8)	2 (28.6)	5 (62.5)
GT	13 (61.9)	5 (71.4)	3 (37.5)
TT	3 (14.3)	0	0
Total risk alleles (T)	19 (45.2%); n=21	5 (35.7%)	3 (18.8%)

* HRCT scans were reviewed by JM

** Genotypes were determined by Sanger sequencing of genomic DNA (primers available upon request).

Age = age at recruitment; IPF = idiopathic pulmonary fibrosis; HP = hypersensitivity pneumonitis; CTD-ILD = connective tissue disease ILD; ILA = interstitial lung abnormality BMI = body mass index; COPD = chronic obstructive pulmonary disease; FVC = forced vital capacity; FEV1 = forced expiratory volume; DLCO = diffusing capacity for carbon monoxide; SGRQ = St. George's Respiratory Questionnaire, *MUC5B* = Mucin 5B, Oligomeric Mucus/Gel-Forming gene.

All measurements are reported as mean(range), unless otherwise indicated. Predicted values (% predicted) were calculated using the Global Lung Function Initiatives for spirometry[8] (FVC and FEV1) and the carbon monoxide transfer factor[9] (DLCO).

better understand disease causation. Here, we provide additional evidence in support of screening relatives of ILD patients to identify those with preclinical ILD.

We defined recruitment criteria as families with multiple first-degree relatives diagnosed with ILD or ILA, where at least one had been diagnosed with IPF (hereafter collectively termed "patients"). Families were identified via a questionnaire sent to all living Australian IPF Registry[6] participants (September-November 2019) or directly recruited by respiratory physicians. Affected living individuals meeting the criteria for inclusion were recruited, in addition to at least one self-reported unaffected first-degree relative (hereafter known as "relative"). Relatives included were $\geq$ 50 years, except for those families with a case diagnosed before the age of 50, where relatives were included if at least as old as the youngest diagnosed case. This study reports all families in which at least one relative participated in a clinic visit. Of the families where a relative was not recruited, 38% did not have a suitably aged, living relative, whilst others were unable to participate due the impact of the global pandemic.

Informed consent and a physical examination were conducted by respiratory physicians, after which participants completed: questionnaires, including the St. George's Respiratory Questionnaire (SGRQ)[7]; a chest high resolution computed tomograph (HRCT) scan; full pulmonary function testing (PFT); and blood/saliva sample collection. To screen relatives for preclinical ILD, HRCT images were blinded and assessed by an ILD physician (JM). Preclinical ILD was classified using the Fleischner Society's ILA definition.[2]

Fifteen relatives participated from 12 families (example, Fig. 1). This included ten siblings, three offspring of patients, and two individuals who had both an affected parent and sibling. Seven relatives were found to have preclinical ILD (46.7%), while eight (53.3%) had no evidence of abnormalities (Table 1). The prevalence of preclinical ILD in our Australian cohort is higher than recent studies in the American families described by Hunninghake et al.[3] (26%) and Salisbury et al.[5] (23%). This may be due to our strict definition of familial ILD with a confirmed family history (as opposed to self-report), although our cohort was also smaller and older (65.8 years compared to 60 years[3] and 53.1 years[5]), which may have contributed to these differences.

A limitation of this study was that we were unable to examine possible ascertainment bias as we did not have access to AIPFR data for those who did not participate. In addition, the small sample size precluded formal statistical analysis to compare groups. Despite this, interesting trends have been observed. Relatives diagnosed with preclinical ILD tended to be older (71.6 *vs* 60.8 years) than the unaffected group. Consistent with a strong genetic predisposition in our familial cohort and earlier reports,[3,5] the frequency of the established IPF risk variant in the *MUC5B* promotor (rs35705950) was 45.2% in the known patients, 35.7% in relatives with preclinical ILD, but only 18.8% in the unaffected group. Counterintuitively, the rate of ever smoking in the preclinical ILD group was only 28.6%, while 50.0% of their unaffected counterparts, and 54.5% of known patients, were ever smokers. This finding is consistent with a previous report,[3] where the rate of ever smoking was lower in relatives from families with familial ILD compared to relatives of apparent sporadic patients (28% *vs* 52%), and may represent environmental risk modification in individuals with familial risk.

Preclinical ILD was only observed in siblings of patients, not offspring, with a prevalence of 58.3% when only considering relatives with an affected sibling. This finding is consistent with Aburto et al.[4], who reported that 52.6% of siblings of apparent sporadic IPF patients had preclinical ILD, whilst only 5.6% of patient's offspring were affected. Given the mean age of the offspring group was only 47.7 years,[4] compared with 59.4 years in our cohort, it is likely that some of these individuals may develop preclinical ILD in the future.

This report provides further evidence that clinical screening of first-degree relatives of ILD patients facilitates early diagnosis. Further research is required to determine appropriate screening for the offspring of ILD patients, however, we propose that the age of diagnosis for known patients in the family is an important consideration. Early diagnosis provides individuals with opportunities to adopt healthy lifestyle interventions, and access to improved clinical management as well as innovative treatments as they are developed.

Ethics approval

This study was conducted in accordance with the amended Declaration of Helsinki. The study was approved by the Sydney Local Health District Human Research Ethics Committee (X18-0193), University of Tasmania Health and Medical Human Research Ethics Committee (17775) and the Prince Charles Hospital Human Research Ethics Committee (53369).

Sources of support

This research was supported by an untied grant from a philanthropic family.

Conflicts of interest

None.

Acknowledgements

We are greatly indebted to our participants and their families for volunteering their time and clinical data; without their participation, this study would not be possible. We also thank the ILD nurses and coordinators, including Catriona Doran from Royal Adelaide Hospital; Elizabeth Ray, Shannon Cleary, Jessica Rhodes and Qi Lin from Royal Prince Alfred Hospital; Amy Cashmore from John Hunter Hospital; Sandra Bancroft from The Prince Charles Hospital; Karen Symons from The Alfred; Shona Knights-Rennie from Border Physicians Group; Samantha Wadham and Helen Rodgers from Sunshine Coast University Hospital and; David Clark from PathWest Albany. The Australian IPF Registry is facilitated by Lung Foundation Australia and is supported by unrestricted educational grants from Foundation Partners, Boehringer Ingelheim and Roche Products, Pty. Limited. SEML, PR, LT, DAS, RWB, SW, YM, SM, HW, DC, TJC and JLD made substantial contributions to the conception and design of the study; SL, KR, SM, TJC, LT, IG,

PNR, DC, CC, CG, JR and PK made substantial contributions to the acquisition of patients and clinical data; SEML and JM conducted data analysis; SEML; KR; JM and TLC and JLD made substantial contributions to the interpretation of the data; SEML and JLD drafted the manuscript; while all authors were involved in revising the manuscript critically for important intellectual content; gave final approval for publishing; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SEML, TJC and JLD are guarantors of this work, taking responsibility for the integrity of the work as a whole, from inception to published article.

References

1. Hunninghake GM, Hatabu H, Okajima Y, et al. MUC5B promoter polymorphism and interstitial lung abnormalities. N Engl J Med. 2013;368(23):2192—200.
2. Hatabu H, Hunninghake GM, Richeldi L, et al. Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. Lancet Respir Med. 2020;8(7):726—37.
3. Hunninghake GM, Quesada-Arias LD, Carmichael NE, et al. Interstitial Lung Disease in Relatives of Patients with Pulmonary Fibrosis. Am J Respir Crit Care Med. 2020;201(10):1240—8.
4. Aburto M, Aguirre U, Arrizubieta MI, et al. Checking Siblings of Patients with Idiopathic Pulmonary Fibrosis as a Scheme for Early Disease Detection. Ann Am Thorac Soc. 2021;18(1):172—4.
5. Salisbury ML, Hewlett JC, Ding G, et al. Development and Progression of Radiologic Abnormalities in Individuals at Risk for Familial ILD. Am J Respir Crit Care Med. 2020;201(10):1230—9.
6. Moodley Y, Goh N, Glaspole I, et al. Australian Idiopathic Pulmonary Fibrosis Registry: vital lessons from a national prospective collaborative project. Respirology. 2014;19(7):1088—91.
7. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis. 1992;145(6):1321—7.
8. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3—95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324—43.
9. Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. Eur Respir J. 2017;50(3):1700010.

S.E.M. Lucas[a], K. Raspin[a], J. Mackintosh[b,c], I. Glaspole[d,e], P.N. Reynolds[f,g], C. Chia[h], C. Grainge[i], P. Kendall[j,k], L. Troy[l,m], D.A. Schwartz[n], R. Wood-Baker[o], S.L.F. Walsh[p], Y. Moodley[q,r], J. Robertson[s], S. Macansh[t], E.H. Walters[a,o], D. Chambers[b,c], T.J. Corte[l,m,1], J.L. Dickinson[a,1,*]

[a] *Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia*
[b] *School of Medicine, The University of Queensland, Brisbane, QLD, Australia*
[c] *QLD Lung Transplant Service, Department of Thoracic Medicine, The Prince Charles Hospital, Brisbane, QLD, Australia*
[d] *Department of Respiratory Medicine, Alfred Health, Melbourne, VIC, Australia*
[e] *Department of Medicine, Monash University, Melbourne, VIC, Australia*
[f] *Royal Adelaide Hospital, Adelaide, SA, Australia*
[g] *University of Adelaide, Adelaide, SA, Australia*
[h] *Launceston General Hospital, Launceston, TAS, Australia*
[i] *School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia*
[j] *Respiratory Medicine Service, Albany, WA, Australia*
[k] *School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia*
[l] *Department of Respiratory Medicine, Royal Prince Alfred Hospital, Camperdown, NSW, Australia*
[m] *School of Medicine, The University of Sydney, Camperdown, NSW, Australia*
[n] *Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA*
[o] *Tasmanian School of Medicine, University of Tasmania, Hobart, TAS, Australia*
[p] *National Heart and Lung Institute, Imperial College London, London, England, UK*
[q] *University of Western Australia, Institute for Respiratory Health, Perth, WA, Australia*
[r] *Department of Respiratory Medicine, Fiona Stanley Hospital, Perth, WA, Australia*
[s] *Border Physicians Group, West Albury, NSW, Australia*
[t] *Lung Foundation Australia, Brisbane, QLD, Australia*

[*] Corresponding author at: Menzies Institute for Medical Research, University of Tasmania, 17 Liverpool St (Private Bag 23), Hobart TAS 7000.
E-mail address: jo.dickinson@utas.edu.au (J.L. Dickinson).

Received 15 July 2022; Accepted 6 September 2022
Available online 7 October 2022

[1] Joint last author

Pulmonology 29 (2023) 261—263

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Transcatheter embolization of pulmonary artery pseudoaneurysm secondary to squamous-cell lung cancer

To the Editor,

Pseudoaneurysm is a rare abnormality of the pulmonary arteries. Pulmonary artery pseudoaneurysm (PAP) may develop due to primary lung cancer or metastatic lung disease, a rare phenomenon; the proposed mechanism for its formation involves direct tumour invasion and erosion of the vessel wall.[1] Due to hemoptysis and the risk of rupture and enlargement, therapy is essential. Transcatheter embolization is a possible approach,[1,2] but little has been reported in this context. In this report, we describe an uncommon case of a PAP secondary to squamous-cell lung cancer and approach with coil embolization.

A 60-year-old male was admitted to the emergency department with a 3-week history of recurrent episodes of moderate hemoptysis. Past medical history was significant for 2-month diagnosis of squamous-cell lung cancer staged as cT4N2M0—IIIB (mass in the right upper lobe involving the upper lobar bronchus and extending into the peribronchovascular regions of the upper and middle lobes) under chemotherapy with Carboplatin and Gemcitabine. Physical examination was normal, except for diminished breath sounds in the right upper lung field. Blood test revealed anaemia (8.4g/dL), leucocytosis (23120/μL) and elevation of serum C-reactive protein levels (14.54mg/dL). Chest radiography showed a cavitary mass with an air-fluid level in the right upper lobe with ipsilateral mediastinal shift.

The diagnosis of superimposed infection secondary to the lung tumour was assumed, and the patient was hospitalized. An empiric antibiotic therapy with Piperacillin/Tazobactam and Aminocaproic Acid intravenous infusion was started. No microbiological isolates were found in blood, urine, or sputum. Contrast-enhanced chest computed tomography (CT) was performed, revealing a cavitary mass involving the pulmonary artery branch to the middle lobe, causing stenosis in its proximal segment and distal ectasia (Fig. 1). Fiberoptic bronchoscopy identified a vascular infiltrative lesion in the right upper lobe bronchus with no evidence of active bleeding at that time, therefore no endoscopic intervention was performed.

Given the persistence of moderate hemoptysis and anaemia, after a multidisciplinary meeting comprising Pulmonology and Interventional Radiology, transcatheter arterial embolization of the vascular lesion was decided upon. Under conscious sedation, the right pulmonary artery was catheterized via the right femoral vein using the ultrasound control. The angiography detected the presence of a fusiform pseudoaneurysm of the middle lobe branch of the pulmonary artery, with a maximum diameter of 5-mm and an extension of 2-cm between the origin and the arterial bifurcation (Fig. 2). After superselective catheterization, the lesion was embolized with several detachable coils of 0.018-inch size and 3-6mm diameter with the proximal coil placed 2-mm from the origin. The final angiographic study demonstrated complete occlusion of the PAP (Fig. 2). There were no complications. The patient was discharged with occasional blood-streaked sputum, and no anaemia. A follow-up chest CT after 1 month showed coils in the middle lobe branch of the pulmonary artery with occlusion of distal branches. The patient remained with only some episodes of blood-streaked sputum, predominantly in the morning, and a blood test without haemoglobin decrease.

Hemoptysis originates from the pulmonary arteries in less than 10% of patients,[3,4] and pseudoaneurysm is the main cause of bleeding.[5] Their wall consists of either a single layer of the arterial wall or the surrounding tissue and thus poses a higher risk of rupture.[1,2] PAP may be associated with various etiologies such as infection, with tuberculosis being the most common, bronchiectasis, trauma, iatrogenesis, vasculitis, and malignancy.[2,5,6] According to some reported cases, PAP due to primary lung cancer is rare and is commonly combined with tumour necrosis.[6] The squamous-cell carcinoma is the most frequent carcinoma involved in PAP, due to its biological features that make it prone to necrosis.[6] In this case, the PAP was secondary to tumour progression involving a peripheral branch of the right pulmonary artery.

PAPs can be treated by interventional radiologists using minimally invasive endovascular techniques as an alternative to surgical management[1]. Due to its rarity, mainly isolated case reports about endovascular treatment have been published.[4,7] To the best of our knowledge, few cases have been reported in the literature on endovascular management of pulmonary artery lesions

https://doi.org/10.1016/j.pulmoe.2022.07.013

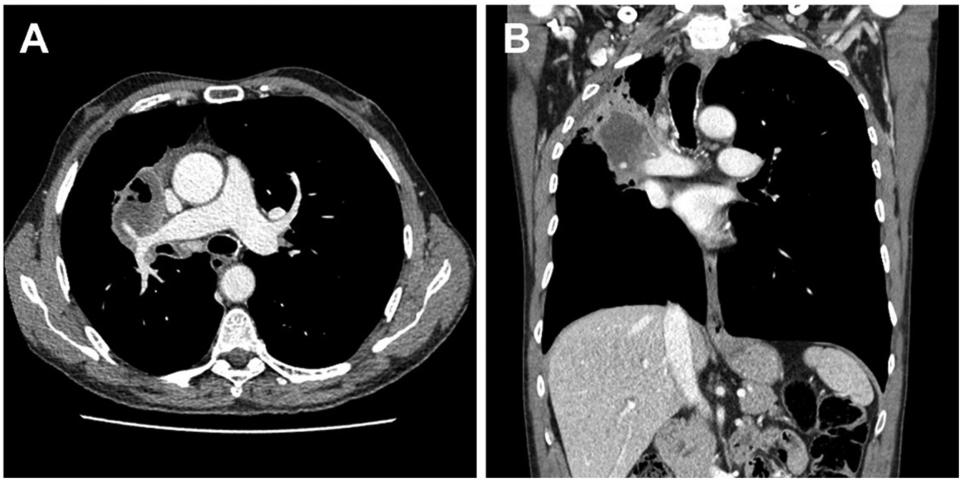

Fig. 1 Contrast-enhanced axial (A) and coronal sectional (B) chest CT with mediastinal setting revealing a cavitary mass completely involving the middle lobe branch of the pulmonary artery causing stenosis in its proximal segment and distal ectasia.

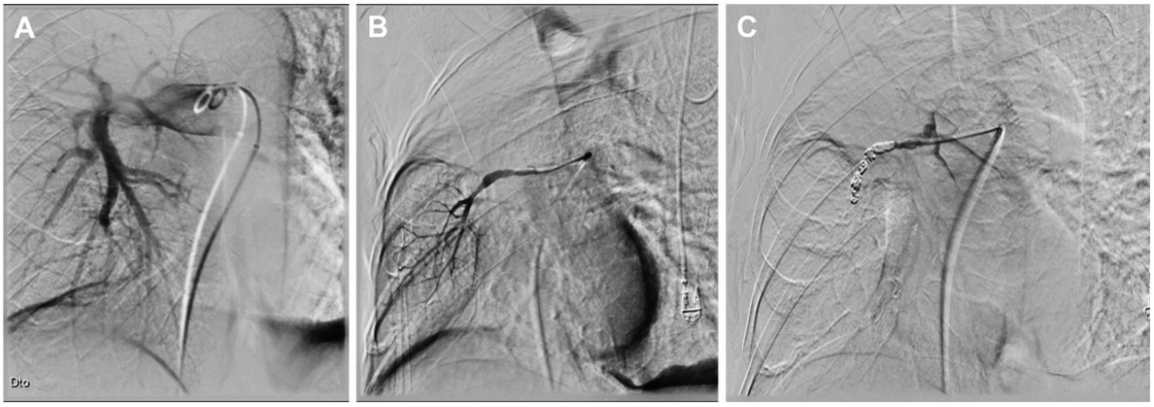

Fig. 2 Angiography studies. (A) Pre-procedure selective right pulmonary angiography (B) shows the fusiform pseudoaneurysm of the middle lobe branch of the pulmonary artery. (C) Angiography post-procedure shows the complete embolization of the pseudoaneurysm with multiple detachable coils.

caused by lung tumours.[4,6] Various techniques for effective embolization have been described using several embolic agents, such as, coils, vascular plugs, stents, and liquid agents.[1,4,6,7] In this case, coil embolization was chosen due to the operator's previous experience with bronchial embolization. Detachable coils have the advantage of allowing better control of their liberation, and so complications, such as coil migration and vessel wall damage are diminished.[7]

The presented case supports the current evidence showing that pulmonary artery endovascular management is an effective, safe, and minimally invasive therapeutic approach for the treatment of hemoptysis in patients with lung tumors[4], although few centres perform it.

Authorship

ARG and EMT wrote the manuscript. ES and TS followed the patient. IM was the radiologist who reported the vascular lesion on contrast-enhanced chest CT. TP was the interventional radiologist who performed the procedure and ARG followed the procedure. ARG, EMT, ES, TS, IM, and TP read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Considerations

Written informed consent was obtained for use of clinical data and publication.

Declaration of Competing Interest

All authors have no conflicts of interest to declare.

References

1. Park HS, Chamarthy MR, Lamus D, Saboo SS, Sutphin PD, Kalva SP. Pulmonary artery aneurysms: diagnosis & endovascular therapy. Cardiovasc Diagn Ther. 2018;8(3):350—61. https://doi.org/10.21037/cdt.2018.04.01.
2. Zugazaga A, Stachno MA, García A, et al. Pulmonary artery pseudoaneurysms: endovascular management after adequate imaging diagnosis. Eur Radiol. 2021;31(9):6480—8. https://doi.org/10.1007/s00330-021-07819-8.
3. Andersen PE. Imaging and interventional radiological treatment of hemoptysis. Acta Radiol. 2006;47(8):780—92. https://doi.org/10.1080/02841850600827577.
4. Marcelin C, Soussan J, Desmots F, Gaubert J-Y, Vidal V, Bartoli JM, Izaaryene J. Outcomes of pulmonary artery embolization and stent graft placement for the treatment of hemoptysis caused by lung tumors. J Vasc Interv Radiol. 2018;29(7):975—80. https://doi.org/10.1016/j.jvir.2018.01.773.
5. Shin S, Shin T-B, Choi H, et al. Peripheral pulmonary arterial pseudoaneurysms: therapeutic implications of endovascular treatment and angiographic classifications. Radiology. 2010;256(2):656—64. https://doi.org/10.1148/radiol.10091416.
6. Zhang J, Jiang S. Massive haemoptysis from a central pulmonary arterial pseudoaneurysm secondary to advanced lung cancer: successful treatment by Guglielmi detachable coil embolization. Clin Respir J. 2017;11(2):258—62. https://doi.org/10.1111/crj.12333.
7. Lal A, Bansal A, Chaluvashetty SB, Sandhu MS, Gorsi U. Percutaneous transthoracic embolisation for massive haemoptysis secondary to peripheral pulmonary artery pseudoaneurysms. Eur Radiol. 2021;31(4):2183—90. https://doi.org/10.1007/s00330-020-07348-w.

A.R. Gigante[a,*], E.M. Tinoco[a], I. Marques[b], E. Silva[a], T. Shiang[a], T. Pereira[c]

[a] *Serviço de Pneumologia, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal*
[b] *Serviço de Imagiologia, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal*
[c] *Unidade Funcional de Radiologia de Intervenção, Grupo Trofa Saúde, Vila Nova de Gaia, Portugal*

[*] Corresponding author at: Serviço de Pneumologia, Centro Hospitalar Vila Nova de Gaia/Espinho. R. Conceição Fernandes S/N, 4434-502 Vila Nova de Gaia, Portugal.
E-mail address: anarita.gigante@gmail.com (A.R. Gigante).

Received 5 May 2022; Accepted 27 July 2022
Available online 28 September 2022

Pulmonology 29 (2023) 264—265

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

A curious presentation of an endobronchial Hodgkin's lymphoma in a sarcoidosis-lymphoma syndrome

Dear Editor,

The simultaneous occurrence of sarcoidosis and lymphoproliferative disease is a rare but well-established entity called sarcoidosis-lymphoma syndrome. Despite being increasingly recognized, it remains a diagnostic challenge due to clinical and imaging similarities.[1] In most cases, sarcoidosis precedes lymphoma, with non-Hodgkin's lymphoma being the most commonly associated type.[1,2] In this case report we describe a rare presentation of endobronchial Hodgkin lymphoma in a patient with sarcoidosis-lymphoma syndrome.

A thirty-seven-year-old male, non-smoker, was diagnosed with lymph node, bone and cutaneous sarcoidosis in 2018, initially treated with prednisolone 40mg/day, later tapered to a maintenance dose of 10mg/day; and with Stage IV classic Hodgkin's Lymphoma (HL), in 2019, treated with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and achieving complete remission in 2020. He was asymptomatic to date.

In February 2021 the patient started to complain of dry cough, fever and night sweats. Physical examination was unremarkable. Laboratory investigations revealed worsening microcytic anemia (hemoglobin of 8.0g/dL) and both high erythrocyte sedimentation rate (72mm/h) and C-reactive protein (11mg/dL). Chest radiograph was normal.

18-FDG Positron emission tomography was performed and showed multiple supra and infradiaphragmatic foci with active metabolism (elevated maximum standardized uptake values (SUVmax)) suggesting active lymphoproliferative disease.

As there was no biopsiable peripheral lymphadenopathy, the patient underwent endobronchial ultrasound (EBUS). The procedure revealed multiple pearly nodular lesions throughout the tracheobronchial tree (Figs. 1 and 2). Bronchial biopsies were performed and mediastinal lymph nodes were punctured at stations 4R and 7 by EBUS-transbronchial needle aspiration.

The anatomopathology of the endobronchial lesions showed HL infiltration and the examination of the lymph nodes showed non-caseating epithelioid granulomas compatible with sarcoidosis. HL relapse was assumed.

The patient was started on chemotherapy treatment with protocol DHAP (dexamethasone, cytarabine, cisplatin and prednisolone), having completed five cycles, with an intermediate response. On reassessment in January 2022, there were signs of disease progression with PET-CT scan showing splenic, multifocal osteomedullary and supra and infra-diaphragmatic lymph nodes involvement. Excisional lymph node biopsy of cervical adenomegaly was performed which, again, confirmed relapse of Hodgkin's Lymphoma and the patient was started on 3rd-line chemotherapy with BV-GVD (brentuximab vedotin + gemcitabine, vinorelbine and doxorubicin) and was proposed for autologous stem cell transplantation.

The sarcoidosis-lymphoma syndrome was first described in 1986 by Brincker.[2]

Lymphoproliferative disease develops relatively frequently in patients with chronic active sarcoidosis, probably as a consequence of immunological abnormalities observed in this pathology, such as an increased number of T-helper cells in granulomatous tissues, a decreased number of circulating T-helper cells and hyperactivity of the B-cell system. The prolonged immunosuppression therapy, may also have an important role.[2,3]

The diagnosis of sarcoidosis-lymphoma syndrome is a challenge, since granulomatous inflammation can occur in infections and neoplasms, and is not, in isolation, a diagnosis of sarcoidosis. In our patient, other analytical changes, such as the increase in angiotensin-converting enzyme (ACE) and hypercalcemia, helped the initial diagnosis of sarcoidosis.

The diagnosis of lymphoma was made later by histologic examination of lymph nodes, thus allowing the diagnosis of sarcoidosis-lymphoma syndrome.[1,2] A rare aspect of this case is the association between Hodgkin lymphoma and sarcoidosis, which, despite being less common, is also described in the literature.

Another unusual aspect that is highlighted in this clinical case is the recurrence of lymphoma with a rare endobronchial presentation. Pulmonary involvement of HL may occur in up to 40% of cases, but endobronchial involvement is rare, or may be underdiagnosed.[4,5] Its frequency varies according to the authors (described in living patients between 1.9-14% of patients with HL). The frequency of endobronchial lymphoma is higher post-mortem.[5] The secondary bronchi and

https://doi.org/10.1016/j.pulmoe.2022.07.006

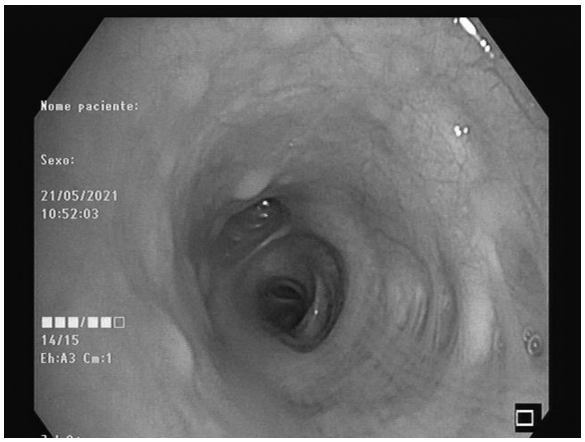

Fig. 1 Multiple pearly nodular lesions throughout the tracheobronchial tree.

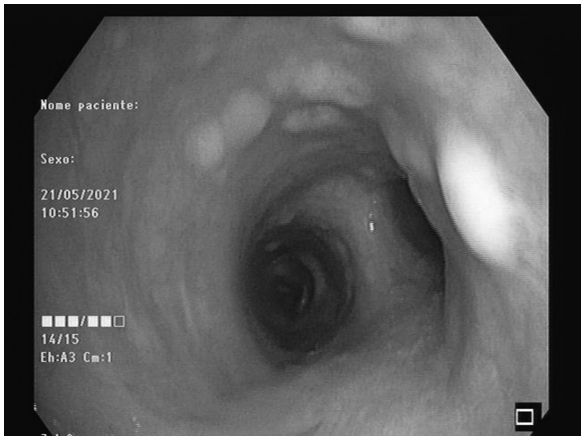

Fig. 2 Multiple pearly nodular lesions throughout the tracheobronchial tree.

bronchioles are most often affected, in relation to the main bronchi and trachea. The origin physiopathology is thought to involve transmural spread of hilar adenopathies or blood spread from an extrathoracic focus.[6] Lesions may present as platyform mucosal infiltrates with superficial ulceration or, more rarely, a single polypoid mass.

In this patient, the diagnosis of endobronchial lymphoma was an incidental finding during EBUS procedure aimed to evaluate mediastinal lymphadenopathy. The presence of non-caseating epithelioid granulomas could be inferred as a recurrence of sarcoidosis.

In summary, this case highlights the differential diagnosis between sarcoidosis and lymphoma, the possibility of their overlap and the need for systematic exploration of the tracheobronchial tree in suspected lymphoma. Bronchoscopy evaluation in these patients might allow the histological diagnosis through lesion biopsy and the evaluation of the extent of HL, which will influence the prognosis and treatment of the disease.

Authors' contribution

Study Conception and design: Catarina Barata, José Pedro Boléo-Tomé.

Data acquisition: Catarina Barata, Margarida Isabel Pereira, Miguel Barbosa.

Data analysis and interpretation: Catarina Barata, Margarida Isabel Pereira, Miguel Barbosa, Filipa Mousinho.

Dafting of the manuscript: Catarina Barata, Margarida Isabel Pereira, Miguel Barbosa

Critical revision of the manuscript for important intelectual content: Filipa Mousinho, José Pedro Boléo-Tomé.

All authors read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Oskuei A, Hicks L, Ghaffar H, Hoffstein V. Sarcoidosis-lymphoma syndrome: a diagnostic dilemma. BMJ Case Rep. 2017;bcr2017220065. https://doi.org/10.1136/bcr-2017-220065. bcr2017220065.
2. Brincker H. The sarcoidosis-lymphoma syndrome. Br J Cancer. 1986;54(3):467—73. https://doi.org/10.1038/bjc.1986.199.
3. Oliwiecki S, Kotecha B, Kingston T, Rothera MP. Sarcoidosis-lymphoma syndrome. J R Soc Med. 1992;85(3):176—7.
4. Kiani B, Magro CM, Ross P. Endobronchial presentation of Hodgkin lymphoma: a review of the literature. Ann Thorac Surg. 2003;76 (3):967—72. https://doi.org/10.1016/S0003-4975(03)00140-1.
5. Amro L, Jridi S, Sajiai H, Serhane H, Batahar SA. Endobronchial localization of Hodgkin's disease. Pan African Med J. 2017;28:9. https://doi.org/10.11604/pamj.2017.28.9.11315.
6. Harper PG, Fisher C, McLennan K, Souhami RL. Presentation of Hodgkin's disease as an endobronchial lesion. Cancer. 1984;53(1):147—50. https://doi.org/10.1002/1097-0142(19840101)53:1<147::AID-CNCR2820530126>3.0.CO;2-J.

C. Barata[a], M.I. Pereira[b], M. Barbosa[c], F. Mousinho[d], J.P. Boléo-Tomé[b]

[a] *Serviço de Pneumologia, Centro Hospitalar de Lisboa Ocidental, EPE, Lisboa, Portugal*
[b] *Serviço de Pneumologia, Hospital Professor Doutor Fernando Fonseca, EPE, Amadora, Portugal*
[c] *Serviço de Pneumologia, Centro Hospitalar Barreiro Montijo, EPE, Montijo, Portugal*
[d] *Serviço de Hematologia, Centro Hospitalar de Lisboa Ocidental, EPE, Lisboa, Portugal*
E-mail address:
Received 2 June 2022; Accepted 10 July 2022
Available online 16 September 2022

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

COVID-19 pandemic mistakes and monkeypox: Correspondence

Dear Editor, we would like to share ideas on the publication by Boschiero et al.[1] Although monkeypox doesn't seem to have the same potential for spreading, Boschiero et al. noted that public health policies should be implemented to reduce the spread and fatality of monkeypox and prevent the emergence of a new "COVID-19." These policies include a proper testing policy, implementation of vaccination, proper clinical management, self-isolation, when necessary, and even the investment in new antivirals to treat monkeypox. We all concur that a strong public health response strategy is required to combat the spread of monkeypox. The knowledge gained through COVID-19 may be helpful. The main issue may be the under-recognition and low awareness of the issue, which can recur. Normal public health measures, including airport screenings to prevent disease importation, are in place in a number of countries, but the disease can still spread to new regions like Southeast Asia. According to our scenario, which takes place in Southeast Asia, the local public health ministry first devised the procedures for conducting airport screening, much like it had just done during COVID-19.[2] However, the issue of faulty diagnosis from screening for monkeypox exists, and the final imported monkeypox case—which could pass the screening at the airport—occurred—just as it did in the recent COVID-19 incident. Specifically, there is one instance where the patient passed immigration disease screening before receiving a diagnosis at a regional hospital inside a nation. This particular patient ultimately evaded hospitalization and again made it through the emigration process into a neighboring country (see details at https://www.thansettakij.com/health/533845). It is important to remember that the initial imported cases typically exhibited abnormal clinical symptoms, a skin lesion on a concealed area of the body, and a lack of fever. Lack of a certain expert with enough experience is typically another serious issue. In developing nations, it occasionally happens that local scientists exaggerate their capabilities to control the disease.[3] In July 2022, the first case of monkeypox was reported. The first article in the regionally cited medical journal of the local Department of Medicine was made available in September 2022 to correspond to the newly emergent concern. Without any specific information from local experience, the local reference's information on basic epidemiology, disease diagnosis, and treatment is taken directly from the WHO reference.[4] Additionally, there are no clear criteria for disease control.[4] This ought to be a moment for open dialogue. It is acceptable to admit that one knows little about a new condition and that asking for advice from knowledgeable colleagues around the world will be helpful.

Conflict of interest

None.

References

1. Boschiero MN, Palamim CVC, Marson FAL. Learning with the COVID-19 pandemic mistakes: facing the progression of the first cases of Monkeypox in Brazil. Pulmonology. 2023;29. https://doi.org/10.1016/j.pulmoe.2022.08.007.
2. Sriwijitalai W, Wiwanitkit V. Positive screening for Wuhan novel coronavirus infection at international airport: What's the final diagnosis for positive cases. Int J Prev Med. 2020;11:30.
3. Sriwijitalai W, Wiwanitkit V. Exaggerated information and COVID-19 outbreak. Eur J Clin Invest. 2020;50(5):e13226.
4. Wichaidit M, Trisukosol P, Kwangsuksathit A, Vorawutthinum N, Suthikulsethi P, Kutthipattanapong P, et al. Monkeypox. Monkeypox, 47. Bull Medical Department (Thai); 2022. p. 5—8.

R. Mungmunpuntipantip[a,*], V. Wiwanitkit, Adjunct professor[b,c]

[a] *Private Academic Consultant, Bangkok Thailand*
[b] *University Centre for Research & Development Department of Pharmaceutical Sciences Chandigarh University Gharuan, Mohali, Punjab, India*
[c] *Joseph Ayobabalola University, Ikeji-Arakeji, Nigeria*

[*] Corresponding author.
E-mail address: rujittika@gmail.com
(R. Mungmunpuntipantip).
Received 3 October 2022; Accepted 10 October 2022
Available online 17 October 2022

https://doi.org/10.1016/j.pulmoe.2022.10.003

Pulmonology 29 (2023) 267—268

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Learning with the COVID-19 pandemic mistakes: Facing the progression of the first cases of Monkeypox in Brazil. Authors' reply

Dear Editor, we read with enthusiasm the correspondence by Mungmunpuntipantip and Wiwanitkit,[1] in which the authors added a valuable discussion to our published paper.[2]

Apart from the public health policies we discussed in our paper, our colleagues also highlighted the importance of normal public health measures (e.g., airport screening) and, especially, the lack of expertise and clinical management of such a new viral disease. They also pointed out that scientists might have overconfidence in their abilities to treat/control new diseases such as Monkeypox,[3] mainly in developing countries, such as Thailand, India, and Brazil which can compromise the disease dispersion causing a possible new pandemic.

On top of proper public health policies, scientists and health professionals should not repeat the same mistakes made during the Coronavirus Disease (COVID)-19 pandemic. Also, it is important to optimize scientific knowledge with caution, enabling the emergence of high-quality science. The first step to do that is to improve the inclusion of science in professional qualifications and to publish high-quality studies rather than just achieving a higher F-impact or improving our own H-index.[4] It was noteworthy how COVID-19 papers were reviewed faster and how pre-print repositories have grown during the COVID-19 pandemic,[5] which may even characterize a "paperdemic".[6,7] Unfortunately, the higher number of published papers was not followed by adequate scientific scrutiny, which translated into a higher retraction rate from COVID-19 papers.[7] Although we do need scientific research regarding Monkeypox, it is our duty, as scientists, not to sacrifice scientific method and quality to the anxiety for publication. As one might say "we need less research, better research, and research done for the right reasons".[8]

Funding

[MNB] Fundação de Amparo à Pesquisa do Estado de São Paulo (Foundation for Research Support of the State of São Paulo, Brazil; #2022/05810-7).

Ethics approval

The data used in our study were made publicly available, not containing consent-free personal data since it does not present risks to the research participants.

Consent to participate

Not required.

Consent for publication

The authors have approved the manuscript and agreed with the submission.

Data and material availability

We accessed the complete data in Our World in Data (https://ourworldindata.org/).

Code availability

Not required.

Authors' contributions

Not applicable.

Declaration of Competing Interest

Not required.

References

1. Mungmunpuntipantip R, Wiwanitkit V. COVID-19 pandemic mistakes and monkeypox: correspondence. Pulmonology. 2022;This issue. https://doi.org/10.1016/j.pulmoe.2022.10.003.
2. Boschiero MN, Palamim CVC, Marson FAL. Learning with the COVID-19 pandemic mistakes: facing the progression of the first cases of Monkeypox in Brazil. Pulmonology. 2022. https://doi.org/10.1016/j.pulmoe.2022.08.007.

https://doi.org/10.1016/j.pulmoe.2022.10.004

3. Sriwijitalai W, Wiwanitkit V. Exaggerated information and COVID-19 outbreak. Eur J Clin Investig. 2020;50(5):e13226. https://doi.org/10.1111/eci.13226.
4. Ambrosino N, Pacini F. Publish or perish? Perish to publish? (Unrequested advices to young researchers). Pulmonology. 2022;28(5):327—9. https://doi.org/10.1016/j.pulmoe.2022.03.008.
5. Else H. How a torrent of COVID science changed research publishing — in seven charts. Nature. 2020;588(7839):553. https://doi.org/10.1038/d41586-020-03564-y.
6. Dinis-Oliveira RJ. COVID-19 research: pandemic versus "paperdemic", integrity, values and risks of the "speed science. Forensic Sci Res. 2020;5(2):174—87. https://doi.org/10.1080/20961790.2020.1767754.
7. Boschiero MN, Carvalho TA, Marson FA de L. Retraction in the era of COVID-19 and its influence on evidence-based medicine: is science in jeopardy? Pulmonology. 2021;27(2):97—106. https://doi.org/10.1016/j.pulmoe.2020.10.011.
8. Altman DG. The scandal of poor medical research. BMJ. 1994;308(6924):283—4. https://doi.org/10.1136/bmj.308.6924.283.

M.N. Boschiero[a,1], C.V.C. Palamim[a,b,1], F.A.L. Marson[a,b,1,*]

[a] *Laboratory of Cell and Molecular Tumor Biology and Bioactive Compounds, São Francisco University, Bragança Paulista, SP, Brazil*
[b] *Laboratory of Human and Medical Genetics, São Francisco University, Bragança Paulista, SP, Brazil*

[*] Corresponding author at: São Francisco University; Post graduate Program in Health Science; Laboratory of Cell and Molecular Tumor Biology and Bioactive Compounds and Laboratory of Human and Medical Genetics. Avenida São Francisco de Assis, 218. Jardim São José, Bragança Paulista, São Paulo, 12916-900, Brazil.
E-mail addresses: fernando.marson@usf.edu.br, fernandolimamarson@hotmail.com (F.A. Marson).
Received 6 October 2022; Accepted 11 October 2022
Available online 24 October 2022

[1] These authors contributed equally to this study.

Pulmonology 29 (2023) 269—270

PULMONOLOGY

www.journalpulmonology.org

PHOTO

Diffuse pulmonary calcification in a patient with renal failure and no alterations in phosphorus—calcium metabolism

T. Cobo Ruiz[a,*], D. Herrán de la Gala[a], M. E. Peña Gómez[b]

[a] *Radiology Department, "Marques de Valdecilla" University Hospital. Santander, Cantabria, Spain*
[b] *Cardiothoracic Imaging Unit, "Marques de Valdecilla" University Hospital. Santander, Cantabria, Spain*

Received 7 April 2022; accepted 13 June 2022
Available online 22 October 2022

Diffuse or metastatic pulmonary calcification is a rare entity of unknown etiology, associated with a wide variety of benign and malignant processes.[1]

In 1855 Virchow first described metastatic pulmonary calcification. It is usually associated with phosphocalcic metabolism or pH alterations, both at a systemic and local level. Its most common cause is chronic kidney disease (CKD), but other causes include hyperparathyroidism, renal transplantation, hypervitaminosis D, and malignant diseases such as myeloma.[2]

We present the case of a 79-year-old male, non-smoker, who had been a marble worker for fifty years. He had a history of CKD with a histological diagnosis of membranoproliferative glomerulonephritis. He presented to the emergency department with dyspnea, cough, and fever, so a chest X-ray was taken showing a bibasal alveolointerstitial pattern (Fig. 1A), not present in the radiological study performed two years earlier (Fig. 1B). With the suspicion of bacterial pneumonia, antibiotic treatment was administrated without success. During admission his kidney function worsened, requiring hemodialysis. Given the persistence of dyspnea and hypoxemia, a CT pulmonary angiogram was performed. There was no evidence of embolism, but the study showed confluent and markedly hyperdense condensations of bibasal predominance (Fig. 1C).

Phosphocalcic metabolism abnormalities, hyperparathyroidism, or hypervitaminosis D were ruled out. Therefore, based on both clinical and radiological evidence, the diagnosis was metastatic pulmonary calcification in the context of CKD undergoing hemodialysis.

Metastatic calcification appears as a metabolic disorder in which calcium deposits accumulate in tissues outside their usual location.[3] Several factors have been implicated in its etiology, although it can also affect patients with normal phosphocalcic metabolism,[4] as in this case.

The lung is one of the main sites of metastatic calcium deposition, predominantly in the alveolar walls but also the bronchial wall, pulmonary arteries, and veins.[4] In autopsy series, metastatic calcification has been shown in 60—80% of hemodialysis patients,[5] although it is rarely detected during the patient's life.

Metastatic pulmonary calcification is a frequently asymptomatic and underdiagnosed condition.[5] It should be suspected when dialysis patients develop radiographic changes or unexplained respiratory symptoms,[5] which include dyspnea and nonproductive cough. The degree of respiratory distress often does not correlate with the amount of macroscopic calcification.[1]

Although its evolution and prognosis are generally favorable, it can sometimes progress to irreversible alveolar damage and respiratory failure.[3] Visceral calcifications usually persist despite treatment, which is none other than suppressing predisposing factors.[2]

Since chest radiography is not sensitive enough to demonstrate small amounts of calcium,[3] high-resolution computed tomography (HRCT) is the most sensitive and effective test

* Corresponding author
E-mail address: teresa.cobo@scsalud.es (T. Cobo Ruiz).

https://doi.org/10.1016/j.pulmoe.2022.06.005

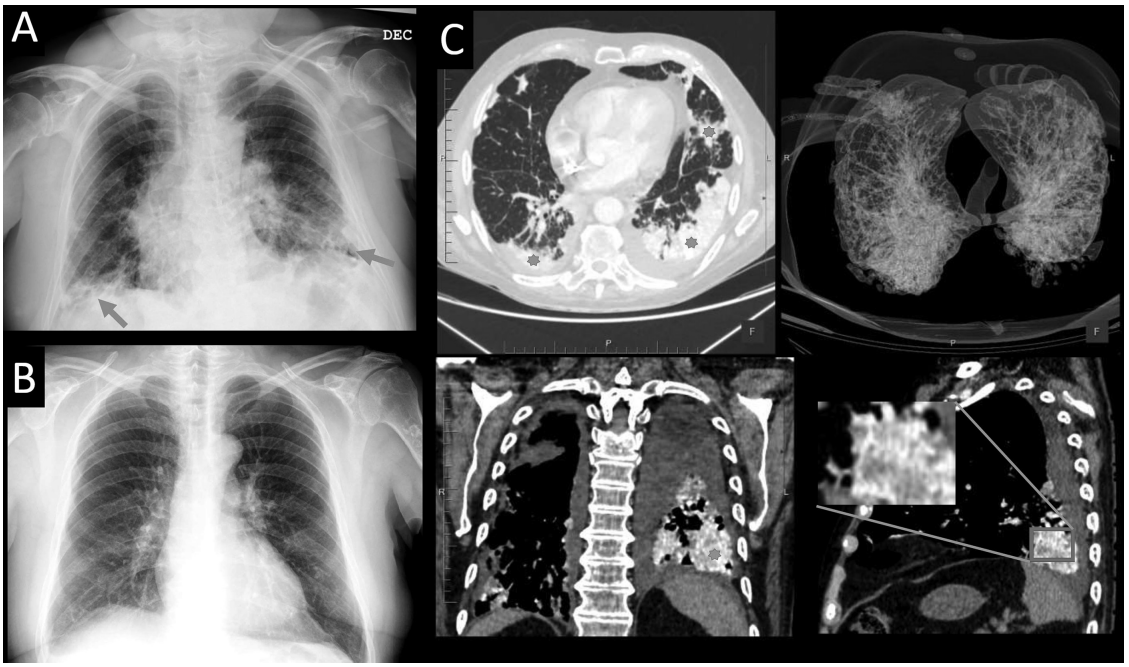

Fig. 1 (A) Chest X-ray performed at the Emergency room showing a bibasal alveolointerstitial pattern (green arrows). (B) Previous X-ray without those findings. (C) CT pulmonary angiogram in axial (up and left), coronal (down left), and sagittal (down right) planes with a 3D-VR reconstruction of the airway (up and right), showing confluent and markedly hyperdense condensations of bibasal predominance (asterisks) because of metastatic calcification.

for diagnosing this entity,[3,4] and lung biopsy is rarely used.[2] Three possible patterns of calcification are described on HRCT: diffusely distributed nodules, patchy areas of ground-glass opacity, and lobular distributed parenchymal consolidation areas.[4]

References

1. Chan ED, Morales DV, Welsh CH, McDermott MT, Schwarz MI. Calcium deposition with or without bone formation in the lung. Am. J. Respir. Cri.t Care Med. 2002;165(12):1654—69.
2. Villalobos S, Becerra R, Naranjo B, Juan M. Calcificación pulmonar metastásica: una rara causa de enfermedad pulmonar intersticial. Arch. Bronconeumol. 2003;39(4):184—6.
3. Lingam RK, Teh J, Sharma A, Friedman E. Case report. Metastatic pulmonary calcification in renal failure: a new HRCT pattern. Br. J. Radiol. 2002;75(889):74—7.
4. Castillo MC, Gimeno MJ, Carro B, Benito JL, Freile E, Sainz JM. Calcinosis pulmonar difusa en paciente con insuficiencia renal. Arch. Bronconeumol. 2005;41(10):587—9.
5. Belém LC, Zanetti G, Souza AS Jr, Hochhegger B, Guimarães MD, Nobre LF, et al. Metastatic pulmonary calcification: state-of-the-art review focused on imaging findings. Respir. Med. 2014;108 (5):668—76.