online

ELSEVIER EDITORIAL SYSTEM

Via the online submission and editorial system from Elsevier (EES).

Submit your paper online to **PULMONOLOGY JOURNAL**

Easy and friendly

Authors will notice that:

1. You can track your paper.
2. You will have your own space where you can view the status of your paper during the review process.
3. It speeds up the peer-review and publication process.

Reviewers and Editors will save time because:

1. It´s easily accessible.
2. It´s easy to submit your comments to the journal.
3. You will have access to different databases:

Direct searches in Medline + 30 days Free-Access to Scopus and ScienceDirect

every time a reviewer accepts and invitation

To submit your manuscript to

PULMONOLOGY JOURNAL

register at:

http://ees.elsevier.com/pulmoe

ELSEVIER

Pulmonology Journal
volume 27 / number 1 / January/February 2021

PULMONOLOGY JOURNAL

Previously **Revista Portuguesa de Pneumologia**

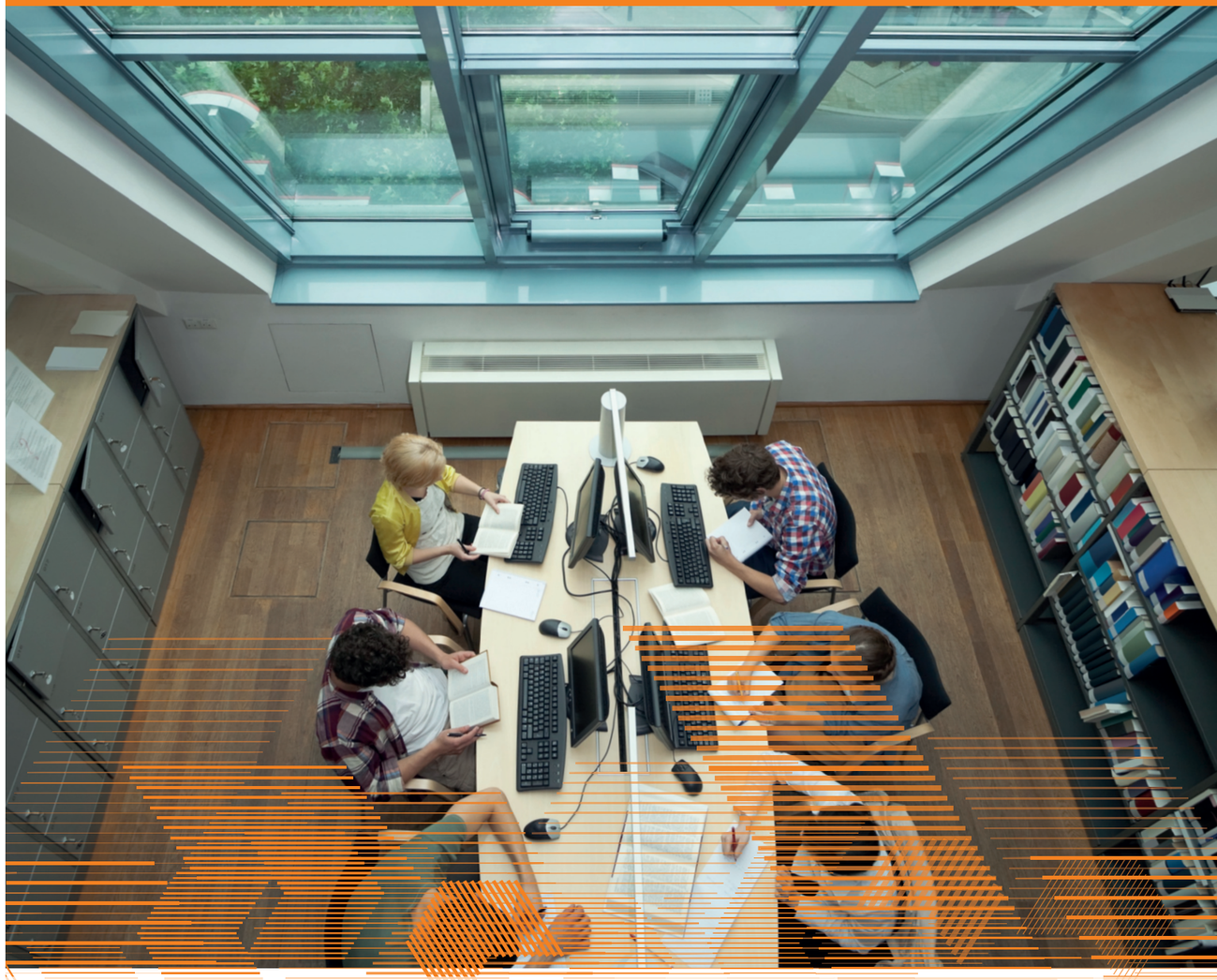
volume 27 / number 1 / January/February 2021

Original Articles

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: sppneumologia@mail.telepac.pt

ELSEVIER
Av. Josep Tarradellas, 20-30, 1°
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

ClinicalKey®

CK

The ClinicalKey Mobile App is here!

Leverage insights for better patient outcomes anytime, anywhere with the ClinicalKey mobile app – available for both Apple® and Android™ devices.

ClinicalKey helps clinicians rapidly access evidence-based, peer reviewed information to improve speed to accurate diagnosis and treatment, with the goal of improving patient outcomes and lowering the high cost of care.

Start your ClinicalKey mobile experience today!

- Open the App Store on your mobile device
- Search for "ClinicalKey" and install at no charge
- Once in the app, two options will appear – Click on ClinicalKey
- Enter your ClinicalKey username and password used for remote access and start using the ClinicalKey App!

Your institution must subscribe to ClinicalKey in order for you to use the app.
To sign up for a free 30-day trial, visit clinicalkey.com.au/info

Lead with answers.

ELSEVIER

PULMONOLOGY

www.journalpulmonology.org

Volume 27. Number 1. January-February 2021

CONTENTS

Letters to the Editor

Correspondence

ELSEVIER

WebShop

Elsevier WebShop's Language Services

Elsevier's Language Editing service offers professional English language editing for researchers preparing articles for publication in international scientific and medical journals.

Elsevier's PhD-level language editors have the expertise and editing experience necessary to ensure that your work is free of grammatical, spelling, and other common language errors before you submit, so that reviewers focus on the quality of your research rather than your language skills.

- ✓ Editing into proper scientific American or British English, by native speakers only
- ✓ PhD-level language editors, selected according to your field of study
- ✓ All work completed within 4 (short documents) or 7 business days
- ✓ Can be used for research papers, reports, books, PhD theses, grant applications, or Powerpoint presentations
- ✓ Exclusive Guarantee: free re-editing or money back

WebShop also offers:

Translation Services

Elsevier's translation services will ensure that your scientific or medical article or other technical documents are translated accurately and are free of language errors before you submit.

Currently available for: *Chinese, Spanish, Portuguese and 12 more languages*

Group Deals

Due to increasing demand from customers in research groups, university departments, and other research institutions, we have created **group deals which offer reduced prices** on bulk purchases for returning customers (or multiple customers at the same institution).

Our customers tell us that group deals have helped their budgets to go further, reduced their submission-to-publication times and positively impacted their research output – take advantage of these benefits for your own group!

ELSEVIER

find out more:
webshop.elsevier.com

Pulmonology 2021;**27(1)**:1–3

PULMONOLOGY

www.journalpulmonology.org

COMMENT

Challenges for the female health-care workers during the COVID-19 pandemic: the need for protection beyond the mask

Claudia Crimi[a,*], **Annalisa Carlucci**[b,c]

[a] *Respiratory Medicine Unit, ''Policlinico-Vittorio Emanuele-San Marco'' University Hospital, Via Santa Sofia, 78, 95123, Catania, Italy*
[b] *Department of Medicina e Chirurgia, Università Insubria Varese-Como, Italy*
[c] *Pulmonary Rehabilitation Unit, Istituti Clinici Scientifici Maugeri, Via S. Maugeri, 10, 27100, Pavia, Italy*

Received 26 June 2020; accepted 13 September 2020

KEYWORDS
Covid-19;
Gender gap;
Work-life balance

The COVID-19 outbreak hit the world with unprecedented consequences on global health, economy and people's lives.

As the virus spread across the countries, it rapidly showed a different impact on the two sexes. Gender analysis and sex-disaggregated data showed different outcomes across groups of similar age and sex, with an overall significantly higher COVID-19-related mortality rate in men compared with women.[1] Beyond epidemiological data, the virus has shed light on a silent gender gap that we need to look at.

Approximately 70% of the global health-care workforce is made up of women,[2] according to an analysis of 104 countries conducted by the World Health Organization, reaching 90% in Hubei province.[3] A first gap sticks out: most of the health-care heroes that tackled COVID-19 in the frontline were women, although they represent only 30% of leaders in Medicine and Science and authors of academic journal submissions on COVID-19.[4]

Moreover, a higher proportion of female health-care workers were infected in Italy, Spain, and USA (69%, 75.5%, 73% respectively).[1] A possible reason for that, besides potential biological mechanisms, is that personal protective equipment has been designed to fit males and even the smallest size is too big for some women.[5,6]

Interestingly, the countries that performed better against COVID-19 were guided by women, even if only 24% of females were involved in national governments' task forces dedicated to pandemic.[7] Notably, in Italy, the pandemic highlighted the lack of female representation in the government scientific committee and hospital organization leadership; therefore, women were not involved in the decision-making of the pandemic response. This represents the ''social paradox'' considering that like nothing in this

* Corresponding author.
E-mail addresses: dott.claudiacrimi@gmail.com (C. Crimi), annalisa.carlucci@icsmaugeri.it (A. Carlucci).

https://doi.org/10.1016/j.pulmoe.2020.09.004

era, women involved in health work showed the best skills in management.

Over the years, global organizations have made incredible efforts to improve gender-related policies, but COVID-19 has proved that it is still not enough. Today, man and woman have equal standing in the battle against COVID-19, but the virus has imposed an extra burden on female health-care workers, highlighting a silent gender difference.

Work-life has changed dramatically for health-care providers, with the high physical demand imposed by wearing the protective equipment for the entire shift, fighting against the fear of contagion and bringing home the virus to relatives, dealing with the anxiety of masks or goggles not fitting properly or involuntary dirty gloves touching the face. Moreover, they feel discouraged by the extreme challenges of caring for COVID-19 patients, coping with the emotional task of difficulty in communicating with patients and their relatives, dealing with people suffering and dying alone and sometimes facing the difficult decision of prioritizing care. In relation to this latter point, studies have shown gender-related behavioral differences in communication to patients among physicians, with females engaged in a more empathic approach compared to their male colleagues[8,9]; this may explain the higher prevalence of burnout among female frontline workers reported in Japan.[10]

On the other hand, life outside work has been incredibly demanding, especially for female workers, since women predominately assume the role of family caregiver.[11] Pandemic lockdowns and restrictions disproportionately impacted female workforces, especially those who also have domestic responsibilities and caregiving duties, affecting most of the services that helped them find a work-life balance, overloading them more than ever, with a permanent, challenging, and invisible extra shift work: the mental load of the planning, scheduling, coordinating, prioritizing, and problem-solving.[12] The daily emotional and mental pressures have been documented, showing a higher prevalence rate of anxiety, depression[13,14] and suicide in female frontline workers.[15]

In Italy, the government has taken measures to support workers with a ''Babysitter bonus'' to pay for home-based childcare, a noble initiative to help but not a practical solution to the problem of how to leave your children the following day. More efficiently, in other European countries some childcare facilities remain open with a skeleton staff to look after the children of essential service workers. Moreover, the alternative possibility of taking paid leave does not represent a proactive solution, jeopardizing women's careers. An innovative initiative was carried out by a private company running supermarkets in Northern Italy, allowing health-care workers to save time ordering their shopping online and collecting from a dedicated point in the hospital: a practical intervention dedicated to the few lucky workers in those areas.[16]

We should support and protect such vulnerable employees better, re-shaping the world around them, taking pressure off ''thoughts work'', having them involved in conceiving and designing tailored strategies to cope with this burden.

Person-directed interventions (such as cognitive-behavioral training and relaxation) and organizational-directed measures (such as task restructuring, decreased job demand, increased job control) should be specifically promoted.[17] Indeed, flexible scheduling,[18] teleworking through telemedicine,[19] back-up/emergency childcare and eldercare may facilitate female employees in combining personal life chores and work duties. These types of services are routinely offered by most businesses in the industry area but occasionally in healthcare workplaces with great heterogeneity among countries. Technological devices and robots may support health care professionals facilitating some operational tasks during the pandemic,[20] performing risky procedures and diverting some of the responsibilities from their shoulders.[19] There is no one-size-fits-all solution and most depend on the local hospital organizations, but it's time to close the gap.

All health-care workers should be protected against the pandemic, leaving no one behind. Female health-care workers need more protection beyond the mask.

References

1. https://data.unwomen.org/resources/covid-19-emerging-gender-data-and-why-it-matters Date: June 26, 2020. Date accessed: June 30, 2020.
2. Boniol M, McIsaac M, Xu L, Wuliji T, Diallo K, Campbell J, Date: March, 2020. Date accessed: June 22, 2020 https://apps.who.int/iris/bitstream/handle/10665/311314/WHO-HIS-HWF-Gender-WP1-2019.1-eng.pdf?sequence=1&isAllowed=y, 2019.
3. Wenham C, Smith J, Morgan R. Gender and COVID-19 Working Group. COVID-19: the gendered impacts of the outbreak. Lancet. 2020;395:846–8, http://dx.doi.org/10.1016/S0140-6736(20)30526-2.
4. Gabster BP, van Daalen K, Dhatt R, Barry M. Challenges for the female academic during the COVID-19 pandemic. Lancet. 2020;395:1968–70, http://dx.doi.org/10.1016/s0140-6736(20)31412-4.
5. https://www.tuc.org.uk/sites/default/files/PPEandwomenguidance.pdf Date: April, 2017. Date accessed: June 30, 2020.
6. Perez Criado, Caroline. Invisible Women: Data Bias in A World Designed for Men. Harry N. Abrams; 2019.
7. Rajan D, Koch K, Rohrer K, Bajnoczki C, Socha A, Voss M, et al. Governance of the Covid-19 response: a call for more inclusive and transparent decision-making. BMJ Global Health. 2020, 5e002655.
8. Roter DL, Hall JA, Aoki Y. Physician gender effects in medical communication: a meta-analytic review. JAMA. 2002;288:756–64, http://dx.doi.org/10.1001/jama.288.6.756.
9. Jefferson L, Bloor K, Birks Y, Hewitt C, Bland M. Effect of physicians' gender on communication and consultation length: a systematic review and meta-analysis. J Health Serv Res Policy. 2013;18:242–8, http://dx.doi.org/10.1177/1355819613486465.
10. Matsuo T, Kobayashi D, Taki F, et al. Prevalence of health care worker burnout during the Coronavirus Disease 2019 (COVID-19) pandemic in Japan. JAMA Netw Open. 2020;3:e2017271, http://dx.doi.org/10.1001/jamanetworkopen.2020.17271. Published 2020 Aug 3.
11. Sharma N, Chakrabarti S, Grover S. Gender differences in caregiving among family - caregivers of people with mental illnesses. World J Psychiatry. 2016;6:7–17, http://dx.doi.org/10.5498/wjp.v6.i1.7.
12. Adams-Prassl A., Boneva T., Golin M., Rauh C. Inequality in the impact of the coronavirus shock: evidence from real time surveys. IZA discussion paper 13183.

https://www.iza.org/publications/dp/13183/inequality-in-the-impact-of-the-coronavirus-shock-evidence-from-real-time-surveys Date: April, 2020. Date accessed: June 22, 2020.
13. Pappa S, Ntella V, Giannakas T, Giannakoulis VG, Papoutsi E, Katsaounou P. Prevalence of depression, anxiety, and insomnia among health-care workers during the COVID-19 pandemic: a systematic review and meta-analysis. Brain Behav Immun. 2020;20, http://dx.doi.org/10.1016/j.bbi.2020.05.026, 30845-X.
14. Rossi R, Socci V, Pacitti F, et al. Mental health outcomes among frontline and second-line health care workers during the Coronavirus Disease 2019 (COVID-19) pandemic in Italy. JAMA Netw Open. 2020;3(5):e2010185, http://dx.doi.org/10.1001/jamanetworkopen.2020.10185.
15. Rahman A, Plummer V. COVID-19 related suicide among hospital nurses; case study evidence from worldwide media reports. Psychiatry Res. 2020;291:113272, http://dx.doi.org/10.1016/j.psychres.2020.113272.
16. https://www.linkedin.com/posts/esselunga_worklifebalance-socialimpact-ecommerce-activity-6672052386787332096—FM/ Date: May, 2020. Date accessed: June 22, 2020.
17. Awa Wl, Plaumann M, Walter U. Burnout prevention: a review of intervention programs. Patient Educ Couns. 2010;78:184–90, http://dx.doi.org/10.1016/j.pec.2009.04.008.
18. Burnham EL, Burns KEA, Moss M, Dodek PM. Burnout in women intensivists: a hidden epidemic? Lancet Respir Med. 2019;7(4):292–4, http://dx.doi.org/10.1016/S2213-2600(19)30029-3.
19. Rubulotta F, Soliman-Aboumarie H, Filbey K, et al. Technologies to optimize the care of severe COVID-19 patients for health care providers challenged by limited resources. Anesth Analg. 2020;131:351–64, http://dx.doi.org/10.1213/ANE.0000000000004985.
20. Mazzoleni S, Turchetti G, Ambrosino N. The COVID-19 outbreak: from ''black swan'' to global challenges and opportunities. Pulmonology. 2020;26:117–8, http://dx.doi.org/10.1016/j.pulmoe.2020.03.002.

Pulmonology 2021;**27(1)**:4–6

PULMONOLOGY

www.journalpulmonology.org

COMMENT

Tuberculosis — Reaping benefits from COVID-19 in Portugal

B.L. Mateiro Gomes[a,b,c,*], **I. Carvalho**[d,e]

[a] *Entre Douro e Vouga I Public Health Unit, Northern Regional Health Administration, Santa Maria da Feira, Portugal*
[b] *Department of Public Health, Northern Regional Health Administration, Porto, Portugal*
[c] *Instituto de Saúde Pública da Universidade do Porto, EPIUnit, Porto, Portugal*
[d] *National Tuberculosis Programme, Portugal*
[e] *Centro Hospitalar de Vila Nova de Gaia, Espinho, Portugal*

Portugal has managed the first national wave of COVID-19 but now it is now time to turn to other priorities in our Health System. Tuberculosis is our old enemy, while SARS-CoV-2 is the new kid on the block. The slow onset of tuberculosis matches its slow mobilization of resources, in contrast to the speed of SARS-CoV-2. While we are living through a pandemic that, so far, has claimed over 700000 lives worldwide,[1] it is easy to forget that TB claims more than 1.2 million lives every year.[2]

There is international concern regarding the cycle of lockdown and slow restoration of tuberculosis services, predicting an additional 1.4 million TB deaths between 2020 and 2025, due to delayed diagnosis, interruption or delay of treatment.[3–6] What can we expect in the next months for tuberculosis incidence in Portugal? The country has been fighting a long war to maintain the incidence under the 20 cases/100.000 inhabitants mark and has a difficult challenge ahead to reach Sustainable Development Goal 3.3 before 2030. It has a unique profile in Western Europe, with an elevated number of cases in natives and a small proportion of cases in foreign-born individuals[7] and high spatial heterogeneity transmission associated with housing conditions, unemployment and vulnerable populations.[8] The COVID-19 threats are clear: disruption of services and supply chains, access to diagnosis and treatment and the already known consequences of the incoming economic crisis that feeds known determinants of tuberculosis and other infectious diseases.[6,9] It is still not clear if COVID-19 and TB co-infection outcomes are relevant or keep on being heavily influenced by age and other known co-morbidities.[10]

Clinical activities related with tuberculosis were not particularly hard hit in Portugal since they were considered a priority in the Portuguese Health System. However, there was some expected disruption in the access to laboratory and imaging investigations, which will almost surely result in some delays in the time from symptoms to proper diagnosis, a known risk factor for outbreaks.[11] On the other hand, investigation of presumptive Covid-19 cases can lead to quicker identification of pre-existing TB,[12] although one must keep TB as differential diagnosis amidst overwhelming attention given to Covid-19.

Due to the partial lockdown, we can expect a contrast of influences in TB: increased transmission in home clusters and decreased transmission in social circumstances, particularly social and occupational settings. Respiratory etiquette and social use of masks can break chains of transmission, give the upper hand to the control of this disease and help reduce the impact of delayed diagnosis and maintenance of index case infectiousness.[13] Stigma associated to mask usage by

* Corresponding author at: Department of Public Health, Northern Regional Health Administration, Porto, Portugal.
E-mail address: bgomes@arsnorte.min-saude.pt (B.L. Mateiro Gomes).

https://doi.org/10.1016/j.pulmoe.2020.08.006

Table 1 Threats and Opportunities in the context of Tuberculosis control in Portugal.

Threats	Opportunities
Disruption of services	Generalized use of masks
Hampered supply chains	Digital transition/telemedicine
TB late presentation	Differential diagnosis of COVID-19
Family cluster increase	Occupational cluster reduction
Unemployment/poverty	Field epidemiology development
Jeopardized international TB programmes	Contact tracing routines

tuberculosis patients or visiting health professionals is also something that will certainly diminish in the next few years.

Crisis also offers a broad set of opportunities. The clearest example is digital transition that has advanced more in two months than in the last two years due to the sheer pressure of physical distancing. DOT monitoring and patient follow-up can benefit from this. The long awaited reform of the tuberculosis dedicated health services could also be favored.

There will be other opportunities, such as the present familiarity with contact tracing among the general population, dedication of public health units to core activities of epidemiologic surveillance and infectious disease control, increasing use of digital technologies (with new developments) for the follow up of patients and the side effects of preventive measures for COVID-19 in pathologies like tuberculosis and influenza. In fact, despite their differences there is much to look forward to in the lessons learnt from SARS-CoV-2 and the accumulated experience with TB.[14] Tuberculosis outpatient centers will certainly take advantage of telemedicine and electronic tools to guarantee improved access. Online meetings and continuous training will also benefit.

Nonetheless, it is clear that we need to keep on prioritizing the vulnerable group multidisciplinary approach: homeless, social housing populations, inmates. Intersectoral collaborations with NGOs continue to prove crucial. Behind Portugal's Universal Health Coverage and TB cost-free treatment, social support and poverty reduction measures are the backbone of a sustainable fight against tuberculosis. It is well known that heterogeneity of epidemiology of the disease favor the targeting of high-risk groups, based on a variety of determinants.[15]

Finally, the expertise of field epidemiology and the pursuit of infectious diseases deserve a proper setting and dedicated multidisciplinary teams to face the myriad of enemies, from the well-known tuberculosis to the new zoonotic threats that can endanger, as we are witnessing, our way of living.

Despite not being able to predict the future, the anticipation of these different threats and opportunities (Table 1) might also help to shape health services and guide clinical, epidemiological and preventive measures. There is a chance that the particular setting of Portugal might help strike a decisive blow in tuberculosis transmission.

Funding

No additional funding sources are to be declared.

Conflicts of interest

The authors have no conflicts of interest to declare.

CRediT authorship contribution statement

B.L. Mateiro Gomes: Writing - original draft. .

References

1. Roser M, Richie H, Ortiz-Ospina E, Hasell J. https://ourworldindata.org/covid-deaths#what-is-the-total-number-of-confirmed-deaths, 2020 [Accessed 12 August 2020].
2. World Health Organization. https://www.who.int/tb/publications/global_report/en/, 2020 [Accessed 12 August 2020].
3. STOP TB Partnership. http://www.stoptb.org/assets/documents/news/Modeling%20Report_1%20May%202020_FINAL.pdf, 2020 [Accessed 12 August 2020].
4. Togun T, Kampmann B, Stoker NG, Lipman M. Anticipating the impact of the COVID-19 pandemic on TB patients and TB control programmes. Ann Clin Microbiol Antimicrob. 2020;19(1):1–6, http://dx.doi.org/10.1186/s12941-020-00363-1.
5. Hogan AB, Jewell BL, Sherrard-Smith E, Vesga JF, Watson OJ, Whittaker C, et al. Potential impact of the COVID-19 pandemic on HIV, tuberculosis, and malaria in low-income and middle-income countries: a modelling study. Lancet Glob Health. 2020;8(9):E1132–41, http://dx.doi.org/10.1016/S2214-109X(20)30288-6.
6. Buonsenso D, Iodice F, Biala JS, Goletti D. COVID-19 effects on Tuberculosis care in Sierra Leone. Pulmonology. 2020, http://dx.doi.org/10.1016/j.pulmoe.2020.05.013.
7. Paulino J, Martins A, Machado M, Gomes M, Gaio AR, Duarte R. Tuberculosis in native-and foreign-born populations in Portugal. Int J Tuberc Lung Dis. 2016;20(3):357–62, http://dx.doi.org/10.5588/ijtld.15.0430.
8. Couceiro L, Santana P, Nunes C. Pulmonary tuberculosis and risk factors in Portugal: a spatial analysis. Int J Tuberc Lung Dis. 2011;15(11):1445–55, http://dx.doi.org/10.5588/ijtld.15.0430.
9. Suhrcke M, Stuckler D, Suk JE, Desai M, Senek M, McKee M, et al. The impact of economic crises on communicable disease transmission and control: a systematic review of the evidence. PLoS One. 2011;6(6), http://dx.doi.org/10.1371/journal.pone.0020724.
10. Motta I, Centis R, D'Ambrosio L, et al. Tuberculosis, COVID-19 and migrants: preliminary analysis of deaths occurring in 69 patients from two cohorts. Pulmonology. 2020;26(4):233–40, http://dx.doi.org/10.1016/j.pulmoe.2020.05.002.
11. Mitruka K, Oeltmann JE, Ijaz K, Haddad MB. Tuberculosis outbreak investigations in the United States, 2002–2008. Emerg Infect Dis. 2011;17(3):425–31, http://dx.doi.org/10.3201/eid1703.101550.
12. Tadolini M, García-García J, Blanc F, Borisov S, Goletti D, Motta I, et al. On tuberculosis and COVID-19 co-infection. Europ Respir J. 2020;56(2):2002328, http://dx.doi.org/10.1183/13993003.02328-2020.

13. Mathema B, Andrews JR, Cohen T, Borgdorff MW, Behr M, Glynn JR, et al. Drivers of tuberculosis transmission. J Infect Dis. 2017;216 Suppl. 6:S644–53, http://dx.doi.org/10.1093/infdis/jix354.
14. Dara M, Sotgiu G, Reichler M, Chiang CY, Chee CBE, Migliori GB. New diseases and old threats: lessons from tuberculosis for the COVID-19 response. Int J Tuberc Lung Dis. 2020;24, http://dx.doi.org/10.5588/ijtld.20.0151.
15. Trauer JM, Dodd PJ, Gomes MGM, Gomez GB, Houben RMGJ, McBryde ES, et al. The Importance of Heterogeneity to the Epidemiology of Tuberculosis. Clin Infect Dis. 2019;69(1):159–66, http://dx.doi.org/10.1093/cid/ciy938.

Pulmonology 2021;**27(1)**:7–13

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Translating Idiopathic pulmonary fibrosis guidelines into clinical practice

C. Robalo-Cordeiro[a], **A. Morais**[b,*]

[a] *Pulmonology Department, Coimbra University Hospital, University of Coimbra, Portugal*
[b] *Pulmonology Department, São João Hospital Centre, Faculty of Medicine of Porto University, Oporto, Portugal*

Received 22 May 2020; accepted 28 May 2020
Available online 16 June 2020

KEYWORDS
Awareness;
Consensus;
Diagnosis;
Guidelines;
Idiopathic pulmonary fibrosis

Abstract
Introduction and objectives: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrotic interstitial lung disease of unknown cause, which predominantly manifests in older males. IPF diagnosis is a complex, multi-step process and delay in diagnosis cause a negative impact on patient survival. Additionally, a multidisciplinary team of pulmonologists, radiologists and pathologists is necessary for an accurate IPF diagnosis. The present study aims to assess how diagnosis and treatment of IPF are followed in Portugal, as well as the knowledge and implementation of therapeutic guidelines adopted by the Portuguese Society of Pulmonology.
Materials and methods: Seventy-eight practicing pulmonologists were enrolled (May–August 2019) in a survey developed by IPF expert pulmonologists comprised of one round of 31 questions structured in three parts. The first part was related to participant professional profile, the second part assessed participant level of knowledge and practice agreement with national consensus and international guidelines for IPF as well as their access to radiology and pathology for IPF diagnosis, and the third part was a self-evaluation of the guidelines adherence for diagnosis and treatment in their daily practice.
Results: Participants represented a wide spectrum of pulmonologists from 14 districts of Portugal and autonomous regions of Azores and Madeira. The majority were female (65%), with 5–19 years of experience (71%) and working in a public clinical center (83%). Importantly, the majority of pulmonologists follow their IPF patients ($n = 45$) themselves, while 26% referred IPF patients to ILD experts in the same hospital and 22% to another center. Almost all pulmonologists (98%) agreed or absolutely agreed that multidisciplinary discussion is recommended to accurately diagnose IPF. No pulmonologists considered pulmonary biopsy as absolutely required to establish an IPF diagnosis. However, 87% agreed or absolutely agree with considering biopsy in a possible/probable UIP context. If a biopsy is necessary, 96% of pulmonologists absolutely agree or agree with considering criobiopsy as an option for IPF diagnosis. Regarding IPF treatment, 98% absolutely agreed or agreed that antifibrotic therapy should be started once the IPF diagnosis is established. Finally, 76% stated that 6 months is the recommended time for follow-up visit in IPF patients.

* Corresponding author.

https://doi.org/10.1016/j.pulmoe.2020.05.017

Conclusions: Portuguese pulmonologists understand and agree with national consensus and international guidelines for IPF treatment but their implementation in Portugal is heterogeneous.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive lung disease, which predominantly manifests in adults over 55 years old and tends to affect more men than women.[1] The exact prevalence of IPF is unknown with estimates ranging from 2 to 29 people per 100 000 in the general population[2–4] and is increasing over time.[4] The etiology and exact pathophysiological mechanism of the disease is still unknown and the median natural survival of patients with IPF is only 2–5 years from the time of diagnosis.[5,6] It is not uncommon for patients to live 5 years or more after receiving the diagnosis but many patients die from progressive respiratory failure.[7] Moreover, given the varied natural history of the disease, it is difficult to determine an accurate clinical course for patients with newly diagnosed IPF. Usual interstitial pneumonia (UIP) is the imaging and histopathological hallmark pattern of IPF contrary to the other idiopathic interstitial pneumonias,[8,9] and diagnosis relies on this feature. Obtaining an accurate diagnosis of IPF can be challenging, because symptoms of exertional dyspnea, cough, and fatigue are nonspecific and often attributed to more common medical conditions like chronic obstructive pulmonary disease, or heart failure.[10]

IPF was initially considered to be a chronic inflammatory[11] process and therefore the first international guidelines on IPF diagnosis and treatment recommended agents to target inflammatory pathways, despite the very low level of evidence supporting this recommendation.[12] However, understanding of the pathobiology of IPF has undergone dramatic changes since then, evolving from an inflammatory process to an aberrant reparative response to alveolar epithelial cell injury, causing irreversible loss of function.[13,14] Several clinical trials addressed the efficacy of compounds targeting the fibrotic process but turned out to be disappointing.[15,16] The following 2011 guideline represented a rigorous joint effort by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT), which did not strongly recommend any pharmacological treatments for patients with IPF.[3] A new updated guideline was published in 2015 considering current alternative therapies[17] such as nintedanib and pirfenidone and a year later, a consensus document for the diagnosis and treatment of idiopathic pulmonary fibrosis was published by *Sociedade Portuguesa de Pneumologia*, *Sociedade Portuguesa de Radiologia e Medicina Nuclear* and *Sociedade Portuguesa de Anatomia Patológica*.[18] This document envisioned increasing awareness among, not only pulmonologists and specialists in interstitial lung diseases, (ILDs) but also general practitioners of the importance of early diagnosis of the disease[19] and the challenge of new approved drugs. More importantly, experts recommended that the evaluation of benefits and risks of the therapeutic strategy as well as the clinical behavior of the disease should be undertaken in each individual patient. Further on, in 2018, a new collaborative recommendation guideline was updated regarding IPF diagnostic criteria.[20]

Along with the clear evolution of IPF management strategy, this study aims at contributing to guidelines disclosure and to evaluate whether the current information on IPF treatment and diagnosis is adequate and implemented by Portuguese pulmonologists according to the Official ATS/ERS/JRS/ALA Clinical Practice Guideline and the Portuguese consensus document.

Material and methods

Study design

A one-round, anonymous, cross-sectional survey was conducted comprised of on a line 31-item questionnaire. The questionnaire was designed to characterize current clinical practice patterns regarding the diagnosis and treatment of IPF patients by pulmonologists, considering the knowledge about national consensus[18] and international guidelines.[20] It comprised three parts. The first part included 10 questions about demographic characteristics and professional profile, such as years working as a health care professional, location of working center, monthly and yearly volume of patients followed, reference or not of patients to an ILD expert within or outside the hospital, and time between visits. The second part was a 4-question self-evaluation of the level of IPF diagnosis and treatment guidelines acceptance and practice. The third part was a group of questions to access the level of agreement with specific national and international recommendations for the diagnosis and treatment of IPF, according to the clinical practice in relation to IPF management. This last part of the survey contained 17 multiple-choice questions with five unique response options.

Data were collected from 78 pulmonologists across Azores, Madeira and 14 districts in mainland Portugal, between May and August 2019. Since 33 pulmonologists refer their patients to a colleague, the remaining 45 were included for further statistical analysis.

Results

Of the total pulmonologists enrolled in this study, 65.4% were female (Table 1). The age among participants varied, with 55.1% of the respondents being under 40 years old and 30.8%

Table 1 Participant sociodemographic characteristics and professional status.

Variables	*n*	Percentage (%)
Total participants (*n* = 78)		
Sex		
Female	51	65.4
Male	27	34.6
Age group (years)		
<40	43	55.1
40–49	24	30.8
50–59	7	9.0
≥60	4	5.1
Years working as healthcare professional		
<5	5	6.4
5–9	25	32.1
10–14	13	16.7
15–19	17	21.8
20–24	8	10.3
25–40	8	10.3
≥40	2	2.6
Monthly volume of patients with any respiratory disease		
20–39	4	5.1
40–59	10	12.8
≥60	64	82.1
Yearly volume of IPF patients		
<5	20	25.6
5–9	25	32.1
10–14	17	21.8
15–29	11	14.1
≥30	5	6.4
Reference of IFP patients to a colleague in the hospital		
No	56	71.8
Yes	20	25.6
Reference of IFP patients to a colleague in other hospital		
No	61	78.2
Yes	17	21.8
Participants who follow IPF patients (*n* = 45)		
Institution where IFP patients are followed		
Public hospital	42	93.3
Private hospital	1	2.2
Both	2	4.4
Time intervals between visits (months)		
<2	2	4.4
2–3	33	73.3
4–5	5	11.1
6–8	1	2.2
Impossible to answer	3	6.7

between 40 and 49 years old. In terms of clinical experience, 32.1% of participants have worked as healthcare professionals for 5–9 years and 21.8% for 15–19 years. The majority of participants (82.1%) attend ≥60 patients per month with different respiratory diseases, while 42.3% follow more than 10 IPF patients per year. Fifty-eight percent (*n* = 45) of participants do not refer their IPF patients, whereas 25.6% refer IPF patients to an ILD expert in the same department and 21.8% to an ILD expert in another hospital (Table 1). Of the 45 pulmonologists who follow IPF patients, the majority (93.3%) follow their patients in a public hospital and 73.3% follow their patients every 2–3 months.

Pulmonologists were also asked about the availability of ILD specialized radiology and pathology as well as multidisciplinary team discussions for IPF diagnosis (Table 2). Approximately half (48.9%) of pulmonologists following IPF patients have ILD specialized radiology with multidisciplinary team discussions in their hospital center and 40.0% have ILD specialized pathology with multidisciplinary team discussions in their hospital center.

Table 2 Idiopathic pulmonary fibrosis management.

Variables	*n*	Percentage (%)
Participants who follow IPF patients (*n* = 45)		
Availability of ILD specialized radiology for IPF Diagnosis		
Availability in my own center with multidisciplinary team discussions	22	48.9
Availability in my own center but without multidisciplinary team discussions	7	15.6
Availability in my own center but is not specialized in ILD	9	20.0
No availability in my own center but I participate in/consult a multidisciplinary team of another hospital	5	11.1
No availability in my own center and I do not participate in/consult a multidisciplinary team of another hospital	1	2.2
Other	1	2.2
Availability of ILD specialized pathology for IPF Diagnosis		
Availability in my own center with multidisciplinary team discussions	18	40.0
Availability in my own center but without multidisciplinary team discussions	3	6.7
Availability in my own center but is not specialized in ILD	12	26.7
No availability in my own center but I participate in/consult a multidisciplinary team of another hospital	6	13.3
No availability of pathology in my own center and I do not participate in/consult a multidisciplinary team of another hospital	4	8.9
Other	2	4.4
A change in absolute FVC of 10%, or a change in absolute DLco of 15% is evidence of disease progression, and a surrogate marker of mortality		
I absolutely agree	29	64.4
I agree	16	35.6
I disagree	0	0.0
I absolutely disagree	0	0.0
Pulmonary rehabilitation in IPF is recommended for the majority of patients		
I absolutely agree	25	55.6
I agree	19	42.2
I disagree	1	2.2
I absolutely disagree	0	0.0
During IPF follow-up, what is the recommended time for the main examinations?		
3 months	9	20.0
6 months	34	75.6
12 months	2	4.4

Most pulmonologists (71.1%) reported to have a high knowledge of national consensus and international guidelines and 66.7% consider those recommendations in clinical practice (results not shown). These considerations were further evaluated through a list of questions regarding IPF diagnosis (Fig. 1). The majority of professionals (75.6%) absolutely agree with multidisciplinary discussion with experienced clinicians, radiologists and pathologists, to accurately diagnose IPF. More than half of the respondents (60.0%) absolutely agree with high-resolution computed tomography (HRCT) as the main procedure for IPF diagnosis, while 62.2% disagree and 37.8% absolutely disagree that pulmonary biopsy is absolutely required. However, if a biopsy is required, 40.0% absolutely agree and 55.6% agree with criobiopsy as a valid option to establish IPF diagnosis. Most participants (80.0%) agree with the term probable usual interstitial pneumonia (UIP), while approximately half (54.5%) agree with the term possible UIP. Upon IPF suspicion, 77.8% absolutely agree to use serologic testing for connective tissue disease screening.

Concerning treatment, the majority of participants (88.9%) absolutely disagree that IPF patients should be treated with corticosteroid monotherapy to prevent treatment-related morbidity, as well as 93.3% absolutely disagreeing with combination therapy of N-acetylcysteine, azathioprine, and prednisone for IPF patient treatment (Fig. 2). In total, approximately 80% of pulmonologists absolutely agree that antifibrotic treatment has benefits for important patient outcomes, Importantly, 66.7% of pulmonologists absolutely agree that antifibrotic therapy should start once IPF diagnosis is established.

Considering IPF management (Table 2), responses varied among pulmonologists. More than a half (64.4%) absolutely agree that disease progression in IPF is defined as a sustained decline of more than 10% in forced vital capacity (FVC) and/or of 15% in diffusion capacity of the lung for

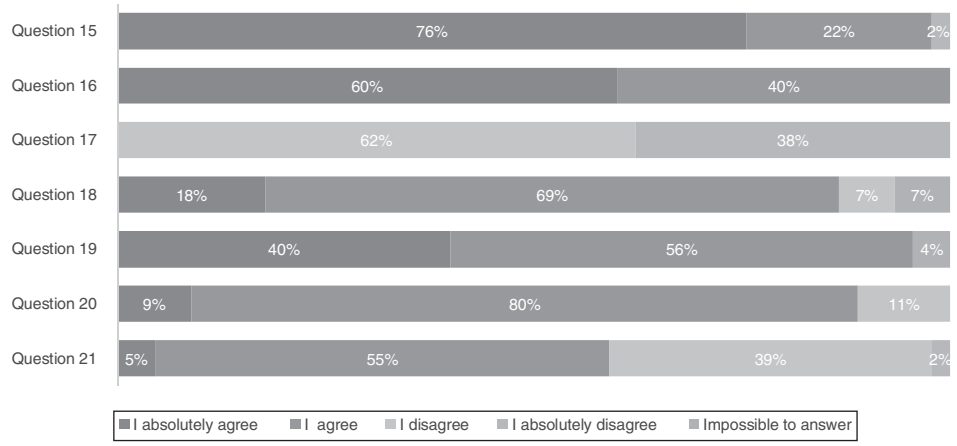


Figure 1 Idiopathic pulmonary fibrosis diagnosis.

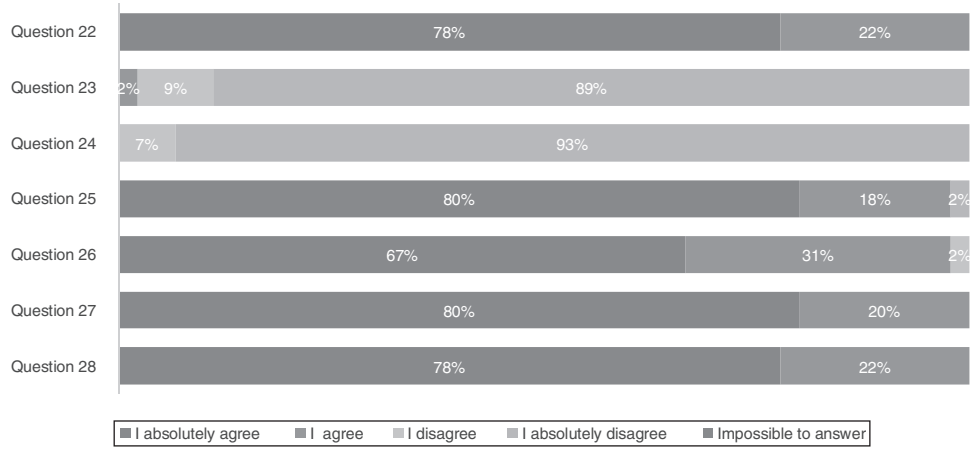


Figure 2 Idiopathic pulmonary fibrosis treatment.

carbon monoxide (DL_{CO}). In addition, 55.6% absolutely agree that pulmonary rehabilitation in IPF is recommended for the majority of patients, long-term oxygen therapy should be provided to patients with clinically significant resting hypoxemia, and the patients with the defined criteria should undergo lung transplantation. Following initiation of IPF treatment, 75.6% consider that 6 months is the recommended time for main appointments.

Discussion

This survey represents the first assessment of clinical practice of Portuguese pulmonologists regarding IPF diagnosis, management and treatment, considering the knowledge of the recent national consensus[18] and international guidelines.[3,20] Despite the wide age range among participants, the selected population is generally young and mostly female and 60% of the participants had more than 10 years of clinical practice. The number of IPF patients attending a monthly/yearly appointment is indicative of a high level of clinical practice. The public hospital appears to be the main care setting for most IPF patients followed by pulmonologists in this survey.

Due to the challenge in reaching a confident IPF diagnosis caused by nonspecific symptoms, guidelines suggest using multidisciplinary teams from different specialties.[21–23] The panel is completely in line with this concept since 76% absolutely agree and 22% agree that a multidisciplinary team including experienced clinicians, radiologists and pathologists as the main process for an accurate diagnosis. Indeed, our results showed that nearly half of the practitioners have multidisciplinary team discussions with specialized radiology and/or pathology available in their institution or in another hospital center. However, a considerable number of participants in the present study admitted that these specialties were not available in their own centers. This delay in IPF diagnosis and further treatment in Portugal[24] is a cause for concern.

Seventy-one percent of pulmonologists that follow IPF patients reported they have a high level of knowledge of IPF national consensus and international guidelines for IPF diagnosis and treatment and 66.7% apply their knowledge in clinical practice. This level of familiarity implies that IPF awareness is a priority within national health programs, which is true considering the number of programs boosted by the national policies. However, the remaining 28% of

participants who are not aware of recommendations may hinder their intervention in clinical practice.

There was some unexpected controversy regarding the use of HRCT as the main procedure for IPF diagnosis with opinions divided among pulmonologists. A confident diagnosis of IPF can be made in the correct clinical setting when HRCT imaging shows a pattern of typical or even probable UIP in a certain context.[3,17,18,20,25] Indeed, the official ATS/ERS/JRS/ALAT Statement on IPF[3] states that a correct IPF diagnosis requires ''the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy (SLB)''. Importantly, for patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of UIP, it is strongly recommended not to perform SLB.[20] Surprisingly, only 37.8% of participants in this study absolutely disagree with the sentence ''A pulmonary biopsy is absolutely required to establish an IPF diagnosis''. On the other hand, ATS/ERS/JRS/ALAT clinical practice guidelines suggest SLB in a probable UIP context; 68.9% of participants agreed with the sentence ''Do you consider biopsy in a possible/probable UIP context?'' The remaining 40% are more in line with Fleishner Society white paper statement that does not require lung biopsy in a probable UIP in an appropriate clinical setting.[23] The fact that the majority of the panel tends to consider lung biopsy by name in possible UIP contexts may be due to the high level of non-IPF fibrotic ILDs in our country, with particular relevance of the high frequency of chronic hypersensitivity pneumonitis related with exposure to birds and molds.[26,27] Considering biopsy as an alternative, lung cryobiopsy although still controversial has been shown to be generally safe and well tolerated.[28] Tomasseti et al. demonstrated that the proportion of IPF cases diagnosed with a high degree of confidence increased from 16 to 63% after performing lung cryobiopsy and in some cases led to a change in the diagnostic suspiction.[28] A recent prospective, multicentre study evaluated the diagnostic accuracy of transbronchial lung cryobiopsy (TBLC) for ILD diagnosis. The results showed good agreement between TBLC and SLB obtained sequentially from the same patients, supporting the clinical utility of TBLC as an alternative to SLB for patients requiring lung tissue for ILD diagnosis.[29] Moreover a comparative study between TBLC and explant lungs from lung transplantation of patients with UIP showed also a high concordance.[30] According to this survey, Portuguese pulmonologists globally agree with the use of this technique as an option for IPF diagnosis.

The recommendations against outmoded therapies for IPF are established, as there is strong evidence against their use.[31] Portuguese pulmonologists absolutely disagreed (95.3%) with triple therapy which is fully compatible with international guidelines.[3] Apart from this, respondents of this survey totally agreed that antifibrotic treatment benefits IPF progression and should be started as soon as this disease is diagnosed. Lung transplantation has been used as an option for IPF treatment worldwide for patients with moderate to severe disease[32] as well as by Portuguese pulmonologists, but mortality is high and one of the potential reasons for this is a late referral of the patients to the transplant units with advanced disease.[33]

Most of participants responded that the time for IPF patients' follow-up and main examinations was every 6 months, this result differs from guidelines in which the range is 3–6 months. Paradoxically, the majority of the participants stated that the usual appointments of IPF patients in their clinical practice was exactly 3 months. More importantly, palliative care is rarely instituted in patients with IPF before the end of life,[7] which should be addressed in our care facilities.

This study presented some potential limitations that should be addressed to avoid misinterpretation of results. First, in the initial part of the questionnaire, 33 participants were eliminated from the study since they referred IPF patients to another colleague. To avoid this statistical pitfall, we could have considered this as the first question. Second, we could have reached a higher number of participants with a telephone-based interview survey or a face-to-face interview. Moreover, this is a cross-sectional study therefore it cannot support conclusions on casual relationships. However, it allowed the analysis of the main concerns regarding IPF management, diagnosis and treatment. In the future, a large-scale survey across all Portuguese geographical areas is needed to confirm the consistency of responses regarding the knowledge of IPF recommendations and further clinical practice.

Conclusions

To the best of our knowledge, this survey represents the largest and most comprehensive assessment of the level of awareness and acceptance of IPF National Consensus and international Official ATS/ERS/JRS/ALAT IPF Guidelines. More importantly, we conclude that most IPF recommendations are followed by Portuguese pulmonologists, but their implementation is heterogeneous.

Conflicts of interest

Funding information

The study and medical writing support for the manuscript was funded by Boehringer Ingelheim Portugal.

Acknowledgments

The authors thank Maria João Almeida (Pulso Ediciones) for editorial assistance in the preparation of the manuscript.

References

1. Coultas D, Zumwalt R, Black W, Sobonya R. The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med. 1994;150:967–72.
2. Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. Eur Respir J. 2015;46:795–806.
3. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An Official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
4. Olson AL, Gifford AH, Inase N, Fernández Pérez ER, Suda T. The epidemiology of idiopathic pulmonary fibrosis and interstitial

lung diseases at risk of a progressive-fibrosing phenotype. Eur Respir Rev. 2018;27.
5. Molina-Molina M, Aburto M, Acosta O, Ancochea J, Rodríguez-Portal JA, Sauleda J, et al. Importance of early diagnosis and treatment in idiopathic pulmonary fibrosis. Expert Rev Respir Med. 2018;12:537–9.
6. Ley B, Collard HR, King TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183:431–40.
7. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018;378:1811–23, http://dx.doi.org/10.1056/NEJMra1705751.
8. Bjoraker JA, Ryu JH, Edwin MK, Myers JL, Tazelaar HD, Schroeder DR, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1998;157:199–203.
9. Travis WD, Costabel U, Hansell DM, King TE, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48.
10. du Bois RM. An earlier and more confident diagnosis of idiopathic pulmonary fibrosis. Eur Respir Rev. 2012;21:141–6.
11. Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. Lancet. 2017;389:1941–52, http://dx.doi.org/10.1016/S0140-6736(17)30866-8.
12. Directors AB, Committie EE. American Thoracic Society Idiopathic Pulmonary Fibrosis: diagnosis and treatment. Am J Respir Crit Care Med. 2000;161:646–64.
13. Günther A, Korfei M, Mahavadi P, von der Beck D, Ruppert C, Markart P. Unravelling the progressive pathophysiology of idiopathic pulmonary fibrosis. Eur Respir Rev. 2012;21:152–60.
14. King TE, Schwarz MI, Brown K, Tooze JA, Colby TV, Waldron JA, et al. Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality. Am J Respir Crit Care Med. 2001;164:1025–32.
15. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005;171:1040–7.
16. Carter NJ. Pirfenidone: in idiopathic pulmonary fibrosis. Drugs. 2011;71:1721–32.
17. Raghu G, Rochwerg B, Zhang Y, Garcia CAC, Azuma A, Behr J, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis: an update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192:e3–19.
18. Robalo Cordeiro C, Campos P, Carvalho L, Campainha S, Clemente S, Figueiredo L, et al. Consensus document for the diagnosis and treatment of idiopathic pulmonary fibrosis: Joint Consensus of Sociedade Portuguesa de Pneumologia, Sociedade Portuguesa de Radiologia e Medicina Nuclear e Sociedade Portuguesa de Anatomia Patológica. Rev Port Pneumol. 2016;22:112–22.
19. Wuyts WA, Wijsenbeek M, Bondue B, Bosnos D, Bresser P, Robalo Cordeiro C, et al. Idiopathic pulmonary fibrosis: best practice in monitoring and managing a relentless fibrotic disease. Respiration. 2020;99:73–82.
20. 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.
21. Walsh S, Maher T, Kolb M, Poletti V, Nusser R. Diagnostic accuracy of a clinical diagnosis of idiopathic pulmonary fibrosis: an international case – cohort study. Eur Respir J. 2017;50.
22. Walsh SLF, Maher T, Kolb M, Poletti V, Nusser R. Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study. Lancet Respir Med. 2016;4:557–65.
23. Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TB, Galvin JR, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med. 2018;6:138–53.
24. Direção Geral de Saúde. Doenças respiratorios; 2015.
25. Gruden JF, Panse PM, Leslie KO, Tazelaar HD, Colby TV. UIP diagnosed at surgical lung biopsy, 2000-2009: HRCT patterns and proposed classification system. Am J Roentgenol. 2013;200:458–67.
26. Santos V, Martins N, Sousa C, Jacob M, Padrão E, Melo N, et al. Hypersensitivity pneumonitis: main features characterization in a Portuguese cohort. Pulmonology. 2020;26:130–7, http://dx.doi.org/10.1016/j.pulmoe.2019.09.004.
27. Pires FS, et al. Fibrose pulmonar idiopática – apresentação clínica, evolução e factores prognósticos basais numa coorte portuguesa. Rev Port Pneumol (English Ed). 2013;19:19–27.
28. Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TB, Rossi G, et al. Bronchoscopic lung cryobiopsy increases diagnostic confidence in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2016;193:745–52.
29. Unterman A, Wand O, Fridel L, Edelstein E, Pertzov B, Kramer MR. High diagnostic accuracy of transbronchial cryobiopsy in fibrotic interstitial lung diseases compared to final explant diagnosis. Respiration. 2019;98:421–7.
30. Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, et al. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. Lancet Respir Med. 2020;8:171–81.
31. Raghu G, Anstrom KJ, King TE, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366:1968–77.
32. Martinez FJ, Collard HR, Pardo A, Raghu G, Richeldi L, Selman M, et al. Idiopathic pulmonary fibrosis. Nat Rev Dis Primers. 2017;3, http://dx.doi.org/10.1038/nrdp.2017.74.
33. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014 – an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Hear Lung Transplant. 2015;34:1–15.

Pulmonology 2021;**27(1)**:14–25

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Low dose computed tomography of the lung for detection and grading of interstitial lung disease: A systematic simulation study

S. Ley[c,f,h,*], L. Fidler[b], H. Schenk[c], M. Durand[d,f], T. Marras[e], N. Paul[f], S. Shapera[g], S. Mittoo[a]

[a] *Department of Rheumatology, Mount Sinai Hospital, Toronto, Ontario, Canada*
[b] *Department of Medicine, University of Toronto, Toronto, Ontario, Canada*
[c] *Surgical Clinic Munich South, Munich, Bavaria, Germany*
[d] *Department of Radiology, Grey's Hospital, Pietermaritzburg, KwaZulu-Natal, South Africa*
[e] *Department of Respirology, Toronto Western Hospital, Toronto, Ontario, Canada*
[f] *Joint Department of Medical Imaging, Toronto General Hospital, Toronto, Ontario, Canada*
[g] *Department of Respirology, Toronto General Hospital, Toronto, Ontario, Canada*
[h] *Institute of Clinical Radiology, Ludwig Maximilians University, Munich, Germany*

Received 5 May 2020; accepted 2 June 2020
Available online 24 June 2020

KEYWORDS
Interstitial Lung Disease;
Computed Tomography;
Low-dose;
Simulation study;
Diagnostic performance

Abstract
Purpose: HRCT is the preferred imaging technique to evaluate Interstitial-Lung-Disease. Optimal Low-Dose-Computed-Tomography protocol for monitoring ILD with lowest radiation dose and optimal diagnostic accuracy and image quality unknown.
Methods: 28 Patients underwent HRCT. Image reconstructions with varying combinations of tube current (50mA, 20mA, 15 mA, 10mA) and image-thickness/increment (1/1mm, 2/2mm, 3/2.4mm, 5/4mm) were simulated from raw data. 448 CTs evaluated by 2 readers on image quality and ILD-specific features (ground glass opacification (ggo), honeycombing (hc), reticulation (ret)).
Results: Reduced dose settings with 20 mA did not show any significant difference to standard dose settings for all parameters in reader 1, while results were significantly altered in reader 2. Slice thickness did not significantly influence rating of typical ILD features like ggo, hc, ret or total disease extent. The correct differentiation between UIP and NSIP could be made on all dose settings and with all slice thickness. It was even found, that an increased slice thickness can compensate for the noise associated image quality degradation. Overall, for ggo detection a combination of 20 mA and 3 or 5 mm slice thickness was not different to the original evaluation.

* Corresponding author.
E-mail address: ley@gmx.net (S. Ley).

https://doi.org/10.1016/j.pulmoe.2020.06.004

Conclusions: Assessment of ILD specific CT features down to 20 mA and a slice thickness of 3 or 5 mm is feasible.

Introduction

Interstitial lung disease (ILD) encompasses a heterogeneous group of disorders affecting the lung parenchyma that can lead to poor quality of life, hospitalization, and death.[1–3] Pulmonary function tests (PFTs) and chest X-rays (CXRs) have insufficient sensitivity to identify early ILD. Thoracic high-resolution computed tomography (HRCT) is the preferred method to detect and differentiate between the different forms of interstitial lung disease, being classified as usual interstitial pneumonia (UIP), probable UIP, indeterminate for UIP and alternative diagnosis (like non-specific interstitial pneumonia (NSIP)).[4–6] In lieu of a surgical biopsy, HRCT is an accepted gold standard for the diagnosis of ILD when certain specific findings are present.[5–8] Both UIP and NSIP can exhibit reticulation and traction bronchiectasis on chest HRCT; distinguishing radiologic features between these two subsets includes a greater degree of ground glass opacities (GGO) relative to reticulation in NSIP compared to UIP and the presence of honeycombing (HC) in UIP.[5,6]

HRCT is defined as a slice thickness less than 1.5 mm using a high-frequency reconstruction kernel.[9] To achieve diagnostic images a certain amount of radiation dose has to be applied to outweigh the image noise. So far, no official recommendations exist regarding latest noise reduction techniques like iterative reconstruction. This may be due to the fact, that each CT vendor uses different algorithms and the inter-study results show varying results of diagnostic accuracy based on the strength of image post-processing.

In light of the malignancy risk associated with exposure to cumulative doses of ionized radiation exposure, there is a trend for clinicians to request lower radiation dose protocols to monitor for ILD progression. These protocols tend to involve helical acquisition of CT data using reduced X-ray exposure parameters.[10] This is particularly relevant in patients with ILD who are already at an increased risk of developing pulmonary malignancy.[11] Especially repeated, long-term CT chest imaging in adults over 20–30 year periods, has been associated with non-trivial doses of radiation, exceeding that of nuclear plant workers and atomic bomb survivors.[12] For imaging of the lung parenchyma – as a high contrast tissue – a high kVp is recommended. Therefore, reduction of radiation dose with CT imaging is achieved by either reducing tube current and/or increasing the image slice interval (i.e. leaving gaps between slices). However, changes in tube current and image slice interval compromise image quality, negatively impact disease detection and estimated disease extent.[13,14] Research focused on finding the appropriate balance between CT imaging radiation exposure and optimal image quality is desperately needed. The problem with the design of systematic dose reduction studies is that a repeated CT examination of the same subject is unethical (and would also mean different breath-holds compromising image comparability). Past studies evaluating LDCT imaging in ILD have therefore chosen imaging parameters arbitrarily, failing to establish an optimal LDCT protocol for detecting and distinguishing ILD and its subsets (UIP and NSIP).

As there is no study out evaluating a steady decrease in dose in the same patient, the aim of this study was to find an optimal imaging protocol to identify and grade specific features of ILD in comparison to standard 3d-HRCT.

Materials and methods

Patient and sample population

Patients treated at the Toronto General Hospital-ILD clinic, a tertiary academic referral clinic, were approached for study enrolment between July 2012 and April 2013. Oral and written consent was recorded when the patients were approached while visiting the clinic for regularly scheduled appointments. Patient consent records were stored securely with their study records. Adult patients ($\geq$18 years of age) with a diagnosis of IPF, idiopathic NSIP, or connective tissue disease (CTD)-ILD and who required a thoracic CT at their visit were included. Patients with a history of pneumotoxic medication use, environmental exposures, granulomatous lung disease (i.e. sarcoidosis) or other idiopathic interstitial pneumonias were excluded from this study. A diagnosis of IPF was based on criteria outlined by American Thoracic Society guidelines.[5,6] A rheumatologist evaluated all patients to confirm the presence of a CTD (rheumatoid arthritis, systemic sclerosis, idiopathic inflammatory myositis, Sjogren's syndrome, mixed connective tissue disease, systemic lupus erythematosus, or undifferentiated connective tissue disease).

Ethics approval was obtained prior to patient enrolment from both the BLINDED FOR REVIEW Research Ethics Board and the BLINDED FOR REVIEW Research Ethics Board.

CT image acquisition and assessment

Patients were scanned in the prone position during full inspiration. Average patient anterior–posterior (AP) and left–right (LR) body size was 253.8 mm (*S.E.* = 8.3) and 328.3 mm (*S.E.* = 6.7) respectively. Images were acquired with a 64 mm $\times$ 0.5 mm detector configuration using two CT scanners: Aquilion 64 (n = 26) or Aquilion One (n = 5) (both Toshiba Medical Systems, Ottawara, Japan). Image acquisition was done with the clinical routine protocol

Table 1 Summary of CT acquisitions and simulation parameters.

Nr patients	Original dose	Simulated dose	Slice thickness/increment	Nr datasets
8	Automatic dose (115–212 mA)	SD 30 SD 40 SD 50	1/1 mm 2/2 mm 3/2.4 mm 5/4 mm	128
20	50 mA	20 mA 15 mA 10 mA	1/1 mm 2/2 mm 3/2.4 mm 5/4 mm	320

(120 kVp, 0.5 s rotation time). The raw data from each clinical scan was stored and used for low dose simulation using the Toshiba low dose simulation software.[15] No iterative reconstruction techniques were used. Some original data were acquired using automatic dose exposure ($n = 8$, 115–212 mA – depending on body habitus), and others with fixed mA settings (50 mA). For low dose simulation, the noise levels were reconstructed for the following standard deviation (SD) of noise of 30, 40 and 50 Hounsfield Units (HU) (as allowed by the software). The fixed mA datasets were simulated at 20 mA, 15 mA and 10 mA. Reconstruction was done with various slice thicknesses/increments: 1 mm/1 mm, 2 mm/2 mm, 3 mm/2.4 mm, and 5 mm/4 mm (for the thicker slice thicknesses an overlap of 20% was chosen to allow for increased characterization benefit[16]). The reconstruction kernel was FC03 (soft tissue kernel) to reduce noise without limiting imaging characteristics known from CAD. This setting allowed for intra-individual comparison of the impact of dose reduction. As the same raw data set was used, there were no variations in physiological conditions, such as inspiratory depth and fluid content. Only one CT scan was performed on each study participant, thus no additional radiation burden was applied.

Overall, 28 patients with 4 different dose settings and 4 slice thickness/increment settings were reconstructed, in total 448 CT datasets were used for evaluation (Table 1).

The clinical dose CT dataset (original dose, no noise) with 1 mm slice thickness was used as reference standard.

All CT images were interpreted in random order and separately by a radiologist (reader 1) with over 15 years of experience in thoracic radiology, and one second year radiology resident (reader 2). Both were blinded to the patients' clinical history. Lung parenchyma was evaluated by individual lobe (right upper, right middle, right lower, left upper, lingua and left lower) for the presence of GGO, reticulation, and HC. Each lobe was scored for extent of these changes from 0 to 100% in 5% intervals. GGO was defined according to the Fleischner Glossary of Terms for Thoracic Imaging as an increase in lung attenuation without obscuring pulmonary vessels, reticulation as fine or thick reticular grid and thickened interlobular septa and honeycombing as peripheral cysts within a coarse reticulation.[17]

An overall estimate of image quality, number of lobes involved and total percent of diseased lung was provided by the readers for each patient's series. Image quality was rated on a scale from 1 to 4, with 1 indicating excellent image quality without any artefacts; 2 indicating good image quality with minor streak artefacts without limiting image interpretation; 3 indicating moderate image quality with more severe streak artefacts limiting image interpretation; and 4 indicating bad image quality with severe artefacts significantly impairing image interpretation. The radiologic pattern was recorded as UIP, NSIP, or non-classifiable fibrosis for all CT scans at each LDCT series. UIP and NSIP were defined in accordance with ATS guidelines for IPF and the idiopathic interstitial pneumonias (IIPs) respectively.[5,6] As mentioned above, HRCT scans with the highest tube current (clinical established dose levels), 1 mm slice thickness were established as the conventional (reference) standard.

The optimal LDCT was selected based on the following three features:(1) diagnostic accuracy, (2) image quality and (3) delivered radiation dose between series. Diagnostic accuracy was considered the most important operating characteristic, given that the overall radiographic pattern often influences clinical diagnosis and treatment decisions. Image quality influences the perception of other CT imaging features (i.e. GGO, reticulation and disease) and hence was chosen as the second most important factor. LDCT imaging series' with similar diagnostic accuracy and image quality were differentiated based on delivered radiation dose, with the lowest dose series deemed most optimal.

Statistical analysis

For statistical analysis the average scores for total involvement of GGO, reticulation and HC across all lobes were enumerated. Also, the total disease extent was used (average of the sum of all three types of radiographic changes between the left and right lungs). Mixed linear models were used to investigate the effects of different series on operating characteristics and imaging features. The estimation method ''REML'' (residual (restricted) maximum likelihood) was used.

Statistical evaluation was done on a per-patient basis using SAS Version 9.3, Cary, North Carolina, USA. A local level of significance (p) of <0.05 was considered statistically significantly.

Results

Patient population and baseline HRCT imaging

Of 35 patients approached for study involvement, seven were excluded (4 due to difficulty attaining stored CT images, 2 with hypersensitivity pneumonitis, and 1 with

Table 2 Demographic, disease, and pulmonary characteristics of 28 patients with ILD.

Demographics	
Females, %	56
Age [years], mean (S.E.)	60.3 (2.8)
Ever smoked tobacco, %	36.0
Body size anterior–posterior [mm], mean (S.E.)	253.8 (8.3)
Body size lateral–radial [mm], mean (S.E.)	328.3 (6.7)
Disease diagnosis	
Idiopathic pulmonary fibrosis, %	20
Non IPF, %	80
Pulmonary function test	
Forced vital capacity, % predicted, mean (S.E.)	66.3 (4.1)
Total lung capacity, % predicted, mean (S.E.)	69.8 (3.2)
Diffusing capacity of carbon monoxide, % predicted, mean (S.E.)	67.3 (3.1)

sarcoidosis). Among 28 patients evaluated (56% female) with approximately one-third having a past history of cigarette smoking (Table 2). A clinical diagnosis of IPF and NSIP were made in 20%, and 80% patients respectively. Routine clinical HRCT imaging (120 kV, fixed 50 mA or dose modulation 115–212 mA, 1 mm slice thickness) (Table 1), was reported as UIP in 6 cases (24%) and NSIP in 19 (76%) cases. In total, 448 individual CT scans were generated, reviewed and analyzed.

To provide the utmost insight into the data, the evaluation results of reader 1 are provided in Table 3. Given the huge amount of primary data, ''Results'' section is focused on the statistical results. As mentioned above, for each radiological feature the percentage of affected/diseased lung was visually assessed for each dose level and slice thickness.

Ground glass opacities (GGO)

The overall analysis found a significant ($p < 0.001$) influence of dose on the correct findings for GGOs (Fig. 1). In detail, for reader 1, the second dose level was not significantly different from the reference standard ($p = 0.21$), while dose level three and four showed significant differences ($p = 0.0003$ and $p < 0.0005$, respectively) (Table 4). For reader 2, even the second dose level led to a significant difference in evaluation of the amount of ggo pattern.

The overall analysis found no significant ($p = 0.25$) influence of slice thickness on the correct findings for GGOs for reader 1. In detail, the 2 mm slice thickness resulted in a p-value of 1, 3 mm and 5 mm in $p = 0.89$ and $p = 0.19$, respectively. The combined evaluation of reader 1 and reader 2 confirmed the findings, that a slice thickness of 3 mm showed no significant difference ($p = 0.55$).

Honey combing (HC)

The overall analysis found a significant ($p = 0.002$ and $p < 0.0001$, respectively) influence of dose on the correct findings for HC. In detail, for reader 1 the second and third dose level were not significantly different ($p = 0.29$ and $p = 0.11$, respectively), while dose level four showed significant difference ($p = 0.002$). For the combined evaluation the second dose level was borderline not significantly different ($p = 0.55$).

The overall analysis for reader 1 found no significant ($p = 0.30$) influence of slice thickness on the correct findings for HC. In detail, the 2 mm slice thickness resulted in a p-value of 1, 3 mm and 5 mm in $p = 1$ and $p = 0.86$, respectively. For reader 2 and the combined analysis a slice thickness of 3 mm showed no significant difference on the evaluation of HC, $p = 0{,}64$ and $p = 0.68$, respectively.

Reticulation (RET)

The overall analysis found no significant ($p = 0.38$) influence of dose on the correct findings for reticulation (Fig. 2). In detail, for reader 1 the second dose level was not significantly different ($p = 0.86$), dose level three and four showed p-values of 0.85 and $p = 0.14$, respectively. For reader 2, all reduced dose levels showed a significant difference ($p < 0.0001$).

The overall analysis (reader 1) found no significant ($p = 0.59$) influence of slice thickness on the correct findings for reticulation. In detail, the 2 mm slice thickness resulted in a p-value of 1, 3 mm and 5 mm in $p = 0.98$ and $p = 0.94$, respectively. For reader 2 the slice thickness had no significant impact on detection rate (mean $p = 0.14$).

Total disease extend

The overall analysis found a significant ($p < 0.0001$ and $p = 0.02$, respectively) influence of dose on the correct findings for total disease extend. In detail, for reader 1 the second dose level was not significantly different ($p = 0.61$), dose level three and four showed p-values of <0.0001 and $p < 0.0001$, respectively.

The overall analysis found a significant ($p = 0.024$ and $p = 0.003$, respectively) influence of slice thickness on the correct total disease extend. In detail, for reader 1 the 2 mm slice thickness resulted in a p-value of 1, 3 mm and 5 mm in $p = 0.98$ and $p = 0.017$, respectively.

Image quality

The overall analysis found a significant ($p < 0.0001$) influence of dose on image quality. In detail, was the second dose level significantly different ($p < 0.0001$), dose level three and four showed p-values of <0.0001 and $p < 0.0001$, respectively.

The overall analysis found a significant ($p < 0.0001$) influence of slice thickness on image quality for both readers. In detail, for reader 1 the 2 mm slice thickness resulted in a p-value of =0.08, 3 mm and 5 mm in $p < 0.001$ and $p = 0.0002$, respectively.

Table 3 Individual results of reader 1 for the different dose levels (doses 1–4) and parameters: ground glass opacification (GGO), honeycombing (HC), reticulations (Ret) and total amount of disease (total).

Pat.	Dose 1				Dose 2				Dose 3				Dose 4			
	GGO	HC	Ret	Total	GGO	HC	Ret	Total	GGO	HC	Ret	Total	GGO	HC	Ret	Total
1 mm																
P1	16	0	16	20	16	0	16	20	21	0	18	23	19	0	18	23
P2	10	18	17	25	10	18	17	25	10	18	17	25	10	18	17	25
P3	37	0	23	60	37	0	23	60	37	0	23	60	37	0	23	60
P5	38	0	6	60	38	0	6	60	38	0	6	60	38	0	6	60
P6	5	0	14	15	8	0	14	20	3	0	14	15	5	0	14	15
P7	12	6	47	45	12	6	47	45	11	6	47	45	14	6	47	45
P8	7	15	22	25	7	15	22	20	7	15	22	20	14	15	22	28
P9	5	0	4	5	5	0	4	5	13	0	4	10	19	0	4	13
P10	8	3	16	10	3	3	16	10	67	3	13	70	100	2	12	100
P11	23	23	27	30	23	23	27	30	33	23	27	38	37	23	27	38
P13	52	0	7	55	100	0	7	100	100	0	8	100	100	0	50	100
P14	100	0	100	100	100	0	100	100	100	0	100	100	100	0	100	100
P15	39	0	5	43	39	0	5	43	58	0	5	58	100	0	13	100
P16	4	28	0	35	32	18	0	35	100	13	0	65	100	13	0	65
P17	58	33	10	55	58	33	10	55	65	33	10	60	73	33	10	65
P19	45	0	35	50	45	0	35	50	58	0	35	60	70	0	35	68
P20	31	0	7	30	31	0	7	30	31	0	7	30	35	0	7	33
P23	10	60	3	60	10	60	3	60	10	60	3	60	17	60	3	65
P24	30	0	0	35	30	0	0	35	30	0	0	35	35	0	0	38
P25	3	60	0	60	7	60	0	60	28	60	0	80	100	47	0	80
P26	21	0	23	33	36	0	29	43	100	0	29	75	100	0	31	75
P27	20	48	0	70	23	48	0	70	27	48	0	75	37	48	0	83
P28	18	0	13	10	18	0	13	10	18	0	13	10	18	0	13	10
P30	5	4	0	5	5	4	0	5	5	4	0	5	7	4	0	10
P31	65	0	53	75	65	0	53	75	60	0	53	73	78	0	53	85
P32	45	43	7	75	45	43	7	75	45	43	7	75	45	43	7	75
P33	40	0	37	65	73	0	37	80	87	0	37	90	100	0	37	100
P34	37	0	0	45	37	0	0	45	37	0	0	45	37	0	0	45
2 mm																
P1	16	0	16	20	16	0	16	20	16	0	16	20	19	0	18	23
P2	10	18	17	25	10	18	17	25	10	18	17	25	10	18	17	25
P3	37	0	23	60	37	0	23	60	37	0	23	60	37	0	23	60
P5	38	0	6	60	38	0	6	60	38	0	6	60	38	0	6	60
P6	5	0	14	15	3	0	14	15	5	0	14	15	5	0	14	15
P7	12	6	47	45	12	6	47	45	12	6	47	45	14	6	47	45
P8	7	15	22	25	7	15	22	20	7	15	22	20	11	15	22	23
P9	5	0	4	5	5	0	4	5	8	0	4	5	13	0	4	10
P10	8	3	16	10	4	3	16	10	33	3	16	35	100	2	13	100
P11	23	23	27	30	23	23	27	30	27	23	27	33	27	23	27	33
P13	52	0	7	55	48	0	7	50	48	0	7	50	100	0	7	100
P14	100	0	100	100	100	0	100	100	100	0	100	100	100	0	100	100
P15	39	0	5	43	39	0	5	43	48	0	5	45	97	0	10	95
P16	4	28	0	35	16	23	0	35	80	18	0	55	100	14	0	65
P17	58	33	10	55	58	33	10	55	58	33	10	55	62	33	10	58
P19	45	0	35	50	45	0	35	50	50	0	35	53	58	0	35	60
P20	31	0	7	30	31	0	7	30	31	0	7	30	31	0	7	30
P23	10	60	3	60	10	60	3	60	10	60	3	60	10	60	3	60
P24	30	0	0	35	30	0	0	35	30	0	0	35	30	0	0	35
P25	3	60	0	60	3	63	0	60	20	60	0	75	70	55	0	75
P26	21	0	23	33	26	0	25	35	50	0	25	50	60	0	31	65
P27	20	48	0	70	20	48	0	70	23	48	0	70	30	48	0	78
P28	18	0	13	10	18	0	13	10	18	0	13	10	18	0	13	10

Table 3 (*Continued*)

Pat.	Dose 1				Dose 2				Dose 3				Dose 4			
	GGO	HC	Ret	Total	GGO	HC	Ret	Total	GGO	HC	Ret	Total	GGO	HC	Ret	Total
P30	5	4	0	5	5	4	0	5	5	4	0	5	5	4	0	5
P31	65	0	53	75	65	0	53	75	65	0	53	75	68	0	53	75
P32	45	43	7	75	45	43	7	75	45	43	7	75	45	43	7	75
P33	40	0	37	65	40	0	37	65	47	0	37	70	88	0	37	90
P34	37	0	0	45	37	0	0	45	37	0	0	45	37	0	0	45
3 mm																
P1	16	0	16	20	21	0	16	28	19	0	18	23	19	0	19	23
P2	12	18	17	25	12	18	17	25	12	18	17	25	12	18	17	25
P3	37	0	23	60	37	0	123	60	37	0	23	60	37	0	23	60
P5	38	0	6	60	38	0	6	60	38	0	6	60	38	0	6	60
P6	5	0	14	15	3	0	14	15	5	0	14	15	5	0	14	15
P7	12	6	47	45	12	6	47	45	12	6	47	45	12	6	47	45
P8	7	15	22	20	7	15	22	20	7	15	22	20	7	15	22	20
P9	5	0	4	5	5	0	4	5	5	0	4	5	8	0	4	5
P10	8	3	16	10	8	3	16	10	8	3	16	10	70	3	16	70
P11	23	23	27	30	23	23	27	30	23	23	27	30	27	23	27	33
P13	52	0	7	55	52	0	7	55	48	0	7	50	63	0	7	70
P14	0	0	18	20	0	0	18	20	100	0	100	100	100	0	100	100
P15	39	0	5	43	39	0	5	43	39	0	5	43	82	0	8	75
P16	4	28	0	35	4	28	0	35	27	18	0	35	80	18	0	55
P17	58	33	10	55	58	33	10	55	58	33	10	55	58	33	10	55
P19	45	0	35	50	45	0	35	50	45	0	35	50	45	0	35	50
P20	31	0	7	30	31	0	7	30	31	0	7	30	31	0	7	30
P23	10	60	3	60	10	60	3	60	10	60	3	60	10	60	3	60
P24	30	0	0	35	30	0	0	35	30	0	0	35	30	0	0	35
P25	3	60	0	60	3	60	0	60	8	60	0	65	37	60	0	70
P26	21	0	23	33	21	0	23	33	36	0	23	43	50	0	31	60
P27	27	48	0	75	27	48	0	75	27	48	0	75	23	48	0	75
P28	18	0	13	10	18	0	13	10	18	0	13	10	18	0	13	10
P30	5	4	0	5	5	4	0	5	5	4	0	5	5	4	0	5
P31	65	0	53	75	65	0	53	75	65	0	53	75	65	0	53	75
P32	45	43	7	75	45	43	7	75	45	43	7	75	45	43	7	75
P33	40	0	37	65	40	0	37	65	40	0	37	65	50	0	37	70
P34	37	0	0	45	37	0	0	45	37	0	0	45	37	0	0	45
5 mm																
P1	19	0	18	28	26	0	18	35	19	0	18	23	19	0	19	23
P2	13	18	17	25	13	18	17	25	13	18	17	25	13	18	17	25
P3	37	0	23	60	38	0	25	60	38	0	25	60	38	0	25	60
P5	37	0	6	60	37	0	6	60	37	0	6	60	37	0	6	60
P6	5	0	14	15	7	0	14	20	5	0	14	15	5	0	14	15
P7	12	6	47	45	14	6	47	45	14	6	47	45	11	6	47	45
P8	7	15	22	25	8	15	22	20	12	15	22	25	9	15	22	23
P9	7	0	4	5	5	0	4	5	5	0	4	5	5	0	4	5
P10	8	3	16	10	5	3	16	10	5	3	16	10	38	3	16	40
P11	30	23	27	35	30	23	27	35	30	23	27	35	30	23	27	35
P13	57	0	7	60	57	0	7	60	57	0	7	53	63	0	7	60
P14	0	0	18	20	0	0	18	20	100	0	100	100	100	0	100	100
P15	41	0	5	43	48	0	10	48	48	0	10	48	82	0	10	75
P16	5	28	0	35	16	23	0	35	18	18	0	28	27	18	0	35
P17	67	33	10	60	67	33	10	60	67	33	10	60	67	33	10	60
P19	58	0	35	60	58	0	35	60	58	0	35	60	58	0	35	60
P20	39	0	7	38	39	0	7	38	39	0	7	38	39	0	7	38
P23	18	60	3	65	18	60	3	65	18	60	3	65	15	60	3	65
P24	33	0	0	38	33	0	0	38	38	0	0	43	35	0	0	38
P25	10	60	0	65	10	60	0	65	10	60	0	65	18	60	0	65
P26	26	0	23	38	26	0	23	38	26	0	23	38	35	0	26	53

Table 3 (*Continued*)

Pat.	Dose 1				Dose 2				Dose 3				Dose 4			
	GGO	HC	Ret	Total	GGO	HC	Ret	Total	GGO	HC	Ret	Total	GGO	HC	Ret	Total
P27	37	48	0	80	37	48	0	80	37	48	0	80	37	48	0	80
P28	16	0	13	10	16	0	13	10	16	0	13	10	16	0	13	10
P30	3	3	0	5	3	3	0	5	3	3	0	5	3	3	0	5
P31	65	0	53	75	72	0	53	78	72	0	53	78	72	0	53	78
P32	45	43	7	75	53	43	7	80	53	43	7	80	53	43	7	80
P33	40	0	37	65	52	0	37	73	52	0	37	73	52	0	37	73
P34	37	0	0	45	37	0	0	45	33	0	0	40	33	0	0	40

For 1 mm slice thickness (increment 1 mm).
For 2 mm slice thickness (increment 2 mm).
For 3 mm slice thickness (increment 2.4 mm).
For 5 mm slice thickness (increment 4 mm).

Diagnosis

Using a logistic regression model the likelihood for establishing the correct diagnosis was calculated (Fig. 3).

The overall analysis found no significant ($p < 0.36$ and $p = 1$, respectively) influence of dose on establishing the diagnosis. In detail, for reader 1 the second dose level was not significantly different ($p = 1$), dose level three and four showed p-values of =0.57 and $p = 0.12$, respectively.

The overall analysis found no significant ($p = 0.77$ and $p = 1$, respectively) influence of slice thickness on establishing the diagnosis. In detail, for reader 1 the 2 mm slice thickness resulted in a p-value of =0.6, 3 mm and 5 mm in $p = 0.6$ and $p = 0.29$, respectively.

Optimal LDCT series

The mixed model analysis allows for a combined analysis of dose and slice settings. The estimate of the linear model provides the offset compared to the optimal dataset; the closer this value is to zero, the better.

By using the aforementioned data, it was obvious that a dose level less than 2 leads to significant errors in rating of GGO and total disease extend. Therefore, this specific analysis was tailored to the slice thickness (Table 5). Using this approach, the least estimate (least difference from the original data set) was found for a combination of dose level 2 and slice thickness 5 mm for reader 1 and 3 mm for reader 2.

Discussion

In this study, we set out to establish an optimal LDCT protocol for the most common forms of chronic ILD, UIP and NSIP, by systematically evaluating LDCT imaging series with varying tube current and image slice thickness for differences in operating characteristics and imaging features. The evaluation was done with 2 readers, one experienced chest radiologist and one resident. A LDCT imaging series with 20 mA tube current (SD 30, respectively) and 3–5 mm slice thickness was most optimal, upholding diagnostic accuracy for pattern detection while delivering the lowest radiation dose. Further reductions in tube current to 10 mA resulted in significant reductions in image quality and increased estimation of disease extent, GGO and reticulation. These preliminary results provide support for applying a specific LDCT protocol in patients with common forms of ILD in larger, prospective studies.

Previous CT protocol studies comparing 150 mA versus 40 mA have found reduced sensitivity in detecting ILD imaging features, including interstitial opacities, reticulation, and GGO at lower tube currents.[14] We found estimated GGO, reticulation and disease extent to increase significantly with reductions in tube current to 10 mA. This is suspected to be as a consequence of reduced image quality with lower tube current, interpreted as an exaggerated burden of diseased lung. Image quality was also reduced in 1 mm slice series', compared with 3 mm and 5 mm, suggesting a higher number of images at low tube currents results in increased noise. Interestingly, we found little difference in disease extent and other imaging features between 50 mA and 20 mA series', suggesting a threshold exists, beyond which noise influences imaging feature interpretation. Accurately measuring disease extent on CT imaging is important, as it has been shown to predict functional decline and mortality in both CTD-ILD and IPF.[18,19]

The diagnostic accuracy of HRCT is quoted between 90 and 100% for UIP and 65 and 90% for NSIP, based on studies employing surgical-lung biopsy confirmation.[6,20,21] However, no studies have evaluated the diagnostic accuracy of LDCT imaging for distinguishing UIP and NSIP in comparison to HRCT. We found comparable agreement, sensitivity and specificity between all LDCT series for ILD pattern in comparison to HRCT. However, diagnostic accuracy was highest in 20 mA tube current series. This likely represents how challenging it can be to differentiate UIP and NSIP patterns, regardless of imaging protocol. A central feature in differentiating UIP and NSIP is the presence and extent of HC. We found no difference between LDCT series' in the reported extent of HC, which may explain why operating characteristics were preserved in the 20 mA series.

We compared LDCT series for diagnostic accuracy, image quality and estimated radiation dose to identify the optimal CT parameters. Diagnostic accuracy was felt to be the operating characteristic of principal importance, given it strongly

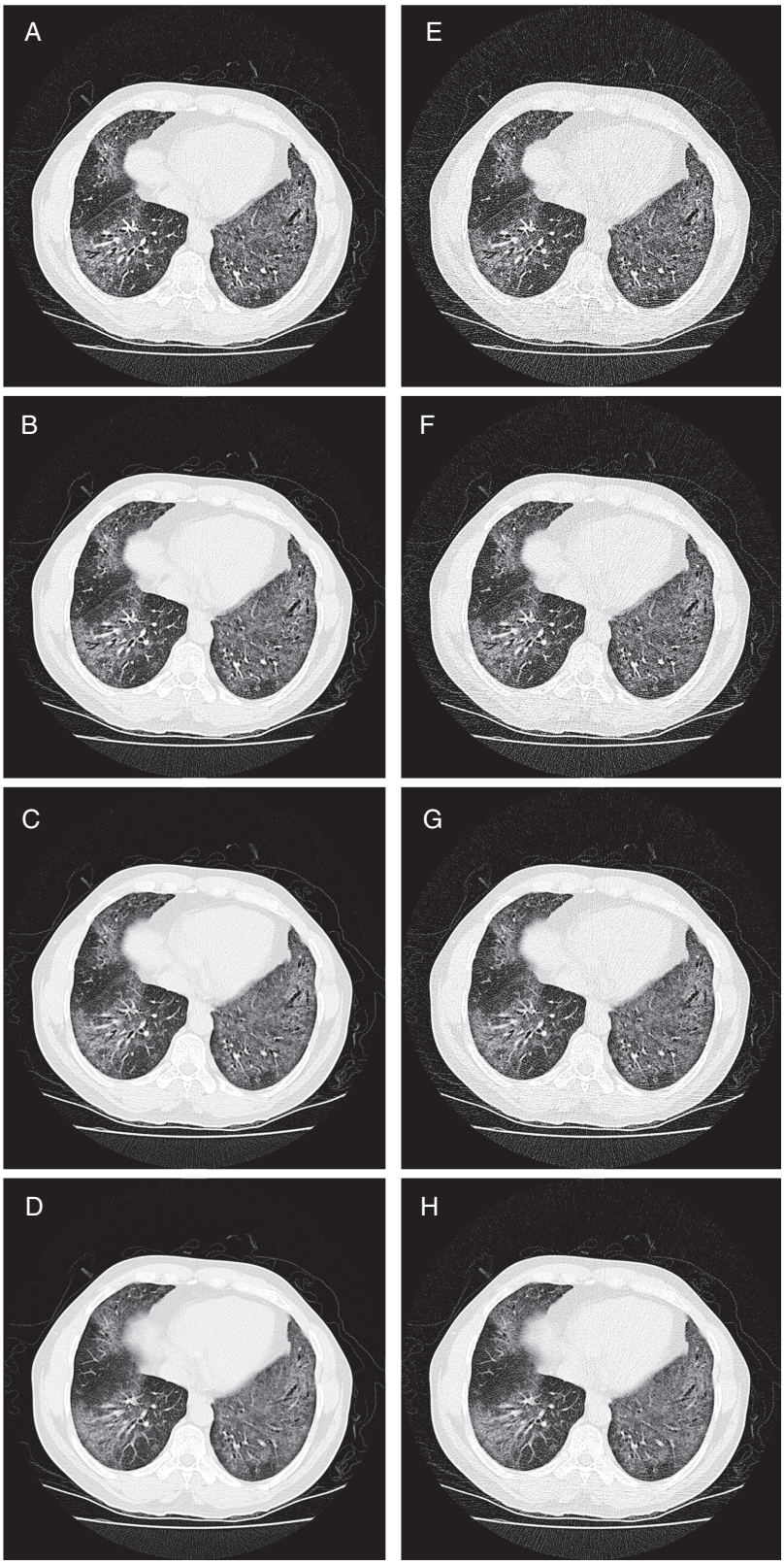


Figure 1 Presentation of ground appearance using 50 mA dose settings simulated 10 mA settings (E–H); images are displayed with W/L: 1600/−600 HU. 1 mm slice thickness (A and E), 2 mm slice thickness (B and F), 3 mm slice thickness (C and G) and 5 mm slice thickness (D and H).

Table 4 Statistical results for reader 1, reader 2, and combined of original and simulated CT datasets with respect to typical ILD features like ground glass opacities (GGO), honeycombing (HC), and reticulation (RET). Mean values were calculated using the SAS procedure ''GLIMMIX''. Also, total disease extend, image quality and diagnostic accuracy are shown.

	GGO	HC	RET	Tot disease	Image qual	Diagn
Reader 1						
Dose 1	–	–	–	–	–	–
Dose 2	=0.21	=0.29	=0.86	=0.61	<0.001	=1
Dose 3	=0.0003	=0.11	=0.85	<0.0001	<0.001	=0.57
Dose 4	<0.0005	=0.002	=0.14	<0.0001	<0.001	=0.12
Mean	<0.001	=0.002	=0.38	<0.001	<0.0001	=0.36
Slice 1 mm	–	–	–	–	–	–
Slice 2 mm	=1	=1	=1	=1	=0.08	=0.6
Slice 3 mm	=0.89	=1	=0.98	=0.98	<0.001	=0.56
Slice 5 mm	=0.19	=0.8591	=0.94	=0.17	=0.0002	=0.29
Mean	=0.248	=0.2966	=0.59	=0.024	<0.0001	=0.77
Dose * slice	=0.1	=0.93	0.48	=0.0078	=0.44	
Reader 2						
Dose 1	–	–	–	–	–	–
Dose 2	=0.01	=0.08	<0.0001	=0.0001	<0.0001	=1
Dose 3	<0.0001	0.0042	<0.0001	<0.0001	<0.0001	=1
Dose 4	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	=1
Mean	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	=1
Slice 1 mm	–	–	–	–	–	–
Slice 2 mm	=0.88	=0.82	=0.74	=0.86	=0.63	=1
Slice 3 mm	=0.46	=0.64	=0.7	=0.89	=0.59	=1
Slice 5 mm	=0.04	=0.02	=0.08	=0.07	=0.29	=1
Mean	<0.0001	=0.004	=0.006	=0.003	=0.08	=1
Dose * slice	=1	=0.97	=0.88	=0.97	=0.28	
Combined						
Dose 1	–	–	–	–	–	–
Dose 2	=0.01	=0.05	=0.003	=0.005	<0.0001	=1
Dose 3	<0.0001	=0.001	<0.0001	<0.0001	<0.0001	=0.67
Dose 4	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	=0.22
Mean	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	=0.56
Slice 1 mm	–	–	–	–	–	–
Slice 2 mm	=0.92	=0.84	=0.8	=0.9	=0.9	=0.68
Slice 3 mm	=0.55	=0.68	=0.77	=0.9	=0.03	=0.68
Slice 5 mm	=0.02	=0.03	=0.22	=0.8	=0.8	=0.4
Mean	=0.003	=0.01	=0.14	=0.002	<0.0001	=0.87
Dose * slice	=0.7	=0.85	=0.89	=0.1	=0.18	

influences the clinical diagnosis and decisions to initiate or withhold immunomodulating therapy. Image quality influences radiologist interpretation of imaging features. We found GGO, reticulation and disease extent to be highest in the 10 mA series, which had the worst image quality. We suspect this is because increased noise leads to an exaggerated quantification of these imaging features. These preliminary results suggest protocols applying 10 mA tube current or less should be avoided, as this could lead to an overestimation of disease extent, and influence projected prognosis. We found the 20 mA/5 mm series to have the best balance of maintaining operating characteristics, while minimizing radiation exposure. However, given the detailed results for each parameter, it appears, that a slice thickness of 3 mm would show even less differences for the individual disease features.

Although there were only 28 subjects involved in this study, each CT performed was used to generate multiple data sets. Comparisons between LDCT series for the same patient removes individual inconsistencies (i.e. differences in breath holding) ensuring only protocol changes influenced CT interpretation. We limited our population to those with UIP and NSIP. This was done to create a homogeneous cohort, but limits the applicability of this protocol to ILD patients with other radiographic patterns. That said, IPF is the most common form of ILD and the approach to interpreting radio-

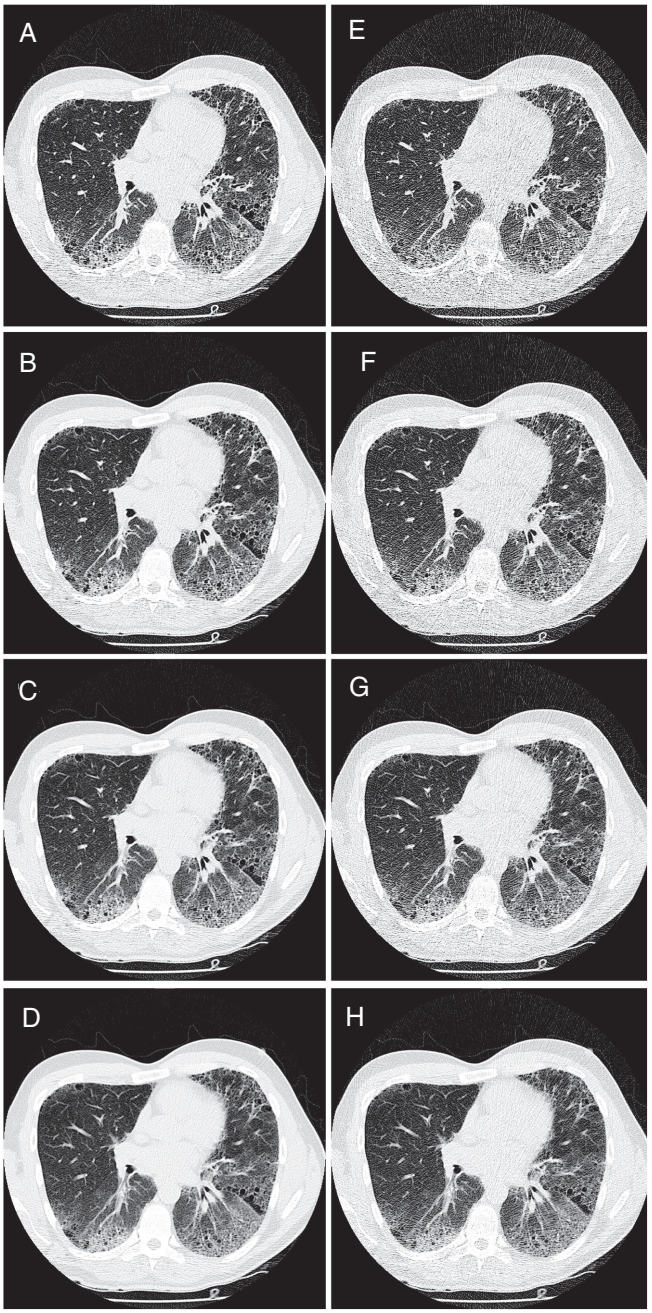


Figure 2 Presentation of reticulation using 50 mA dose settings (A–D) and simulated 10 mA settings (E–H); images are displayed with W/L: 1600/−600 HU. 1 mm slice thickness (A and E), 2 mm slice thickness (B and F), 3 mm slice thickness (C and G) and 5 mm slice thickness (D and H).

graphic UIP outlined in ATS guidelines are often applied to those with undefined ILD [Raghu, 2011 #4452].[4]

Our results suggest that LDCT imaging may accurately distinguish and characterize radiographic UIP and NSIP. A threshold appears to exist for LDCT parameters, below which operating characteristics are compromised. Most of the CT scanners use software-based dose modulation techniques for optimization of the image quality and radiation dose exposure. The dose limits can be adjusted be the user. In case an examination is too low dose due to a challenging body habitus, our results indicate, that it is possible to use even 3–5 mm slice thickness for compensation of the noise without losing the diagnostic capability of the examination (and to avoid re-scan). Additional studies investigating the diagnostic utility of various LDCT protocols in ILD are required.

Clinical relevance

- Low-dose CT imaging for diagnostic characterization of typical ILD changes with 20 mA possible.

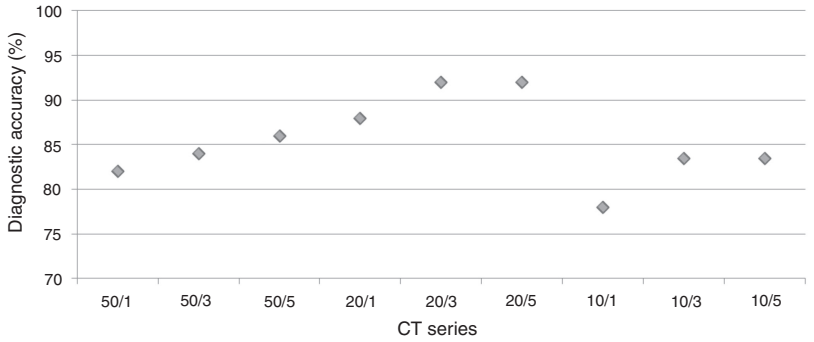


Figure 3 Diagnostic accuracy based on CT imaging parameters. CT series in milliamperes (mA)/millimetres (mm).

- Slice thickness of 3 mm (increment 2.4 mm) and even 5 mm (increment 4 mm) does not impair evaluation of interstitial lung disease.

Funding

Own funding, no external funding.

Conflicts of interest

None declared.

Acknowledgements

We would like to thank Hatem Mehrez for data preparation, and Antonio Cassano for help with the manuscript revision and submission process.

Statistical analysis was performed by Dr. A. Crispin (The Institute for Medical Information Processing, Biometry, and Epidemiology; LMU Munich).

References

1. Solomon JJ, Ryu JH, Tazelaar HD, Myers JL, Tuder R, Cool CD, et al. Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). Respir. Med. 2013;107:1247–52, http://dx.doi.org/10.1016/j.rmed.2013.05.002. PubMed PMID: 23791462 [Epub 25.06.13].
2. Winstone TA, Assayag D, Wilcox PG, Dunne JV, Hague CJ, Leipsic J, et al. Predictors of mortality and progression in scleroderma-associated interstitial lung disease: a systematic review. Chest. 2014;146:422–36, http://dx.doi.org/10.1378/chest.13-2626. PubMed PMID: 24576924 [Epub 01.03.14].
3. Carrington CB, Gaensler EA, Coutu RE, FitzGerald MX, Gupta RG. Natural history and treated course of usual and desquamative interstitial pneumonia. N. Engl. J. Med. 1978;298:801–9, http://dx.doi.org/10.1056/NEJM197804132981501. PubMed PMID: 634315 [Epub 13.04.1978].
4. 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, http://dx.doi.org/10.1164/rccm.201807-1255ST. PubMed PMID: 30168753 [Epub 01.09.18].
5. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am. J. Respir. Crit. Care Med. 2013;188:733–48, http://dx.doi.org/10.1164/rccm.201308-1483ST. PubMed PMID: 24032382; PubMed Central PMCID: PMC5803655 [Epub 17.09.17].
6. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am. J. Respir. Crit. Care Med. 2011;183:788–824, http://dx.doi.org/10.1164/rccm.2009-040GL. PubMed PMID: 21471066 [Epub 08.04.11].
7. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am. J. Respir. Crit. Care Med. 2008;177:1248–54, http://dx.doi.org/10.1164/rccm.200706-877OC. PubMed PMID: 18369202 [Epub 29.03.08].
8. Assayag D, Elicker BM, Urbania TH, Colby TV, Kang BH, Ryu JH, et al. Rheumatoid arthritis-associated interstitial lung disease: radiologic identification of usual interstitial pneumonia pattern. Radiology. 2014;270:583–8, http://dx.doi.org/10.1148/radiol.13130187. PubMed PMID: 24126367; PubMed Central PMCID: PMC4228744 [Epub 16.10.13].
9. ACR-STR. ACR-STR practice parameter for the performance of high-resolution computed tomography (HRCT) of the lungs in adults; 2015. Available from: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/HRCT-Lungs.pdf [cited 2018].
10. Brenner DJ, Hall EJ. Computed tomography – an increasing source of radiation exposure. N. Engl. J. Med. 2007;357:2277–84. PubMed PMID: 18046031.
11. Bouros D, Hatzakis K, Labrakis H, Zeibecoglou K. Association of malignancy with diseases causing interstitial pulmonary changes. Chest. 2002;121:1278–89. PubMed PMID: 11948064 [Epub 12.04.02].
12. McCunney RJ, Li J. Radiation risks in lung cancer screening programs: a comparison with nuclear industry workers and atomic bomb survivors. Chest. 2014;145:618–24, http://dx.doi.org/10.1378/chest.13-1420. PubMed PMID: 24590022 [Epub 05.03.14].
13. Winklehner A, Berger N, Maurer B, Distler O, Alkadhi H, Frauenfelder T. Screening for interstitial lung disease in systemic sclerosis: the diagnostic accuracy of HRCT image series with high increment and reduced number of slices. Ann. Rheum. Dis. 2012;71:549–52, http://dx.doi.org/10.1136/annrheumdis-2011-200564. PubMed PMID: 22121134 [Epub 29.11.11].
14. Christe A, Charimo-Torrente J, Roychoudhury K, Vock P, Roos JE. Accuracy of low-dose computed tomography (CT)

Table 5 Specific analysis of the influence of slice thickness on diagnostic accuracy. As ground glass opacities were the most susceptible parameter for the influence of reduced dose this parameter was chosen. For reader 1 and the combined analysis the estimate is closest to zero with the highest slice thickness of 5 mm, while 2 mm and 3 mm slice thickness were equal. For reader 2, a slice thickness of 3 mm showed the best sensitivity for detection of ground glass opacities in a reduced dose setting.

	Slice thickness	Estimate	*p*-Value
Reader 1			
Dose 2	2	−2.74	0.42
Dose 2	3	−2.93	0.38
Dose 2	5	−1.08	0.75
Reader 2			
Dose 2	2	−0.5	0.88
Dose 2	3	−0.0004	0.99
Dose 2	5	0.4	0.9
Combined			
Dose 2	2	−1.6	0.5
Dose 2	3	−1.5	0.6
Dose 2	5	−0.3	0.9

for detecting and characterizing the most common CT-patterns of pulmonary disease. Eur. J. Radiol. 2013;82:e142–50, http://dx.doi.org/10.1016/j.ejrad.2012.09.025. PubMed PMID: 23122673 [Epub 06.11.12].
15. Zaporozhan J, Ley S, Weinheimer O, Eberhardt R, Tsakiris I, Noshi Y, et al. Multi-detector CT of the chest: influence of dose onto quantitative evaluation of severe emphysema: a simulation study. J. Comput. Assist. Tomogr. 2006;30:460–8. PubMed PMID: 16778622.
16. Gavrielides MA, Zeng R, Myers KJ, Sahiner B, Petrick N. Benefit of overlapping reconstruction for improving the quantitative assessment of CT lung nodule volume. Acad. Radiol. 2013;20:173–80, http://dx.doi.org/10.1016/j.acra.2012.08.014. PubMed PMID: 23085408 [Epub 23.10.12].
17. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246:697–722. PubMed PMID: 18195376.
18. Moore OA, Goh N, Corte T, Rouse H, Hennessy O, Thakkar V, et al. Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. Rheumatology (Oxford). 2013;52:155–60, http://dx.doi.org/10.1093/rheumatology/kes289. PubMed PMID: 23065360 [Epub 16.10.12].
19. Lee HY, Lee KS, Jeong YJ, Hwang JH, Kim HJ, Chung MP, et al. High-resolution CT findings in fibrotic idiopathic interstitial pneumonias with little honeycombing: serial changes and prognostic implications. Am. J. Roentgenol. 2012;199:982–9, http://dx.doi.org/10.2214/AJR.11.8192. PubMed PMID: 23096169 [Epub 26.10.12].
20. Johkoh T. Nonspecific interstitial pneumonia and usual interstitial pneumonia: is differentiation possible by high-resolution computed tomography? Semin. Ultrasound CT MR. 2014;35:24–8, http://dx.doi.org/10.1053/j.sult.2013.10.004. PubMed PMID: 24480140 [Epub 01.02.14].
21. Sumikawa H, Johkoh T, Fujimoto K, Arakawa H, Colby TV, Fukuoka J, et al. Pathologically proved nonspecific interstitial pneumonia: CT pattern analysis as compared with usual interstitial pneumonia CT pattern. Radiology. 2014;272:549–56, http://dx.doi.org/10.1148/radiol.14130853. PubMed PMID: 24661246 [Epub 26.03.14].

Pulmonology 2021;**27(1)**:26–34

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

The effect of different treatment modalities on survival in elderly patients with locally advanced non-small cell lung cancer

A. Sakin[a,*], S. Sahin[b], M.M. atci[c], A. Sakin[d], N. Yasar[c], C. Geredeli[c], F. Aksaray[e], S. Cihan[c]

[a] *Department of Medical Oncology, Yuzuncu Yil University Medical School, 65030, Van, Turkey*
[b] *Department of Medical Oncology, University of Health Sciences, Van Research and Training Hospital, Van, Turkey*
[c] *Department of Medical Oncology, University of Health Sciences, Okmeydani Training and Research Hospital, 34384, Istanbul, Turkey*
[d] *Department of Internal Medicine, University of Health Sciences, Van Research and Training Hospital, Van, Turkey*
[e] *Department of Radiation Oncology, University of Health Sciences, Okmeydani Training and Research Hospital, 34384, Istanbul, Turkey*

Received 23 October 2019; accepted 22 November 2019
Available online 12 December 2019

KEYWORDS
Chemotherapy;
Non-small cell lung cancer;
Chemoradiotherapy;
Survival;
Elderly patients;
Locally advanced disease

Abstract
Purpose: The aim of this study is to investigate the effect of treatment modalities on survival among unoperat ed and locally-advanced non-small cell lung cancer (NSCLC) patients aged 70 years and older, representing real-life data.
Methods: From 2005 through 2017, medical records of 2259 patients with lung cancer from Okmeydani Training and Research Hospital-Istanbul/Turkey were reviewed retrospectively. Patients with locally advanced NSCLC $\geq$ 70 years of age who did not undergo surgery for lung cancer were reviewed. In total, 130 patients were eligible for the final analysis. Patients were stratified into four groups as: chemotherapy (CT), concurrent chemoradiotherapy (cCRT), sequential chemoradiotherapy (sCRT), and radiotherapy (RT) only.
Results: Of the 130 patients included in the analysis; CT, cCRT, sCRT, and RT only were applied to 25(19.2%), 30(23.1%), 31(23.8%), and 44(33.8%) patients, retrospectively. Twelve (9.2%) patients were female. Median age was 72 years (range, 70–88). Sixty (46.2%) patients had stage IIIA disease and 70(53.8%) patients had stage IIIB disease. Median progression-free survival(mPFS) in patients treated with CT, cCRT, sCRT, and RT were 8.0, 15, 10, and 9.0 months, respectively($p = 0.07$). Corresponding median overall survival (mOS) were 10, 33, 20, and 15 months ($p = 0.04$). In multivariate analysis, stage IIIB disease [hazard ratio (HR), 2.8], ECOG-PS 2(HR,

* Corresponding author at: Department of Medical Oncology, Yuzuncu Yil University Medical School, Van, Turkey.
E-mail addresses: drsakin@hotmail.com, drsahins@hotmail.com (S. Sahin), dr_mmatci@hotmail.com (M.M. atci), Mdaysegulsakin@gmail.com (A. Sakin), yasarnurgul@yahoo.com (N. Yasar), caglayange@hotmail.com (C. Geredeli), aksarayf@hotmail.com (F. Aksaray), Sener70@yahoo.com (S. Cihan).

https://doi.org/10.1016/j.pulmoe.2019.11.007

2.10), and ECOG-PS 3–4(HR, 5.13) were found to be the negative factors affecting survival, while cCRT (HR, 0.45) and sCRT (HR, 0.50) were the independent factors associated with better survival.

Conclusion: This study showed that the use of combined treatment modality was associated with better survival in elderly patients with locally advanced NSCLC, with the greatest survival observed in patients treated with cCRT. We therefore suggest that cCRT, when feasible, should be strongly considered in locally advanced NSCLC patients 70 years and over.

Introduction

Lung cancer (LC) is the most common cancer in the world, causing a large number of cancer-related deaths. In 2012, approximately 1.8 million patients had LC worldwide, with an estimated 1.6 million deaths in the same year. About 95% of all LC cases are classified as small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC).[1,2]

The treatment plan in LC depends on several factors such as cell type (e.g. SCLC, NSCLC), patient medical condition, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), and tumor stage. Surgery, chemotherapy (CT), radiotherapy (RT), or chemoradiotherapy (CRT) are widely used to treat patients with a curative intent in stage I, II, or III NSCLC.[2,3]

Stage III NSCLC involves a very heterogeneous group of patients. In addition, many aspects of treatment in stage III disease are still controversial. The definition of stage III disease in LC has changed over time. Moreover, many improvements in LC treatment, including the use of new CT agents, recent advances in RT, and new surgical techniques, limit the interpretation of the results from previous clinical trials.[3–5]

Indeed, LC is an elderly population disease. The median age at diagnosis in LC is 71. Therefore, it becomes increasingly important to establish an effective treatment for elderly patients with LC. Concurrent chemoradiotherapy (cCRT) is the mainstay of treatment for patients with locally advanced and inoperable NSCLC. However, few clinical studies have been designed to specifically examine the treatment outcomes of elderly patients with stage III NSCLC and it is unclear whether cCRT is appropriate for elderly patients.[6,7]

This was a real-world study and aimed to analyze the factors affecting survival along with the effects of different treatment modalities (CT, sCRT, cCRT, and RT) on treatment outcomes in unoperated and locally-advanced NSCLC patients aged 70 years and older.

Methods

Study population

Hospital records and written archive files of 2259 patients with LC, who were followed up and treated between 2005 and 2017 in Okmeydanı Training and Research Hospital-

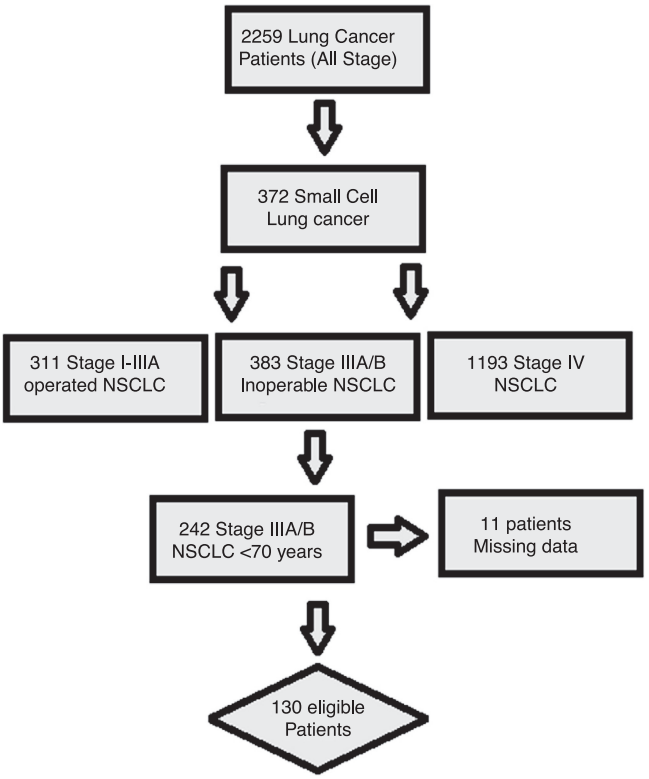


Figure 1 Patient selection for study; a flow diagram.

Istanbul, Turkey, were reviewed retrospectively. Patients with a second primary malignancy, age <70 years, those with missing data, metastatic disease at diagnosis, and patients undergoing surgery for LC were excluded from the study. In total, 130 locally advanced (clinical stage IIIA-IIIB) and unoperated NSCLC patients aged 70 and over were subtracted for the analysis (Fig. 1). The staging procedure was performed by using ^{18}F-FDG-Positron emission tomography/computed tomography and brain magnetic resonance imaging before the treatment. Patients were restaged according to the AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 8th edition.

Data collection

Clinical and demographic features including age, gender, smoking status, body mass index (BMI), presence of comor-

bid disease (e.g. hypertension, diabetes mellitus, ischemic heart disease), ECOG-PS, histological subtype, recurrence, treatment modality, CT regimen, response to treatment, first-line CT regimen used in the metastatic setting, and data regarding the patient final status were obtained from written archive files. According to the treatment modality, patients were divided into four groups as CT, cCRT, sequential chemoradiotherapy (sCRT), and RT only. In patients receiving RT (cCRT, sCRT, and RT), RT was administered at a total dose of 60—66 Gy, 2 Gy/day per fraction.

Treatment modalities and CT regimens were described as follows; *CT, single-agent platinum (carboplatin or cisplatin) or combined cytotoxic CT, *cCRT; carboplatin (AUC 2) + paclitaxel (50 mg/m^2 iv, on day 1 weekly) + concurrent thoracic RT, or cisplatin (75 mg/m^2 iv, on day 1 and 8) + etoposide (100 mg/m2 iv, on day 1–5), cycled every 28 days + concurrent thoracic RT, or cisplatin (20 mg/m2 iv, on day 1 weekly) + docetaxel (20 mg/m2 iv, on day 1 weekly) + concurrent thoracic RT, *sCRT; single-agent platinum (carboplatin or cisplatin) or combined cytotoxic CT was delivered within 30 days before or after initiation of RT.

BMI was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). Progression free survival (PFS) was calculated as the time interval from the beginning of treatment to the date of progression. Overall survival (OS) was defined as the time period from the date of diagnosis to the date of death or last alive contact.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and reviewed and approved by the Ethics Committee of the Okmeydani Training and Research Hospital, University of Health Sciences (48670771-514.10).

Statistical analysis

Statistical Package for Social Sciences 22.0 for Windows software (Armonk NY, IBM Corp. 2013) was used for statistical analysis. For numerical variables, descriptive statistics were reported as mean, standard deviation, minimum, and maximum. For categorical variables, descriptive statistics were presented as number and percentage. Student's *t*-test was used when numerical variable provided a normal distribution condition between the two independent groups and Mann Whitney *U* test was used when the normal distribution condition was not met. Chi square analysis was used to compare the ratios among the groups. Monte Carlo simulation was applied when the conditions were not met. Survival was analyzed using Kaplan Meier method. The determinant factors were examined by Cox Regression Analysis. Forward stepwise model was used for values <0.150 in univariate analysis. Statistical significance level was accepted as $p < 0.05$.

Results

Of the 130 patients included in the analysis; CT, cCRT, sCRT, and RT were applied in 25 (19.2%), 30 (23.1%), 31 (23.8%), and 44 (33.8%) patients, retrospectively. Twelve (9.2%) patients were female and 118 (90.8%) patients were male, with a median age of 72 years (range, 70–88). A total of 125 (96.2%) patients had smoking history. Nearly half of the patients (47.7%) had HT at the time of diagnosis. The information of histological subtype in 38 (29.2%) patients was not available. Sixty (46.2%) patients were stage IIIA and 70 (53.8%) patients were stage IIIB. During the follow-up, 106 (81.5%) patients died and 121 patients experienced disease recurrence, of the patients who developed recurrence, only 27 (20.8%) were able to receive first-line CT (Table 1).

In patients receiving cCRT, radiotherapy was administered concurrently with cisplatin + etoposide (CE) in 7 (23.3%) patients, carboplatin + paclitaxel (CP) in 15 (50%) patients, and cisplatin + docetaxel (CD) in 8 (26.7) patients. In total, 18 patients received a consolidation CT following cCRT; 12 of 15 patients receiving cCRT with CP received 2 more cycles of carboplatin (AUC 5–6 iv, on day 1) + paclitaxel (175 mg/m2, on day 1), cycled every 21 days and 6 of 8 patients receiving cCRT with CD received 2 more cycles of cisplatin (75 mg/m2 iv, on day 1) + docetaxel (75 mg/m2 iv, on day 1), cycled every 21 days (Table 1).

Median PFS and mOS durations according to the disease stage were 16 and 33 months in patients with stage IIIA disease versus 7.0 and 9.0 months in those with stage IIIB, respectively (log rank $p < 0.001$, log rank $p < 0.001$, respectively). Stage IIIA patients treated with CT, cCRT, sCRT, or RT alone had mOS of 22, 36, 30, and 23.0 months, respectively (Log rank $p = 0.549$). Corresponding mOS durations in stage IIIB were 6, 23, 10, and 8.0 months (Log rank $p = 0.014$) (Fig. 2). Median PFS in all patients treated with CT, cCRT, sCRT, and RT alone were 8, 15, 10, and 9 months, respectively (Log rank $p = 0.077$). Corresponding mOS durations were 10, 33, 20, and 15 months (Log rank $p = 0.04$). No significant differences were observed in mOS and mPFS between the CT regimens given concurrently with RT (Log rank $p = 0.497$, Log rank $p = 0.498$, respectively) (Fig. 3).

In univariate analysis, ECOG-PS 2 [hazard ratio (HR), 1.927; 95% Confidence interval (CI), 1.258–2.953], ECOG-PS 3–4 (HR, 3.274; 95% CI, 1.874–5.729), and stage IIIB disease (HR, 2.656; 95% CI, 1.768–3.989) were the factors adversely affecting survival, whereas cCRT and sCRT (HR, 0.434; 95% CI, 0.231–0.813 and HR, 0.547; 95% CI, 0.309–0.967) were observed to be associated with favorable survival. Likewise, In multivariate analysis, stage IIIB disease (HR,2.899; 95% CI,1.894–4.438), ECOG-PS 2 (HR, 2.106; 95 % CI, 1.346–3.296), and ECOG-PS 3–4 (HR,5.139; 95%CI, 2.689–9.822) were found to be the negative factors affecting survival, while cCRT and sCRT were the independent factors associated with better survival (HR, 0.452; 95% CI, 0.239-0.857 and HR, 0.509; 95% CI, 0.284-0.912, respectively) (Table 2)

Discussion

It is known that the feasibility rates of definitive treatment in elderly patients with locally advanced NSCLC are lower than those of non-elderly patients.[8] In this study, we investigated the factors affecting survival in stage III NSCLC patients aged 70 years and older who were treated with CT, cCRT, sCRT, or RT alone. We showed that survival was significantly decreased as ECOG-PS increased. However, the use of combined treatment modality significantly increased sur-

Table 1 Patient data.

	Characteristics	All patients (n = 130)		CT (n = 25)		cCRT (n = 30)		sCRT (n = 31)		RT alone (n = 44)		
	n	%	n	%	n	%	n	%	n	%	P	
Gender	Female	12	9.2	3	12.0	1	3.3	2	6.5	6	13.6	0.446
	Male	118	90.8	22	88.0	29	96.7	29	93.5	38	86.4	
Age	Years (min–max)	72.0 (70–88)		73.0 (70–78)		71.5 (70–81)		71.0 (70–80)		75.0 (70–88)		0.001
Smoking history		125	96.2	24	96.0	29	96.7	30	96.8	42	95.5	0.990
BMI	Kg/m^2 (Mean ± SD)	24.3 ± 4.8		24.5 ± 3.9		25.1 ± 5.0		24.3 ± 6.1		23.0 ± 3.7		0.617
Hypertension		62	47.7	3	12.0	15	50.0	17	54.8	27	61.4	0.001
Diabetes mellitus		11	8.5	2	8.0	4	13.3	1	3.2	4	9.1	0.546
Chronis ischemic heart disease		14	10.8	2	8.0	1	3.3	1	3.2	10	22.7	0.022
ECOG-PS	0–1	74	56.9	12	48.0	23	76.7	17	54.8	22	50.0	0.005
	2	37	28.5	9	26.0	6	20.0	13	41.9	9	20.5	
	3–4	19	14.6	4	16.0	1	3.3	1	3.2	13	29.5	
Stage	IIIA	60	46.2	8	32.0	15	50.0	16	51.6	21	47.7	0.456
	IIIB	70	53.8	17	68.0	15	50.0	15	48.4	23	52.3	
Tumor histology	Unknown	38	29.2	5	20.0	6	20.0	13	41.9	14	31.8	0.222
	SCC	60	46.2	10	40.0	17	56.7	14	45.2	19	43.2	
	AC	32	24.6	10	40.0	7	23.3	4	12.9	11	25.0	
Grade	Moderate	75	90.4	6	100.0	22	91.7	18	90.0	29	87.9	0.905
	Poor	8	9.6	0	0.0	2	8.3	2	10.0	4	12.1	
CT regimen used with RT	Cisplatin + etoposide	7	23.3			7	23.3					
	Carboplatin + paclitaxel	15	50.0			15	50.0					
	Cisplatin + docetaxel	8	26.7			8	26.7					
Maintenance therapy after cCRT	Platine + docetaxel					6	66.7					
	Platine + paclitaxel					12	33.3					
CT regimen	Platine + docetaxel			4	16.0			9	29.0			
	Platine + paclitaxel			7	28.0			13	41.9			
	Platine + gemcitabine			9	36.0			3	9.7			
	Gemcitabine			4	16.0			2	6.5			
	Platine + vinorelbine			0	0.0			3	9.7			
	Vinorelbine			1	4.0			1	3.2			
Response to treatment	Complete response	13	10.0	1	4.0	5	16.7	5	16.1	2	4.5	0.076
	Partial response	63	48.5	8	32.0	16	53.3	13	41.9	26	59.1	
	Stabil disease	29	22.3	6	24.0	7	23.3	7	22.6	9	20.5	
	Progression	25	19.2	10	40.0	2	6.7	6	19.4	7	15.9	
Recurrence		121	93.1	25	100.0	24	80.0	29	93.5	43	97.7	0.012
First-line treatment in metastatic setting		27	20.8	3	12.0	12	40.0	7	22.6	5	11.4	0.022

Table 1 (*Continued*)

	Characteristics	All patients (n = 130)		CT (n = 25)		cCRT (n = 30)		sCRT (n = 31)		RT alone (n = 44)		
	n	%	n	%	n	%	n	%	n	%	P	
	Platine + paclitaxel	1	3.7	0	0.0	1	8.3	0	0.0	0	0.0	0.257
	Platine + gemcitabine	7	25.9	1	33.3	3	25.0	2	28.6	1	20.0	
	Gemcitabine	8	29.6	0	0.0	5	41.7	0	0.0	3	60.0	
	Vinorelbine	6	22.2	1	33.3	1	8.3	3	42.9	1	20.0	
	Alectinib	1	3.7	0	0.0	1	8.3	0	0.0	0	0.0	
	Docetaxel	2	7.4	0	0.0	0	0.0	2	28.6	0	0.0	
	Pemetrexed	2	7.4	1	33.3	1	8.3	0	0.0	0	0.0	
Follow up time	Months(Median)	15		10		19		20		15		0.048
Final status	Alive	24	18.5	2	8.0	13	43.3	4	12.9	5	11.4	0.002
	Dead	106	81.5	23	92.0	17	56.7	27	87.1	39	88.6	

Abbreviations: AC, Adenocarcinoma; ECOG-PS, Eastern cooperative oncology group performance status; CT, Chemotherapy; cCRT, Concurrent chemoradiotherapy; RT, Radiotherapy; SCC, Squamous cell carcinoma; sCRT: Sequential chemoradiotherapy; BMI, body mass index.

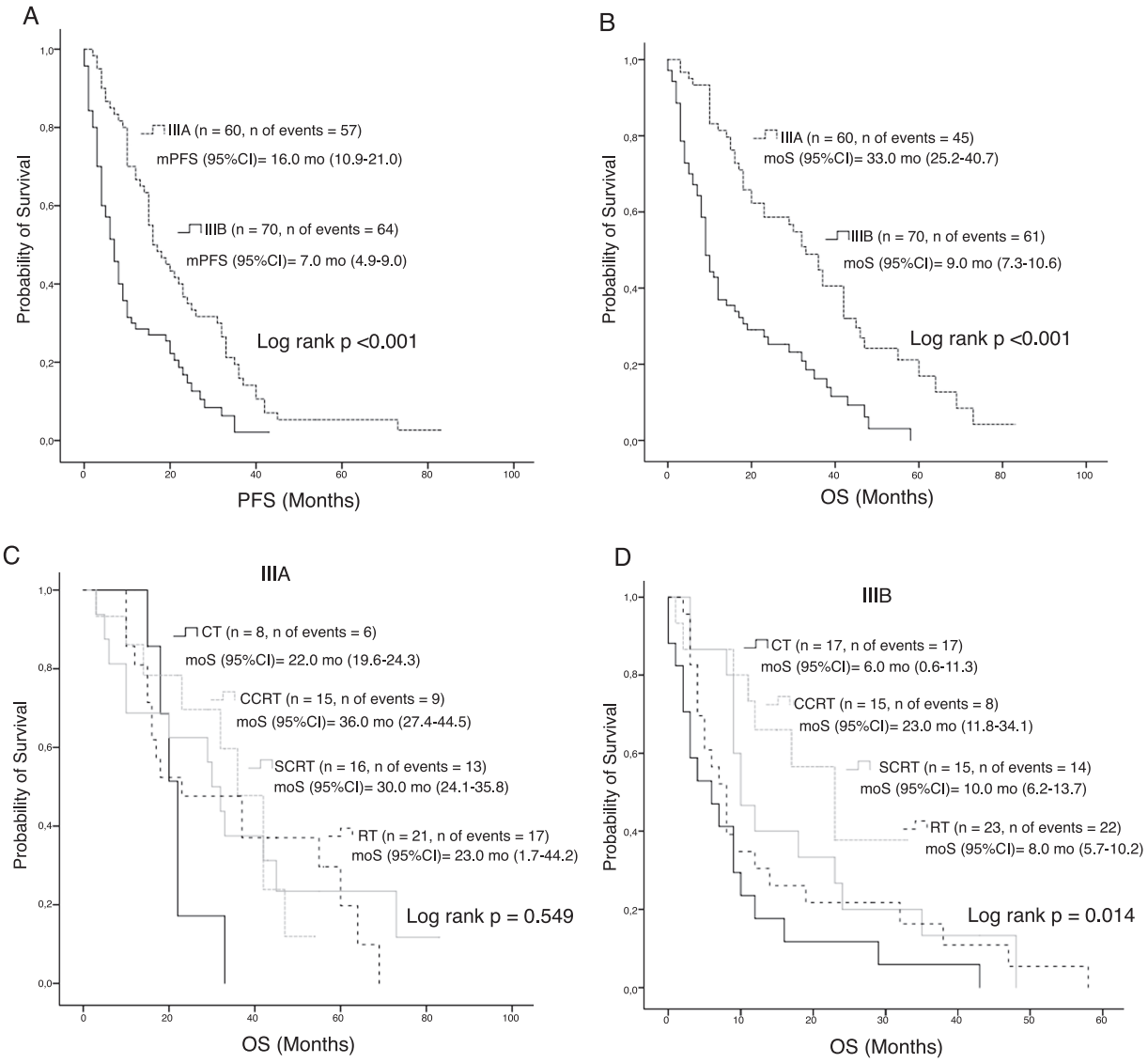


Figure 2 Survival according to stage; A, PFS according to stage; B, OS according to stage; C, OS according to treatment groups in stage IIIA; D, OS according to treatment groups in stage IIIB.
Abbreviations: CT, Chemotherapy; cCRT, Concurrent chemoradiotherapy; OS, Overall survival; RT, Radiotherapy; PFS, Progression-free survival: sCRT, Sequential chemoradiotherapy.

vival, with the best outcomes observed in patients treated with cCRT.

NSCLC accounts for approximately 85% of all cases of LC. In spite of the progress achieved in treatment modalities, NSCLC still has a poor prognosis. Age, gender, histology, and stage are known prognostic factors and new biological markers are being investigated.[9] Stage III NSCLC represents approximately 30% of newly-diagnosed cancer patients and this patient population is extremely heterogeneous, hence requiring a multidisciplinary treatment approach. Elderly patients with LC account for more than one third of all LC patients However, limited data is currently available to guide decision-making in the elderly population. Given the conflicting and inadequate data on this patient population, the optimal treatment strategy for elderly patient with stage III NSCLC needs to be further defined.[10–13]

Driessen et al. performed a multicenter retrospective study including 216 stage III NSCLC patients and reported mOS to be 18 months for patients treated with cCRT, 12 months for those receiving sCRT, 11 months for patients treated with RT alone, and 5 months for patients not undergoing a curative treatment. The authors also concluded that there was no improvement in OS in patients aged 70 and over treated with cCRT, compared with patients receiving sCRT or RT alone.[14] On the contrary, in the study by Davidoff et al. using Survival Epidemiology and End Results-Medicare, stage IIIA and IIIB patients over 65 years of age treated with cCRT had significantly improved overall survival rates. In addition, stage and ECOG-PS were found to be independent factors affecting survival.[15] Similarly, in a subgroup analysis of 2 prospective studies by Schild et al. analyzing 166 patients with NSCLC aged 65 and over, mOS was 10.5 months in patients receiving RT alone and

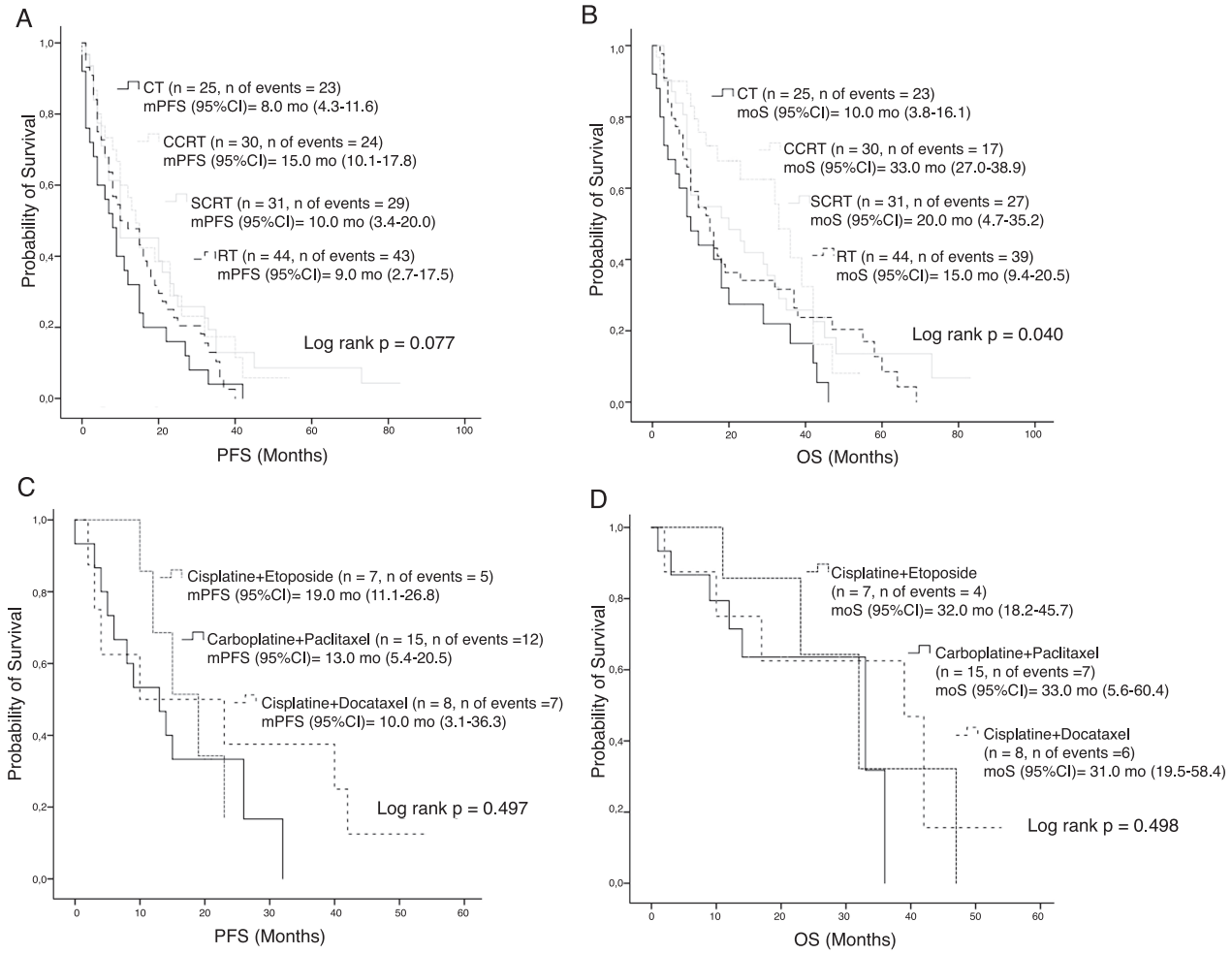


Figure 3 OS according to the treatment; A, PFS according to the treatment modality; B, OS according to the treatment modality; C, PFS according to the CT regimen in patients treated with cCRT; D, OS according to the CT regimen in patients treated with cCRT. Abbreviations: CT, Chemotherapy; cCRT, Concurrent chemoradiotherapy; OS, Overall survival; RT, Radiotherapy; PFS, Progression-free survival: sCRT, Sequential chemoradiotherapy.

13.7 months in those treated with cCRT, demonstrating a significantly longer survival with cCRT.[16] Additionally, in a multicenter and prospective study by Atagi et al. including 200 patients with stage IIIA-IIIB NSCLC treated with either RT alone (n = 100) or cCRT (n = 100), mOS was found to be 16.9 in patients receiving RT alone versus 22.4 months in those treated with cCRT, with a statistically significant survival difference.[17] Our results were similar to those reported by Atagi et al., with corresponding OS durations of 15 and 33 months. Moreover, in our study, stage, ECOG-PS, and receiving cCRT were found to be independent factors affecting survival, as shown by Atagi et al.

In the phase-II SWOG-9019 study, 50 patients with stage IIIB NSCLC received cCRT with CE and demonstrated a mOS of 15 months.[18] In a later phase III study, mOS was detected 23.2 months and it was shown that maintenance treatment with docetaxel following cCRT with CE had no survival advantage.[19] In another phase II study by Belani et al. who analyzed inoperable and locally advanced NSCLC patients, 2 cycles of additional CP were given after cCRT with CP and mOS was found to be 16 months.[20] In a later phase III 3 study comparing the cCRT with CE vs. cCRT with CP, mOS was found to be 23.3 months and 20.7 months, respectively.[21] Yamamoto et al. and Kiura et al. reported mOS of 23.1 and 23.4 months, respectively, in locally advanced and inoperable NSCLC patients treated with cCRT with CD.[22,23] Our study also included stage IIIA NSCLC patients and no maintenance CT was given after cCRT with CE, whereas most patients treated with cCRT with CP and cCRT with CD received maintenance CT. In our study, although patients receiving cCRT with CE had the best survival durations, there was no statistically significant difference in mOS duration between the CT regimens given concurrently with RT.

Compared with the previous studies, the treatment groups in our study were more homogeneous and the follow up period was relatively longer.[14–16] In addition, survival analysis could be performed according to the treatment regimens concurrently used with RT. Although real life data were presented in this study, this was a single-centered study of a retrospective nature, including a relatively small number of cases. The results of this study may therefore be flawed by selection bias inherent in retrospective studies. Another major limitation for this study was the failure

Table 2 Factors affecting survival.

	Characteristics	Univariate analysis for OS			Multivariate analysis for OS		
	HR	95 % CI	P	HR	95 % CI	P	
Gender	Male vs. female	0.856	0.468–1.566	0.615			
Age	Years	0.995	0.944–1.047	0.837			
Smoking	Yes vs. no	1.081	0.439–2.660	0.866			
BMI	Kg/m^2	0.995	0.936–1.058	0.875			
Hypertension	Yes vs. no	1.577	0.691–1.851	0.436			
Diabetes mellitus	Yes vs. no	0.857	0.416–1.766	0.675			
Ischemic heart failure	Yes vs. no	1.604	0.974–4.251	0.150			
ECOG-PS	0–1 (ref)	Reference		<0.001	1		<0.001
	2	1.927	1.258–2.953	0.003	2.106	1.346–3.296	0.001
	3–4	3.274	1.871–5.729	<0.001	5.139	2.689–9.822	<0.001
Stage	IIIA vs. IIIB	2.656	1.768–3.989	<0.001	2.899	1.894–4.438	<0.001
Histology	Unknown(ref.)	1		0.769			
	SCC	1.179	0.753–1.846	0.472			
	AC	1.121	0.670–1.874	0.663			
Grade	Poor vs. moderate	1.292	0.581–2.873	0.530			
Treatment	CT	Reference		0.052			0.057
modality	cCRT	0.434	0.231–0.813	0.009	0.452	0.239–0.857	0.015
	sCRT	0.547	0.309–0.967	0.038	0.509	0.284–0.912	0.023
	RT alone	0.632	0.374–1.069	0.087	0.673	0.338–1.049	0.076

Abbreviations: AC, Adenocarcinoma; ECOG PS, Eastern cooperative oncology group performance status; CT, Chemotherapy; cCRT, Concurrent chemoradiotherapy; RT, Radiotherapy; SCC, Squamous cell carcinoma; sCRT: Sequential chemoradiotherapy.

to reach the side effect profile in the entire population. In addition, a detailed geriatric evaluation could not be performed.

In conclusion, the present study demonstrated that ECOG-PS and CRT were found to be the most important factors affecting survival in locally advanced and unoperated stage III NSCL patients aged 70 years and over. The best survival was achieved in patients treated with cCRT. In light of these data, we think that cCRT should be strongly considered in elderly patients with locally advanced NSCLC, taking into account the performance status and comorbidities in the elderly population. Nevertheless, our results need to be confirmed by larger prospective studies.

Author contributions

Concept – AS, SC, SS; Design – NY, CG, SS; Supervision – SC, SS, CD, AS; Resources – CG, SC, SA; Materials – AS, NY, SA, CG; Data Collection and/or Processing – AS, NY FA,CD; Analysis and/or Interpretation – SC, FA, AS; Literature Search – CD, AS, FA, SS; Writing Manuscript – AS,SS; Critical Review – SC,CD, FA; Other – CG, FA, SC, NY.

Informed consent statement

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data, which were obtained after each patient agreed to treatment by written consent.

Funding source

None.

Conflict-of-interest statement

All authors declare no conflicts-of-interest related to this article.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(January (1)):7–34.
2. Kvale PA, Simoff M, Prakash UB, American College of Chest P. Lung cancer. Palliative care. Chest. 2003;123 January (1 Suppl):284S–311S.
3. Rodrigues G, Choy H, Bradley J, et al. Definitive radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline. Pract Radiat Oncol. 2015;5(May-June (3)):141–8.
4. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med. 1985;312(June 20 (25)):1604–8.
5. Sakin A, Secmeler S, Arici S, et al. Prognostic Significance of Mean Platelet Volume on Local Advanced Non-Small Cell Lung Cancer Managed with Chemoradiotherapy. Sci Rep. 2019;9(March 8 (1)):3959.
6. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol. 1999;17(September (9)):2692–9.

7. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103(October 5 (19)):1452–60.
8. Miller ED, Fisher JL, Haglund KE, et al. Identifying patterns of care for elderly patients with non-surgically treated stage III non-small cell lung cancer: an analysis of the national cancer database. Radiat Oncol. 2018;13(October 5 (1)):196.
9. Machado D, Marques C, Dias M, Campainha S, Barroso A. Inflammatory prognostic biomarkers in advanced non-small cell lung cancer. Pulmonology. 2019;25(May–June (3)):181–3.
10. Crino L, Weder W, van Meerbeeck J, Felip E, Group EGW. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 May (Suppl 5):v103–115.
11. Sacher AG, Le LW, Leighl NB, Coate LE. Elderly patients with advanced NSCLC in phase III clinical trials: are the elderly excluded from practice-changing trials in advanced NSCLC? J Thorac Oncol. 2013;8(March (3)):366–8.
12. Langer CJ. Neglected and underrepresented subpopulations: elderly and performance status 2 patients with advanced-stage non-small-cell lung cancer. Clin Lung Cancer. 2006;7 May (Suppl 4):S126–137.
13. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol. 2003;21(April 1 (7)):1383–9.
14. Driessen EJ, Bootsma GP, Hendriks LE, et al. Stage III Non-Small Cell Lung Cancer in the elderly: Patient characteristics predictive for tolerance and survival of chemoradiation in daily clinical practice. Radiother Oncol. 2016;121(October (1)):26–31.
15. Davidoff AJ, Gardner JF, Seal B, Edelman MJ. Population-based estimates of survival benefit associated with combined modality therapy in elderly patients with locally advanced non-small cell lung cancer. J Thorac Oncol. 2011;6(May (5)):934–41.
16. Schild SE, Mandrekar SJ, Jatoi A, et al. The value of combined-modality therapy in elderly patients with stage III nonsmall cell lung cancer. Cancer. 2007;110(July 15 (2)):363–8.
17. Atagi S, Kawahara M, Yokoyama A, et al. Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301). Lancet Oncol. 2012;13(July (7)):671–8.
18. Albain KS, Crowley JJ, Turrisi AT 3rd, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. J Clin Oncol. 2002;20(August 15 (16)):3454–60.
19. Hanna N, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol. 2008;26(December 10 (35)):5755–60.
20. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol. 2005;23(September 1 (25)):5883–91.
21. Liang J, Bi N, Wu S, et al. Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. Ann Oncol. 2017;28(April 1 (4)):777–83.
22. Yamamoto N, Nishimura Y, Nakagawa K, Matsui K, Fukuoka M. Phase I/II study of weekly docetaxel dose escalation in combination with fixed weekly cisplatin and concurrent thoracic radiotherapy in locally advanced non-small cell lung cancer. Cancer Chemother Pharmacol. 2006;58(September (3)):285–91.
23. Kiura K, Ueoka H, Segawa Y, et al. Phase I/II study of docetaxel and cisplatin with concurrent thoracic radiation therapy for locally advanced non-small-cell lung cancer. Br J Cancer. 2003;89(September 1 (5)):795–802.

Pulmonology 2021;**27(1)**:35–42

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Risk factors for early mortality in patients with pulmonary tuberculosis admitted to the emergency room

R. Singla[a,*], B. Raghu[a], A. Gupta[a], J.A. Caminero[b,c], P. Sethi[a], D. Tayal[d], A. Chakraborty[a], Y. Jain[e], G.B. Migliori[f,g]

[a] *Department of Tuberculosis and Chest Diseases, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, 110030, India*
[b] *Pneumology Department, Hospital General de Gran Canaria ''Dr. Negrin'', Las Palmas de Gran Canaria, 35010, Spain*
[c] *MDR-TB Unit, Tuberculosis Division, International Union against Tuberculosis and Lung Disease, Paris 75006, France*
[d] *Department of Biochemistry, National Institute of Tuberculosis and Respiratory Diseases, New Delhi 110030, India*
[e] *Jan Swasthya Sahyog, Bilaspur, Ganiyari, Chhattisgarh 495112, India*
[f] *Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri IRCCS, Tradate, 21049, Italy*
[g] *Blizard Institute, Queen Mary University of London, 4 Newark St, Whitechapel, London E1 2AT, United Kingdom*

Received 3 December 2019; accepted 6 February 2020
Available online 29 February 2020

KEYWORDS
Pulmonary tuberculosis;
Risk factors;
Mortality;
Prediction score;
Intensive care;
Pulmonary rehabilitation

Abstract
Background and objectives: Mortality of patients with pulmonary tuberculosis (TB) admitted to emergency departments is high. This study was aimed at analysing the risk factors associated with early mortality and designing a risk score based on simple parameters.
Methods: This prospective case-control study enrolled patients admitted to the emergency department of a referral TB hospital. Clinical, radiological, biochemical and microbiological risk factors associated with death were compared among patients dying within one week from admission (cases) and those surviving (controls).
Results: Forty-nine of 250 patients (19.6%) experienced early mortality. Multiple logistic regression analysis showed that oxygen saturation (SaO_2) $\leq$90%, severe malnutrition, tachypnoea, tachycardia, hypotension, advanced disease at chest radiography, severe anaemia, hyponatremia, hypoproteinemia and hypercapnia were independently and significantly associated with early mortality. A clinical scoring system was further designed to stratify the risk of death by selecting five simple parameters ($SpO_2 \leq 90\%$, tachypnoea, hypotension, advanced disease at chest radiography and tachycardia). This model predicted early mortality with a positive predictive value of 94.88% and a negative predictive value of 19.90%.

* Corresponding author at: Department of Tuberculosis and Chest Diseases, National Institute of Tuberculosis and Respiratory Diseases, New Delhi 110030, India.
E-mail address: drrupaksingla@yahoo.com (R. Singla).

https://doi.org/10.1016/j.pulmoe.2020.02.002

Conclusions: The scoring system based on simple parameters may help to refer severely ill patients early to a higher level to reduce mortality, improve success rates, minimise the need for pulmonary rehabilitation and prevent post-treatment sequelae.

Introduction

Tuberculosis (TB) is a major public health problem worldwide. A significant number of patients die due to TB across the globe despite good control programmes in many countries including India.[1] The best WHO estimate is that around 10.0 million people developed TB disease in 2018, with 1.2 million deaths from TB, including 251,000 Human Immunodeficiency Virus (HIV) positive people.[1] In India the estimated number of new TB cases was 2,700,000 accounting for about a quarter of the world's TB burden with 440,000 deaths in 2018.[1–3] The India National TB Elimination Plan 2017–2025 introduced a mortality target (90% reduction by 2025, i.e. global reduction from 32 to 3 death per 100,000 population)[3] to contribute to monitoring this core parameter.

The literature on factors associated with early mortality of patients with TB is scanty. The available studies are based on cohort analysis of treatment outcomes and, with a single exception,[4] analysed long-term mortality with a retrospective approach.[5–11] These studies identified drug-resistant TB and HIV infection as the main determinants of mortality.[4–8] The risk factors for early and long-term mortality are likely to be different. Adequate identification of early mortality predictors would allow clinicians to early identify patients at risk. Moreover, as after Intensive Care Unit (ICU) admission the surviving patients often need pulmonary rehabilitation, a more precise risk stratification of these cases would be very useful, both from a clinical and public health perspective.[12–16]

The aims of this prospective case-control study were: 1) to identify risk factors of patients with TB associated with early mortality (within one week from admission); 2) to develop a simple risk score to be easily assessed in peripheral units to call for rapid clinical action and prevention of avoidable mortality.

Methods

This is an international collaborative prospective case-control study consisting of two steps: 1: to identify the risk factors independently associated to early mortality; and 2: based on them, to design a simple risk score which can be applied in all health facilities to prevent early mortality.

Setting and patients

This collaborative study was conducted between May 2017 and May 2019 at the National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India (a referral, tertiary level institute for TB management) in collaboration with the Maugeri Institute, Tradate, Italy (a reference centre with interest in TB research and rehabilitation).[13] In India one of four admissions to the emergency department are due to patients with diagnosed or presumptive TB. All consecutive bacteriologically confirmed (at direct sputum smear and XPERT® MTB/RIF assay) patients admitted at the emergency department with symptoms and/or signs suggestive of TB (e.g. cough, fever, or hemoptysis, for more than two weeks) were enrolled in the study upon consultation with the Maugeri Institute. The patients who died within 7 days after admission within the study period were defined as cases and those surviving were defined as controls. All causes of death were documented.

The study was approved by the ethics and research committee of the participating institutions (N° 12,007/2017 dated 07-02-2017 and 12,733/2017 dated 01-03-2017, respectively). Patients (when not possible, the relatives) signed the informed consent.

Study design

All enrolled patients underwent a comprehensive clinical examination and a detailed medical history. All the findings were entered in a clinical data-collection form, including:

1 Demographics and anthropometrics; socio-economic status as per Kuppuswamy scale.[17]; smoking history (number of bidis and cigarettes smoked per day multiplied by the year of smoking); alcohol use history according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (DSM-IV) criteria for alcohol dependence[18];
2 Duration of signs and symptoms; history of previous anti-TB treatment; direct sputum smear for acid fast bacilli; co-morbidities (diabetes mellitus, chronic obstructive pulmonary disease, co-infection with HIV and cardiovascular diseases);
3 Clinical signs: arterial blood pressure, pulse rate, respiratory rate, body temperature, and presence/absence of wheezing;
4 Laboratory: Pulse oximetry (SpO_2) and arterial blood gases; blood count, renal and liver function tests, serum electrolytes;
5 As per Indian guidelines all patients were tested for HIV co-infection.
6 All patients underwent a postero-anterior chest radiography read by two independent expert clinicians and

classified according to the USA National Tuberculosis Association criteria[19] as follows:

(7) *Minimal lesions*. Without cavities and of slight to moderate density. They may involve a small part of one or both lungs, but the total extent (regardless of distribution) should not exceed the volume of lung on one side that occupies the space above the second chondrosternal junction and the spine of the forth -or body of the fifth- vertebra.
(8) *Moderately advanced lesions*. Localized in one or both lungs, cavities (if present) with a total diameter below 4 cm, with total extent not exceed the following: a. disseminated lesions of slight to moderate density throughout the total volume of one lung or the equivalent in both lungs; b. dense and confluent lesions limited in extent to one-third the volume of a single lung.
(9) *Far advanced lesions*. More extensive than the moderately advanced ones.

Other chest X-ray details (such as unilateral/ bilateral, with/without cavities) were also recorded.

Discrepancies in reading were resolved by consensus.

Statistical analysis

Sample size calculation

Preliminary data from the emergency department (first quarter 2016) indicate that out of 175 admissions, 69 were due to bacteriologically confirmed TB patients, with high mortality within the first week following admission (5/69, 7.2%). The hypothesis guiding the study design and the sample size calculation is that a fraction of this mortality is preventable via rapid referral to higher clinical level, given adequate criteria to identify the patients are available and that a suitable cut-off to define early mortality is one week.

Therefore, considering these assumptions with 95% confidence interval and 3% absolute precision, the sample size was calculated as follows:

$$n = \frac{Z^2_{(1-\alpha/2)}PQ}{d^2} = \frac{(1.96)^2\,(0.07)\,(0.93)}{(0.1)\,(0.1)}$$

n = Sample size; $\alpha = 0.05$; P = Percentage of patient with diagnosis of PTB; Q = (1-P); Z = 1.96 at significance level of 5%; d = Absolute precision

The resulting sample size of 243, was rounded up to 250.

Step 1: defining risk factors for early mortality

Both univariate and multivariate logistic regression models were used to assess the risk factors independently associated with early mortality. A p value of <0.05 was considered statistically significant.

Step 2: defining a simple risk score to predict early mortality

Among the independent factors significantly associated to early mortality in the multiple logistic regression analysis, we identified those which could be easily evaluated in a peripheral health unit; they were used to design a clinical prediction model able to stratify the risk of death among TB patients. A specific weight was assigned to each variable based on their Odds Ratios (i.e., the risk factor with a higher odds ratio got a higher weighted score). The scores were then used to classify patients into levels of increasing risk of mortality.

The study data was analysed and the scores assigned with several simulations in such a way that no patient group with lower mortality risk would be placed at a higher level (and vice-versa). A higher risk score was therefore expected to be associated with a higher probability of early mortality.

Proportions were calculated for categorical variables and mean $\pm$ Standard Deviation (SD) for continuous variables. The data were entered in Microsoft® Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (IBM, Armonk, NY, USA) version 21.0.

Results

The analysis was performed on 250 patients out of which 49 were cases (patients who died within one week from admission) and 201 controls (those who survived). Their characteristics are summarized in Table 1.

Step 1: risk factors for early mortality

From the univariate analysis the factors significantly associated with mortality were: lower socio-economic status, longer treatment duration, severe malnutrition (assessed by Body Mass Index — BMI), previous history of anti-TB treatment, advanced disease on chest radiography, tachycardia, hypotension and tachypnoea, anaemia, sepsis, thrombocytopenia, electrolyte dis-balance including hyponatremia and hypokalemia, $SpO_2 \leq 90\%$, hypercapnia, hypoxaemia and hypoproteinemia.

As shown in Table 2, the factors independently and significantly associated with mortality at the multiple logistic regression analysis were $SpO_2 \leq 90\%$, severe malnutrition, tachypnea, tachycardia, hypotension, advanced disease at chest radiography, severe anaemia, hypoxaemia, hyponatremia, hypoproteinemia and hypercapnia.

Only four patients diagnosed with TB were co-infected with HIV. Four patients were infected by rifampicin-resistant strains of *Mycobacterium tuberculosis* among cases and 18 among controls.

Step 2: simple risk score to predict early mortality

The five significant risk parameters from the multivariate logistic regression analysis and easy to measure in field conditions include: $SpO_2 \leq 90\%$, tachypnoea, hypotension, advanced disease at chest radiography and tachycardia (Table 3A).

Using the weights summarised in Table 3A, the scoring system to stratify the risk of death was designed assigning a score from 0 to 6+ to each patient (Table 3B). The mortality rate associated with a risk score of 1–2, 3–5 and $\geq$6 was found to be 15%, 33% and 87.5%, respectively. The prediction model had area under receiver operating characteristic (ROC) curve (Fig. 1) of 0.86 indicating a very good predictability of the model. This model predicted early

Table 1 Summary of the patients' characteristics.

	Cases (n = 49)	Controls (n = 201)	p-Value
Age (years)			
a) >60	7 (14.3%)	46 (22.9%)	p = 0.206
b) <60	42 (85.7%)	155 (77.1%)	
Sex			
a) Male	36 (73.5%)	134 (66.7%)	p = 0.360
b) Female	13 (26.5%)	67 (33.3%)	
Social class (Kuppuswamy scale)[12]			
a) Upper middle	1 (2.0%)	2 (0.1%)	p = 0.00094
b) Lower middle	6 (12.2%)	33 (16.4%)	
c) Upper lower	5 (10.2%)	74 (36.8%)	
d) Lower	37 (75.5%)	92 (45.8%)	
Smoking habit			
a) Yes	23 (46.9%)	83 (41.3%)	p = 0.4733
b) No	26 (53.1%)	118 (58.7%)	
Smoking index			
a) >500	5 (10.2%)	25 (12.4%)	p = 0.666
b) 0-500	44 (89.8%)	176 (87.6%)	
History of alcoholism			
a) Yes	18 (36.7%)	64 (31.8%)	p = 0.5129
b) No	31 (63.2%)	137 (68.1%)	
BMI, Kg/m^2			
a) <16	46 (93.9%)	161 (80.1%)	p = 0.0219
b) >16	3 (6.1%)	40 (19.9%)	
Past history of ATT			
a) Yes	34 (69.4%)	106 (52.7%)	p = 0.0054
b) No	15 (30.6%)	95 (47.2%)	
Duration of treatment in previous TB episodes			
a) >1 year	8 (23.5%)	16 (15.9%)	p = 0.0014
b) 6 months-1 year	16 (47.0%)	22 (20.6%)	
c) <6 months	10 (29.4%)	68 (63.5%)	
Number of times ATT taken			
a) >2	8 (23.5%)	13 (12.3%)	p = 0.134
b) 2	12 (35.3%)	27 (24.5%)	
c) 1	14 (41.2%)	66 (62.3%)	
Drug sensitive TB			
a) Yes	44 (89.9%)	179 (89.05%)	P = 0.89
a) No	5 (10.1%)	22 (10.95%)	
Health service			
a) Private	22 (64.7%)	70 (66.0%)	p = 0.900
b) Public	8 (23.5%)	27 (25.5%)	
c) Public and private	4 (11.8%)	9 (8.5%)	
SpO_2			
a) $\leq$90%	37 (75.5%)	110 (54.7%)	p = 0.00012
b) >90%	12 (24.5%)	91 (45.3%)	
$PaCO_2$, mmHg			
a) >45	2 (4.1%)	1 (0.5%)	p = 0.038
b) <45	47 (95.9%)	200 (99.5%)	
PaO_2, mmHg			
a) <70	40 (81.6%)	98 (49.2%)	p = 0.000044
b) >70	9 (18.4%)	101 (50.7%)	
Haemoglobin, gm/dl			
a) <7	23 (46.9%)	40 (19.1%)	p = 0.00627
b) 7–10	18 (36.7%)	95 (47.3%)	
c) 10–12	2 (4.1%)	34 (16.9%)	
d) >12	6 (12.2%)	32 (15.9%)	

Table 1 (*Continued*)

	Cases (n = 49)	Controls (n = 201)	p-Value
White cells, cells/μL			
a) <4000 and >11000	32 (65.3%)	96 (47.8%)	p = 0.027
b) 4000–11000	17 (34.7%)	105 (52.2%)	
Platelet count,			
a) <150 × 103/μL	9 (18.4%)	171 (85.9%)	p = 0.00001
b) ≥150 × 103/μL	40 (81.6%)	28 (14.1%)	
Heart rate per minute			
a) >100	9 (18.3%)	91 (45.3%)	p = 0.00056
b) <100	40 (81.6%)	110 (54.7%)	
Systolic blood pressure, mmHg			
a) <90	32 (65.3%)	75 (37.3%)	p = 0.00038
b) >90	17 (34.7%)	126 (62.7%)	
Respiratory rate, per minute			
a) ≥20	39 (79.5%)	109 (54.2%)	p = 0.00119
a) <20	10 (20.4%)	92 (45.8%)	
Serum sodium, mEq/L			
a) <135	37 (75.5%)	109 (54.2%)	p = 0.0067
b) 135–145	12 (24.5%)	92 (45.8%)	
Serum potassium, mEq/L			
a) <3.5	45 (91.8%)	88 (43.8%)	p = 0.00001
b) 3.5–5.0	4 (8.2%)	113 (56.2%)	
Total serum proteins, gm/dl			
a) <6.5	41 (83.7%)	132 (65.7%)	p = 0.014
b) 6.5–8	8 (16.3%)	69 (34.3%)	
Chest radiography			
a) Advanced disease	16 (32.6%)	22 (10.9%)	p = 0.0005
b) Moderate disease	31 (63.3%)	158 (78.6%)	
c) Minimal disease	2 (4.1%)	21 (10.4%)	
Cavities			
a) Yes	44 (89.8%)	150 (74.6%)	p = 0.022
b) No	5 (10.2%)	51 (25.4%)	
Cavities	(n = 44)	(n = 150)	
a) Single	1 (2.3%)	14 (9.3%)	p = 0.123
b) Multiple	43 (97.7%)	136 (90.7%)	

Data shown as n (%), unless otherwise stated. BMI: body mass index; ATT: anti-tuberculosis treatment; ABG: arterial blood gas; TLC: total leucocyte count; BP: blood pressure; AFB: acid fast bacilli; RBC: red blood cell; SpO_2: estimate of arterial oxygen saturation $PaCO_2$: partial pressure of oxygen in the arterial blood.

Table 2 Variables independently associate with early mortality at the multivariate logistic regression analysis.

	Odds ratio (95% CI)	p Value
a) BMI <16 kg/m^2	3.80 (1.12–12.88)	p = 0.0202
b) Hb < 7 gm/dl		p = 0.02796
c) SpO_2 < 90%	4.25 (4.01–6.17)	p = 0.0004301
d) Serum sodium, <135 mEq/L	2.60 (1.28–5.28)	p = 0.044456
e) Total serum proteins, <6.5 gm/dl	2.88 (0.98–8.47)	p = 0.02497
f) Advanced disease on chest radiography		p = 0.00011
g) Cavity	2.99 (1.12–7.95)	p = 6.03E-05
h) $PaCO_2$ > 45 mmHg	8.51 (0.75–9.58)	p = 0.04445
i) Heart rate > 100 per minute	2.27 (1.12–2.59)	p = 0.00012
j) Systolic blood pressure < 90 mmHg	3.16 (1.64–6.08)	p = 0.01255
k) Respiratory Rate > 20 per minute:	3.29 (1.55–6.95)	p = 0.04201
l) PaO_2 < 70 mmHg	4.58 (2.11–9.93)	p = 4.98E-06

Abbreviations: OR: odds ratio; CI: confidence interval; BMI: Body Mass Index; SpO_2: estimate of arterial oxygen saturation; $PaCO_2$: partial pressure of oxygen in the arterial blood.

Table 3A Five core risk parameters composing the clinical scoring system to predict early mortality.

Predicting factor	Multivariate OR (95% CI)	Weight for risk score
$SpO_2 \leq 90\%$	6.1 (3.37–7.75)	4
Respiratory rate > 20 per minute	4.95 (2.32–10.4)	2
Systolic blood pressure < 90 mmHg	4.8 (2.46–9.12)	2
Advanced disease on chest radiography	4.0 (1.68–11.92)	1
Heart rate > 100 per minute	3.6 (1.68–3.88)	1

Abbreviations: OR: odds ratio; CI: confidence interval; SpO_2: estimate of arterial oxygen saturation;

Table 3B Stratification of the pulmonary TB patients admitted to emergency care according to the newly developed risk assessment tool'.

Risk score	Risk class	Mortality
a) 1–2	Low	15%
b) 3–5	Moderate	33%
c) >6	High	87.5%

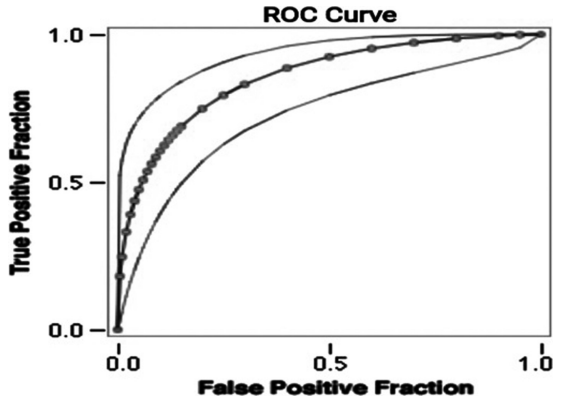


Figure 1 Receiver operating characteristic (ROC) curve for the clinical scoring system and mortality rate.
Area under ROC curve: 0.86; Accuracy 88%.

mortality with a positive predictive value of 94.88% and a negative predictive value of 19.90%.

Discussion

This prospective study assessed the risk factors of patients with TB associated with early mortality at the emergency department level in a developing country. Furthermore, it allowed us to stratify the mortality risk by using basic and easy measurable parameters. To the best of our knowledge, our study is also the first prospective study specifically designed and powered to study early mortality of these patients admitted to the emergency department and to propose a clinical prediction model to stratify all the patients admitted to an emergency department for early mortality.[9–11] Although the evidence raised is limited to India, and more evidence is needed, the model is likely to be useful in other intermediate and low-income settings, being based on simple parameters. Early referral to intensive care is likely to reduce preventable early mortality.

Our study suggests that severe malnutrition is an independent risk factor for mortality. In a study by Yung-Feng Yen et al.[20] severe malnutrition was significantly associated with higher risk of all-cause mortality in these patients. The Indian Government has considered malnutrition in patients with TB as a serious concern and framed a national policy to provide financial aid to all patients by transferring cash incentives every month to their accounts till the completion of treatment as an initiative to improve their nutritional status.[2] In our study severe anaemia was observed in 46.9% of cases, as compared to 19.1% of controls. Anaemia was associated with mortality in a retrospective case-control study in South Africa in which 50% of patients died.[10]

Interestingly enough, the factors independently and significantly associated with mortality in our study did not include history of previous treatment. As the treatment of drug-susceptible TB has not changed over the last four decades and the prevalence of drug resistance is alarming in several countries (including India), new drugs and regimens are urgently needed.[21,22]

The use of clinical prediction rules (CPRs) gained recent relevance in the field of pulmonary diseases. Most of the prediction rules available so far in the area of TB cover diagnosis, with only three studies providing prognosis-centred CPRs.[11,23–29] Wejse et al.[28] proposed the first CPR (the BandimTBscore) in a low-resource country (Guinea-Bissau), based on five symptoms and six clinical signs. However, the study included HIV-positive patients who might have been independent risk factors for mortality.[24] Horita et al.[30] developed a CPR to predict in-hospital TB mortality. However, exclusion of multi-drug resistant cases might have biased the conclusions as well as excluding co-morbidities (e.g. diabetes) from their prediction model.[30] Bastos et al.[11] conducted a retrospective cohort study in Portugal and selected five risk parameters in patients with pulmonary TB to formulate a risk assessment tool. They stratified patients into low (score 2), moderate (score 3–5) and high (score 6) mortality risk. However, six-month mortality was taken as the outcome measure.

Patients with higher scores are likely to benefit from early admission to intensive/advanced medical care units. Importantly, the prediction of mortality is independent from both the patients' collaboration and the clinician's subjective judgement.

Recent evidence suggests that a significant proportion of TB cases are affected by functional abnormalities (obstruction, restriction, mixed pattern) at the end of their treatment as a consequence of sequelae.[12–16] Recent evidence is also available on the need for pulmonary rehabilitation following surgery for TB.[31–32] A more accurate

evaluation of severely ill patients with pulmonary TB with earlier access to intensive care for those for which indication exists will minimise mortality, increase the proportion of patients successfully cured and probably lower the occurrence of post-treatment sequelae. Further studies on this are needed.

Study limitations

Some demographic factors like age and sex did not match between cases and controls. Only four patients were HIV-TB co-infected, as the prevalence of HIV-TB co-infection in the Delhi population is much lower when compared to national figures.[33] Therefore, the influence of this important factor on early mortality could not be properly evaluated. Furthermore, the study was conducted in a TB hospital where usually patients with advanced disease are admitted, so the mortality rates might be skewed. Furthermore, the 7 days cut-off to define early mortality (cases) is arbitrary and the proposed score needs to be tested in different settings and countries to define its generalisability.

Conclusions

The five significant risk parameters which are independently and significantly associated with mortality in TB patients and are easy to measure in field conditions include: SpO_2 $\leq$90%, tachypnoea, hypotension, advanced disease at chest radiography and tachycardia. We propose a scoring system to predict a mortality rate in patients with severe pulmonary TB admitted to an emergency department. The study may help clinicians at the periphery level to early identify severely ill patients using a scoring system based on simple parameters. These parameters, easily measurable in peripheral health institutions of any setting would allow early referral of such patients to specialised centres to reduce mortality, improve success rates, minimise the need for pulmonary rehabilitation and prevent post-treatment sequelae. Further studies are necessary to evaluate the workplace safety when potentially infectious TB cases are admitted, and the role of appropriate airborne infection control measures in reducing the risk of transmission to other patients, health care workers and visitors.[34] Finally, although internal validation of the risk score was performed, additional studies validating the score in similar and different settings would allow us to clearly define a potentially useful prognostic score for severe TB patients.

Authors' contributions

RS and BR conceived and drafted the manuscript with the support of GBM. All authors critically reviewed and edited the final version prior to submission.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding source

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

Acknowledgements

The project is part of the activities of the Global Tuberculosis Network (GTN) and of the WHO Collaborating Centre for Tuberculosis and Lung Diseases, Tradate, ITA-80, 2017-2020-GBM/RC/LDA.

The Authors wish to thank, Rosella Centis, Dina Visca (Istituti Clinici Maugeri, Tradate, Italy) and Lia D'Ambrosio (Public Health Consulting Group; Lausanne, Switzerland) for their useful comments on the manuscript.

References

1. World Health Organization, License: CCBY-NC-SA3.0IGO. Avaialble at: https://www.who.int/tb/publications/global_report/en/, 2019.
2. Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Nirman Bhawan, New Delhi. India TB Report 2019. Revised National TB Control Programme. Annual Status Report. Available at: https://tbcindia.gov.in/WriteReadData/India%20TB%20Report%202019.pdf. [Accessed 2 December 2019].
3. Central TB Division, Directorate General of Health Services, Ministry of Health with Family Welfare, Nirman Bhavan, New Delhi. Revised National Tuberculosis Control Programme. National Strategic Plan for Tuberculosis Elimination 2017–2025. March 2017. Available from: https://tbcindia.gov.in/WriteReadData/NSP Draft 20.02.2017 1.pdf. [Accessed 26 November 2019].
4. Feng J-Y, Su W-J, Chiu Y-C, Huang S-F, Lin Y-Y, Huang R-M, et al. Initial presentations predict mortality in pulmonary tuberculosis patients - a prospective observational study. PLoS One. 2011;6(9):e23715.
5. Churchyard GJ, Kleinschmidt I, Corbett EL, Murray J, Smit J, De Cock KM. Factors associated with an increased case-fatality rate in HIV-infected and non-infected South African gold miners with pulmonary tuberculosis. Int J Tuberc Lung Dis. 2000;4(8):705–12.
6. Mathew TA, Ovsyanikova TN, Shin SS, Gelmanova I, Balbuena DA, Atwood S, et al. Causes of death during tuberculosis treatment in Tomsk Oblast, Russia. Int J Tuberc Lung Dis. 2006;10(8):857–63.
7. Jung RS, Bennion JR, Sorvillo F, Bellomy A. Trends in tuberculosis mortality in the United States, 1990-2006: a population-based case-control study. Public Health Rep. 2010;125(3):389–97.
8. Dos Santos JDO junior, de Pereira B. Estudo dinâmico da mortalidade por tuberculose no Estado de São Paulo, Brasil: uma abordagem bayesiana. Dynamic study of tuberculosis mortality in São Paulo State, Brazil: a Bayesian approach (english). Cadernos de Saúde Pública. 2011;27(7):1415–22, http://dx.doi.org/10.1590/S0102-311X2011000700016. ISSN 0102-311X. Available at: http://www.scielo.br/pdf/csp/v27n7/16.pdf. [Accessed 26 November 2019].
9. Kwon Y-S, Kim YH, Song J-U, Jeon K, Song J, Ryu YJ, et al. Risk factors for death during pulmonary tuberculosis treatment in Korea: a multicenter retrospective cohort study. J Korean Med Sci. 2014;29(9):1226–31.
10. Sacks LV, Pendle S. Factors related to in-hospital deaths in patients with tuberculosis. Arch Intern Med. 1998;158(September (17)):1916–22.

11. Bastos HN, Osório NS, Castro AG, Ramos A, Carvalho T, Meira L, et al. A Prediction rule to stratify mortality risk of patients with pulmonary tuberculosis. PLoS One. 2016;11(9):e0162797.
12. Muñoz-Torrico M, Rendon A, Centis R, D'Ambrosio L, Fuentes Z, Torres-Duque C, et al. Is there a rationale for pulmonary rehabilitation following successful chemotherapy for tuberculosis? J Bras Pneumol. 2016;42(September–October (5)):374–85, http://dx.doi.org/10.1590/S1806-37562016000000226.
13. Visca D, Zampogna E, Sotgiu G, Centis R, Saderi L, D'Ambrosio L, et al. Pulmonary rehabilitation is effective in patients with tuberculosis pulmonary sequelae. Eur Respir J. 2019;53(3), http://dx.doi.org/10.1183/13993003.02184-2018, pii: 1802184.
14. Tiberi S, Torrico MM, Rahman A, Krutikov M, Visca D, Silva DR, et al. Managing severe tuberculosis and its sequelae: from intensive care to surgery and rehabilitation. J Bras Pneumol. 2019;45(April (2)):e20180324, http://dx.doi.org/10.1590/1806-3713/e20180324.
15. Akkerman OW, ter Beek L, Centis R, Maeurer M, Visca D, Muñoz-Torrico M, et al. Rehabilitation, optimized nutritional care and boosting host internal milieu to improve long-term treatment outcomes in TB patients. Int J Infect Dis. 2020;(Jan 23), http://dx.doi.org/10.1016/j.ijid.2020.01.029, pii: S1201-9712(20)30031-X. [Epub ahead of print].
16. Muñoz-Torrico M, Cid-Juárez S, Gochicoa-Rangel L, Torre-Bouscolet L, Salazar-Lezama MA, Villarreal-Velarde H, et al. Functional impact of sequelae in drug susceptible and multidrug-resistant tuberculosis cases. Int J Tuberc Lung Dis. 2020, in press.
17. Kuppuswamy B. Manual of socioeconomic status (Urban). 1st ed. Delhi: Manasayan; 1981. p. 66–72.
18. Office of the Surgeon General (US), National Institute on Alcohol Abuse and Alcoholism (US), Substance Abuse and Mental Health Services Administration (US). The surgeon general's call to action to prevent and reduce underage drinking. Rockville (MD): Office of the Surgeon General (US); 2007. Appendix B: DSM-IV-TR Diagnostic Criteria for Alcohol Abuse and Dependence. Available from: https://www.ncbi.nlm.nih.gov/books/NBK44358/. [Accessed 26 November 2019].
19. National Tuberculosis Association, National Tuberculosis and Respiratory Disease Association. Diagnostic standards and classification of tuberculosis. 11th ed; 1961. New York. https://catalog.hathitrust.org/Record/010152594. [Accessed 26 November 2019].
20. Yen Y-F, Chuang P-H, Yen M-Y, Lin S-Y, Chuang P, Yuan M-J, et al. Association of body mass index with tuberculosis mortality: a population-based follow-up study. Medicine (Baltimore). 2016;95(January (1)):e2300.
21. Tiberi S, Muñoz-Torrico M, Duarte R, Dalcolmo M, D'Ambrosio L, Migliori GB. New drugs and perspectives for new anti-tuberculosis regimens. Pulmonology. 2018;24(2):86–98.
22. Pontali E, Raviglione MC, Migliori GB, the writing group members of the Global TB Network Clinical Trials Committee. Regimens to treat multidrug-resistant tuberculosis: past, present and future perspectives. Eur Respir Rev. 2019;28(May (152)), http://dx.doi.org/10.1183/16000617.0035-2019, pii: 190035.
23. Mello FCde Q, Bastos LGdo V, Soares SLM, Rezende VMC, Conde MB, Chaisson RE, et al. Predicting smear negative pulmonary tuberculosis with classification trees and logistic regression: a cross-sectional study. BMC Public Health. 2006;6:43.
24. Fournet N, Sanchez A, Massari V, Penna L, Natal S, Biondi E, et al. Development and evaluation of tuberculosis screening scores in Brazilian prisons. Public Health. 2006;120(10):976–83.
25. Wisnivesky JP, Henschke C, Balentine J, Willner C, Deloire AM, McGinn TG. Prospective validation of a prediction model for isolating inpatients with suspected pulmonary tuberculosis. Arch Intern Med. 2005;165(4):453–7.
26. Solari L, Acuna-Villaorduna C, Soto A, Agapito J, Perez F, Samalvides F, et al. A clinical prediction rule for pulmonary tuberculosis in emergency departments. Int J Tuberc Lung Dis. 2008;12(6):619–24.
27. Pontali E, Centis R, D'Ambrosio L, Migliori GB. Monitoring predictors of mortality: a necessary action to reach TB elimination. Revista Portuguesa de Pneumologia (English Edition). 2015;21(6):295–8.
28. Wejse C, Gustafson P, Nielsen J, Gomes VF, Aaby P, Andersen PL, et al. TB score: signs and symptoms from tuberculosis patients in a low-resource setting have predictive value and may be used to assess clinical course. Scand J Infect Dis. 2008;40(2):111–20.
29. Meira L, Chaves C, Araújo D, Almeida L, Boaventura R, Ramos A, et al. Predictors and outcomes of disseminated tuberculosis in an intermediate burden setting. Pulmonology. 2019;25(6):320–7.
30. Horita N, Miyazawa N, Yoshiyama T, Sato T, Yamamoto M, Tomaru K, et al. Development and validation of a tuberculosis prognostic score for smear-positive in-patients in Japan. Int J Tuberc Lung Dis. 2013;17(1):54–60.
31. Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of multidrug and extensively drug-resistant tuberculosis: a multicentre study. Eur Respir J. 2017;49(5), pii: 1700387.
32. Borisov SE, D'Ambrosio L, Centis R, Tiberi S, Dheda K, Alffenaar JW, et al. Outcomes of patients with drug-resistant-tuberculosis treated with bedaquiline-containing regimens and undergoing adjunctive surgery. J Infect. 2019;78(January (1)):35–9, http://dx.doi.org/10.1016/j.jinf.2018.08.003.
33. National Institute of Medical Statistics, National AIDS Control Organization. Technical report India HIV estimates; 2006. Available at http://naco.gov.in/sites/default/files/Technical%20Report%20on%20HIV%20Estimation%202006.pdf. [Accessed 26 November 2019].
34. Migliori GB, Nardell E, Yedilbayev A, D'Ambrosio L, Centis R, Tadolini M, et al. Reducing tuberculosis transmission: a consensus document from the World Health Organization Regional Office for Europe. Eur Respir J. 2019;53(June (6)), http://dx.doi.org/10.1183/13993003.00391-2019, pii: 1900391.

Pulmonology 2021;**27(1)**:43–51

PULMONOLOGY

www.journalpulmonology.org

REVIEW

The role of non-invasive ventilation in weaning and decannulating critically ill patients with tracheostomy: A narrative review of the literature

Miguel Guia[a,*], Laura D Ciobanu[b], Jithin K Sreedharan[c], Mohamed E. Abdelrahim[d], Gil Gonçalves[e], Bruno Cabrita[f], Jaber S. Alqahtani[g], Jun Duan[h], Mohamad El-Khatib[i], Montserrat Diaz-Abad[j], Jakob Wittenstein[k], Habib M.R. Karim[l], Pradipta Bhakta[m], Paolo Ruggeri[n], Giancarlo Garuti[o], Karen E.A. Burns[p], Guy W. Soo Hoo[q], Raffaele Scala[r], Antonio Esquinas[s], on behalf of International Association of Non Invasive Ventilation

[a] *Pulmonology Department, Hospital Professor Doutor Fernando Fonseca, IC19, 2720-276 Amadora, Lisbon, Portugal*
[b] *Clinical Hospital of Rehabilitation, Iasi University of Medicine and Pharmacy ''Grigore T Popa'', Strada Universităţii 16, Iaşi 700115, Romania*
[c] *Prince Sultan Military College of Health Sciences, Al Amal Dhahran 34313, Saudi Arabia*
[d] *Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Qism Bani Sweif, Bani Sweif, Beni Suef Governorate, Egypt*
[e] *Pulmonology Department, Centro Hospitalar e Universitário de Coimbra, Praceta, R. Prof. Mota Pinto, 3004-561 Coimbra, Portugal*
[f] *Pulmonology Department, Hospital Pedro Hispano, R. de Dr. Eduardo Torres, Sra. da Hora, Matosinhos, Portugal*
[g] *Department of Respiratory Care, Prince Sultan Military College of Health Sciences, Al Amal, Dhahran 34313, Saudi Arabia*
[h] *Department of Respiratory and Critical Care Medicine, The first Affiliated Hospital of Chongqing Medical University, 275 Jinlong Rd, Longxi, Yubei District, Chongqing, China*
[i] *Department of Respiratory Therapy, American University of Beirut - Medical Center, Beirut, Lebanon*
[j] *Department of Medicine, University of Maryland School of Medicine, 655 W Baltimore St S, Baltimore, MD 21201 USA*
[k] *Department of Anesthesiology and Intensive Care Medicine, University Hospital Carl Gustav Carus, Fetscherstraße 74, 01307 Dresden, Germany*
[l] *Department of Anaesthesiology and Critical Care, All India Institute of Medical Sciences, Great Eastern Rd, AIIMS Campus, Tatibandh, Raipur, Chhattisgarh 492099, India*
[m] *Department of Anaesthesia and Intensive Care, Cork University Hospital, Wilton, Cork, Ireland*
[n] *Pulmonology Unit, Department of Biomedical and Dental Sciences, Morphological and Functional Images (BIOMORF), University of Messina, Piazza Pugliatti, 1, 98122 Messina ME, Italy*
[o] *Pulmonology Unit, Santa Maria Bianca Hospital, Mirandola, AUSL Modena, Via S. Giovanni del Cantone, 23, 41121 Modena MO, Italy*

Abbreviations: COPD, Chronic obstructive pulmonary disease; EPAP, Expiratory positive airway pressure; FiO_2, Fraction of inspired oxygen; HFT, High-flow tracheal oxygen; ICU, Intensive care unit; IPAP, Inspiratory positive airway pressure; IMV, Invasive mechanical ventilation; NIV, Non-invasive ventilation; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen.

* Corresponding author at: Rua Tenente General Zeferino Sequeira, number 20, 13ºA, Carnaxide, Lisbon, Portugal.
E-mail address: miguelguia7@gmail.com (M. Guia).

https://doi.org/10.1016/j.pulmoe.2020.07.002

[p] *Interdepartmental Division of Critical Care Medicine, University of Toronto, 27 King's College Cir, Toronto, ON M5S, Canada*
[q] *Pulmonary, Critical Care and Sleep Section, VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA*
[r] *Pulmonology Department an RICU, San Donato Hospital, Via Pietro Nenni, 20/22, 52100 Arezzo AR, Italy*
[s] *Intensive Care Unit, Hospital Morales Meseguer, Av Marqués de los Vélez, s/n, 30008 Murcia, Spain*

Received 10 May 2020; accepted 1 July 2020
Available online 25 July 2020

KEYWORDS
Non-invasive ventilation;
Tracheostomy;
Ventilator weaning;
Decannulation

Abstract:
Introduction: Invasive mechanical ventilation (IMV) is associated with several complications. Placement of a long-term airway (tracheostomy) is also associated with short and long-term risks for patients. Nevertheless, tracheostomies are placed to help reduce the duration of IMV, facilitate weaning and eventually undergo successful decannulation.
Methods: We performed a narrative review by searching PubMed, Embase and Medline databases to identify relevant citations using the search terms (with synonyms and closely related words) ''non-invasive ventilation'', ''tracheostomy'' and ''weaning''. We identified 13 publications comprising retrospective or prospective studies in which non-invasive ventilation (NIV) was one of the strategies used during weaning from IMV and/or tracheostomy decannulation.
Results: In some studies, patients with tracheostomies represented a subgroup of patients on IMV. Most of the studies involved patients with underlying cardiopulmonary comorbidities and conditions, and primarily involved specialized weaning centres. Not all studies provided data on decannulation, although those which did, report high success rates for weaning and decannulation when using NIV as an adjunct to weaning patient off ventilatory support. However, a significant percentage of patients still needed home NIV after discharge.
Conclusions: The review supports a potential role for NIV in weaning patients with a tracheostomy either off the ventilator and/or with its decannulation. Additional research is needed to develop weaning protocols and better characterize the role of NIV during weaning.

Introduction

Invasive mechanical ventilation (IMV) with an endotracheal tube may lead to ventilator associated pneumonia and development of other ventilator-related complications including ventilator-induced lung injury, muscular atrophy, diaphragmatic dysfunction,[1] tracheal stenosis[2] and high sedation requirements. Factors associated with prolonged IMV include chronic cardiopulmonary diseases, sepsis, critical illness myoneuropathy, the use of prolonged and excessive sedation, neuromuscular blocking agents, diaphragmatic weakness, tracheo-bronchial obstruction, ineffective cough, retained secretion, nutritional and metabolic deficits.[3]

Tracheostomy is often placed in patients needing extended duration of endotracheal intubation. The most common indications for tracheostomy are acute respiratory failure with demonstrated or expected prolonged duration of mechanical ventilation, failure to wean from IMV, upper airway obstruction and copious secretions.[4] It may diminish risks associated with prolonged endotracheal tube use such as ventilator-associated pneumonia, sinusitis and laryngeal and tracheal damage. In addition, it also improves patient comfort, reducing the need for sedation, and lowers airway resistance.[4] Tracheostomy may also facilitate patient recovery as it allows more effective airway access and secretion clearance, reduces work of breathing, improves patient comfort, and promotes progression of care in and outside the intensive care unit (ICU).[5]

However, tracheostomy or placement of an artificial airway in the neck also has a host of short and long-term risks and complications that mirror those associated with IMV. The tracheostomy tube is a foreign body and can lead to infectious and respiratory complications, along with impaired swallowing. Moreover, patients with a tracheostomy are unable to engage in pursed-lips breathing and lose the contribution of the vocal cords in maintaining subglottic pressure.[6] In most cases, the use of tracheostomy also leads to aphonia and loss of spoken communication. Early tracheostomy complications include haemorrhage, structural damage to trachea, aspiration, pneumothorax, pneumomediastinum, subcutaneous emphysema, stoma infection and stoma ulceration. Late complications include tracheal stenosis, granulation tissue formation, tracheomalacia,

pneumonia, trachea-arterial fistula and tracheoesophageal fistula. Accidental decannulation and dysphagia are both early and/or late complications.[4] Also, mechanical ventilation through a tracheostomy tube is associated with more demanding out-hospital management and potential respiratory incidents. In a study by Stieglitz et al. on out-of-hospital IMV patients, almost half presented with respiratory incidents, the most common being oxygen desaturation and dyspnea, requiring other interventions such as bag valve mask ventilation, need for pulmonologist consultation and replacement of the tracheostomy tube.[7]

As more patients with multiple co-morbidities undergo tracheostomy and develop difficulty with weaning, new innovative concepts are urgently needed for their management. Chronic ventilator dependent patients with tracheostomies are at risk of aforementioned infections and tracheal complications which further prolong duration of mechanical ventilation as well as increased mortality, so weaning from these artificial airways should start as soon as possible.[8] Surprisingly, there is very little data dealing with tracheostomy patients in weaning from mechanical ventilation and subsequent tracheostomy tube decannulation. The former requires the unassisted respiratory muscles to function well enough to manage the work of breathing, the latter is feasible only if airways patency, glottic function and cough efficiency are preserved. It is not surprising that many of these patients are unable to overcome these obstacles and remain ventilator dependent. There is growing support for the use of non-invasive ventilation (NIV) to facilitate this transition off ventilatory support.

NIV has been used extensively to manage patients with acute and chronic respiratory failure,[9] as well as in patients not capable of totally independent breathing after extubation.[10] NIV does not usually require sedation, allowing patients to communicate, eat and drink. In a Cochrane review[11] of 16 trials that compared NIV with IMV weaning, NIV significantly reduced mortality, weaning failures, ventilator associated pneumonia, ICU and hospital length of stay, total duration of IMV and rates of tracheostomy. In subgroup analysis, the authors found that the mortality benefit was greater in COPD versus non-COPD patients. The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines suggest that in hypercapnic respiratory failure NIV may be used to facilitate weaning from IMV. It can also be used to prevent post-extubation acute respiratory failure (ARF) in high-risk patients. However, NIV is not recommended for use in the treatment of patients with established post-extubation acute respiratory failure.[12]

The role of NIV in mechanically ventilated patients with tracheostomy tubes to facilitate both weaning off from the ventilator and removal of the tracheostomy tube has a solid physiological rationale, but most clinical evidence is derived from limited observational studies. Therefore, to better outline the role of NIV in management in these patients with tracheostomies and chronic ventilatory failure, we conducted the following literature search and provide a narrative review on this topic.

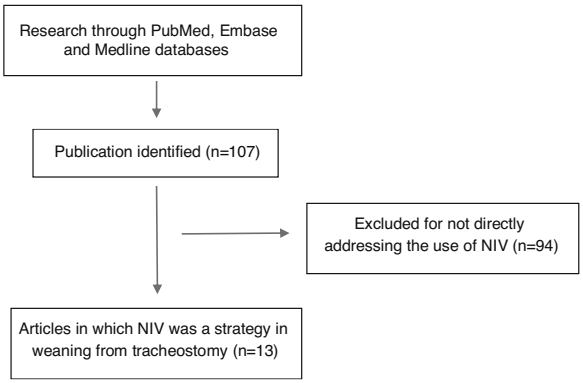


Fig. 1 Flowchart of the study selection process.

Methods

We searched PubMed, Embase and Medline databases for relevant citations using the search terms (with synonyms and closely related words) ''non-invasive ventilation'', ''tracheostomy'' and ''weaning'' from January 1992 to February 2020. We have reviewed the bibliographies of selected studies for additional references.

We identified 13 publications comprising retrospective or prospective studies in which NIV was one of the strategies used for patients with tracheostomies during weaning from IMV and/or decannulation. These studies were analyzed in relation to number of patients with tracheostomies, clinical location and setting of NIV application, success in weaning patient with tracheostomies from IMV, success of decannulation of the tracheostomy tube and necessity for home NIV after discharge. A flowchart of the study process is reported in Fig. 1.

Due to limited and heterogeneous data, it was not feasible to perform a statistical analysis or provide high quality evidence-based recommendations, but consensus recommendations and opinions are provided where appropriate.

Rationale

Factors associated with difficulties in weaning patients with tracheostomies from IMV include an imbalance between the workload and the force efficacy of the ventilatory pump, further limited by any compromise of the upper airways (for example, bulbar dysfunction, low cough efficiency, vocal cord dysfunction and airway stenosis and/or oedema).

Even brief periods of IMV may result in diaphragm weakness due to a major decline of diaphragmatic contractile force together with atrophy of diaphragm muscle fibres. IMV, sepsis and malnutrition leading to mitochondrial oxidative stress and inflammation, resulting in diaphragmatic muscle atrophy and contractile dysfunction.[13] Other factors contributing to respiratory muscle dysfunction are advanced age and use of medications like corticosteroids and neuromuscular blocking agents.[14] The loss of efficacy from the ventilatory pump contributes to imbalance between the work of breathing and respiratory muscle reserve.[3] Therefore, the first step in weaning from tracheostomy comprises reconditioning the respiratory pump and reducing workload imposed during spontaneous breathing.[8]

Generally, tracheostomy tubes are placed to facilitate weaning as they do decrease dead space, are generally more comfortable for the patient and permit a gradual decrease in ventilatory support until the patient has recovered enough to maintain independent unassisted ventilation. Often this involves nocturnal ventilatory support with increasing duration of unassisted breathing during waking hours until no longer requiring assisted ventilation. However, there is a subset of patients who are not able to discontinue mechanical ventilation with this approach, in whom NIV may be able to facilitate this transition. This favourable effect is due to several physiological advantages with NIV, as it allows: reduction of inspiratory effort and work of breathing, counters intrinsic positive end-expiratory pressure, recruitment of collapsed alveoli and thereby increase dynamic compliance.[15] In addition, NIV may play a decisive role in allowing decannulation, since patients can initiate NIV with the tracheostomy tube still in place and continue to receive non-invasive support during and after decannulation. As NIV applies positive airway pressure, it may help maintain upper airway patency by preventing oro-pharyngeal collapse and potentially minimizing effects of vocal cord dysfunction. However, in some patients after tracheostomy, the continuity and integrity of the trachea may be damaged, which adds extra difficulties to NIV.[16]

One approach is to confirm upper airway patency using bronchoscopy, after which NIV can be applied using a facial mask, with the cuff deflated and the tracheostomy capped. This will permit a check for tolerance and clinical stability, after which decannulation could be considered.[17]

In patients with neuromuscular respiratory weakness or failure, combined non-invasive assistance of both the ventilatory pump and forced expiratory flow is needed to wean these patients off ventilatory support. Cough augmentation techniques (CAT) may play a decisive role in secretions management and reducing weaning failure rates, especially in those patients with neuromuscular respiratory weakness and clinical conditions associated with excessive respiratory secretions. The CAT is a useful adjunct and should be applied before each period of NIV application.[18]

The creation and development of respiratory high-dependence care units is crucial for the management of patients with tracheostomies, especially in view of the weaning process.[19] It is also important to highlight that the process of decannulation includes a multidisciplinary approach between doctors, nurses, physiotherapist and speech therapists.[20]

Clinical studies

Udwadia et al.[2] performed a study in ICU enrolling 22 patients with difficult weaning from IMV, 9 of them had tracheostomies. Nasal NIV was used while the cuff was deflated and the tube was occluded. Patients who tolerated NIV were transferred from the ICU to a general or high dependency ward within 24—48 h (only two patients did not tolerate NIV, but not explicitly specified whether they had a tracheostomy or endotracheal tube). In this study tracheostomies were closed in all patients who were weaned from IMV (Table 1).

Körber W et al.[21] reported that 32 of 37 patients with tracheostomy who had been on long-term ventilation were successfully weaned off IMV using a volume-controlled intermittent ventilation via an individually adapted face mask. Out of 37 weaned patients, 29 were discharged with home NIV.

Schöenhofer et al.[22] reported their ten-year experience, in weaning centre, on 306 tracheostomy patients, 59% with COPD, using a protocol directed T-piece weaning strategy. They applied NIV in patients with ongoing hypercapnia ($PaCO_2$ > 50 mmHg (COPD) or >45 mmHg (restrictive disease) after 24 h without ventilatory support (after capping the tracheostomy). They identified 114 hypercapnic patients, 96 of whom were maintained off IMV and discharged home on NIV; the most common condition was COPD and the rest had either thoracic cage disorders or neuromuscular disease. No data was presented on the percent undergoing successful decannulation, but it was clear that NIV was fundamental in maintaining independent ventilation to permit discharge home.

In a similar report, Quinnell et al.[23] described a nine-year experience in their weaning centre, focusing on 67 COPD patients with prolonged mechanical ventilation and tracheostomy tubes. They were able to wean 65 (96%) with 62 surviving to discharge, of which NIV was initiated in patients who were unable to tolerate unsupported spontaneous breathing trials without developing respiratory distress or hypercapnia, defined as $PaCO_2$ > 56 mmHg. NIV was used to wean 40 and used as long term ventilatory support in 25. Although not explicitly stated, all except two were discharged without tracheostomies, with NIV provided via a nasal or orofacial mask. A one-way speaking valve was also used to facilitate communication and speech. NIV was associated with a better long-term survival.

Heinemann et al.[24] analysed 117 COPD patients admitted to a weaning centre. Weaning was achieved in 82 patients (although it was not discriminated how many had tracheostomies). In patients with tracheostomies, NIV was applied according to clinical and laboratory (arterial blood gas analysis) evidence of respiratory failure. NIV was initiated in 62 patients after extubation or decannulation, and 39 patients were discharged home on NIV. However, the study did not clearly state the number/percent of patients in which NIV was necessary to achieve weaning from tracheostomy after decannulation. The overall success rate in weaning from IMV was 70.1% (no distinction made between endotracheal tube and tracheostomy). The initiation of home NIV after successful weaning was an independent prognostic factor for survival to one year.

In a retrospective observational study on 26 patients with tracheostomies, Ibrahim et al.[25] proposed the use of NIV as an alternative technique to facilitate discharge of patients with tracheostomies who leave the ICU and eventually leave the hospital. NIV was connected to the tracheostomy tube, and 20 patients were discharged from the ICU and 16 from the hospital (no data on decannulation or need for home NIV).

Ceriana et al.[26] reviewed their experience with patients requiring prolonged mechanical ventilation and tracheostomies. Over a 13-year period, they retrospectively analysed prospectively collected data on their cohort of patients. Out a total of 587 patients, they were able to enrol 51 (9%) into their NIV decannulation protocol, of which 46 (8%) were successfully weaned and discharged on home

Table 1 Characteristics of included studies reported NIV as weaning procedure from tracheostomy.

Study	Type	Conditions	NIV (n)	NIV interface	Weaning from IMV success rate	Decannulation Success rate (in weaned patients)	Home NIV (weaned patients)	Setting
Udwadia et al.[2]	Prospective	Various	9	Nasal	No specific data on tracheostomy patients			ICU
Körber et al.[21]	Retrospective	Various	37	No data	86%	No data	91 %	Weaning centre
Schönhofer et al.[22]	Retrospective	Various	114	No data	84%	No data	100%	Weaning centre
Quinnell et al.[23]	Retrospective	COPD	40	Nasal Full-face	96%	100%	63%	Weaning centre
Heinemann et al.[24]	Retrospective	COPD	62 [a]	Nasal Oronasal	No specific data on NIV	No data	63%[a]	Weaning centre
Ibrahim et al.[25]	Retrospective	Various	26	Tracheos-tomy	No data	No data	21%[b]	ICU
Ceriana et al.[26]	Retrospective	Various	51	Not specified	90%	100%	100%	Weaning centre
Sancho et al.[27]	Prospective	Various	40	Nasal Oronasal	100%	100%	100%	Respiratory care unit
Bonnici et al.[28]	Prospective	Various	No data	No data	No specific data on relation to NIV			Weaning centre
Bach et al.[29]	Prospective	Neuromuscular	37	Nasal Mouth-piece	No specific data	86%	81%	Respiratory care unit
Duan et al.[30]	Prospective randomized	Various	15	Face-mask	93%	43%	No data	Respiratory intensive care unit
Pu el al.[16]	Retrospective	Various	26	Nasal Full-face	81%	100%	No data	Respiratory department
Budweiser et al.[31]	Retrospective	Various	135	No data	No data	No specific data on relation to NIV		Weaning centre

COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; NIV: non-invasive ventilation.
[a] Not mention exactly how many of them had tracheostomies.
[b] At discharge from the ICU (intensive care unit).

NIV. They identified patients as candidates for NIV weaning as those who could maintain unassisted breathing and had favourable criteria for decannulation, but with signs of inadequate ventilation defined as a $PaCO_2 > 50$ mmHg, and/or an increase in $PaCO_2 \geq 5$ mmHg since suspension of IMV, and/or pH < 7.33 within seven days of spontaneous breathing. These patients underwent a protocol which included downsizing by 1 mm the cannula internal diameter without fenestration, capping of the tracheostomy cannula, and increasing periods of nocturnal NIV with the goal of achieving at least 4 consecutive hours of NIV (after two nights with good adherence they were switched to a domiciliary bilevel ventilator). After conducting an upper endoscopy to check the airways, the investigators decannulated patients who were admitted to a domiciliary NIV program. The mean time needed to protocol completion was 7.2 days. Home ventilators were set with a mean IPAP of 17.1 cmH_2O and mean EPAP of 4.2 cmH_2O. None of the patients required surgical closure of their tracheal stoma. Five patients failed due to claustrophobia associated with the mask and/or poor adherence to the mask. After one year, the survival rate was 82% and only one of the surviving patients was switched back to IMV. It was possible to decannulate all patients in whom NIV was successfully used for weaning from IMV.

In a one-year, prospective, multicentre study of respiratory care units in Spain, Sancho et al.[27] identified 231 patients with tracheostomies out of a population of 4609, requiring prolonged mechanical ventilation. Of these 231 patients, 198 (86%) were successfully weaned and of that group, 40 (21%) needed NIV during weaning, which was applied when patients were not able to progress beyond 18 h on their spontaneous breathing trial for 5 consecutive days. The ventilator was set in pressure-support mode to achieve a tidal volume of approximately 8—10 mL/Kg. In this study, the tracheostomy stoma was either capped with a tracheal button or the tracheostomy tube was capped, with the cuff deflated and inner cannula replaced with a fenestrated tube. Bronchoscopy was performed to evaluate upper and lower airways for possible lesions. No differences were found between those with a capped tracheostomy tube or tracheal button. Treatment focused on nocturnal support and ventilatory goals included a $PaCO_2 < 45$ mmHg and less than 5% of time with oxygen saturation under 90%. In subgroup analysis, they found obstructive sleep apnea, congestive heart failure and chronic renal failure as underlying conditions of patients requiring NIV. Prior use of home CPAP, NIV or chronic hypercapnia identified those most likely to need NIV during weaning. Baseline hypercapnia was also significantly increased with an average $PaCO_2$ of 50 ± 10 mmHg. Although not explicitly reported, it appears that all the 40 NIV patients were successfully decannulated.

Bonnici DM et al.[28] conducted a prospective study of patients with tracheostomies and neuromuscular and/or chest wall disorders, postsurgical, COPD and obesity-related respiratory failure. They found that 382% of the patients were weaned to self-ventilation. In this cohort, 24% of patients were discharged with nocturnal NIV and 1.9% of patients were discharged with both nocturnal and intermittently daytime NIV. However, numbers for patients on NIV and the decannulation success rate were not explicitly reported.

Bach et al.[29] conducted a prospective study on 49 patients, including 37 with tracheostomies, with primarily neuromuscular insufficiency. When patients were clinically stable, the tracheostomy tube was switched to a fenestrated cuffed one, which was then capped, and the patients were started on NIV using mouthpiece and nasal mask while awake (during sleep they would use a nasal interface or lipseal). Mechanical insufflation-exsufflation was applied when needed. After decannulation (n = 32), 26 patients required home NIV (later, it was possible to stop NIV in 9). Decannulation was successful in 32 of the 37 patients.

Duan et al.[30] performed a single center feasibility study to compare the NIV vs. a conventional strategy to accelerate weaning of patients with tracheostomies. This study enrolled 15 patients in the NIV group and 17 cases in control group. At the initial stages, all of the patients underwent conventional weaning strategies. If multiple spontaneous breathing tests failed, the patient was enrolled in this study. In the NIV group, the tracheostomy cuff was deflated, and the tube was capped. NIV was initially set to an IPAP 10 cmH_2O and EPAP 4 cmH_2O (titration to 8 mL/kg tidal volume), with facemask. During the application of NIV, airway management was especially important especially in patients with weak cough. If the sputum production decreased and was thin, and the ability to cough was strong, the tracheostomy tube was capped for more than 48 h. If the patient tolerated this trial, the tracheostomy tube could be removed. NIV allowed weaning from IMV in 14 patients. In this study, NIV reduced nosocomial pneumonia, shortened the days on ventilator weaning and ICU length of stay for these patients with tracheostomies. From the 14 patients weaned from IMV using NIV, decannulation was possible in 6.

In a retrospective study by Pu et al.[16] conventional weaning approach in those with a tracheostomy (n = 24) was compared to a sequential invasive-noninvasive ventilation strategy (n = 26). The latter patients were started on NIV with a nasal of full-face mask, while tracheostomy was plugged and the cuff deflated. Weaning was possible in 21 patients from the sequential group (however it was not disclosed whether continued nocturnal NIV was required). PaO_2 at 1 and 24 h after withdrawal of IMV was significantly higher in the sequential group. Also, the sequential group presented significantly shorter duration of IMV and incidence of ventilator-associated pneumonia, and a significantly higher rate of successful weaning. Although the decannulation success rate was not explicitly reported, it appears that all the 21 patients weaned from IMV in the NIV group were decannulated.

A retrospective study by Budweiser et al.[31] evaluated the usefulness of a tracheostomy retainer during decannulation. From 384 prolonged weaning patients, a tracheostomy retainer was inserted in 166. After decannulation, NIV was applied to 135 of them, with a first decannulation success rate of nearly 72% (119 of 166), and 63 patients adapted to home NIV.

Discussion

Due to advances in medical care, there is an increasing number of patients surviving admissions to the ICU who require

long-term care due to prolonged IMV with tracheostomy tube in place. This is associated with increasing healthcare costs and organizational challenges for health systems related to these patients' debilitated state and poor long-term outcomes of these patients.[3] Few studies have evaluated the role of NIV in weaning and decannulating patients with a tracheostomy.

Based on the analysed results from studies using NIV to facilitate weaning from IMV, several key points are evident: 1) the majority of the studies were retrospective analyses; 2) most occurred in weaning centres; 3) NIV appears to be effective even with a tracheostomy tube in place; 4) NIV may be a useful adjunct for the very difficult to wean patient requiring prolonged mechanical ventilation and a tracheostomy, resulting in successful weaning and discontinuation from mechanical ventilation in more than 80%, and with an equally high percentage tolerating decannulation); 5) hypercapnia during or after a spontaneous breathing trial may identify patients who may benefit the most from this modality); 6) In some patients, NIV will need to be continued, typically as nocturnal support in as many as 60% or more of those weaned.

The studies[16,30] comparing conventional weaning with NIV suggest that NIV can provide enough support to result in higher weaning and decannulation success rates. There may be reduction in infection as well as the length of the weaning period.

However, there are considerable limitations and lack of ability to generalize results. First of all, in some studies, the distinction between patients with tracheostomies or those with endotracheal tube is unclear. The process of decannulation is not mentioned in a significant number of the studies, and decannulation success is not uniformly reported.

There is considerable heterogeneity in the patients treated and the methods by which NIV is applied. The best NIV modality and settings during weaning require additional physiological studies. Variables of interest included the volume of dead space, upper airways resistance and resistance of the tracheostomy tube.[32] It is probably safe to assume that the level of NIV inspiratory and expiratory pressure needed during the weaning process is probably greater than that applied via tracheostomy during assisted ventilation. However, this may not be borne out as most of the studies did not report on exact ventilator settings during NIV.

Of course, the underlying cause of acute respiratory failure needs to be considered when planning the weaning process with NIV.[33] An underlying obstructive or restrictive disease such as COPD or a neuromuscular respiratory failure require completely different NIV settings. Not surprisingly, based on our review the patients who may benefit the most from NIV during weaning have the same conditions which are best treated with NIV during acute respiratory failure, specifically COPD, neuromuscular respiratory failure disease and obesity/hypoventilation syndrome or obstructive sleep apnea.

The choice of the optimal NIV interface is another critical point.[34] Nasal mask or mouthpiece intermittent positive pressure could facilitate expectoration and air staking manoeuvre during daytime hours as opposed to an oronasal mask which could be preferable during night-time NIV to avoid excessive leaks with open mouths.

It should also be noticed that tracheal manometry was not used in any of the reported studies. This could provide objective measurements of airway pressure during capping[17] and may be a useful tool to include in future studies.

On the other hand, some studies and proposed decannulation protocols[35,36,37] are not directly linked to NIV use but may be the foundation for future research. Studies directed to airway secretion quantification[8] and secretion clearance are important as they may contribute to weaning failure, NIV effectiveness and safety.

High-flow tracheal oxygen (HFT) has been considered as an alternative to NIV or as an integrative tool and adjunct. However, although HFT allows a more accurate FiO_2,[38] bypassing upper airways with administration through a tracheostomy tube forfeits some potential benefits associated with high-flow nasal cannula.[38,39] The flow should be at least 50 L/min for greatest benefit.[38,40] High-flow oxygen has been successfully used in liberating intubated patients from IMV when compared to both conventional oxygen and NIV. However, evidence of the role of HFT alone or combined with NIV to facilitate weaning from those with tracheostomy tubes and decannulation is still lacking.

Conclusions

There are increasing number of reports that incorporate NIV into the weaning of patients with a tracheostomy. Most call for NIV delivered through the facial interface while the tracheostomy tube is capped. This seems to facilitate the transition off ventilatory support and eventual decannulation. Additional research is needed to develop weaning protocols and compare NIV weaning to other weaning approaches and strategies in this population.

Authors contribution

The study has more than 6 authors, since it was initiated and revised by an international panel. Miguel Guia, Raffaele Scala and Antonio Esquinas conceived and designed this study. All authors have participated in data acquistion and/or analysis, and also in manuscript revision.

Funding

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

Conflict of interest

None.

Acknowledgments

Guy W. Soo Hoo, who revised English; Yasmin M. Madney, Hadeer S. Harb and Haitham Saeed (members of International Association of Non Invasive Ventilation) for their contribution.

References

1. Petrof BJ, Jaber S, Matecki S. Ventilator-induced diaphragmatic dysfunction. Curr Opin Crit Care. 2010;16(1):19–25.
2. Udwadia ZF, Santis GK, Steven MH, Simonds AK. Nasal ventilation to facilitate weaning in patients with chronic respiratory insufficiency. Thorax. 1992;47:715–8.
3. Ambrosino N, Vitacca M. The patient needing prolonged mechanical ventilation: a narrative review. Respir Med. 2018;13(6):1–10.
4. Cheung NH, Napolitano LM. Tracheostomy: epidemiology, indications, timing, technique, and outcomes. Respir Care. 2014;59(6):895–919.
5. Terragni P, Faggiano C, Martin EL, Ranieri VM. Tracheostomy in mechanical ventilation. Semin Respir Crit Care Med. 2014;35(4):482–91.
6. Kent CL. Tracheostomy decannulation. Respir Care. 2005;50(4):538–41.
7. Stieglitz S, George S, Priegnitz C, Hagmeyer L, Randerath W. Frequency and management of respiratory incidents in invasive home ventilation. Chron Respir Dis. 2013;10(3): 135–40.
8. Ghiani A, Paderewska J, Sainis A, Crispin A, Walcher S, Neurohr C. Variables predicting weaning outcome in prolonged mechanically ventilated tracheotomized patients: a retrospective study. J Intensive Care. 2020;8:19–28.
9. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet. 2009;374:250–9.
10. Vitacca M, Ambrosino N, Clini E, Porta R, Rampulla C, Lanini B, et al. Physiological response to pressure support ventilation delivered before and after extubation in patients not capable of totally spontaneous autonomous breathing. Am J Respir Crit Care Med. 2001;164:638–41.
11. Burns KEA, Meade MO, Premji A, Adhikari NKJ. Noninvasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: a Cochrane systematic review. CMAJ. 2014;186(3):112–22.
12. Rochwerg B, Brochard L, Elliot MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidleines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50:1602426.
13. Peñuelas O, Keough E, López-Rodríguez L, Carriedo D, Gonçalves G, Barreiro E, et al. Ventilator-induced diaphragm dysfunction: translational mechanisms lead to therapeutical alternatives in the critically ill. Intensive Care Med Exp. 2019;7(1): 48–72.
14. Díaz Mc, Ospina-Tascón Ga, Salazar Bc. Respiratory muscle dysfunction: a multicausal entity in the critically ill patient undergoing mechanical ventilation. Arch Bronconeumol. 2014;50(2):73–7.
15. Kallet RH, Diaz JV. The physiologic effects of nonivasive ventilation. Respir Care. 2009;54(1):102–15.
16. Pu X, Wang J, Yan X, Jiang X. Sequential invasive-noninvasive mechanical ventilation weaning strategy for patients after tracheostomy. World J Emerg Med. 2015;6(3):196–200.
17. O'Connor HH, White AC. Tracheal decannulation. Respir Care. 2010;55(8):1076–81.
18. Spinou A. A review on cough augmentation techniques: assisted inspiration, assisted expiration and their combination. Physiol Res. 2020;69(1):93–103.
19. Scala R, Corrado A, Confalonieri M, Marchese S, Ambrosino N. Increased number and expertise of Italian Respiratory High-Dependency Care Units: the second national survey. Respir Care. 2011;56(8):1100–7.
20. Medeiros GC, Sassi FC, Lirani-Silva C, Andrade CRF. Criteria for tracheostomy decannulation: literature review. Codas. 2019;31(6), e20180228:1-9.
21. Körber W, Laier-Groeneved G, Criée CP. Endotracheal complications after long-term ventilation. Noninvasive ventilation in chronic thoracic diseases as an alternative to tracheostomy. Med Klin. 1999;94:45–50.
22. Schönhofer B, Euteneuer Nava S, Suchi S, Köhler D. Survival of mechanically ventilated patients admitted to a specialised weaning centre. Intensive Care Med. 2002;98:908–16.
23. Quinnell TG, Pilsworth S, Shneerson JM, Smith IE. Prolonged invasive ventilation following acute ventilatory failure in COPD. Chest. 2006;129(1):133–9.
24. Heinemann F, Budweiser S, Jörres R, Michael ARZT, Rösch F, Kollert F. The role of non-invasive home mechanical ventilation in patients with chronic obstructive pulmonary disease requiring prolonged weaning. Respirology. 2011;16: 1273–80.
25. Ibrahim SG, Silva JM, Borges LG, Savi A, Forgiarini LA Júnior, Teixeira C. Use of a nonivasive ventilation device following tracheostomy: an alternative to facilitate ICU discharge? Rev Bras Ter Intensiva. 2012;24(2):167–72.
26. Ceriana P, Nava S, Vitacca M, Carlucci A, Paneroni M, Schreiber A, et al. Noninvasive ventilation during weaning from prolonged mechanical ventilation. Pulmonology. 2019;25(6): 328–33.
27. Sancho J, Servera E, Jara-Palomares L, Barrot E, Sanchez-Oro-Gómez R, Gómez de Terreros FJ, et al. Noninvasive ventilation during weaning process inc chronically criticalyy ill patients. ERJ Open Res. 2016;2(4):1–8.
28. Bonnici DM, Sanctuary T, Warren A, Murphy PB, Steier J, Marino P, et al. Prospective observational cohort study of patients with weaning failure admitted to a specialist weaning, rehabilitation and home mechanical ventilation centre. BMJ Open. 2016;6:e010025–32.
29. Bach JR, Saporito LR. Criteria for extuation and tracheostomy tube removal for patients with ventilatory failure. Chest. 1996;110:1566–71.
30. Duan J, Guo S, Han X, Tang X, Xu L, Liu Y, et al. Dual-mode weaning strategy for difficult-weaning tracheotomy patients: a feasibility study. Anesth Analg. 2012;115(3):597–604.
31. Budweiser S, Baur T, Jörres RA, Kollert F, Pfeifer M, Heinemann F. Predictors of successful decannulation using a tracheostomy retainer in patients with prolonged weaning and persisting respriatory failure. Respiration. 2012;84:469–76.
32. Dellweg D, Barchfeld T, Haidl P, Appelhans P, Kohler D. Tracheostomy decannulation: implication on respiratory mechanics. Head Neck. 2007;29:1121–7.
33. Hill N. Noninvasive mechanical ventilation for post acute care. Clin Chest Med. 2001;22:35–54.
34. Nava S, Navalesi P, Gregoretti C. Interfaces and humidification for noninvasive mechanical ventilation. Respir Care. 2009;54:71–84.
35. Ceriana P, Carlucci A, Navalesi P, Rampulla C, Delmastro M, Piaggi G, et al. Weaning from tracheostomy in long-term mechanically ventilated patients: feasibility of a decisional flowchart and clinical outcome. Intensive Care Med. 2003;29:845–8.
36. Santus P, Gramegna A, Radovanovic D, Raccanelli R, Valenti V, Rabbiosi D, et al. A systematic review on tracheostomy decannulation: a proposal of a quantitative semiquantitative clinical score. BMC Pulm Med. 2014;14:201–8.
37. Marchese S, Corrado A, Scala R, Corrao S, Ambrosino N. Intensive Care Study Group, Italian Association of Hospital Pul-

monologists (AIPO). Tracheostomy in patients with long-term mechanical ventilation: a survey. Respir Med. 2010;104(May (5)):749–53.
38. Corley A, Edwards M, Spooner AJ, Dunster KR, Anstey C, Fraser JF. High-flow oxygen via tracheostomy improves oxygenation in patients weaning from mechanical ventilation: a randomised crossover study. Intensive Care Med. 2017;43: 465–7.
39. Stripoli T, Spadaro S, Di mussi R, Volta CA, Trerotoli P, De Carlo F, et al. High-flow oxygen therapy in tracheostomized patients at high risk of weaning failure. Ann Intensive Care. 2019;9:4–13.
40. Natalini D, Grieco DL, Santantonio MT, Mincione L, Toni F, Anzellotti GM, et al. Physiological effects of high-flow oxygen in tracheostomized patients. Ann Intensive Care. 2019;9:114–22.

Pulmonology 2021;**27(1)**:52–66

PULMONOLOGY

www.journalpulmonology.org

REVIEW

Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review

A. Cortegiani[a,*], M. Ippolito[a], M. Greco[b,c], V. Granone[b,c], A. Protti[b,c], C. Gregoretti[a,d], A. Giarratano[a], S. Einav[e], M. Cecconi[b,c]

[a] *Department of Surgical, Oncological and Oral Science (Di.Chir.On.S.), University of Palermo. Department of Anesthesia Intensive Care and Emergency, Policlinico Paolo Giaccone, Palermo, Italy*
[b] *Department of Anesthesiology and Intensive Care, Humanitas Clinical and Research Center – IRCCS, Milan, Italy*
[c] *Department of Biomedical Science, Humanitas University, Milan, Italy*
[d] *Fondazione ''Giglio'', Cefalù, Italy*
[e] *IntensiveCare Unit of the Shaare Zedek Medical Medical Centre and Hebrew University Faculty of Medicine, Jerusalem, Israel*

Received 6 July 2020; accepted 7 July 2020

KEYWORDS
COVID-19;
Tocilizumab;
SARS-CoV-2;
Pneumonia;
Coronavirus

Abstract
Background: Tocilizumab is an IL-6 receptor-blocking agent proposed for the treatment of severe COVID-19. The aim of this systematic review was to describe the rationale for the use of tocilizumab for the treatment of COVID-19 and to summarize the available evidence regarding its efficacy and safety.
Methods: MEDLINE, PubMed, EMBASE, pre-print repositories (bioRxiv and medRxiv) and two trial Registries were searched for studies on the use of tocilizumab in COVID-19 or SARS-CoV-2 infection, viral pneumonia, and/or sepsis until 20th June 2020.
Results: We identified 3 indirect pre-clinical studies and 28 clinical studies including 5776 patients with COVID-19 (13 with a comparison group, 15 single-arm). To date, no randomized trials have been published. We retrieved no studies at low risk of bias. Forty-five ongoing studies were retrieved from trial registries.

Abbreviations: AIFA, Agenzia Italiana del Farmaco; ARDS, Acute respiratory distress syndrome; COVID-19, Coronavirus disease 2019; CPAP, Continuous positive airway pressure; CRS, CAR-T cell-induced cytokine release syndrome; GCA, Giant cell arteritis; ICTRP, International Clinical Trials Registry Platform; IDSA, Infectious Diseases Society of America; IMV, Invasive mechanical ventilation; NIH, U.S. National Institutes of Health; NIV, Noninvasive mechanical ventilation; pJIA, Pediatric juvenile idiopathic arthritis; RA, Rheumatoid arthritis; SIMIT, Italian Society of Infectious and Tropical disease; sJIA, Juvenile idiopathic arthritis; TNF, Tumor necrosis factor; WHO, World Health Organization.

* Corresponding author.
E-mail addresses: andrea.cortegiani@unipa.it (A. Cortegiani), ippolito.mariachiara@gmail.com (M. Ippolito), massimiliano.greco@hunimed.eu (M. Greco), veronica.granone@gmail.com (V. Granone), alessandro.protti@hunimed.eu (A. Protti), c.gregoretti@gmail.com (C. Gregoretti), antonino.giarratano@unipa.it (A. Giarratano), einav_s@szmc.org.il (S. Einav), maurizio.cecconi@hunimed.eu (M. Cecconi).

https://doi.org/10.1016/j.pulmoe.2020.07.003

Conclusions: There is insufficient evidence regarding the clinical efficacy and safety of tocilizumab in patients with COVID-19. Its use should be considered experimental, requiring ethical approval and clinical trial oversight.

Introduction

The search for the holy grail of medical treatment for COVID-19 (Coronavirus Disease-2019) has led researchers to propose, among other options, the use of IL-6 receptor blocking agents for treatment of symptomatic patients.[1] With a death toll of nearly 400.000 worldwide and nearly 7 million known cases[2,3] the current lack of targeted effective medication and ongoing reliance on supportive treatment alone remains a major cause of concern.[1]

Patients with the most severe COVID-19 symptoms (i.e. severe lung damage, septic shock and multiple organ failure) also exhibit what seems to be a hyper-inflammatory syndrome.[4] Early serology analyses identified higher IL-6 serum levels in patients with severe COVID-19 (particularly non-survivors) when compared to patients with mild and moderate disease.[5,6] As it has been proposed that elevated IL-6 levels may be associated with greater disease severity, the assumption is that they are also associated with worse clinical outcomes[7] and vice versa. This assumption underlies the current interest in anti-inflammatory therapies for the treatment of COVID-19.[8]

One of the IL-6 receptor blocking agents proposed for treatment of COVID-19, tocilizumab, was introduced in the early 2000's for treatment of autoimmune disorders such as refractory rheumatoid arthritis and systemic juvenile idiopathic arthritis (sJIA)[9,10] and has been approved by the FDA since 2017 for treatment of the cytokine release syndrome (CRS) that may occur following some forms of immunotherapy (e.g. CAR-T).[11] The aim of this review was to describe the rationale and summarize the available evidence, direct and indirect, regarding the use of tocilizumab for treatment of SARS-CoV-2 infection and to identify and describe ongoing clinical trials with this drug.

Methods

A preliminary search conducted prior to formal study initiation suggested the evidence on the topic is likely to be limited, and yet patients are already receiving the drug, making the issue urgent. Therefore, the protocol of this systematic review was not registered.

PICO question

We sought information regarding the use of tocilizumab (I) for treatment of COVID-19, SARS-CoV-2 infection, viral pneumonia, and/or sepsis in any population (adults and children) or laboratory model (P) with or without a comparator (C). We aimed to describe any treatment outcome whether solicited or unsolicited (O).

Search methods and article/trial inclusion/exclusion criteria

We conducted a systematic search of the MEDLINE, PubMed and EMBASE databases from inception to 20th June 2020. We sought pre-clinical and clinical studies addressing the use of tocilizumab for treating COVID-19, SARS-CoV-2 infection, viral pneumonia, and/or sepsis. Our search included the keywords 'tocilizumab', 'covid-19', 'coronavirus', 'sepsis, 'pneumonia, and 'viral infection' as exact phrases and a combination of subject headings according to databases syntax. We also searched the references of retrieved papers for additional potentially relevant papers. In order to find prepublication manuscripts, we surveyed the pre-print repositories biorRxiv and medRxiv from inception to 20th June 2020 for clinical or pre-clinical studies about the use of tocilizumab in COVID-19 or SARS-CoV-2 infection, viral pneumonia, and/or sepsis. No language restrictions were imposed in any of the searches. Finally, to identify clinical trials studying treatment with tocilizumab for COVID-19, SARS-CoV-2 infection, viral pneumonia, and/or sepsis, we sought trials registered prior to 20th June 2020 in the Chinese Clinical Trial Registry and Clinicatrial.gov. The databases and the trial registries were all screened independently and in duplicate by two of the authors (MI, VG).

In the second stage, the abstracts of all potentially relevant papers and pre-publication manuscripts were screened to identify relevant papers to be downloaded in full. After downloading potentially relevant articles, case reports, case series and reviews were excluded. Discrepancies and doubts regarding the relevance of papers downloaded in full were resolved by discussion and consensus with two additional authors (AC, MG).

Risk of bias assessment

Two of the authors (AC, MI) assessed the risk of bias (RoB) of the included studies independently and in duplicate. Disagreements over RoB were resolved by consensus or, if necessary, adjudicated by a third author (AG). The ROBINS-I tool (Risk Of Bias in Non-randomized Studies of Interventions) was used for nonrandomized studies with a comparison group.[12] The Newcastle Ottawa Scale (NOS) was used for single-arm nonrandomized studies.[13] The domains were rated in accordance with the requirements of the assessment tool used, with the lowest score achieved predominating as accepted. We used the Risk-of-Bias VISual-

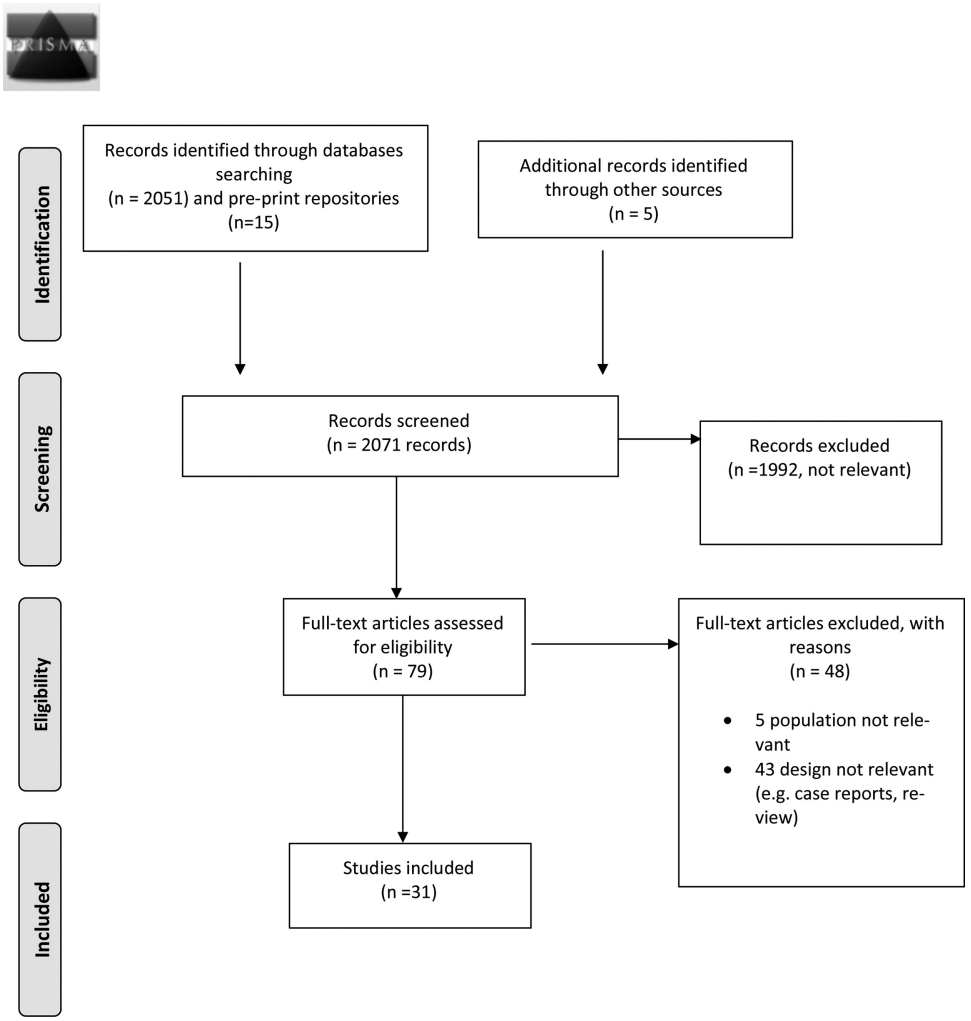


Figure 1 PRISMA flow-chart.
The figure shows the PRISMA flow-chart with inclusion/exclusion process in details.

ization (robvis) tool[14] to present the risk of bias assessments as either a plot or a table.

Results

The initial search identified 2071 records from MEDLINE, PubMed and EMBASE, pre-print repositories and other sources. After screening of titles and abstracts, removal of duplicates and evaluation of the additional sources retrieved, overall 31 published peer-reviewed papers and preprint non peer-reviewed papers were included (see the PRISMA flow diagram, available in Fig. 1 for the study selection process). Three papers described preclinical studies and 28 papers described clinical studies. The characteristics of the clinical studies included were summarized (see Table 1). In addition, forty-five ongoing clinical studies were retrieved from the trial Registries. These too were tabulated (see Table A1, Appendix A).

Pre-clinical studies and rationale

The hypothetical justification for treating patients with tocilizumab in the context of COVID-19 stems from indirect findings. These include several pre-clinical studies describing a beneficial effect in cellular and murine models of sepsis and influenza.[15–17]

In a cell model of sepsis (Human monocyte cell line THP-1), tocilizumab reduced the expression of *TNF* and *IL-10*, down-regulated inflammasome activation (reduced levels of NLRP3 and CASP1) and inhibited monocyte phagocytic activity. The authors of the study suggested that if suppressing the 'cytokine storm' is important when treating sepsis, these effects may be beneficial.[15]

Tocilizumab has also been evaluated in a murine model of Influenza A virus infection. Mice were anesthetized, intubated, and infected with mouse-adapted H1N1. The tocilizumab treated group (8 mg/kg 24 h before infection) and the controls were compared. Reduced skeletal muscle weakness (measured as digital grip strength), preserved muscle weight and increased short-term and long-term mortality were registered in the treated group, in comparison with controls. The mice manifesting distress were sacrificed and their deaths were also recorded as mortality.[16]

In a rat model of sepsis-induced acute lung and kidney injury, tocilizumab (4—8 mg/kg) reduced mortality. The authors also observed normalization of persistently high

Table 1 Characteristics of the included studies.

Author	Study type (Country)	Population (N)	Treatment	Comparison	Outcomes	Main findings	Overall risk of bias
Alattar et al.[18]	Single-centre retrospective observational study (Qatar)	Patients with severe COVID-19 (n = 25)	Median of tocilizumab dose 1 mg/kg (IQR, 1–3); median total dose 5.7 mg/kg (IQR, 4.8–9.5). Median time to treatment 1 day (IQR, 1–3) from admission to ICU.	No comparison	Alive ICU discharge at day 14; ventilatory support; inflammatory markers; adverse events	Nine patients (36%) were discharged alive from ICU by day 14. Of the remaining 16, three (12%) patients died and 13 (52%) were still in ICU. Twenty-three (92%) patients experienced adverse events.	Poor quality score (NOS)
Campochiaro et al.[19]	Single-centre prospective observational study (Italy)	Patients with severe COVID-19 and hyperinflammation (n = 65)	Tocilizumab i.v. at 400 mg. Second dose 400 mg after 24 h in case of respiratory worsening after the first infusion. (n = 32)	Not receiving tocilizumab (n = 33)	Overall survival and the proportion of discharge alive from hospital or decrease of at least 2 points from baseline on the six-category ordinal scale at 28 days; adverse events.	By day 28: 16% of TCZ group compared to 33% of standard treatment group died (p = 0.150). 63% of TCZ group compared to 49% of standard treatment group were discharged from the hospital (p = 0.32), with a similar median time to discharge. Clinical improvement in 69% of the TCZ group and in 61% of the standard treatment group, p = 0.61. Serious adverse events in 25% of the TCZ group and in 27% of the standard treatment group. Bacteremia in 13% of the TCZ group and 12% of the standard treatment group (p = 0.99).	Serious risk of bias (ROBINS-I)
Capra et al.[23]	Single-centre retrospective observational study (Italy)	Hospitalized patients with non critical respiratory failure and COVID-19 (n = 85)	Tocilizumab 400—800 mg i.v. or 324 mg s.c. administered within 4 days from admission (n = 62)	Not receiving tocilizumab admitted earlier than 4 days before tocilizumab availability in the centre (n = 23)	Survival rate; clinical improvement; infections	TCZ group had significantly greater survival rate compared to control (HR for death, 0.035; 95% CI, 0.004—0.347; p = 0.004). No infections related to tocilizumab and no increased levels of serum procalcitonin.	Moderate risk of bias (ROBINS-I)

Table 1 (*Continued*)

Author	Study type (Country)	Population (N)	Treatment	Comparison	Outcomes	Main findings	Overall risk of bias
Colaneri et al.[24]	Single-centre retrospective observational study (Italy)	Hospitalized patients with COVID-19 (n = 112)	Tocilizumab i.v. 8 mg/kg (up to a maximum 800 mg per dose), repeated after 12 h if no side effects (n = 21)	Not receiving tocilizumab (n = 91)	ICU admission and 7-day mortality rate; clinical and laboratory data; adverse events	No adverse event. TCZ did not significantly affect ICU admission (OR 0.11; 95% CI 0.00–3.38; p = 0.22) or 7-day mortality (OR 0.78; 95% CI 0.06–9.34; p = 0.84) compared with standard care. Analysis performed on propensity score matched cohort (42 patients)	Moderate risk of bias (ROBINS-I)
Guaraldi et al.[22]	Multicentre retrospective observational study (Italy)	Patients with severe COVID-19 (n = 544)	Tocilizumab 8 mg/kg (up 800 mg) twice, 12 h apart or 162 mg in two simultaneous doses, (324 mg in total) (n = 179)	Not receiving tocilizumab (n = 365)	Composite of death or invasive mechanical ventilation	Tocilizumab associated with a reduced risk of invasive mechanical ventilation or death (adjusted hazard ratio 0·61, 95% CI 0·40–0·92; p = 0·020). 24 (13%) of the treated were diagnosed with new infections vs. 14 (4%) of the controls (p < 0·0001)	Moderate risk of bias (ROBINS-I)
Kewan et al.[21]	Single-centre retrospective observational study (USA)	Patients with severe COVID-19 (n = 51)	Tocilizumab 8 mg/kg and received (up to 400 mg) single administration (n = 28)	Not receiving tocilizumab (n = 23)	Live discharge from hospital without worsening or at least 2 points decrease in a six point scale including death	Clinical improvement at 21 days in treated vs. control: 76.5% (95% CI: 57.3–95.6) vs. 79.4% (95% CI: 56.0–100) and 67.9% (95% CI: 43.2–92.7) vs. 61.9% (95% CI: 21.9–100) among mechanical ventilated patients (p = 0.3)	Serious risk of bias (ROBINS-I)
Luo et al.[28]	Single-centre retrospective observational study (China)	Patients with COVID-19 (n = 15)	TCZ 80—600 mg per time. Five (33.3%) patients received two or more TCZ doses	No comparison	Laboratory data and clinical course	3/15 (20%) death; 2/15 (13%) aggravation; 9/15 (60%) stabilization; 1/15 (7%) improvement	Poor quality score (NOS)
Morena et al.[30]	Single-centre prospective nonrandomized study (Italy)	Patients with severe or critical COVID-19 and high IL-6 levels (n = 51)	Tocilizumab intravenously either at fixed first dose of 400 mg followed by 400 mg after 12 h or 8 mg/kg at T0 followed by 8 mg/kg after 12 h (in patients with body weight $\geq$ 60 Kg)	No comparison	Mortality; adverse events; clinical course	30-day mortality: 27%. 61% discharged and 6 still hospitalized at last follow-up (median 34days (IQR 32—37)). Hepatic enzymes increased of at least 3 times the normal values in 29%, thrombocytopenia in 14%, neutropenia in 6% and cutaneous rash in 2%. Bacteremia in 14 patients (27%).	Poor quality score (NOS)

(*Continued*)

Author	Study type (Country)	Population (N)	Treatment	Comparison	Outcomes	Main findings	Overall risk of bias
Price et al.[20]	Single-centre prospective nonrandomized observational study (USA)	Hospitalized patients with confirmed COVID-19 (n = 153)	Tocilizumab 8 mg/kg i.v. (up to 800 mg); second dose if elevated body mass index	No comparison	Survival at day 14; adverse events	87% survival at day 14; 6 patients had neutropenia, 6 bacteremia	Poor quality score (NOS)
Quartuccio et al.[25]	Single-centre retrospective observational study (Italy)	Patients with COVID-19 (n = 111)	Tocilizumab 8 mg/kg i.v. single administration (n = 42)	Not receiving tocilizumab (n = 69)	Clinical course; laboratory findings; complications	TCZ group 9.5% mortality, 43% experienced bacterial complications. No deaths or complication in the standard care group.	Serious risk of bias (ROBINS-I)
Sciascia et al.[26]	Multicentre prospective single-arm study (Italy)	Patients with severe COVID-19 (n = 63)	Tocilizumab i.v. 8 mg/kg or s.c. 324 mg. Single additional dose allowed within 24 h	No comparison	Safety; improvement of laboratory and respiratory parameters	Mortality at day 14 was 11% (7/63). No severe or moderate adverse events related to TCZ. No significant difference in mortality between different routes of administration	Poor quality score (NOS)
Toniati et al.[29]	Single-centre prospective non-randomized study (Italy)	Patients with COVID-19 and respiratory failure (BCRSS score $\geq$3) (n = 100)	Tocilizumab 8 mg/kg (max800 mg) two consecutive i.v. infusions 12 h apart. A third infusion, 24 h apart from the second was allowed	No comparison	Clinical and laboratory data at day 10; adverse events	At 24—72 h after TCZ, 58% had clinical improvement, 37% stabilized and 5% worsened (of whom 4% died). At day 10, 77% improved or stabilized and 23% worsened (of whom 20% died). Two patients developed septic shock and died, one had gastrointestinal perforation requiring urgent surgery	Poor quality score (NOS)
Xu et al.[27]	Multicentre retrospective observational study (China)	Patients with severe or critical COVID-19 (n = 21)	Tocilizumab first dose 4–8 mg/kg (recommended dose 400 mg through an i.v. drip up to a maximum of 800 mg). In case of fever within 12 h, single additional dose	No comparison	Clinical improvement; adverse events	No adverse reactions observed. All patients discharged on average 15.1 day after tocilizumab. By day 5 after TCZ, 75.0% of patients had lower oxygen intake	Poor quality score (NOS)

(*Continued*)

Author	Study type (Country)	Population (N)	Treatment	Comparison	Outcomes	Main findings	Overall risk of bias
Pre-print not peer reviewed studies							
Fomina et al.[37]	Single-centre retrospective observational study (Russia)	Hospitalized patients with COVID-19 (n = 89)	Tocilizumab 400 mg	No comparison	Clinical course	63/72 not mechanically ventilated patients were discharged, 1/72 died, 8/72 remained in hospital; 10/17 mechanically ventilated patients died and 7/10 remain in hospital	Poor quality score (NOS)
Gorgolas et al.[36]	Single-centre retrospective observational study (Spain)	Hospitalized patients with COVID-19 (n = 186)	Tocilizumab single dose of 400—600 mg (16 received two doses and 1 received three doses)	No comparison	Intubation or death after 24 h from administration	51 patients were intubated or dead at day 15; 19 patients needed intubation (of whom 4 died) and 36 died (32 of whom were not intubated). 11 (5·9%) patients had serious adverse reactions, 13 cases (6·3%) of secondary acquired infections	Poor quality score (NOS)
Ip et al.[31]	Multicentre, retrospective, observational, study (USA)	ICU patients with COVID-19 (n = 547)	Tocilizumab: 400 mg (96%), followed by 800 mg (1%), 8 mg/kg (1%), 4 mg/kg (1%), and missing dosing (1%).(n = 134)	Not receiving tocilizumab (n = 413)	Mortality; adverse events	Secondary bacteremia in 11% of the non-treated group, 13% of the treated. Secondary pneumonia in 6% of the non-treated group, 9% of the treated. Propensity modeling showed a trend association between survival and tocilizumab (HR, 0.76 [95% CI, 0.57—1.00]). The unadjusted 30-day mortality favored tocilizumab (46% vs. 56%)	Moderate risk of bias (ROBINS-I)
Kimmig et al.[32]	Single-centre nonrandomized observational study (USA)	ICU patients with critical COVID-19 (n = 60)	400 mg flat dosing of tocilizumab with possible redosing based on clinical response (n = 28)	Not receiving tocilizumab(n = 32)	Bacterial and fungal infections	TCZ associated with higher incidence of secondary bacterial infections (64.3% vs. 31.3% p = 0.010). In a logistic regression model, TCZ was independently associated with secondary bacterial infections (OR 3.96 (95% CI 1.351—11.607), p = 0.033)	Serious risk of bias (ROBINS-I)

(*Continued*)

Author	Study type (Country)	Population (N)	Treatment	Comparison	Outcomes	Main findings	Overall risk of bias
Martinez-Sanz et al. [33]	Multicentre retrospective observational study (Spain)	Hospitalized patients with COVID-19 (n = 1229)	Tocilizumab median dose 600 mg (IQR 600–800 mg). First dose at a median time of 4 (IQR 3–5) days (n = 260)	Not receiving tocilizumab (n = 969)	Time to death; composite including ICU admission or death	Tocilizumab associated with higher risk of death (HR 1.53, 95% CI 1.20–1.96, p = 0.001) and ICU/death (HR 1.77, 95% CI 1.41–2.22, p < 0.001).The effect disappeared in the adjusted analyses	Moderate risk of bias (ROBINS-I)
Moreno-Garcia et al.[45]	Single-centre retrospective observational study (Spain)	Non-ICU patients with COVID-19 (n = 171)	Tocilizumab 400 mg/24 h iv for patients with ≤75 kg and 600 mg/24 h iv for those with >75 kg. Up to 3 doses (12 h apart) if partial response (n = 77)	Not receiving tocilizumab (n = 94)	Composite of ICU admission or death	Tocilizumab group had significantly less ICU admissions (10.3% vs. 195 27.6%, P = 0.005) and less invasive ventilation (0 vs 13.8%, P = 0.001). Findings confirmed at propensity score matched analysis (OR: 0.03, CI 95%: 0.007—0.1, P = 0.0001)	Moderate risk of bias (ROBINS-I)
Perrone et al.[44]	Multicentre, open-label trial, including a single-arm phase 2 study (Italy)	Hospitalized patients with COVID-19 (n = 1221)	Tocilizumab 8 mg/kg (up to 800 mg). Second dose allowed after 12 h, if not recovered	No comparison	Lethality rates at day 14 and day 30 days; adverse events	In phase 2, lethality was 18.4% (97.5%CI: 13.6—24.0, P = 0.52) and 22.4% (97.5%CI: 17.2—28.3, P < 0.001) at 14 and 30 days. Lower rates (15.6% and 20.0%) among the treated (mITT, n = 708).	Poor quality score (NOS)
Petrak et al.[35]	Multicentre retrospective observational study (USA)	Hospitalized patients with COVID-19 (n = 145)	135 patients received 4 mg/kg (up to 400 mg), 5 received a single dose of 600 mg and 4 a dose of 800 mg. Early administration (<1 day) or delayed (>1 day)	No comparison	Mortality; LOS; discharge	48.3% discharged and 29.3% expired. For each additional day that the tocilizumab dose is delayed from admission, the odds of requiring MV increase by 21%, holding all other covariates constant (95% CI: [1.08, 1.38], p = 0.002).	Poor quality score (NOS)
Ramaswamy et al.[40]	Multicentre retrospective observational study (USA)	Hospitalized patients with COVID-19 (n = 86)	Tocilizumab dosed at either 400 mg fixed dose or 8 mg/kg (up to 800 mg) (n = 21)	Not receiving tocilizumab (n = 65)	In-hospital mortality	Reduced risk of inpatient death in the treated (HR 0.25; 95% CI 0.07—0.90, Cox model). Association confirmed in the treatment effects model (RR 0.472; 95% CI 0.449—0.497).	Moderate risk of bias (ROBINS-I)

(*Continued*)

Author	Study type (Country)	Population (N)	Treatment	Comparison	Outcomes	Main findings	Overall risk of bias
Rimland et al.[39]	Single-centre retrospective observational study (USA)	Hospitalized patients with COVID-19 (n = 11)	Tocilizumab median dosage 7.9 mg/kg (IQR 5.8—8.1), median time to administration: one day (IQR 1—4) from admission and nine days (IQR 7—14) after symptom onset	No comparison	Clinical course	Mortality 27%; 45% remained in ICU on mechanical ventilation, receiving vasopressors or hemodialysis; 9% were transferred from the ICU to floor and weaned to room air; 18% were discharged home without oxygen; 64% had minimally elevated liver function tests. Two patients were diagnosed with ileus and two with bacterial pneumonia. No serious adverse events.	Poor quality score (NOS)
Rossi et al.[34]	Single-centre retrospective observational study (France)	Patients with severe COVID-19 (n = 246)	Tocilizumab 400 mg single dose (n = 106)	Not receiving tocilizumab (n = 140)	Composite of all-cause mortality and invasive mechanical ventilation	Tocilizumab associated with fewer primary outcomes 47 (HR = 0.49 (95% CI 0.3—0.81), p value = 0.005) in the matched cohort (n = 168), and full cohort (adjusted HR = 0.26 50 (95CI0.135—0.51, p = 0.0001), confirmed by IPSW analysis (p < 0.0001)	Moderate risk of bias (ROBINS-I)
Roumier et al.[38]	Single-centre nonrandomized observational study (France)	Patients with severe COVID-19 and inflammatory markers (n = 59)	8 mg/kg at the discretion of treating physicians, renewable once in case of insufficient response to therapy (n = 30)	Not receiving tocilizumab (n = 29)	Clinical course	TCZ significantly reduced the need for mechanical ventilation (weighted OR: 0.42; 95%CI[0,20—0,89]; p = 0,025). Unadjusted analysis showed a reduction of mortality (OR: 0.25 95%CI [0.05—0.95], p = 0.04), statistical significance disappeared after weighted analysis.	Moderate risk of bias (ROBINS-I)

(*Continued*)

Author	Study type (Country)	Population (N)	Treatment	Comparison	Outcomes	Main findings	Overall risk of bias
Sánchez-Montalvá et al.[43]	Single-centre prospective and retrospective observational study (Spain)	Patients with severe COVID-19 and high IL-6 (n = 82)	Patients over 75 kg received 600 mg, otherwise 400 mg. A second dose was considered in case of poor early response	No comparison	Mortality at 7 days after tocilizumab administration; admission to the ICU; development of ARDS and respiratory failure	41.5% had been discharged, 26.8% had died, 17.1% were in ICU, 11.0% in medical wards, 3.7% had been transferred to another institution. By 7-day follow-up, the mortality rate was 4.0% per person-day (95% confidence interval [CI], 2.4%–6.2%) by Kaplan-Meier analysis. No adverse events attributed to tocilizumab.	Poor quality score (NOS)
Somers et al.[41]	Single-centre retrospective observational study (USA)	Patients with severe COVID-19 under mechanical ventilation (n = 154)	Tocilizumab 8 mg/kg (maximum 800 mg); additional doses discouraged (n = 78)	Not receiving tocilizumab (n = 76)	Survival probability post-intubation; ordinal illness severity scale integrating superinfections	TCZ associated with adjusted lower hazard of death at multiple analyses [Model A: HR 0.54 (95% CI 0.29, 1.00)], [Model B: n = 116, HR 0.55 (95% CI 0.33, 0.90); [Model C: HR 0.54 (0.35, 0.84)]; TCZ treated patients were more than twice as likely to develop a superinfection than untreated controls (54% vs. 26%; p < 0.001)	Moderate risk of bias (ROBINS-I)
Wadud et al.[42]	Single-centre retrospective observational study (USA)	Hospitalized patients with COVID-19 (n = 94)	Tocilizumab (n = 44)	Not receiving tocilizumab (n = 50)	Length of stay; length of ventilation; mortality; survival and discharge (home, rehab, transfer to outside facility)	Length of stay was longer, in the TCZ group. Survival rate 48% in the control group vs 61.36% in patients receiving TCZ (p < 0.00001)	Serious risk of bias (ROBINS-I)

The table shows the main characteristics of the included studies.
ARDS, acute respiratory distress syndrome; BCRSS, Brescia COVID-19 Respiratory Severity Scale; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; mITT, modified intention to treat; OR, Odds ratio; SARS, severe acute respiratory syndrome; TCZ, tocilizumab; USA, United States of America.

serum levels of IL-6 in septic rats after treatment with tocilizumab and improved lung wet/dry weight ratio and total protein content in the treatment group, in comparison with the sham group.[17]

Clinical studies

We retrieved 13 published clinical studies[18–30] and 15 preprint (i.e. pre peer review) clinical studies,[31–45] respectively evaluating 1396 and 4380 patients, for a total of 5776 patients. The main characteristics of the included clinical studies are presented in Table 1. Only three peer reviewed papers[22,26,27] and five prepublications[31,33,35,40,44] were multicenter studies. Thirteen studies included more than 100 patients, but in these studies the number of patients receiving tocilizumab was not large. One published trial included 112 patients but only one in five patients (n = 21) received tocilizumab.[24] Another published trial included 111 patients among whom less than half (n = 49) were treated.[25] One prepublication included 547 patients of which a third (n = 134) were treated[31] and another included 1229 patients of which 260 received tocilizumab.[33] Seven of the 13 published papers and six of the 15 prepublications presented no comparator.

The risk of bias assessments are shown in Fig. 2 (nonrandomized studies with comparison) and in Appendix A, Table A2 (nonrandomized single-arm studies). Ten studies were at moderate and five at serious risk of bias (ROBINS-I); thirteen studies were judged to be of ''poor quality'' (NOS). None of the studies were assessed as having a low risk of bias.

Discussion

The mechanism of action and pharmacological properties of tocilizumab

Tocilizumab is a humanized monoclonal antibody capable of interfering with the IL-6 soluble and membrane binding site of the receptor (IL-6R), thereby blocking the assembling of the activated complex with the transmembrane protein (gp130-IL-6-sILr). Tocilizumab is also able to block IL-6 trans-signaling[46] which is strongly related to the pro-inflammatory effects of IL-6 (e.g. release of acute phase proteins). Tocilizumab has a non-linear pharmacokinetic profile, with a dose-response curve that plateaus at an approximate dose of 800 mg.[46] The half-life of tocilizumab is dose-dependent and comparable to the half-life of IgG1.[47]

Interleukin-6 (IL-6) and COVID-19

IL-6 is a pleiotropic cytokine secreted by neutrophils, monocytes and macrophages and involved in the inflammatory response. It has a soluble (sIL-6R) and a membrane binding site (mIL-6R), constituting its receptors. IL-6 can bind its mIL-6R at low doses or, at higher doses, its sIL-6R (trans-signaling), creating the activated complex with gp130 protein.[48] Signaling is mediated by Janus kinases (JAK) and Ras/mitogen-activated protein kinase (MAPK)/NF-κB-IL-6.[48] IL-6 promotes B and T cells differentiation, acute phase protein production and osteoclast activation.[46] High levels of IL-6 have been listed among the main features of cytokine storm and cytokine release syndrome (CRS), both of which are characterized by an exaggerated release of pro-inflammatory cytokines and potentially life-threatening multiorgan damage.[48] IL-6 also seems to be involved, through these mechanisms, in the pathophysiology of COVID-19, especially in the most severe forms of the disease.[5,6,49,50] Furthermore, elevated levels of IL-6 have been associated with a hypercoagulable state in both animals and humans,[51,52] and coagulopathy is another characteristic of patients with COVID-19 at high risk of death.[53]

Evidence on efficacy and safety of tocilizumab for COVID-19

The current systematic review shows that although indirect preclinical data suggests rationale for using tocilizumab and observational studies suggest that treatment with tocilizumab may be associated with more favorable outcomes compared to standard care in patients with severe or critical COVID-19, up till now no RCTs have been published or made available pre-print regarding either the effectiveness or the safety of tocilizumab in the context of COVID-19.

The effects of tocilizumab against IL-6 related pro-inflammatory and pro-coagulant status[53] partially explain its potential role in COVID-19.[54] However, it is worth remembering that there is yet no evidence that suppressing the physiological inflammatory response to the virus is indeed beneficial. Previous experience with pharmaceutic inflammatory response modulation in patients with ARDS[55] and sepsis[56] have been notoriously unsuccessful.

Several observational studies have examined whether tocilizumab has any effect in patients with COVID-19. Although many of the patients included in these studies had severe or critical disease and many were admitted to ICUs, drawing conclusions from the findings of these studies is a leap of faith, given that most had small sample sizes and high or moderate risk of bias, mostly due to confounding. The identified studies also varied in dosing (single or double), and drug availability issues emerged in some centres, which may have influenced both sample sizes and study designs. Finally, the literature suggests the presence of two phases in the pathophysiology of COVID-19. An early phase characterized by a high viral load and limited systemic impairment, and a late phase, with elevated cytokine levels and a hyperinflammatory state.[4] Regarding the timing of drug administration, that could therefore potentially determine treatment outcomes, a pre-print study evaluated the effect of early vs late administration of the drug on the outcomes, but the association remains unclear and understudied.[35] The authors found that for each additional day of delay from the admission to tocilizumab administration, the odds of receiving mechanical ventilation independently increase by 21% (95% CI: [1.08, 1.38], p = 0.002).[35]

Clinical studies on patients with COVID-19 have also evoked some safety concerns. The risk of secondary infection complications is unclear. Among the studies with a comparison group, six found a higher rate of infections among treated, compared to untreated,

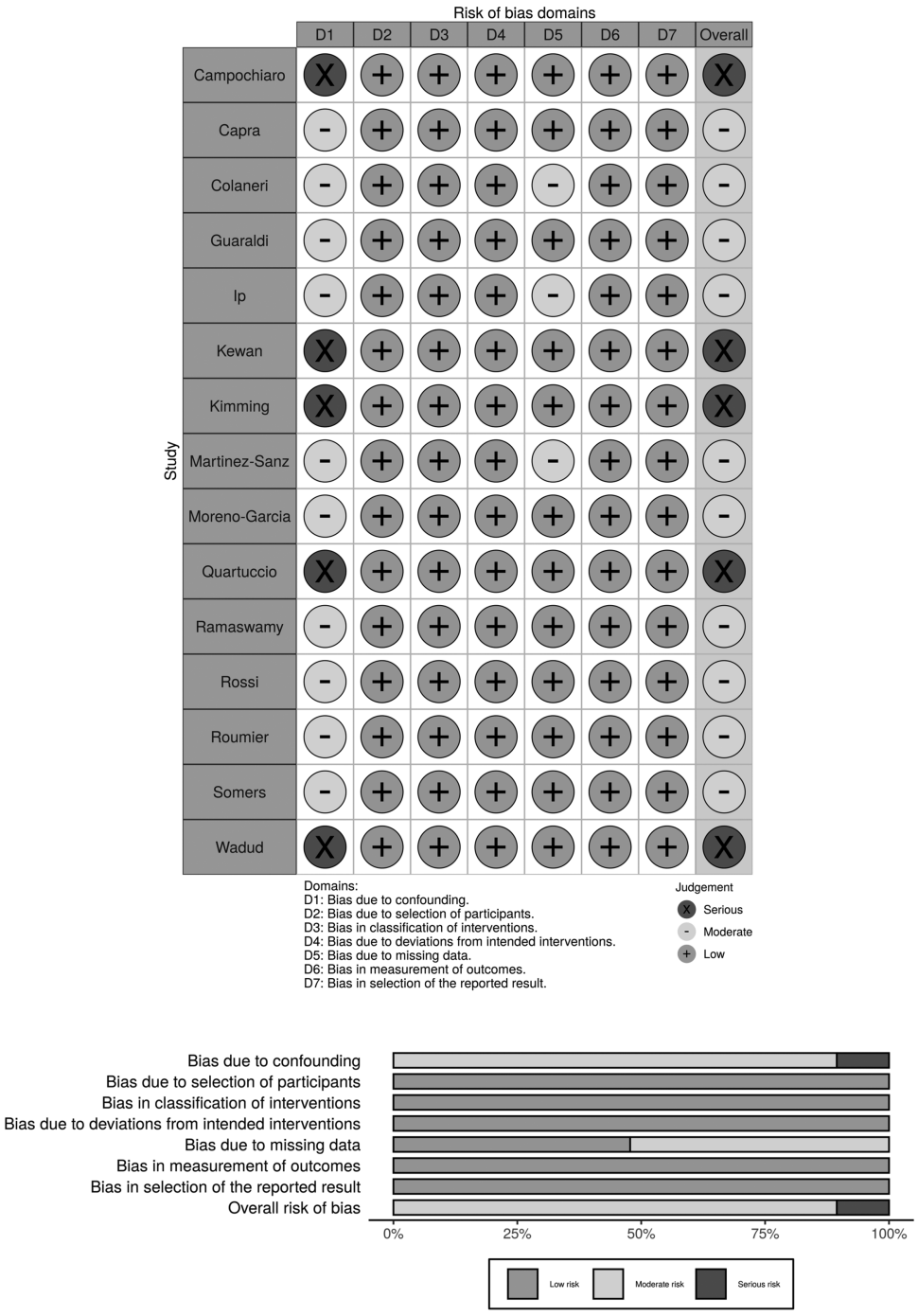


Figure 2 Risk of bias of nonrandomized studies with comparison groups.
The risk of bias of the included nonrandomized studies with comparison groups is reported per single study and per domain. RoB was assessed using Risk of Bias in Non-randomized Studies of Interventions, as appropriate.

patients.[19,22,25,31,32,41] Hepatotoxic effects, neutro- and thrombocytopenia and intestinal perforation have also been described.[57–59] This is worrying, particularly given that data from a clinical study promoted by the Italian agency for medicines (Agenzia Nazionale del Farmaco - AIFA) suggests no significant benefit in terms of either mortality (3.3% vs. 3.2%) or ICU admission (10.0% vs 7.9%) in patients not requiring mechanical respiratory support, when treated with tocilizumab vs. controls.[60]

Recommendations ad ongoing studies

Several clinical practice guidelines already include tocilizumab as a therapeutic option for COVID-19. The most recent Chinese guideline[61] suggests tocilizumab, at a dose of 4—8 mg/kg, for patients with extensive lung lesions and for severe cases with increased levels of IL-6 or with complications.[61] The Italian Society of Infectious and Tropical disease (SIMIT - Lombardy section),[62] recommends

selection of patients who have recovered from the initial high viral load (i.e. afebrile from >72 h or with symptoms for >7 days), those with high IL-6 levels (>40 pg/mL), those with increasing levels of D-dimer, C-reactive protein, ferritin or fibrinogen levels and those needing ventilation support (CPAP, NIV or IMV) for treatment with tocilizumab. However, both the 'Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19) and the U.S. National Institutes of Health (NIH) state that the evidence does not suffice to issue recommendations regarding the use of tocilizumab for COVID-19.[63,64] The World Health Organization (WHO)[65] and the Infectious Diseases Society of America (IDSA)[66] both recommend that tocilizumab only be administered within the context of a clinical trial.

Our search identified 45 registered ongoing trials, including 18 multicentre randomized trials in several countries across 4 continents. The details of the studies underway are provided in Appendix A (Table A1). The results of these trials will hopefully provide sufficient data regarding the role of tocilizumab in the context of COVID-19.

Conclusion

Although basic science suggests rationale for administration of IL-6 receptor antagonists to patients with COVID-19, the clinical evidence regarding the efficacy and safety of tocilizumab for COVID-19 remains observational only and is methodologically flawed. As concerns have also been raised regarding the possibility of secondary infection, the use of this drug should be limited to the context of a clinical trial and accompanied by ethical committee approval and/or informed consent, as well as appropriate monitoring for side effects.

Funding

None.

Conflicts of interest

All authors declare to have no competing interests.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Available.

Code availability

Not applicable.

Authors' contributions

AC conceived the content, drafted the manuscript, approved the final version to be submitted. MI, MG, VG, AP helped in writing the manuscript and revised it critically for important intellectual content, approved the final version to be submitted. CG, AG, SE, MC conceived the content, drafted the manuscript, approved the final version to be submitted.

Acknowledgment

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pulmoe.2020.07.003.

References

1. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA. 2020, http://dx.doi.org/10.1001/jama.2020.6019.
2. WHO. COVID-19 Situation report – 139. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200607-covid-19-sitrep-139.pdf?sfvrsn=79dc6d08_2. 2020. [Accessed June 7, 2020].
3. Johns Hopkins University & Medicine. Coronavirus resource center. https://coronavirus.jhu.edu/map.html. 2020. [Accessed June 7, 2020].
4. Shi Y, Wang Y, Shao C, Huang J, Gan J, Xiaoping H, et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ. 2020;27:1451–4, http://dx.doi.org/10.1038/s41418-020-0530-3.
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020, http://dx.doi.org/10.1016/S0140-6736(20)30566-3.
6. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46:846–8, http://dx.doi.org/10.1007/s00134-020-05991-x.
7. Coomes EA, Haghbayan H. Interleukin-6 in COVID-19: a systematic review and meta-analysis. medRxiv. 2020, http://dx.doi.org/10.1101/2020.03.30.20048058.
8. Cortegiani A, Ippolito M, Ingoglia G, Einav S. Chloroquine for COVID-19: rationale, facts, hopes. Crit Care. 2020, http://dx.doi.org/10.1186/s13054-020-02932-4.
9. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367:2385–95, http://dx.doi.org/10.1056/NEJMoa1112802.
10. Singh JA, Beg S, Lopez-Olivo MA. Tocilizumab for rheumatoid arthritis. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2010, http://dx.doi.org/10.1002/14651858.cd008331.

11. Roche. FDA approves Roche's Actemra/RoActemra (tocilizumab) for the treatment of CAR T cell-induced cytokine release syndrome. https://www.roche.com/media/releases/med-cor-2017-08-30.htm.htm. [Accessed June 7, 2020].
12. Sterne JA, Hernán MA, Reeves BC, Berkman ND, Viswanathan M, Henry D, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016, http://dx.doi.org/10.1136/bmj.i4919.
13. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603–5, http://dx.doi.org/10.1007/s10654-010-9491-z.
14. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2020, http://dx.doi.org/10.1002/jrsm.1411.
15. Sheng F, Han M, Huang Z, Zhang L. Interleukin 6 receptor inhibitor tocilizumab suppresses cytokine expression, inflammasome activation and phagocytosis in a cell model of sepsis. Pharmazie. 2016;71:636–9, http://dx.doi.org/10.1691/ph.2016.6713.
16. Radigan KA, Nicholson TT, Welch LC, Chi M, Amarelle L, Angulo M, et al. Influenza A virus infection induces muscle wasting via IL-6 regulation of the E3 ubiquitin ligase atrogin-1. J Immunol. 2019;202:484–93, http://dx.doi.org/10.4049/jimmunol.1701433.
17. Ibrahim YF, Moussa RA, Bayoumi AMA, Ahmed ASF. Tocilizumab attenuates acute lung and kidney injuries and improves survival in a rat model of sepsis via down-regulation of NF-κB/JNK: a possible role of P-glycoprotein. Inflammopharmacology. 2020;28:215–30, http://dx.doi.org/10.1007/s10787-019-00628-y.
18. Alattar R, Ibrahim TBH, Shaar SH, Abdalla S, Shukri K, Daghfal JN, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. J Med Virol. 2020, http://dx.doi.org/10.1002/jmv.25964.
19. Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. Eur J Intern Med. 2020;76:43–9, http://dx.doi.org/10.1016/j.ejim.2020.05.021.
20. Price CC, Altice FL, Shyr Y, Koff A, Pischel L, Goshua G, et al. Tocilizumab treatment for cytokine release syndrome in hospitalized COVID-19 patients: survival and clinical outcomes. Chest. 2020, http://dx.doi.org/10.1016/j.chest.2020.06.006.
21. Kewan T, Covut F, Al–Jaghbeer MJ, Rose L, Gopalakrishna KV, Akbik B. Tocilizumab for treatment of patients with severe COVID–19: a retrospective cohort study. EClinicalMedicine. 2020, http://dx.doi.org/10.1016/j.eclinm.2020.100418.
22. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol. 2020, http://dx.doi.org/10.1016/S2665-9913(20)30173-9.
23. Capra R, De Rossi N, Mattioli F, Romanelli G, Scarpazza C, Sormani MP, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med. 2020, http://dx.doi.org/10.1016/j.ejim.2020.05.009.
24. Colaneri M, Bogliolo L, Valsecchi P, Sacchi P, Zuccaro V, Brandolino F, et al. Tocilizumab for treatment of severe COVID-19 patients: preliminary results from SMAtteo COvid19 REgistry (SMACORE). Microorganisms. 2020;8:695, http://dx.doi.org/10.3390/microorganisms8050695.
25. Quartuccio L, Sonaglia A, McGonagle D, Fabris M, Peghin M, Pecori D, et al. Profiling COVID-19 pneumonia progressing into the cytokine storm syndrome: results from a single Italian Centre study on tocilizumab versus standard of care. J Clin Virol. 2020, http://dx.doi.org/10.1016/j.jcv.2020.104444.
26. Sciascia S, Aprà F, Baffa A, Baldovino S, Boaro D, Boero R, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol. 2020;38:529–32.
27. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci. 2020, http://dx.doi.org/10.1073/pnas.2005615117.
28. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol. 2020, http://dx.doi.org/10.1002/jmv.25801.
29. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. Autoimmun Rev. 2020;19:102568, http://dx.doi.org/10.1016/j.autrev.2020.102568.
30. Morena V, Milazzo L, Oreni L, Bestetti G, Fossali T, Bassoli C, et al. Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. Eur J Intern Med. 2020;76:36–42, http://dx.doi.org/10.1016/j.ejim.2020.05.011.
31. Ip A, Berry DA, Hansen E, Goy AH, Pecora AL, Sinclaire BA, et al. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients—an observational study. medRxiv. 2020, http://dx.doi.org/10.1101/2020.05.21.20109207.
32. Kimmig LM, Wu D, Gold M, Pettit NN, Pitrak D, Mueller J, et al. IL6 inhibition in critically ill COVID-19 patients is associated with increased secondary infections. medRxiv. 2020, http://dx.doi.org/10.1101/2020.05.15.20103531.
33. Martinez-Sanz J, Muriel A, Ron R, Herrera S, Ron R, Perez-Molina JA, et al. Effects of tocilizumab on mortality in hospitalized patients with COVID-19: a multicenter cohort study. medRxiv. 2020, http://dx.doi.org/10.1101/2020.06.08.20125245.
34. Rossi B, Nguyen LS, Zimmermann P, Boucenna F, Baucher L, Dubret L, et al. Effect of tocilizumab in hospitalized patients with severe pneumonia COVID-19: a cohort study. medRxiv. 2020, http://dx.doi.org/10.1101/2020.06.06.20122341.
35. Petrak R, Skorodin N, Van Hise NW, Fliegelman RM, Pinsky J, Didwania V, et al. Tocilizumab as a therapeutic agent for critically Ill patients infected with SARS-CoV-2. medRxiv. 2020, http://dx.doi.org/10.1101/2020.06.05.20122622.
36. Gorgolas M, Cabello A, Perez LP, Alvarez FV, Alvarez BA, Rodriguez Nieto MJ, et al. Compassionate use of tocilizumab in severe SARS-CoV2 pneumonia. When late administration is too late. medRxiv. 2020, http://dx.doi.org/10.1101/2020.06.13.20130088.
37. Fomina DS, Lysenko M, Beloglazova IP, Mutinova ZY, Poteshkina NG, Samsonova IV, et al. Temporal clinical and laboratory response to interleukin-6 receptor blockade with Tocilizumab in 89 hospitalized patients with COVID-19 pneumonia. medRxiv. 2020, http://dx.doi.org/10.1101/2020.06.12.20122374.
38. Roumier M, Paule R, Groh M, Vallee A, Ackermann F. Interleukin-6 blockade for severe COVID-19. medRxiv. 2020, http://dx.doi.org/10.1101/2020.04.20.20061861.
39. Rimland CA, Morgan CE, Bell GJ, Kim MK, Hendrick T, Marx A, et al. Clinical characteristics and early outcomes in patients with COVID-19 treated with tocilizumab at a United States academic center. medRxiv. 2020, http://dx.doi.org/10.1101/2020.05.13.20100404.
40. Ramaswamy M, Mannam P, Comer R, Sinclair E, McQuaid DB, Schmidt ML, et al. Off-label real world experience using tocilizumab for patients hospitalized with COVID-19 disease in a regional community health system a case-control study. medrxiv. 2020, http://dx.doi.org/10.1101/2020.05.14.20099234.

41. Somers EC, Eschenauer GA, Troost JP, Golob JL, Gandhi TN, Wang L, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. medRxiv. 2020, http://dx.doi.org/10.1101/2020.05.29.20117358.
42. Wadud N, Ahmed N, Shergil MM, Khan M, Krishna MG, Gilani A, et al. Improved survival outcome in SARs-CoV-2 (COVID-19) acute respiratory distress syndrome patients with tocilizumab administration. medRxiv. 2020, http://dx.doi.org/10.1101/2020.05.13.20100081.
43. Sanchez-Montalva A, Selares-Nadal J, Espinosa-Pereiro J, Fernandez-Hidalgo N, Perez-Hoyos S, Salvador F, et al. Early outcomes of tocilizumab in adults hospitalized with severe COVID19. An initial report from the Vall dHebron COVID19 prospective cohort study. medRxiv. 2020, http://dx.doi.org/10.1101/2020.05.07.20094599.
44. Perrone F, Piccirillo MC, Ascierto PA, Salvarani C, Parrella R, Marata AM, et al. Tocilizumab for patients with COVID-19 pneumonia. The TOCIVID-19 phase 2 trial. medRxiv. 2020, http://dx.doi.org/10.1101/2020.06.01.20119149.
45. Garcia EM, Caballero VR, Albiach L, Aguero D, Ambrosioni J, Bodro M, et al. Tocilizumab is associated with reduction of the risk of ICU admission and mortality in patients with SARS-CoV-2 infection. medRxiv. 2020, http://dx.doi.org/10.1101/2020.06.05.20113738.
46. Sheppard M, Laskou F, Stapleton PP, Hadavi S, Dasgupta B. Tocilizumab (actemra). Hum Vaccines Immunother. 2017;13:1972–88, http://dx.doi.org/10.1080/21645515.2017.1316909.
47. Nishimoto N, Mima T. Tocilizumab. In: Rheumatoid Arthritis. Elsevier Inc.; 2009, http://dx.doi.org/10.1016/B978-032305475-1.50050-1.
48. Zhang S, Li L, Shen A, Chen Y, Qi Z. Rational use of tocilizumab in the treatment of novel coronavirus pneumonia. Clin Drug Investig. 2020;40:511–8, http://dx.doi.org/10.1007/s40261-020-00917-3.
49. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020, http://dx.doi.org/10.1016/j.ebiom.2020.102763.
50. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506, http://dx.doi.org/10.1016/S0140-6736(20)30183-5.
51. Van Der Poll T, Levi M, Hack CE, Cate H, van Deventer SJH, Eerenberg AJM, et al. Elimination of interleukin 6 attenuates coagulation activation in experimental endotoxemia in chimpanzees. J Exp Med. 1994;179:1253–9, http://dx.doi.org/10.1084/jem.179.4.1253.
52. Stouthard JML, Levi M, Hack CE, Veenhof CHN, Romijn HA, Sauerwein HP, et al. Interleukin-6 stimulates coagulation, not fibrinolysis, in humans. Thromb Haemost. 1996;76:738–42, http://dx.doi.org/10.1055/s-0038-1650653.
53. Levi M. Tocilizumab for severe COVID-19: a promising intervention affecting inflammation and coagulation. Eur J Intern Med. 2020;76:21–2, http://dx.doi.org/10.1016/j.ejim.2020.05.018.
54. Cecconi M, Forni G, Mantovani A. Ten things we learned about COVID-19. Intensive Care Med. 2020, http://dx.doi.org/10.1007/s00134-020-06140-0.
55. Shankar-Hari M, Calfee CS. Lack of clinical benefit of interferon β-1a among patients with severe acute respiratory distress syndrome: time to overhaul drug trials in ARDS? JAMA - J Am Med Assoc. 2020;323:713–5, http://dx.doi.org/10.1001/jama.2019.22524.
56. Abraham E, Anzueto A, Gutierrez G, Tessler S, San Pedro G, Wunderink R, et al. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. Lancet. 1998;351:929–33, http://dx.doi.org/10.1016/S0140-6736(05)60602-2.
57. EMA. RoActemra - Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_en.pdf. [Accessed June 8, 2020].
58. Fda. ACTEMRA - HIGHLIGHTS OF PRESCRIBING INFORMATION. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf. [Accessed June 8, 2020].
59. Sepriano A, Kerschbaumer A, Smolen JS, van der Heijde D, Dougados M, van Vollenhoven R, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2020;79:760–70, http://dx.doi.org/10.1136/annrheumdis-2019-216653.
60. AIFA. COVID-19: Studio randomizzato italiano, nessun beneficio dal tocilizumab. https://www.aifa.gov.it/web/guest/-/covid-19-studio-randomizzato-italiano-nessun-beneficio-dal-tocilizumab. [Accessed June 18, 2020].
61. National Health Commission & State Administration, Traditional Chinese Medicine. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia. 2020. https://www.chinalawtranslate.com/wp-content/uploads/2020/03/Who-translation.pdf. [Accessed June 29, 2020].
62. SIMIT. Vademecum per la cura delle persone con malattia da COVID-19. https://www.simit.org/news/11-vademecum-per-la-cura-delle-persone-con-malattia-da-covid-19. Published 2020. [Accessed June 29, 2020].
63. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020, http://dx.doi.org/10.1007/s00134-020-06022-5.
64. NIH. Immune-Based Therapy | Coronavirus Disease COVID-19. https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/. [Accessed June 8, 2020].
65. WHO. Clinical Management of COVID-19 - Interim guidance 27 May 2020. 2020. https://www.who.int/publications-detail/clinical-management-of-covid-19. [Accessed June 29, 2020.
66. IDSA. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. 2020. [Accessed May 26, 2020].

Pulmonology 2021;**27(1)**:67–83

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

COVID-19 effects on tuberculosis care in Sierra Leone

After the first description in China, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) spread all over the world, reaching also the poorest countries of sub-Saharan Africa. Despite several authors and organizations raising issues and fears about the potentially devastating effects of SARS-CoV-2 in Africa and unpreparedness of African Health Systems to face Coronavirus Disease 2019 (COVID-19),[1] the real effects in this continent are far from being established.

COVID-19 is posing several challenges in the richest areas of the world which were unable to deal promptly with shortages of intensive care units, health personnel and personal protective equipment[2] leading to hundreds of thousands of severe outcome and deaths.

Whereas, in Africa, while COVID-19 cases and deaths are increasing, other major killers are still there. Tuberculosis (TB) is still the number-one infectious disease killer in the world and containing it during the COVID-19 pandemic is seriously at risk.

Appropriate TB management comprises prompt diagnosis of active TB cases, identification of people exposed and infected people, access to treatment and drug-adherence control. With the rising number of multidrug-resistant TB (MDR), direct observed therapy (DOT) is pivotal to ensuring that people regularly take medications. For appropriate care, a close link between the health centres and patients is needed. However, after the arrival of COVID-19 in Africa, this connection is at risk.

Several African countries are declaring lockdown to prevent contagions. In poor settings, quarantine has heavy economic implications and people are losing their daily income. For most families, this generates difficulties in paying transport fees to reach health centres. In Sierra Leone, the government allowed health facilities to provide patients with enough TB medication for weeks, aiming to reduce movement and flatten the COVID-19 curve. This may lead to low treatment adherence with potential consequences for TB cure rates, development of drug resistant TB and spread in the community.

Importantly, many sub-Saharan peripheral health centres are experiencing a reduction in clinical visits.[3] Matilda Yamba, a community health worker from Bureh Town, Sierra Leone, declared that ''people do not seek medical care for two reasons: they are either scared of getting SARS-CoV-2 infection in the health facilities, or are scared of being diagnosed with it''. Africa knows well the social stigma associated with infectious diseases, HIV and TB being historical models, and it is not unexpected to be scared of being recognized as COVID-19 patients and blamed for spreading the virus in the community.[4]

To understand the impact of COVID-19 on TB care, we evaluated the gross numbers of patients assessed for presumptive TB in the Community Health Post of Tombo, a village of Western Rural Area in Sierra Leone, with a government recognized TB outpatient unit, referral for an area of about 5000 people. Presumptive TB patients undergo sputum smear for Acid Fast Bacilli (AFB) and receive free TB-medications if the diagnosis is confirmed. We collected the number of patients tested and confirmed AFB-positive during the first 4 months of the year 2020 (January, February, March, April), and compared it with the cases reported in 2018 and 2019. The study was approved by the authorities for the TB unit of the local health centre (J.S.B.).

In Sierra Leone, the first COVID-19 presumptive cases were documented at the end of March 2020 and lockdown declared in April 2020. On May 6th, 225 COVID-19 cases and 14 deaths were confirmed by the government in Sierra Leone.

As shown in Fig. 1, on April 2020, a significant drop of confirmed TB cases was documented. Also, the number of TB presumptive cases, that might have other respiratory diseases, gradually decreased in March and April 2020. Similarly, no DOTs were administered in April 2020. No cases of COVID-19 and TB co-infections have been detected. Although our study has several limitations, due to its retrospective and descriptive nature and reference to a specific epidemiological area, this is the first description of an indirect impact of COVID-19 on TB care in a low-resource high-TB burden setting. Conversely, it is difficult to obtain data about TB in children during this pandemic. In poor, peripheral settings, paediatric TB is diagnosed on a clinical basis according to medical history and clinical assessment, since children are not able to expectorate and gastric lavages cannot be performed. For this reason, paediatric TB has been historically considered a neglected condition, since it is difficult to obtain microbiological identification of the disease and children, who usually have a paucibacillary illness, do

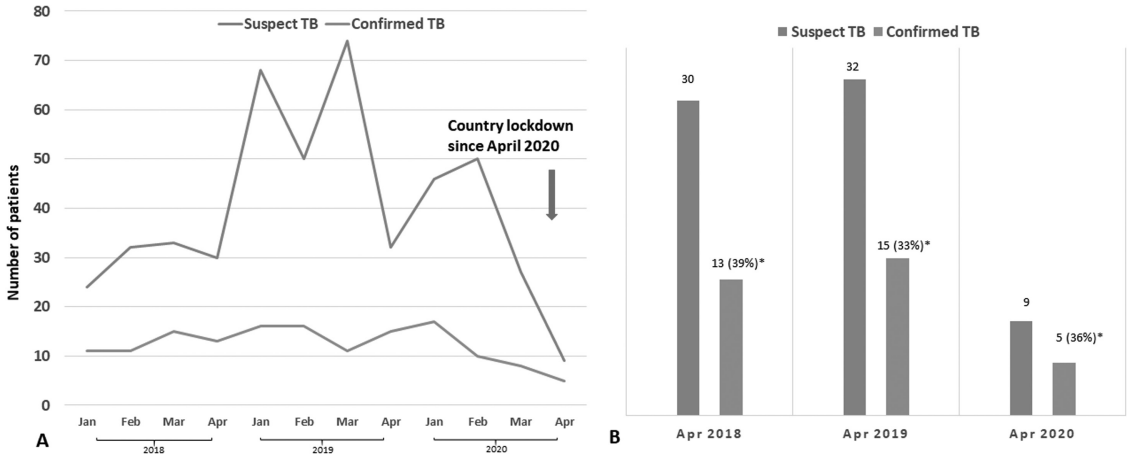


Figure 1 Number of presumptive TB and confirmed TB cases in Tombo Health Centre, Sierra Leone. While a stable trend in TB diagnosis during the first months of 2018, 2019 and 2020 was observed (a), a significant drop was reported in April 2020 (b), after lockdown was declared by the government. * Proportion of TB cases over the total patients enrolled as ''presumptive TB patients'' coming to the outpatient TB unit of Tombo, Western Rural Area, Sierra Leone.

not significantly spread the infection. Since in poor settings they are usually evaluated after an adult member is diagnosed with active TB, now, with the COVID-19 pandemic and ongoing restrictive measures, child TB is disappearing. Paradoxically, now, children with TB may be at risk of being forgotten, not only neglected.

In this context, the International Community is called on to provide massive support to poor countries. Before COVID-19, African health systems were struggling to provide appropriate care, although improvements have been made since the last Ebola outbreak. Now, Africa is not only having to face the historical enemies, but has to deal with both the direct costs of COVID-19 and the indirect consequences of COVID-19. While rich countries are now gaining more experience about the direct effects of COVID-19 on human health, the consequences on the major killers in poor countries are far from being understood. Here, endemic diseases that can present with symptoms similar to COVID-19 (TB, measles, pneumococcal disease and others), must not be forgotten.[5] Importantly, in these settings where advanced forms of TB frequently occur and are caused by drug-resistant strains of *M. tuberculosis*, higher mortality rates due to both TB and COVID-19 can be expected in young individuals.[6,7] Africa needs support not only to strengthen promptness of response to COVID-19 pandemic in hospitals and health centres but also appropriate communication strategies, basic instruments for telemedicine, economic support for patients and healthcare workers, are all needed tools to guarantee TB care. Otherwise, all results achieved in recent years in the fight against TB, may be lost.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgments

Delia Goletti is a professor at Saint Camillus International University of Health and Medical Sciences in Rome.

We are grateful to all our colleagues that supported the development of local health services and training of community health workers in the Western Rural Area of Sierra Leone and, in particular, Ismail Jaber, Matilda Yamba, Prince Williams, Memunatu N. Kallon, Nee Turay, Pietro Sollena, Francesca Vassallo, Vittorio Sabatino, Mara Caramia, Gregory Leeb, Valeria Pansini, Filippo Bruno, Andrea Deidda, Arianna Cafarotti, Davide Guglielmi, Maria Giulia Conti, Jessica Balerna, Francesco Madeddu, Mattia Belardinelli, Daniele Barbuto, Luigi Torricelli, Rachel Mannings, Surf4Children Onlus.

The study was partially supported by the Italian Ministry of Health, Ricerca Corrente Linea 1 and 3.

References

1. Martinez-Alvarez M, Jarde A, Usuf E, et al. COVID-19 pandemic in west Africa. Lancet Glob Health. 2020;8:e631–2.
2. The Lancet. COVID-19: too little, too late? Lancet. 2020;395:755.
3. Adepoju P. Tuberculosis and HIV responses threatened by COVID-19. Lancet HIV. 2020.
4. Alagna R, Besozzi G, Codecasa LR, et al. Celebrating world tuberculosis day at the time of COVID-19. Eur Respir J. 2020;55.
5. Ong CWM, Goletti D. Impact of the global COVID-19 outbreak on the management of other communicable diseases. Int J Tuberc Lung Dis. 2020;24.
6. Motta I, Centis R, D'Ambrosio L, et al. Tuberculosis, COVID-19 and migrants: preliminary analysis of deaths occurring in 69 patients from two cohorts. Pulmonology. 2020, http://dx.doi.org/10.1016/j.pulmoe.2020.05.002.

7. Tadolini M, Codecasa LR, García-García JM, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. Eur Respir J. 2020, http://dx.doi.org/10.1183/13993003.01398-2020 [in press].

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

[a] *Department of Woman and Child Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy*
[b] *Istituto di Microbiologia, Università Cattolica del Sacro Cuore, Rome, Italy*
[c] *Institute of Neurology, Fondazione Policlinico Universitario A. Gemelli IRCCS, 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, Rome, Italy*

[*] Corresponding author.
E-mail address: danilo.buonsenso@policlinicogemelli.it (D. Buonsenso).
Available online 6 June 2020

https://doi.org/10.1016/j.pulmoe.2020.05.013

Extracorporeal membranous oxygenation for a severe case of vaping associated lung injury

In the United States, cases of severe acute respiratory distress syndrome (ARDS), pneumonitis, lipoid pneumonia, and organizing pneumonia secondary to vaping have been rising since June 2019.[1] This syndrome is termed as e-cigarettes or vaping product use-associated lung injury (EVALI) by centers of disease control (CDC).[1] We report the case of a young female who was diagnosed with EVALI and required mechanical ventilation with extracorporeal membrane oxygenation (ECMO).

A 26-year old female with a history of asthma, depression, and substance abuse presented to the emergency department (ED) with two weeks of dyspnea on exertion and whitish productive cough. She had a history of smoking cigarettes and vaping tetrahydrocannabinol. The patient reported receiving a new tetrahydrocannabinol cartridge from a different supplier 2.5 weeks ago. Her oxygen saturation was 84% on room air with respiratory rate (RR) in the 30s and she had crackles in the lungs bilaterally. Initial labs were significant for leukocytosis (WBC: 16.7 k/mm^3) and EKG was normal. Chest X-ray showed bilateral opacities, and CTA chest revealed bilateral ground-glass opacities and no pulmonary embolism (Fig. 1). Echocardiography showed normal ejection fraction. Broad-spectrum antibiotics and furosemide were started. ABG on 12 L of oxygen showed pH: 7.40, PCO_2: 39, bicarbonate: 23.8, and PO_2: 93 with a persistent RR of 30–35. She was intubated for respiratory failure. Bronchoscopy was performed, and bronchoalveolar lavage was sent for analysis and culture. High dose methylprednisolone was started after no bacterial growth was seen on initial sputum culture. While on mechanical ventilation, she continued to be hypoxic showing features of severe ARDS ($PaO_2/FiO_2 = 68$), following which she was placed in prone position. After 20 min of pronation, she was on a ventilator setting of tidal volume: 6 mL/kg, FIO_2: 100%, PEEP: 15 cm H_2O, and driving pressure of 15 cm H_2O. ABG showed pH: 7.33, PCO_2: 46, bicarbonate: 26, PO_2: 69. After 4 h of pronation, the patient was placed in a supine position. Given the severity of respiratory distress, a veno-venous ECMO (31 French ProtekDuo, flow: 4.4 L/m, sweep: 2) was cannulated through the right internal jugular vein with the plan to adjust settings based on frequent ABGs. She was then placed on an ultraprotective ventilator setting (tidal volume: 250 mL, PEEP: 10 cm H_2O, RR: 10 with FIO_2: 40%).

Results from cultures remained negative. Further tests were negative for fungus, influenza, atypical organisms, HIV, and other rheumatological diseases. After 3 days of methylprednisolone 500 mg IV, she was switched to prednisone 60 mg IV twice a day. After she showed clinical and radiological signs of improvement (Fig. 2), ECMO was weaned off on the 8th day. She was extubated on the 10th day. Subsequently, she got out of the ICU on the 15th day and was discharged on the 20th day of her hospital stay.

The management of EVALI comprises of respiratory supportive care, antibiotics, and corticosteroids. The initiation of antibiotics on presentation is important as pneumonia is a common cause of respiratory failure. Once no evidence of infection has been identified, the de-escalation of antibiotics should be considered. Corticosteroids have known to show excellent clinical results. However, caution must be applied while starting corticosteroid if there is a strong suspicion of infection. At times, if the presentation is less severe, corticosteroid could be held until infectious causes are ruled out. Although up to 35% of patients may require intubation and mechanical ventilation, the overall prognosis is usually good, and improvement is seen within weeks of starting corticosteroids.[2]

Three criteria define EVALI: pulmonary infiltrates in imaging, use of electronic cigarettes within the previous 90 days, and the absence of other possible infectious, cardiac, neoplastic, or rheumatological causes.[2] Our patient met all three. Escalation of care with intubation and mechanical ventilation was performed because of severe ARDS. Due to the worsening hypoxia, early ECMO was initiated with a protective ventilation strategy to facilitate faster recovery of the lung injury. In a case series by Maddock et al., one out of six patients required ECMO for seven days.[3] In a case report, Baxter et al. report that early initiation of ECMO for a young male helped improve the condition within 72 h.[4] In another case series by Choe et al., one out of four patients required ECMO for 14 days for refractory hypoxia.[5]

This case highlights the complicated course and the devastating effects of EVALI. In addition to expanding the scant literature, to the best of the authors' knowledge, this is

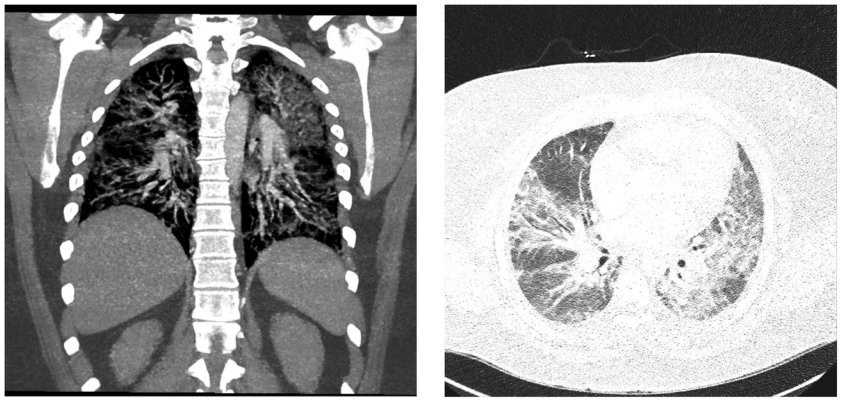


Figure 1 Chest CT scan on presentation showing bilateral infiltrates. Left: coronal view; right: axial view.

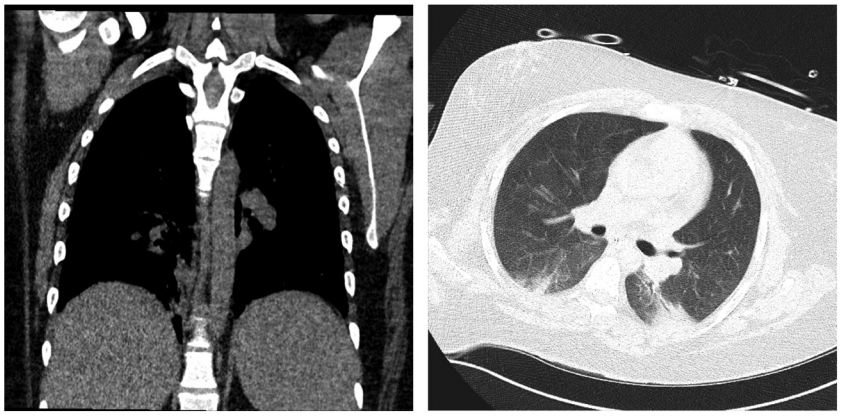


Figure 2 Chest CT scan follow up showing resolution of the bibasilar infiltrates. Left: coronal view; right: axial view.

also the first case where ECMO was performed for EVALI on a female patient. Early initiation of ECMO with lung-protective ventilation strategies could be considered as a potential management strategy for selected individuals suffering from severe ARDS due to EVALI, and this case serves as a data point for such situations.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Christiani DC. Vaping-induced lung injury. N Engl J Med. 2019;6, http://dx.doi.org/10.1056/NEJMe1912032.
2. Kalininskiy A, Bach CT, Nacca NE, Ginsberg G, Marraffa J, Navarette KA, et al. E-cigarette, or vaping, product use associated lung injury (EVALI): case series and diagnostic approach. Lancet Respir Med. 2019;7:1017–26, http://dx.doi.org/10.1016/S2213-2600(19)30415-1.
3. Maddock SD, Cirulis MM, Callahan SJ, Keenan LM, Pirozzi CS, Raman SM, et al. Pulmonary lipid-laden macrophages and vaping. N Engl J Med. 2019;381:1488–9, http://dx.doi.org/10.1056/NEJMc1912038.
4. Baxter RD, Vaquera K, George TJ. Extracorporeal membrane oxygenation support for vaping-induced acute lung injury. Ann Thorac Surg. 2020, http://dx.doi.org/10.1016/j.athoracsur.2020.01.028.
5. Choe J, Chen P, Falk JA, Nguyen L, Ng D, Parimon T, et al. A case series of vaping-associated lung injury requiring mechanical ventilation. Crit Care Explor. 2020;2, http://dx.doi.org/10.1097/CCE.0000000000000079.

M.R. Regmi[a,*], N. Tandan[a], P. Parajuli[a], R. Maini[a], O.E. Lara Garcia[a], P. Jagtap[c], A. Kulkarni[b]

[a] *Department of Internal Medicine, Southern Illinois University School of Medicine, Springfield, IL, United States*
[b] *Division of Cardiology Medicine, Southern Illinois University School of Medicine, Springfield, IL, United States*
[c] *Division of Critical Care Medicine, HSHS St. John's Hospital, Springfield, IL, United States*

* Corresponding author.
E-mail addresses: mregmi81@siumed.edu, manjariregmi08.mr@gmail.com (M.R. Regmi).

https://doi.org/10.1016/j.pulmoe.2020.05.008

The ''Big Five'' Lung Diseases in CoViD-19 Pandemic – a Google Trends analysis

To the Editor:

Google Trends (GT), a popular and freely accessible tool in big data analytics, has been widely used to study perceptions in various medical topics. The monitoring of online queries using GT may provide insight into human behaviour in the CoViD-19 pandemic, as this field is continuously growing and uses data that could not have been accessed otherwise.[1]

In December 2019, a novel coronavirus was identified in Wuhan City, Hubei Province, China and later the disease was named coronavirus disease 2019 (CoViD-19).[2] On March 11, 2020, the World Health Organization (WHO) officially announced that CoViD-19 had reached global pandemic status.[3] In the first months of the pandemic, not only the research community, but also the global population, urged for more information about CoViD-19.

The Forum of the International Respiratory Society identified, in 2017, five major lung diseases, the ''big five'', which include asthma, chronic obstructive pulmonary disease (COPD), acute lower respiratory tract infections, lung cancer and tuberculosis. These diseases are among the most common causes of severe illness and death worldwide.[4]

To identify a possible increase in online interest about lung diseases in the first months of the CoViD-19 pandemic, we conducted a GT worldwide search of five topics measuring the Relative Search Volume (RSV) over time. GT topics are a group of terms that share the same concept in any language. RSV represents search interest relative to the highest point on the chart for the given region and time, but doesn't convey absolute search volume.

Our search included five GT topics: ''Asthma (Disease)''; ''Chronic Obstructive Pulmonary Disease (Disease)'', ''Pneumonia (Medical condition)'', ''Lung Cancer (Topic)'' and ''Tuberculosis (Disease)''. We conducted a visual analysis of the worldwide RSV over the past 5 years (May 2015 till April 2020) (Fig. 1a). In addition, we compared four major European countries RSV-timelines (Spain, Italy, United Kingdom and France) in the past 5 years (May 2015 till April 2020) (Fig. 1b–e).

We uncovered a worldwide peak in RSV-timelines of Pneumonia, Asthma, COPD and Tuberculosis in the first months of the CoViD-19 pandemic (Fig. 1a). Comparing the RSV-timelines from different European countries we perceive peaks with different magnitudes for the four GT topics above and a flat or downward RSV-timeline of Lung Cancer in this pandemic (Fig. 1b–e).

To measure the possible variation in worldwide RSV we compared the median-RSV in March-April 2019 with median-RSV in March-April 2020 of the five GT topics separately. Pneumonia, Asthma, COPD and Tuberculosis median-RSV had a 244%, 50%, 16% and 14% increase, respectively. Lung cancer had a 21% decrease in median-RSV. Using Wilcoxon-test (IBM SPSS Statistics Version 25.0. Armonk, NY: IBM Corp), every score between median-RSV of March-April 2019 and 2020, was statistically significant ($p < 0.001$).

The GT topic that had the highest percentage increase of worldwide median-RSV was Pneumonia, with a two peaks RSV-timeline: first peak in January-February 2020 and a second peak in March-April 2020. These peaks may be explained by the fact that pneumonia is a major and already well-known phenotype of CoViD-19.[5] Asthma worldwide RSV-timeline revealed a visual peak in March-April 2020, with a substantial gain in the median-RSV compared to the same period in 2019. Bousquet et al.[6] stated that in most countries searches for asthma are made during local thunderstorm-induced asthma outbreaks. Our findings suggest also a worldwide online peak search after outbreaks of other diseases masquerading asthma exacerbations, such as CoViD-19, which was particularly relevant in the UK and in France, as asthma surpassed the ''pneumonia'' searches (Fig. 1d, e). COPD and Tuberculosis topics showed less relevant visual peaks, but still a gain in the median-RSV compared to the same period in 2019. Lung cancer showed no visual peak, and less median-RSV in the first months of the CoViD-19 pandemic compared with the same months of 2019. We note this decrease in online search interest about lung cancer, as opposed to other lung diseases, with concern as cancer mortality and morbidity might be on the rise because of late diagnosis in CoVid-19 pandemic.[7]

In conclusion, GTs of the ''big five'' lung diseases, except lung cancer, have increased during CoViD-19 epidemics. It is clear from the 5-year trends that these peaks are not related to the diseases but to a variation in alertness or a misinterpretation of respiratory symptoms. Besides every recent clinical guidelines and efforts by hospitals to admit, treat and follow patients in the pandemic, a possible late diagnosis and/or treatment of lung diseases, especially cancer,[7] is still a major concern. We believe that this pandemic is a unique opportunity to increase awareness in the global population about lung-health and, lung diseases other than CoViD-19 which remain important causes of severe illness and death worldwide.

Conflict of interest

The authors have no conflicts of interest to declare.

Support

No funding was received in the publication of this letter.

Author's contributions

MTB and MMA participated in study design and study conception. MTB performed data analysis and drafted the manuscript. All authors provided critical review of the manuscript and approved the final draft for publication.

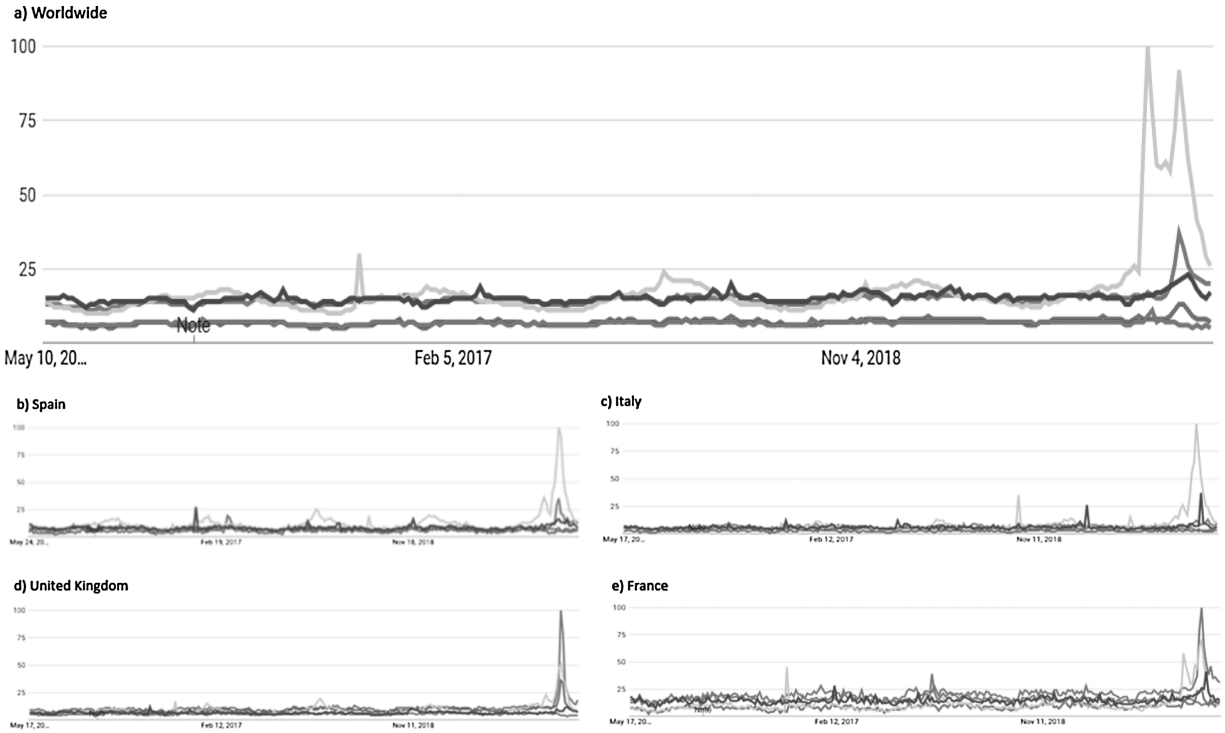


Figure 1 Relative search volume over time in the past 5 years (May 2015 till April 2020): Pneumonia (yellow line), Asthma (blue line), COPD (red line), Tuberculosis (purple line) and Lung cancer (green line). The highest interest on a search query is quantified as 100 relative search volume (RSV), decreasing to 0 RSV, indicating no interest. - Data source: Google Trends (https://www.google.com/trends).

References

1. Springer S, Menzel LM, Zieger M. Google Trends provides a tool to monitor population concerns and information needs during COVID-19 pandemic. Brain Behav Immun. 2020;(April), http://dx.doi.org/10.1016/j.bbi.2020.04.073. S0889-1591(20)30696-6.
2. World Health Organization, WHO Director - General's Remarks at the Media Briefing on 2019-nCoV on 11 February 2020; 2020 https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020
3. WHO Novel coronavirus (2019-nCoV) situation report - 51 (11 March 2020). Geneva: World Health Organization; 2020 https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf
4. Forum of International Respiratory Societies. The Global Impact of Respiratory Disease. 2nd edition Sheffield, European Respiratory Society; 2017.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506, http://dx.doi.org/10.1016/S0140-6736(20)30183-5.
6. Bousquet J, O'Hehir RE, Anto JM, et al. Assessment of thunderstorm-induced asthma using Google Trends. J Allergy Clin Immunol. 2017;140(3):891–3, http://dx.doi.org/10.1016/j.jaci.2017.04.042, e7.
7. Kutikov A, Weinberg DS, Edelman MJ, Horwitz EM, Uzzo RG, Fisher RI. A war on two fronts: cancer care in the time of COVID-19 [published online ahead of print, 2020 Mar 27]. Ann Intern Med. 2020, http://dx.doi.org/10.7326/M20-1133. M20–1133.

M.T. Barbosa[a,b,*], M. Morais-Almeida[b], C.S. Sousa[b,c], J. Bousquet[d]

[a] *Pulmonology Department, Hospital Centre of Barreiro-Montijo, Barreiro, Portugal*
[b] *Allergy Centre, CUF Descobertas Hospital, Lisboa, Portugal*
[c] *Pulmonology Department, Central Hospital of Funchal, Portugal*
[d] *Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Comprehensive Allergy Center, Department of Dermatology and Allergy, Berlin, Germany and MACVIA-France, Montpellier, France*

* Corresponding author at: Pulmonology Department, Hospitalar Centre of Barreiro-Montijo, Avenida Movimento das Forças Armadas, 2834-003 Barreiro, Portugal.
E-mail address: migueltrbarbosa@gmail.com (M.T. Barbosa).

28 May 2020

https://doi.org/10.1016/j.pulmoe.2020.06.008

Total volume/week of physical activity: an underused variable of physical activity in daily life in patients with copd and its association with exercise capacity

Subjects with chronic obstructive pulmonary disease (COPD) may be characterized by muscle dysfunction and symptoms such as dyspnea and fatigue, which may lead to reduced physical activity (PA) levels.[1]

In COPD, functional exercise capacity as measured by the 6-minute walking test (6MWT) is known to be significantly associated with different PA variables such as walking time/day,[2] number of steps/day and time spent/day in different PA intensities, mainly moderate-to-vigorous (MVPA).[3] However, a large systematic analysis concluded that the quality of the evidence for these associations is still relatively low.[4] Furthermore, Mesquita et al.[5] corroborated these findings by showing that changes in the 6MWT are very weakly related to changes in time spent/day in different PA intensities (sedentary: $r = -0.26$, light: $r = 0.25$ and moderate-to-vigorous [MVPA]: $r = 0.24$).

Total volume is a composite variable that corresponds to the product of duration versus intensity of a given effort. It is often used in the context of exercise training, including in patients with COPD.[6] However, it is rarely considered in the context of the total volume of PA in daily life (PADL), especially in the literature of patients with COPD. One can reach the same total PA volume in a certain period through many combinations of time spent in different intensities of PADL, i.e., sedentary, light and MVPA. Moreover, the association of the 6MWT with total PA volume/week has not yet been investigated. Therefore, the aim of this study was to investigate the independent association of functional exercise capacity (assessed by the 6MWT) with total PA volume/week in patients with COPD, as well as to compare this association with those concerning 6MWT and time spent/day in different PA intensities.

A retrospective study was conducted comprising baseline data from subjects with COPD assessed for admission in a pulmonary rehabilitation program performed at the University Hospital of Londrina, Brazil. The present sample concerns the combination of patients from a previously published study[7] and an ongoing study (ClinicalTrials.gov number, NCT03127878). Both studies were approved by the institutional Research Ethics Committee and all participants signed an informed consent term prior to inclusion. Data collection occurred from 2010 to 2019, and the initial assessments, inclusion and exclusion criteria from the two abovementioned studies were similar. Inclusion criteria were: diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1]; absence of any regular physical training in the preceding year; clinical stability defined as absence of exacerbations within the last month; and absence of severe comorbidities that could interfere with the assessment protocol (e.g., orthopedic, rheumatological, neurological or cardiovascular). Concerning the analysis of the present study, individuals were excluded in cases of unavailable data from the 6MWT or incomplete data from the PADL assessment, i.e., not achieving the pre-established minimum wearing time for a valid day (see below).

Objective assessment of PADL was performed using a validated PA monitor (SenseWear® Armband, BodyMedia, USA).[8] Subjects were instructed to wear the monitor during daytime for 7 consecutive days. A valid day was considered as containing at least 8 h/day of wearing time, excluding sleep periods during the day.[9] Total energy spent during the week was defined as the ''total PA volume/week''. Time spent/day in PA performed at specific intensities (i.e., sedentary [<1.5 metabolic equivalents of task, METs], light [1.5–3 METs], and MVPA [>3 METs]) was also quantified, both in absolute values and adjusted as a percentage of the respective wearing time. Functional exercise capacity was assessed by the best of two 6MWT, performed according to international standards.[10]

Normality in data distribution was evaluated using the Shapiro–Wilk test and results were described as mean ± standard deviation or median [interquartile range 25–75%], accordingly. Correlations were evaluated by the Spearman's coefficient. Multiple regression model was performed to investigate the associations between 6MWT and total PA volume/week, with adjustments for sex, age and FEV_1 %predicted.

The statistical softwares used were SPSS 22.0 (IBM, USA) and GraphPad Prism 6.0 (GraphPad Software Inc., USA). Significance level was defined as $P < 0.05$.

Data from 125 subjects with COPD were screened but 33 of them were excluded due to incomplete assessments. Therefore, 92 subjects were analyzed (46 male; 66 ± 8 years; FEV_1 50 ± 16%predicted; 6MWT 472 ± 73 m; wearing time of the PA monitor 14.4 ± 1.5 h/day; mean ± SD). Median [interquartile range] of total PA volume/week was 1281[1089–1585] MET.min, whereas time spent/day in sedentarism, light activities and MVPA were 569[465–641], 254[147–338] and 32[12–72] min/day, respectively.

There was positive correlation between total PA volume/week and 6MWT ($r = 0.30$; $P = 0.004$). In the multiple regression analysis, total PA volume/week explained 26% of the variation in the 6MWT (independently of sex, age and FEV_1%pred) (Table 1). Time spent/day in each specific intensity (sedentary, light and MVPA) both in absolute values and in percentage of the wearing time, was more weakly correlated with the 6MWT ($0.06 < r < 0.27$), corroborating the previous literature.[4] Furthermore, total PA volume/week was strongly correlated with time spent/day in sedentarism, light activities and MVPA ($r = -0.59$, $r = 0.84$ and $r = 0.79$, respectively; $P < 0.0001$ for all).

This was the first study to show a significant and independent association between functional exercise capacity (i.e., 6MWT) and PADL assessed from a different perspective in COPD: total PA volume/week. This association is welcome in the sense that improvements in exercise capacity may be necessary to make patients more active and less sedentary.[5] Moreover, it was highly correlated with traditional PADL outcomes (time spent/day at different PA intensities). The ''PA volume/week'' perspective reflects

Table 1 Summary of the multiple regression analysis.

Variable	*B*	SE_B	β	95 %CI (LB; UP)
6MWT (m)				
Constant	411.647	65.842		(280.774; 542.510)
Total PA volume/week (MET.min)	0.059	0.021	0.260*	(0.018; 0.100)
Sex	45.593	13.540	0.312*	(18.679; 72.506)
Age (years)	−1.727	0.850	−0.193*	(-3.417; −0.037)
FEV_1 (%pred)	1.478	0.420	0.322*	(0.644; 2.313)

* $P < 0.05$; *B* = unstandardized regression coefficient; SE_B = standard error of the coefficient; β = standardized coefficient; 95% CI = 95% Confidence Interval; LB = Lower Bound; UB = Upper Bound; 6MWT = 6-minute walking test; PA = physical activity; FEV_1 = forced expiratory volume in the first second.

PA guidelines' recommendations and incorporates different intensities of PA into a single and comprehensive outcome. Therefore, this preliminary report suggests that this is a reasonable and promising approach, since increasing total PA volume/week (regardless of whether this increase occurred at any intensity) may be a more realistic way of achieving PADL improvements in severely debilitated patients. Further investigation of its measurement properties (i.e., sensitivity to changes due to interventions such as pulmonary rehabilitation) may advance the understanding of its usefulness. In conclusion, total PA volume/week in daily life is significantly and independently associated with functional exercise capacity in patients with COPD.

Funding information

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. However, all authors were supported by individual scholarships or grants from Fundação Araucária, CAPES, CNPq or FUNADESP, Brazil.

Conflict of interest

The authors have no conflict of interest to disclose.

Acknowledgments

We acknowledge the support of Fundação Araucária, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação Nacional de Desenvolvimento do Ensino Superior Particular (FUNADESP), Brazil. In addition, we are grateful to colleagues from the Laboratory of Research in Respiratory Physiotherapy for their contributions to this study.

References

1. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, 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(5), http://dx.doi.org/10.1183/13993003.00164-2019.
2. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;171(9):972–7, http://dx.doi.org/10.1164/rccm.200407-200855OC.
3. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. Eur Respir J. 2009;33(2):262–72, http://dx.doi.org/10.1183/09031936.00024608.
4. Gimeno-Santos E, Frei A, Steurer-Stey C, de Batlle J, Rabinovich RA, Raste Y, et al. Determinants and outcomes of physical activity in patients with COPD: a systematic review. Thorax. 2014;69(8):731–9, http://dx.doi.org/10.1136/thoraxjnl-2013-204763.
5. Mesquita R, Meijer K, Pitta F, Azcuna H, Goertz YMJ, Essers JMN, et al. Changes in physical activity and sedentary behaviour following pulmonary rehabilitation in patients with COPD. Respir Med. 2017;126:122–9, http://dx.doi.org/10.1016/j.rmed.2017.03.029.
6. Ward TJC, Plumptre CD, Dolmage TE, Jones AV, Trethewey R, Divall P, et al. Change in VO2peak in response to aerobic exercise training and the relationship with exercise prescription in people with COPD: a systematic review and meta-analysis. Chest. 2020, http://dx.doi.org/10.1016/j.chest.2020.01.053.10.1016/j.chest.2020.01.053.
7. Furlanetto KC, Donaria L, Schneider LP, Lopes JR, Ribeiro M, Fernandes KB, et al. Sedentary behavior is an independent predictor of mortality in subjects with COPD. Respir Care. 2017;62(5):579–87, http://dx.doi.org/10.4187/respcare.05306.
8. Patel SA, Benzo RP, Slivka WA, Sciurba FC. Activity monitoring and energy expenditure in COPD patients: a validation study. COPD. 2007;4(2):107–12, http://dx.doi.org/10.1080/15412550701246658.
9. Demeyer H, Burtin C, Van Remoortel H, Hornikx M, Langer D, Decramer M, et al. Standardizing the analysis of physical activity in patients with COPD following a pulmonary rehabilitation program. Chest. 2014;146(2):318–27, http://dx.doi.org/10.1378/chest.13-1968.
10. 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(6):1428–46, http://dx.doi.org/10.1183/09031936.00150314.

Lorena P. Schneider[a], Felipe V.C. Machado[b,c], Antenor Rodrigues[d], Raquel P. Hirata[a], Daniele C. Dala Pola[a], Mariana P. Bertoche[a], Letícia F. Belo[a], Ana Carolina dos Reis Andrello[a], Jéssica Fonseca[a], Leandro C. Mantoani[a], Karina C. Furlanetto[a,e], Fabio Pitta[a,*]

[a] *Laboratory of Research in Respiratory Physiotherapy (LFIP), Department of Physiotherapy, State University of Londrina (UEL) - Londrina, Brazil*
[b] *Department of Research and Education, CIRO+, Center of Expertise for Chronic Organ Failure, Horn, Netherlands*
[c] *NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, Maastricht, Netherlands*
[d] *Rehabilitation Aimed at Muscle Performance Laboratory – RAMP, Department of Physiotherapy, University of Toronto, Toronto, Canada*
[e] *Biological and Health Sciences Research Center, University Pitágoras UNOPAR, Londrina, Brazil*

[*] Corresponding author.
E-mail addresses: fabiopitta@uol.com.br, fabiopitta@uel.br (F. Pitta).

14 April 2020

https://doi.org/10.1016/j.pulmoe.2020.05.007

Rhodococcus equi infection as inaugural manifestation of idiopathic CD4$^+$ lymphopenia: A rare entity and a therapeutic challenge

Introduction

Rhodococcus equi (R. equi) is a facultative intracelular gram-positive coccobacillus which primarily causes zoonotic infection.[1,2] This bacteria is becoming an emerging opportunistic agent in humans.[3] As far as we know, we present the first case of *R. equi* infection in a patient with idiopathic T-CD4$^+$ lymphopenia (ICL), a rare condition defined by the repeated presence of a T-CD4$^+$ lymphocyte count <300 cells/mm^3 or less than 20% of total T cells without evidence of human immunodeficiency virus (HIV) infection or other condition that might lead to decreased T-CD4$^+$ counts.[4]

Case description

In April 2017, a 69-year-old never smoker male presented to the emergency department with cough, left pleuritic thoracalgia and fever during the previous month. He was a retired driver who owned a farm with several animals. Past medical history included hypothyroidism treated with levothyroxine and chronic hepatitis B under entecavir. He had undergone lower left lobectomy in 2004 for a pulmonary mass, but histology of the operative specimen suggested an infectious etiology and the patient received no further treatment or follow-up.

On admission, he had peripheral oxygen saturation of 97% on room air and decreased respiratory sounds in the left pulmonary field.

Blood test revealed white blood cells count of 10 030/μL (83.3% neutrophils and 7.5% lymphocytes) and C-reactive protein of 14.7 mg/dL. Chest X-ray revealed a pleural-based consolidation in the left pulmonary field (Fig. 1A) which was characterized by contrast-enhanced chest computed tomography (CT) showing a 67 × 41 × 24 mm mass on the periphery of the left upper lobe (LUL) with heterogeneous contrast uptake and hypodense areas suggestive of necrosis (Fig. 1B).

The diagnosis of necrotizing pneumonia was established and the patient was hospitalized. Urine was negative for pneumococcal and *Legionella* antigens. Blood cultures were collected. Intravenous amoxicillin/clavulanic acid and azithromycin were started. Bronchofibroscopy and bronchoalveolar lavage (BAL) were conducted without endobronchial lesions. *R. equi* was isolated in both blood cultures and BAL. Antimicrobial susceptibility test (AST) showed sensitivity to imipenem and levofloxacin and intermediate sensitivity to ceftriaxone and ciprofloxacin. Treatment was adjusted for a combination of rifampicin and levofloxacin. Although sensitivity to rifampicin could not be tested, it was included due to its intracellular action and because it is a first choice drug.[3,5] The patient underwent transthoracic aspiration biopsy of the LUL lesion that excluded malignancy and showed signs of *R. equi* infection, namely, histiocyte foci with granulomatous configuration, necrosis and coccoid elements in the macrophage cytoplasm. The diagnosis of necrotizing pneumonia by *R. equi* with hematogenous dissemination was established. Central nervous system, cardiac, abdominal and cutaneous involvement were excluded. HIV and human T-lymphotropic infections were ruled out. Further extensive work-up to detect any other immunodeficiency condition was made leading to the diagnosis of ICL with an initial T-CD4$^+$ lymphocyte count of 28 cells/μL.

The patient was discharged after two weeks of intravenous treatment with rifampicin and levofloxacin and instructed to continue oral antibiotic treatment at home.

After one month, blood cultures were negative and radiological improvement was documented with a significant reduction in the LUL mass. After six months of treatment, bronchofibroscopy revealed persistence of *R. equi* in BAL, albeit with significant reduction in the number of colonies.

In April 2018, nearly one year after starting treatment, the patient developed stridor. Rigid bronchoscopy showed obstruction of the lumen of the lower third of the trachea in about 50% due to a protruding lesion (Fig. 1C) in which endoscopic treatment was conducted. Tracheal lesion biopsy revealed chronic inflammation with intracellular bacteria, malakoplakia and no signs of malignancy. Relapse of *R. equi* infection was assumed based on these histopathological findings, but since microbiological isolation was not obtained it was not possible to determine AST. Other potential recurrence sites were investigated leading to the diagnosis of an asymptomatic small brain abscess in magnetic resonance without indication for surgical treatment (Fig. 1D). A new antibiotic regimen was started with ertapenem, gentamycin and linezolide according to the literature.[3,5] One-year treatment was proposed and a central line was placed allowing outpatient parenteral treatment.

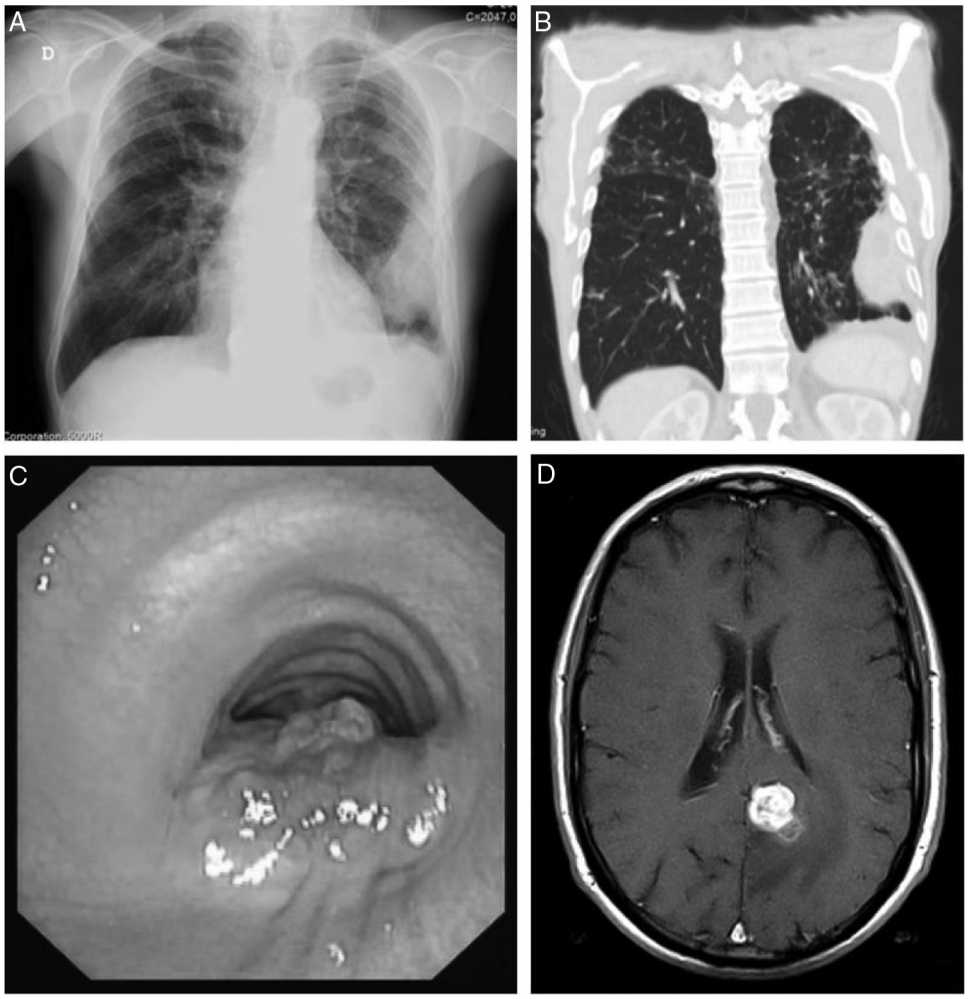


Figure 1 Sites of *Rhodococcus equi* infection. (A) Lung as a consolidation in the left pulmonary field on posteroanterior X-ray; (B) lung as a mass on the periphery of the left upper lobe on chest computed tomography; (C) trachea as a protruding lesion leading to obstruction of about 50% of the lumen; (D) brain as an abscess in the left parasagital occipitoparietal location on magnetic resonance.

On July 2018 linezolid was replaced by clarithromycin due to myelotoxicity and on January 2019 gentamycin was replaced by doxycycline due to nephrotoxicity and ototoxicity.

On July 2019 the patient was under ertapenem (14 months), clarithromycin (12 months) and doxycycline (7 months) with a favorable clinical response, resolution of cerebral abscess and no evidence of infection recurrence. These antibiotics were discontinued and it was decided to start prophylactic treatment with cotrimoxazole. So far the patient has been under surveillance and has not undergone any further treatment.

Discussion

Diagnostic approach of *R. equi* infection requires high clinical suspicion. Multidisciplinary discussion with microbiology expert is of vital importance since *R. equi* may be misdiagnosed as a contaminant or other bacteria. Due to its partial alcohol-acid resistance, *R. equi* infection may lead to misdiagnosis of mycobacteriosis.[2,6] *R. equi* infection may also mimic malignancy since pulmonary nodules or masses may be the radiological manifestation.[3] We believe that the lesion treated with lobectomy in 2004 could already correspond to infection by *R. equi*, since at that time the patient had contact with animals and signs of infection by a supposed atypical mycobacteria on the operative specimen were found. A radical treatment such surgery, the insidious course of the disease and continued contact with animals could explain why the infection only manifested again over ten years later.

R. equi infection prompted the investigation of an immunosuppressive condition leading to the inaugural diagnosis of ICL. T-CD4$^+$ cells, mainly Th1 cells, are involved in acquired resistance against facultative intracellular bacteria and increase bactericidal activity of macrophages by producing gamma interferon.[7] Th1 response seems to be crucial in pulmonary clearance of *R. equi*.[3] Recombinant human IL-7 may be a promising therapeutic intervention in ICL, leading to an increase in T-CD4$^+$ cells in both peripheral blood and tissues.[8] It may be questionable to assume the diagnosis of ICL since opportunistic infections may themselves lead to a depression of T-CD4$^+$ cell count.[9] Because low T-CD4$^+$ cell count persisted for over two years after the first analysis and no apparent cause had been determined, the diagnosis of ICL was made by exclusion.

Regarding treatment there are no consensus guidelines. Because acquired resistances are of concern, combination treatment is recommended with two or three antibiotics to which the agent is susceptible and at least one drug should have good intracellular activity.[3] First line drugs in humans include rifampicin, levofloxacin, erythromycin, imipenem, vancomycin and aminoglycosides.[5] For immunocompromised patients at least six months of antibiotic therapy are advised.[10] The placement of a central venous catheter allows intravenous treatment on an outpatient basis, reducing risks of nosocomial infection and costs. Side-effects from multi-drug treatment over such a long period of time may be a concern and should be closely monitored. Antibiotics withdrawal and substitution may be needed, making *R. equi* infection treatment a dynamic process.

Relapse may occur requiring close surveillance. We scheduled hospital medical consultation whenever the patient presented any complaint and every three months with hemogram, serum biochemistry, blood and sputum cultures and chest computed tomography. After relapse with a brain abscess, brain magnetic resonance was performed every three months until its resolution. No further bronchoscopy was performed following endoscopic treatment of tracheal pseudotumor as the patient refused further invasive examinations and remained asymptomatic.

Funding

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

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Prescott JF. *Rhodococcus equi*: an animal and human pathogen. Clin Microbiol Rev. 1991;4:20–34.
2. Meijer WG, Prescott JF. *Rhodococcus equi*. Vet Res. 2004;35:383–96.
3. Weinstock DM, Brown AE. *Rhodococcus equi*: an emerging pathogen. Clin Infect Dis. 2002;34:1379–85.
4. Unexplained CD4+ T-lymphocyte depletion, persons without evident HIV infection. MMWR. 1992;41:541–5.
5. Cisek AA, Rzewuska M, Witkowski L, Binek M. Antimicrobial resistance in *Rhodococcus equi*. Acta Biochim Pol. 2014;61:633–8.
6. Faria J, Simões J, Eiras EFA. Lung infection by *Rhodococcus equi* in HIV+ patient. A case report. Galicia Clín. 2013;74(Figura 3):2012–4.
7. Nordmann P, Ronco E, Nauciel C. Role of T-lymphocyte subsets in *Rhodococcus equi* infection. Infect Immun. 1992;60:2748–52.
8. Sheikh V, Porter BO, DerSimonian R, Kovacs SB, Thompson WL, Perez-Diez A, et al. Administration of interleukin-7 increases CD4 T cells in idiopathic CD4 lymphocytopenia. Blood. 2016;127:977–88.
9. Laurence J. T-cell subsets in health, infectious disease, and idiopathic CD4+ T lymphocytopenia. Ann Intern Med. 1993;119:55–62.
10. Gundelly P, Suzuki Y, Ribes JA, Thornton A. Differences in *Rhodococcus equi* infections based on immune status and antibiotic susceptibility of clinical isolates in a case series of 12 patients and cases in the literature. Biomed Res Int. 2016;2016:2737295.

A. Alves[a,*], E. Silva[a], T. Teixeira[b], C. Figueiredo[b], A. Lameirão[c], M. Vanzeller[a], C. Ribeiro[a]

[a] *Pulmonology Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, Rua Conceição Fernandes, 4434-502 Vila Nova de Gaia, Portugal*
[b] *Infectious Diseases Unit of Internal Medicine Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, Rua Conceição Fernandes, Portugal*
[c] *Department of Clinical Pathology, Centro Hospitalar de Vila Nova de Gaia/Espinho, Rua Conceição Fernandes, Portugal*

Corresponding author.
E-mail address: adelaide.pereira.alves@gmail.com (A. Alves).

5 January 2020 2 June 2020

https://doi.org/10.1016/j.pulmoe.2020.06.002

First case report in Latin America: Oral treatment of multidrug-resistant tuberculosis with delamanid and bedaquiline in combination with linezolid, moxifloxacin and clofazimine following a DRESS syndrome in a peruvian patient

Dear Editor,

The World Health Organization recommends the use of oral medications for the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB).[1–3] However, few countries have adopted these recommendations, either due to lack of medication or because of outdated local recommendations, as in the case of Peru.[4] The combination of some medications for the treatment of MDR TB such as delamanid (Dlm) with bedaquiline (Bdq) has been associated with a potential risk of cardiovascular symptoms such as prolongation of the QT interval corrected by Fridericia interval (QTcF).[5] Other medications that may enhance the prolongation of this interval are fluroquinolones, especially moxifloxacin (Mfx) and clofazimine (Cfz). We present a case of the simultaneous use of these medications in a patient who provided informed consent. There was no prolongation of the QTcF interval, and no sig-

nificant cardiac symptoms were observed throughout the entire treatment. (1) This patient was the first Peruvian to receive a completely oral combination of medications for the treatment of MDR tuberculosis.[8] (2) This was the first Peruvian case to receive a combination of 4 drugs (Mfx, Bdq, Cfz, and Dlm) considered potentially dangerous because of their sum effects on QTcF.

The patient was a single, nulliparous 23-year-old female with no pathological history living in Lima, Peru. At the beginning of August 2018, she presented hemoptysis and malaise and underwent a chest tomography on August 4th, 2018 showing exudative lesions in the right upper pulmonary lobe associated with a cavity of 3 cm in diameter. On August 14th, 2018, bronchofibroscopy was performed, obtaining a smear-positive in bronchial lavage. Tuberculosis treatment was initiated on August 15th with isoniazid, rifampicin, ethambutol and pyrazinamide.[4] The patient weighed 64 Kg at this time. This treatment was suspended on September 10th, 2018 following results of a Line Probe Assay study (Line ProbeAssay, Genotype® MTBDR Plus Version 2.0) of a sputum sample from August 16th, 2018 showing the presence of primary resistance to rifampicin and isoniazid (Gen KatG). On September 12th, 2018, a new empirical treatment was begun with ethambutol, pyrazinamide, kanamycin, levofloxacin, ethionamide and cycloserine.[4] On October 16, 2018, the patient presented cervical lymphadenopathy (>3 cm in diameter) and axillary lymphadenopathy, in addition to a temperature of 38.5 °C and rash in the following days. On October 23, 2018, eosinophils in peripheral blood were found to be elevated (7%) and proteins were also found in a urine sample. On October 28th, 2018, antituberculosis treatment was suspended. Eosinophils in peripheral blood continued to increase to a maximum of 21% on November 19th and then normalized on January 17th, 2019. Aspartate aminotransferase (AST) values increased to 78 IU/L on November 19th and normalized on December 3rd (AST: 26 IU/L). Alanine aminotransferase (ALT) values reached a maximum of 152 IU/L on November 10th and normalized on December 3rd (ALT: 34 IU/L). The patient was diagnosed with Drug Rash and Eosinophilia with Systemic Symptoms (DRESS) syndrome, with a score of 6 points in the Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) secondary to the treatment received.[6]

The patient was hospitalized on January 25th, 2019 with the aim of designing a new tuberculosis treatment schedule. She was stable with normal vital signs and with a weight of 65 kg. Laboratory tests showed a normal blood count, mild anemia, normal renal, hepatic and cardiac function (normal echocardiogram, electrocardiogram, QTcF, and cardiac enzymes), normal glycosylated hemoglobin, and negative viral hepatitis studies (HAV, HBV, HCV). Antibiotic susceptibility testing showed sensitivity to: ethambutol, pyrazinamide, streptomycin, kanamycin, capreomycin, ethionamide, cycloserine, ethionamide, para-aminosalicylic acid (PAS), levofloxacin and Mfx. The MDR TB unit decided to use new tuberculosis drugs that had not previously been combined in Peru, and the new antituberculosis treatment was begun on March 13th, 2019. This treatment consisted of linezolid (Lzd) at a dose of 600 mg/day, Mfx 400 mg/day, Cfz 200 mg/day, Bdq at a dose of 400 mg/day for the first 14 days and then 200 mg 3 times/week for 22 weeks for a total of 24 weeks, and Dlm at 100 mg bid for 24 weeks. After 24 weeks of treatment, Bdq and Dlm[2,7] were suspended. The patient continued to receive Lzd at the dose described. Cfz was decreased to 100 mg daily from the fourth month due to changes in skin color. The dose of Mfx was increased from 400 mg to 800 mg daily from week 24. Throughout this period laboratory tests were normal. There was no prolongation of the QTcF interval, and no significant cardiac symptoms were observed during the entire treatment. Fig. 1 shows the results of the periodic controls of the QTcF Interval in the timeline of this case. Direct sputum smear and cultures taken monthly were negative from the first month of treatment and throughout the treatment. The 2 tomographic controls taken at months 4 and 8 of treatment showed no lung lesions.

Several aspects are of note in the present case: (1) This patient was the first Peruvian and the first Latin American patient to receive a completely oral combination of medications for the treatment of MDR tuberculosis.[8] (2) This was the first Peruvian and the first Latin American case to receive a combination of 4 drugs (Mfx, Bdq, Cfz, and Dlm) considered potentially dangerous because of their sum effects on QTcF.[1] (3) According to the study of Borisov et al.[9] only 39 out of a total of 658 cases (6.1%) have received Bdq and Dlm consecutively or in combination, none being from Peru. In addition, of the 9 cases presenting severe cardiological events, none had received the same combination as our patient. (4) In Latin America, only Chile and Mexico together have reported 4 cases treated with the combination of Bdq and Dlm, with apparently none using Cfz and Mfx simultaneously.[9] The treatment was well tolerated by our patient, with no adverse cardiovascular events like those reported in other series of patients using this combination.[5,10] Cfz produced slight pigmentation of the skin that did not bother the patient. Lastly, clinical response was excellent with notable radiological improvement.

This drug combination was demonstrated to be safe and effective and well tolerated. None of the frequent adverse reactions that occur with the use of kanamycin injectable medications that are still used in Peru for the treatment of MDR tuberculosis[4] were observed. Moreover, this treatment is highly effective since the sensitivity of bacteria to Bdq, Dlm and Lzd is high.[11] The patient will be followed every 3 months for 2 years to record possible development of relapse. The results of this case are important for demonstrating that oral treatment of MDR tuberculosis is possible and can be carried out safely with suitable monthly clinical controls and periodic QTcF controls.

Statement of ethics

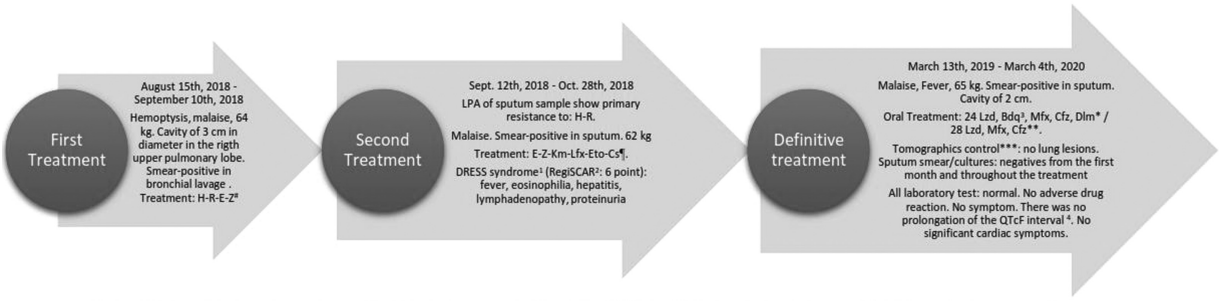
The authors have no ethical conflicts to disclose.

Funding

The authors have not received any funding specifically for this correspondence.

Author contributions

All authors contributed equally to this correspondence.



H: isoniazid, R: rifampicin, E: etambutol, Z: pyrazinamide. ¶ Kanamycin (Km), Levofloxacin (Lfx), Ethionamide (Eto), Cycloserine (Cs). 1 Drug Rash and Eosinophilia with Systemic Symptoms Syndrome.
2 Registry of Severe Cutaneous Adverse Reaction. * Lzd: linezolid (600 mg qd), Mfx: moxifloxacin (400 mg qd), Cfz: clofazimine (200 mg qd), Dlm: delamanid 100 mg bid) for 24 weeks
** Lzd (600 mg qd), Mfx (800 mg qd), Cfz (100 mg qd) for 28 weeks. 3 Bdq (bedaquiline) at a dose of 400 mg / day for the first 14 days and then 200 mg 3 times / week for 22 weeks for a total of 24 weeks
*** Taken at months 4 and 8 of treatment. 4: QT interval values corrected by Fridericia expressed in milliseconds during the year 2019 during combined treatment with Lzd, Bdq, Mfx, Cfz, Dlm

Period/months	Pre-Treatment Period			0		1	2	3	4	5	6
mm/dd	02/27	03/05	03/12	03/19	03/28	April	May	June	July	August	Sept
msec	371	437	372	370	409	424	388	402	395	395	405

Figure 1 Results of the periodic controls of the QTcF interval in the timeline of this case.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

The authors would like to thank Delia Loayza Tamayo, Félix Alcántara Virú, and Javier Torres Valencia for their generous assistance during the treatment of the patient. The authors would like to thank Partners In Health – Perú for the donation of medicines: delamanid, clofazimine, bedaquiline.

References

1. Sharma SK, Dheda K. Whatis new in the WHO consolidatedguidelinesondrug-resistant tuberculosis treatment? Indian J Med Res. 2019;149:309–12, http://dx.doi.org/10.4103/ijmr.IJMR_579_19.
2. Rapid communication: key changes to the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.26). Licence: CC BY-NC-SA 3.0 IGO.
3. Dravniece G, Gebhard A, Mhazo A, Wares F, Nyaruhirira AU, Zagorski A, et al. Frequently asked questions on the WHO rapid communication: key changes to the treatment of multidrug-and rifampicin-resistant TB prepared by the WHO Task Force to support country transition towards new recommendations for the treatment of MDR-TB; 2018 (August). Available from: www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf
4. Ministerio del Perú. Modificatoria de la NTS° 104 - Minsa/DGSP V.01 norma técnica de salud para la atención integral de las personas afectadas por tuberculosis; aprobada por R.M. N° 752-2018 - Minsa [Internet]. Minsa; 2018. p. 38. Available from: http://www.tuberculosis.minsa.gob.pe/portaldpctb/recursos/20190404114640.PDF
5. Hafkin J, Hittel N, Martin A, Gupta R. Compassionate use of delamanid in combination with bedaquiline for the treatment of multidrug-resistant tuberculosis. Eur Respir J. 2019;53:180154, http://dx.doi.org/10.1183/13993003.01154-2018.
6. Pannu AK, Saroch A. Diagnostic criteria for drug rash and eosinophilia with systemic symptoms. J Fam Med Prim Care. 2017;6:693–4.
7. WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA IGO. Available from: http://apps.who.int/iris/handle/10665/258941
8. Milstein M, Brzezinski A, Varaine F, Mitnick CD. (Re)moving the needle: prospects for all-oral treatment for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2016;20:S18–23.
9. Borisov S, Danila E, Maryandyshev A, Dalcolmo M, Miliauskas S, Kuksa L, et al. Surveillanceof adverse events in thetreatmentofdrug-resistant tuberculosis: first global report. Eur Respir J. 2019;54:1901522, http://dx.doi.org/10.1183/13993003.01522-2019.
10. Pontali E, Sotgiu G, Tiberi S, Tadolini M, Visca D, D'Ambrosio L, et al. Combined treatment of drug-resistant tuberculosis with bedaquiline and delamanid: a systematic review. Eur Respir J. 2018;52:1800934, http://dx.doi.org/10.1183/13993003.00934-2018.
11. Pang Y, Zong Z, Huo F, Jing W, Ma Y, Dong L, et al. In vitro drug susceptibility of bedaquiline, delamanid, linezolid, clofazimine, moxifloxacin, and gatifloxacin against extensively drug-resistant tuberculosis in Beijing, China. Antimicrob Agents Chemother. 2017;61:1–8, http://dx.doi.org/10.1128/AAC.00900-17.

S. Pecho-Silva [a,*,1], A.C. Navarro-Solsol [b]

[a] *Universidad Cientifica del Sur Facultad de Ciencias de la Salud, Peru*
[b] *Universidad Nacional de Ucayali, Universidad Nacional de Ucayali Facultad de Medicina Humana, Peru*

* Corresponding author.
E-mail address: samuelpechosilva@gmail.com (S. Pecho-Silva).
[1] Hospital Nacional Edgardo Rebagliati Martins, Peru

https://doi.org/10.1016/j.pulmoe.2020.03.005

Alpha-1-antitrypsin deficiency (AATD) and spontaneous pneumothorax: Guidelines do not recommend screening for AATD in patients with pneumothorax – What did we find in 10 years of clinical evidence?

Genetic influence on spontaneous pneumothoraces is supported by several lines of evidence: (1) pneumothorax can cluster in families – a family history of pneumothorax can be elicited in 10% of individuals presenting with spontaneous pneumothorax – familial spontaneous pneumothorax[1]; (2) mutations in the *FLCN* gene have been found in both familial and sporadic cases; and (3) pneumothorax is a known complication of several genetic syndromes.[2] These can be divided into three mechanistic classes: (1) those arising from mutations in tumour suppressor genes – Birt-Hogg-Dubé syndrome (BHDS), pulmonary lymphangioleiomyomatosis (LAM occurs both sporadically and in association with tuberous sclerosis complex – TSC); (2) connective tissue disorders – Marfan syndrome, vascular Ehlers-Danlos syndrome, Loeys-Dietz syndrome, homocystinuria, cutis laxa; and (3) those in which normal lung architecture is effaced – alpha-1-antitrypsin deficiency (AATD), cystic fibrosis and others.[2]

AATD is a genetic autosomal codominant disorder caused by mutations in *SERPINA1* gene.[3] It is one of the most prevalent genetic disorders, affecting 1/2000–5000 individuals, a similar or higher incidence than cystic fibrosis. However, it is an underdiagnosed condition.[4]

Alpha-1-antitrypsin (AAT) is the prototypic member of the serine protease inhibitor (SERPIN) superfamily of proteins and is mainly produced in the liver, reaching the lungs by diffusion from the circulation. AAT reacts with neutrophil elastase and provides over 90% of defense against the lower airway elastolytic load. In AATD, loss of the natural antiprotease screen against neutrophil elastase (and other proteases), as well as the loss of the anti-inflammatory effects of AAT, predisposes patients to emphysema.[5]

AATD primarily involves the lungs, liver and, less frequently, the skin. In the lung, AATD predisposes individuals to the premature onset of chronic obstructive pulmonary disease (COPD), with 1–2% of all cases estimated to be due to severe AATD.[3] The premature onset of panacinar emphysema is the most prevalent clinical correlate of AATD and the major cause of morbidity and mortality. Spontaneous pneumothorax may be the presenting manifestation of the disease or a complication of emphysema. Bronchiectasis has also been associated with severe AATD.[3]

Recommendations and guidelines of healthcare institutions, such as the World Health Organization, the Portuguese Society of Pneumology (SPP), the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and the American and European Thoracic/Respiratory Societies (ATS/ERS), indicate that all COPD subjects and adults with nonreversible asthma should be tested for AATD at least once during their lifetime.[5] According to the Portuguese guidelines, screening should include an AAT serum level and, if it is <110 mg/dL, genotyping or phenotyping should be done.[3] As AAT behaves like an acute-phase protein, serum levels may be falsely augmented during inflammatory and infectious processes, so measurements should be done outside of acute episodes.

Current guidelines do not recommend screening for AATD in patients with pneumothorax, although this is a matter of controversy. Few studies have addressed this issue. Some support the measurement of AAT serum levels in patients with spontaneous pneumothorax while others failed to prove AAT deficiency was present in these patients.[6,7] A study published by Danielius Serapinas et al. revealed 7.7% of studied patients with spontaneous pneumothorax had AAT deficiency phenotypes including severe deficiency-related ZZ and SZ phenotypes.[8] Daniel and Teba reported spontaneous pneumothorax to be observed in patients with an abnormally low level of AAT.[9]

Our study was designed to evaluate the prevalence of AATD in patients with a first episode of primary spontaneous pneumothorax (PSP).

Clinical files of patients with a first episode of PSP admitted to Coimbra Hospital and University Centre between 2007 and 2017 were reviewed. Patients with an AAT serum level measurement were included in the study. Serum AAT levels were determined by nephelometry. In patients with low serum levels, phenotyping was done.

A total of 122 patients were admitted to our hospital with a first episode of PSP between 2007 and 2017, 103 of whom had an AAT serum level measurement and were included in the study. The mean age was 29.1 ± 12.8 years and 74.8% were males. Seventy-five patients had a chest CT done. Two (1.9%) patients had AAT <57 mg/dl, indicating severe deficiency. Genotyping was done in one patient that was found to be an SZ. The other patient was lost to follow up. Five (4.9%) additional patients had serum levels 57–110 mg/dl, indicating that an intermediate deficiency (heterozygosity) could be present. Genotyping was not done in any of these cases. Among the 7 patients with serum levels <110 mg/dL, only 3 patients were examined by chest computed tomography. One of them had no emphysema and another one had only subpleural blebs in chest CT, both of these had AAT levels between 57 and 110 mg/dl. Only the patient with severe AATD (genotype SZ), presented apical centrilobular and paraseptal emphysema.

In order to prevent or at least slow down the development of AATD related complications including the development of COPD and emphysema, early recognition of the disease is essential. Among patients with PSP we found 2 patients (1.9%) with severe AATD. This detection rate is similar to the detection rate of AATD in COPD patients (1–2%),[6] where screening is recommended, thus supporting the argument that patients with PSP should be routinely screened for AATD.

Additionally, we found 5 patients (4.9%) with AATD serum levels 57–110 mg/dL, some of which could have an intermediate deficiency, raising the detection rate of AATD in patients with PSP even higher.

Furthermore, as AAT is an acute-phase protein it may be elevated when pneumothorax occurs.[8] For that reason, there could be additional patients with an intermediate deficiency whose AATD levels were in the normal range during the episode of pneumothorax and so escaped detection in our study, once again making the detection rate higher. In order to solve this problem, we suggest that all patients

with PSP should have AAT serum levels measured outside the episode of pneumothorax or repeated later on.

Among the 103 patients included in the study, 75 were studied by chest CT. Current clinical guidelines do not recommend chest CT in first-time, unilateral spontaneous pneumothorax.[7,8] However, a recent study demonstrating the cost-effectiveness of CT to detect diffuse, cystic lung diseases in patients with first-time pneumothorax is among the reasons some authors argue for the adoption of this practice.[9] The presence of emphysema might raise the suspicion of AATD, like it did in our SZ patient.

In conclusion, our study supports screening of AATD in patients with primary spontaneous pneumothorax, as the detection rate was at least as high as in other conditions where screening is recommended.

Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgement

None declared.

References

1. Scott RM, Henske EP, Raby B, Boone PM, Rusk RA, Marciniak SJ. Familial pneumothorax: towards precision medicine. Thorax. 2018;73:270–6.
2. Boone PM, Scott RM, Marciniak SJ, Henske EP, Raby BA. The genetics of pneumothorax. Am J Respir Crit Care Med. 2019;199(S1):1344–57.
3. 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. Pulmonology. 2018;24(S1):1–21.
4. Costa CH, Filho AJ, Marques e Silva RM, Cruz TF, Monteiro VO, Pio M, et al. Alpha 1-antitrypsin deficiency in patients with chronic obstructive pulmonary disease patients: is systematic screening necessary? BMC Res Notes. 2019;12:10.
5. Graham RB, Nolasco M, Peterlin B, Garcia CK. Nonsense mutations in folliculin presenting as isolated familial spontaneous pneumothorax in adults. Am J Respir Crit Care Med. 2005;172:39–44.
6. Pawlowicz A, Droszcz W. Pulmonary function and alpha 1-antitrypsin levels in patients after so-called idiopathic spontaneous pneumothorax. Bull Eur Physiopathol Respir. 1987;23:1–4.
7. Chen Y. The change of serum alpha 1-antitrypsin level in patients with spontaneous pneumothorax. Zhonghua Jie He He Hu Xi Za Zhi. 1995;18, 228–9, 256.
8. Serapinas D, Obrikyte V, Vaicius D, Balciuviene R, Valavicius A, Sakalauskas R. Alpha-1 antitrypsin deficiency and spontaneous pneumothorax: possible causal relationship. Pneumologia. 2014;63:32–5.
9. Daniel R, Teba L. Spontaneous pneumothorax and alpha 1-antitrypsin deficiency. Respir Care. 2000;45:327–9.

E. Dias*, I. Farinha, F. Costa

Serviço de Pneumologia do Centro Hospitalar e Universitário de Coimbra, EPE, Coimbra, Portugal

* Corresponding author.
E-mail address: eunicedias7@gmail.com (E. Dias).

https://doi.org/10.1016/j.pulmoe.2020.05.014

Secondary pulmonary alveolar proteinosis in a patient with systemic lupus erythematosus

Dear Editor,

Pulmonary alveolar proteinosis (PAP) is a rare respiratory disease and is pathogenetically classified into the following three types: autoimmune PAP, secondary PAP (sPAP), and congenital PAP.[1] sPAP is not associated with anti-granulocyte macrophage colony-stimulating factor (GM-CSF) antibody and accounts for 5–10% of PAP cases. sPAP is primarily caused by hematological disorders; sPAP caused by autoimmune diseases is extremely rare[2,3]; therefore, clinicians may not always consider the possibility of sPAP when abnormal findings on chest radiography and/or computed tomography (CT) are seen in patients with autoimmune diseases. We report here, a case of sPAP in a patient with systemic lupus erythematosus (SLE).

A 70-year-old woman presented to our hospital with a 1-month history of exertional dyspnea. She was a known case of SLE and had a 37-year-history of treatment with corticosteroids and immunosuppressive agents. Her respiratory sounds were normal, and she had no fever or cough; her oxygen saturation was 94% in room air. Chest radiography and computed tomography revealed diffuse ground-glass opacities in the lung fields bilaterally (Fig. 1A–C). Serum level of Krebs von den Lungen-6, a marker of interstitial pneumonia, was elevated (6416 U/mL); β-D-glucan and cytomegalovirus antigenemia were absent. Non-infectious acute interstitial pneumonia was suspected, and a high-dose corticosteroid was administered; however, radiographic findings and symptoms did not improve. Furthermore, multiple nodules with cavitation appeared in the lower lobe of the left lung. Bronchoscopy was performed; the bronchoalveolar lavage fluid (BALF) was markedly cloudy (Fig. 1D), and showed deposition of acidophilic granular material and foamy macrophages on microscopy. Additionally, *Nocardia* was detected in the nodules of the left lower lobe. Serum anti-GM-CSF antibody was absent. Finally, she was diagnosed with sPAP associated with SLE, and pulmonary nocardiosis. Early treatment of nocardiosis was necessary; therefore, antibiotics were administered, while the corticosteroid dose was tapered.

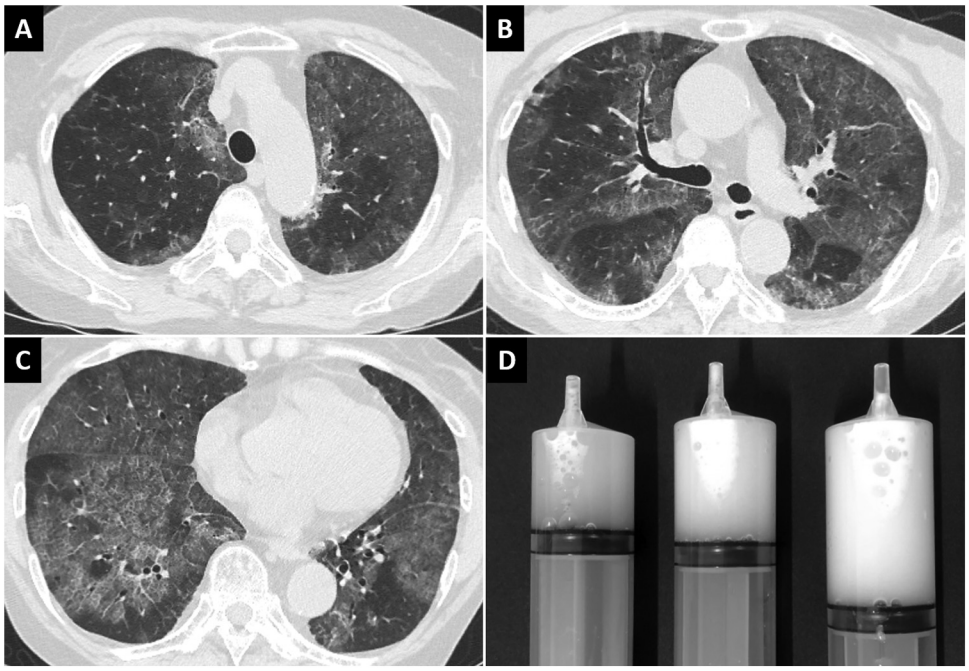


Figure 1 (A–C) Computed tomography image depicting diffuse ground-glass opacities in both lung fields. (D) Bronchoalveolar lavage fluid with a markedly cloudy appearance.

Unfortunately, pulmonary nocardiosis was refractory to treatment; furthermore, complications set in due to the cytomegalovirus pneumonia and non-tuberculous mycobacteriosis. Two months later, the patient died of exacerbating infections.

In this case report, there were two important clinical observations. First, sPAP might develop in a patient with SLE. To the best of our knowledge, only one case of sPAP with SLE has been reported in the literature until date.[4] According to previous reports, autoimmune diseases account for approximately 7% of the underlying causes of sPAP[2,3]; however, autoimmune diseases include Behcet's disease, Wegener's granulomatosis, microscopic polyangiitis, Sjogren's syndrome, and dermatomyositis.[2,3] There are few specific diseases; therefore, every autoimmune disease should be considered as a potential cause of sPAP.

Second, chest CT findings of sPAP might be confused with those of acute interstitial pneumonia and pulmonary alveolar hemorrhage. In many cases of sPAP, such as the present one, chest CT shows ground-glass opacities in the lung fields bilaterally,[5] which are also seen in acute interstitial pneumonia and diffuse alveolar hemorrhage, which are pulmonary disorders of SLE.[6–8] The treatment of acute interstitial pneumonia and diffuse alveolar hemorrhage requires administration of high-dose corticosteroid and frequently an immunomodulatory agent as well. The treatment of sPAP needs to be quite different (Table 1) but as the mechanism underlying sPAP is still uncertain, there are no specific treatment indications for sPAP This may lead to high-dose corticosteroid and/or immunomodulatory agent being administered for pulmonary infections, as in case here presented. It is therefore important that in patients with SLE and diffuse pulmonary ground-glass opacities, clinicians should consider sPAP in addition to acute interstitial pneumonia and diffuse alveolar hemorrhage in the differential diagnosis.

sPAP has a poor prognosis compared to autoimmune PAP.[2] Acute interstitial pneumonia and diffuse alveolar hemorrhage associated with SLE have sudden onset with severe symptoms, while the progression of sPAP is relatively slow and symptoms are relatively mild. Regular and close follow-up on chest radiography is necessary for early detection of sPAP in patients with SLE. For early initiation of appropriate treatment, awareness of the possibility of sPAP in patients with ground-glass opacities in both lung fields is important.

Author contributions

Study conception and design: Masahiro Yamasaki.

Data acquisition: Masahiro Yamasaki, Kazuma Kawamoto, Shota Nakano, Masaya Taniwaki, Naoko Matsumoto, Shinji Nabeshima.

Data analysis and interpretation: Masahiro Yamasaki, Kazuma Kawamoto, Shota Nakano, Noboru Hattori.

Drafting of the manuscript: Masahiro Yamasaki.

Critical revision of the manuscript for important intellectual content: Noboru Hattori.

All authors had access to the data and played a role in writing this manuscript.

Conflict of interest

None declared.

Table 1 Characteristics of secondary alveolar proteinosis compared to acute interstitial pneumonitis and diffuse alveolar hemorrhage in SLE.

Characteristics	sPAP	AIP in SLE	DAH in SLE
Progression rate	Relatively slowly progression	Sudden onset	Sudden onset
Symptoms	Dyspnea; cough	Dyspnea; cough; fever; sometimes hemoptysis	Dyspnea; cough; hemoptysis
HRCT findings	Diffuse GGO; patchy geographic pattern; crazy paving pattern	Diffuse GGO and areas of consolidation	Diffuse or patchy GGO and/or consolidation
BAL findings	Cloudy appearance; acidophilic granular material deposition and foamy macrophages	Incleased cellularity with activated polymorphonuclear leukocytes	Bloody appearance
Treatment	Removing offending exposure or treating the underlying disorder; whole lung lavage	High-dose corticosteroid and/or immunomodulatory agent	High-dose corticosteroid and/or immunomodulatory agent, occasionally plasmapheresis
Prognosis	Poorer than autoimmune PAP; median survival time <20 months	Short-time mortality of 50%	Short-time mortality of 50%

SLE, systemic lupus erythematosus; sPAP, secondary alveolar proteinosis; AIP, acute interstitial pneumonitis; DAH, diffuse alveolar hemorrhage; HRCT, high resolution computed tomography; GGO, ground-glass opacities; BAL, bronchoalveolar lavage.

Acknowledgments

We thank Editage (www.editage.jp) for English language editing.

References

1. Kumar A, Abdelmalak B, Inoue Y, Culver DA. Pulmonary alveolar proteinosis in adults: pathophysiology and clinical approach. Lancet Respir Med. 2018;6:554–65, http://dx.doi.org/10.1016/s2213-2600(18)30043-2.
2. Ishii H, Tazawa R, Kaneko C, Sarayu T, Inoue Y, Hamano E, et al. Clinical features of secondary pulmonary alveolar proteinosis: pre-mortem cases in Japan. Eur Respir J. 2011;37:465–8, http://dx.doi.org/10.1183/09031936.00092910.
3. Zhang D, Tian X, Feng R, Guo X, Wang P, Situ Y, et al. Secondary pulmonary alveolar proteinosis: a single-center retrospective study (A case series and literature review). BMC Pulm Med. 2018;18:15, http://dx.doi.org/10.1186/s12890-018-0590-z.
4. Silva-Díaz M, Freire González M, Romero TH. Pulmonary alveolar proteinosis in a patient with systemic lupus erythematosus. J Rheumatol. 2020;47:779–80, http://dx.doi.org/10.3899/jrheum.181410.
5. Ishii H, Trapnell BC, Tazawa R, Inoue Y, Akira M, Kogure Y, et al. Comparative study of high-resolution CT findings between autoimmune and secondary pulmonary alveolar proteinosis. Chest. 2009;136:1348–55, http://dx.doi.org/10.1378/chest.09-0097.
6. Lynch DA. Lung disease related to collagen vascular disease. J Thorac Imaging. 2009;24:299–309, http://dx.doi.org/10.1097/rti.0b013e3181c1acec.
7. Swigris JJ, Fischer A, Gillis J, Meehan RT, Brown KK. Pulmonary and thrombotic manifestations of systemic lupus erythematosus. Chest. 2008;133:271–80, http://dx.doi.org/10.1378/chest.07-0079.
8. Kamen DL, Strange C. Pulmonary manifestations of systemic lupus erythematosus. Clin Chest Med. 2010;31:479–88, http://dx.doi.org/10.1016/j.ccm.2010.05.001.

M. Yamasaki[a,*], K. Kawamoto[a], S. Nakano[b], M. Taniwaki[a], N. Matsumoto[a], N. Hattori[c]

[a] *Department of Respiratory Medicine, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Naka-ku, Hiroshima, Japan*
[b] *Department of Rheumatology, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Naka-ku, Hiroshima, Japan*
[c] *Department of Molecular and Internal Medicine, Institute of Biomedical & Health Sciences, Hiroshima University, Minami-ku, Hiroshima, Japan*

* Corresponding author at: Department of Respiratory Medicine, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, 1-9-6 Senda-machi, Naka-ku, Hiroshima 730-8619, Japan.
E-mail address: myamasanjp@yahoo.co.jp (M. Yamasaki).

16 June 2020

https://doi.org/10.1016/j.pulmoe.2020.07.008

Pulmonology 2021;**27(1)**:84–89

PULMONOLOGY

www.journalpulmonology.org

CORRESPONDENCE

Potential survival paradox in pneumonia

Dear editor,

I read with great interest the article entitled ''Pneumonia mortality, comorbidities matter?'' by Hespanhol V and Bárbara C.[1] Epidemiology of pneumonia varies among countries. Interestingly, pneumococcus accounted for 40% of bacterial isolates in Portugal. The result of this study may suggest the target of vaccinations and other prevention strategies. However, there are some concerns; some factors which can contribute to impaired outcomes were associated with better outcomes in this study.

Obesities, chronic obstructive pulmonary disease, asthma, and diabetes mellitus were associated with improved hospital mortality in this study. These diseases can develop at a relatively young age, and this result may reflect the potential confounding factors, especially the accessibility to physicians (obesity survival paradox).[2] The existence of past medical history may mean patients go to hospital at an early stage of pneumonia. Tabacco also seemed associated with improved outcomes. If this variable referred to the current smoking habit, it could mean the patients' general condition was not bad.

Among the factors mentioned above, chronic obstructive disease and diabetes mellitus have been reported to result in impaired survival.[3,4] Due to the nature of the retrospective design, it may be complicated to investigate the patients' habits in detail; however, we should be aware of these limitations when interpreting the result of this study. Further investigations are needed to confirm the risk factors for hospital death among patients with pneumonia in Portugal.

Funding

None.

Conflicts of interest

The author declares no potential conflicts of interest.

CRediT authorship contribution statement

H. Ito: Conceptualization, Writing - review & editing.

Acknowledgments

The author is grateful to the members of the Division of Hospital Medicine, University of Tsukuba Hospital for the support of daily clinical practices.

References

1. Hespanhol V, Bárbara C. Pneumonia mortality, comorbidities matter? Pulmonology. 2020;26(3):123–9.
2. Nie W, Zhang Y, Jee SH, Jung KJ, Li B, Xiu Q. Obesity survival paradox in pneumonia: a meta-analysis. BMC Med. 2014; 12:61.
3. Restrepo MI, Mortensen EM, Pugh JA, Anzueto A. COPD is associated with increased mortality in patients with community-acquired pneumonia. Eur Respir J. 2006;28(2):346–51.
4. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. Diabetes Care. 2007;30(9):2251–7.

H. Ito

Division of Hospital Medicine, University of Tsukuba Hospital, 2-1-1 Amakubo, Tsukuba, Ibaraki 305-8576, Japan
E-mail address: itohirokan@yahoo.co.jp
Available online 2 September 2020

https://doi.org/10.1016/j.pulmoe.2020.07.012

Pneumonia mortality, comorbidities matter? Authors' answer

Dear Editor,

Thank you for inviting me to reply to the letter published in Pulmonology journal by H. Ito ''Potential survival paradox in pneumonia''[1] concerning the recent published article in Pulmonology ''Pneumonia Mortality, comorbidities matter?''

Thanks for reading and commenting our article, ''Pneumonia Mortality, comorbidities matter?''

Regarding the results described in your letter to the editor,one comment and some matters for concern raised about the results described in our paper.[2] The comment refers to the possible high proportion of pneumococcal pneumonia identified in the etiology of pneumonia in Portugal, pointing to its possible relationship with vaccination policy. In fact, in Portugal the target populations for pneumococcal vaccination are people under five and older than 64, and patients with any kind of immunodeficiency. Interestingly, most of pneumococcal isolates we obtained in our study, were identified with young-adult patients with no comorbidities, which are not usually included in the target population for pneumococcal vaccination. This is probably one of the explanations for the fact that, that this etiology was not associated with a higher mortality risk.

The concerns are linked to the fact that in our study, smoking habits, obesity, COPD and diabetes are not associated with an increased risk of dying of pneumonia, whereas these comorbidities are usually associated with an increased risk of death from pneumonia. However, the studies[3–5] used to justify the doubts raised in our research, have very different designs, populations, methodologies and analyses, so they can hardly serve for comparison.

In our study, all patients admitted to National Health Service (NHS) hospitals with pneumonia or sepsis with pneumonia, during 2015, were evaluated. The NHS hospitals are responsible for the overwhelming majority of hospitalizations in Portugal. The evaluation and classification of inpatient episodes is permanently carried out, prospectively, by medical doctors specialized in disease coding. This data was used in our study and, whenever necessary, electronic patient records of pneumonia episodes were evaluated. It is not possible, when the investigation is carried out on a retrospective basis, to eliminate all types of bias, due to information/recall or if a particular patient characteristic was included or not in the protocol. However, we believe this was controlled by the nature of our data and by the negligible number of missing values of the 36,366 patients we studied. The risk of misclassification, as we pointed out in the article, is impossible to eliminate completely and we assume that it existed. However, we think that these limitations do not explain the results. The prevalence of severe limiting comorbidities, such as the high number of bedridden patients, patients with stroke, sequelae, dementia, cachexia, cancer and patients living in Care Homes, accounting, in that year, for about 50% of the pneumonia mortality requiring hospital admission. The interpretation of ''non concordant'' results from different research designs, seeking the same goals, but using different data, is not unusual.[6] One way of dealing with this, is using Bayesian approach for interpretation of to the data and results.[7,8] This way of thinking, requiresnot only current data assessment, but also, use of ''prior knowledge'' of the context where the study was conducted, using the prevalence of the patients characteristics in the study population, the way of living and the access to medical care. The variable distribution and prevalence are determinant in the subsequent interpretation of the results and their external validity. The data we used included the great majority of the hospital admissions for pneumonia during 2015 in Portugal. The main goal of the study was to seek for explanations for the high mortality rate for pneumonia in our country,[9,10] and in our view, comorbidities play an important role in this. Using the available data from lastyears,[9,10] it is easy to conclude that chronic illnesses appear early, limiting quality of life. Our study allowed us to identify the coexistence, in a large number of patients, of multiple comorbidities (eg.: smoker + obese + diabetic + COPD + stroke sequelae + bedridden, ...) highly limiting. The impact of any comorbidity, will always depend on their prevalence but also, if in each patient, it exist alone or in combination with others, leading to a different impact in the outcome we are studying.

The results we obtained must be interpreted according to the particularities of the studied population and the access to health care. The large number of elderly patients with concomitant multiple serious comorbidities and the universal access to NHS facilities, may justify the results we found. In fact in other study in our country, the authors found that hospital mortality was particularly related to the aging process and unfavorable socioeconomic conditions[11].The risk model obtained will be tested prospectively in the near future, so we hope to be able to validate the results obtained for this population.

Conflicts of interest

The authors have no conflicts of interest.

References

1. Ito H. Potential survival paradox in pneumonia. Pulmonology. 2020;(September), http://dx.doi.org/10.1016/j.pulmoe.2020.07.012.
2. Hespanhol V, Barbara C. Pneumonia mortality comorbidities matter? Pulmonology. 2020;26(3):126–9.
3. Nie W, Zhang Y, Jee SH, Jung KJ, Li B, Xiu Q. Obesity survival paradox in pneumonia: a meta-analysis. BMC Med. 2014;12:61.
4. Restrepo MI, Mortensen EM, Pugh JA, Anzueto A. COPD is associated with increased mortality in patients with community-acquired pneumonia. Eur Respir J. 2006;28(2):346–51.
5. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. Diabetes Care. 2007;30(9):2251–7.
6. Regina Nuzzo. P values, the gold standard of statistic validity, are not so reliable as many scientist assume. Nature. 2014;150(506):47–8.
7. Gurin NC, Kurinczuc JJ, Burtun PR. Bayesian statistics in medical research: an intuitive alternative to conventional data analysis. J Eval Clin Pract. 2000;6(2):193–204.

8. Davidoff F. Standing statistics right stand up. Ann Internal Med. 1999;12(130):1019–21.
9. OECD. Health at a Glance: Europe 2014. OECD Publishing; 2014, http://dx.doi.org/10.1787/health_glance_eur-2014-en.
10. OECD. Health at a Glance 2019: OECD Indicators. Paris: OECD Publishing; 2019, http://dx.doi.org/10.1787/4dd50c09-en.
11. Pessoa E, Bárbara C, Viegas L, Coata A, Rosa M, Nogueira P. Factors associated with in-hospital mortality from community-acquired pneumonia in Portugal: 2000-2014. BMC Pulm Med. 2020;20:18.

V. Hespanhol[a,*], Cristina Bárbara[b]

[a] *Faculdade Medicina do Porto, Porto, Portugal - Centro Hospitalar e Universitário S. João*

[b] *Faculdade Medicina de Lisboa - Centro Hospitalar e Universitário Lisboa Norte*

* Corresponding author.
E-mail address: vhespanhol@chsj.min-saude.pt (V. Hespanhol).

4 September 2020

https://doi.org/10.1016/j.pulmoe.2020.09.005

Interleukin-6 blockade with tocilizumab in COVID-19: Does it live up to its hype?

A recent systematic review by Cortegiani et al.[1] reviewed the evidence and appraised the quality of evidence concerning the use of tocilizumab in patients with coronavirus disease 2019 (COVID-19). Despite a thorough appraisal of a large number of clinical studies (n = 28) on tocilizumab in patients with COVID-19, Cortegiani et al.[1] concluded that there is still insufficient evidence on its clinical efficacy in patients with COVID-19 because these studies are associated with a high risk of bias and poor quality. We would like to complement the discussion on the evidence of tocilizumab use in patients with COVID-19.

Interleukin (IL)-6 blocking agents such as tocilizumab have been touted as the potential treatment for COVID-19 since the recognition of the cytokine storm associated with a severe course of COVID-19, which involves increased levels of several cytokines where one of them is IL-6. However, a more pressing question is ''Do increased concentrations of an IL-6 imply that its neutralisation will be effective in COVID-19?'' While a recent observational study[2], not included in the systematic review, demonstrated mortality benefits associated with the use of COVID-19, the two recent randomized controlled trials[3,4] did not replicate the findings. The randomized, double-blinded, placebo-controlled COVACTA trial[3] among hospitalized patients with COVID-19 reported no difference in 28-day mortality between the tocilizumab arm and placebo arm (19.7% and 19.4%, respectively). Furthermore, based on the results released on September 18, 2020, from the randomized, double-blind, placebo-controlled EMPACTA trial[4], there was no statistical difference in 28-day mortality between patients who received tocilizumab and patients who received a placebo (10.4% and 8.6%, respectively).

The findings from randomized controlled trials have proved that the use of tocilizumab in COVID-19 did not live up to the hype, where the increased concentration of IL-6 does not imply that its neutralization will be effective in COVID-19. There is a possibility that the wrong cytokine was targeted to dampen the cytokine storm in COVID-19. A recent prospective study by Blot et al.[5] compared the concentrations of IL-6 between 27 patients with COVID-19 pneumonia and 36 patients with non-COVID-19 pneumonia. It was reported that the plasma concentrations of IL-6 were significantly lower in the patients with COVID-19 pneumonia compared to the patients with pneumonia other than COVID-19 (121.0 pg/mL versus 460.4 pg/mL).

The findings of this prospective study, coupled with the findings from two randomized controlled trials that failed to detect mortality benefits with tocilizumab, suggest that IL-6 may not be the cytokine that drives the progression of COVID-19. The use of tocilizumab is not harmless since it may predispose patients to the development of secondary infections. We suggest a shift in focus and to target other mediators of hyperinflammatory state in patients with COVID-19.

Conflicts of interest

The authors have no conflicts of interest.

References

1. Cortegiani A, Ippolito M, Greco M, Granone V, Protti A, Gregoretti C, et al. Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review. Pulmonology. 2020, http://dx.doi.org/10.1016/j.pulmoe.2020.07.003 [published online ahead of print, 2020 Jul 20] S2531-0437(20)30153-30157. Online ahead of print.
2. Biran N, Ip A, Ahn J, Go RC, Wang S, Mathura S, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. Lancet Rheumatol. 2020;2:e603–12, http://dx.doi.org/10.1016/S2665-9913(20)30277-0.
3. Rosas I, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. Preprint. medRxiv. 2020, 2020.08.27.20183442.
4. Roche. Roche's phase III EMPACTA study showed Actemra/RoActemra reduced the likelihood of needing mechanical ventilation in hospitalised patients with COVID-19 associated pneumonia. [Accessed 24 September 2020]. https://www.roche.com/media/releases/med-cor-2020-09-18.htm.
5. Blot M, Bourredjem A, Binquet C, Piroth L, LYMPHONIE Study Group. Is interleukin 6 the right target in COVID-19 severe pneumonia? Am J Respir Crit Care Med. 2020, http://dx.doi.org/10.1164/rccm.202007-202924LE [published online ahead of print, 2020 Sep 21].

C.S. Kow[a,*], S.S. Hasan[b,c]

[a] *School of Postgraduate Studies, International Medical University, Kuala Lumpur, Malaysia*
[b] *Department of Pharmacy, University of Huddersfield, Huddersfield, United Kingdom*
[c] *School of Biomedical Sciences & Pharmacy, University of Newcastle, Callaghan, Australia*

* Corresponding author.
E-mail address: chiasiang_93@hotmail.com (C.S. Kow).

2 October 2020

https://doi.org/10.1016/j.pulmoe.2020.10.004

Rationale and evidence on the use of tocilizumab in COVID-19: A systematic review. Authors' reply

Dear Editor,

We read with interest the Letter from Siang Kow et al.[1] commenting on our systematic review[2] and their discussion of the preliminary evidence from recent randomized controlled trials (RCTs) on the efficacy and safety of tocilizumab for COVID-19. We concur with the authors that it may indeed be time to divert some of our attention from IL-6 to other mediators of inflammation in COVID-19 patients. In fact, previous pharmacological attempts to modulate the inflammatory response in patients with ARDS and sepsis have repeatedly proven unsuccessful. It is therefore reasonable to also question whether suppressing the pathophysiological inflammatory response, or blocking a single mediator for that matter, will be beneficial for patients with COVID-19.

The authors commented on the absence of significant difference in mortality between patients who received tocilizumab (Actemra/RoActemra) or placebo in the industry funded COVACTA (NCT04320615 - https://www.roche.com/dam/jcr:6d8de90d-2e31-43c8-b4e1-0a24a2675015/en/29072020-mr-covacta.pdf) and EMPACTA (NCT04372186 - https://www.roche.com/media/releases/med-cor-2020-09-18.htm) trials.

The results of these trials confirm that findings from non-randomized trials should be interpreted with caution and that such caution is warranted particularly during public health emergencies when large numbers of patients may subsequently receive redundant treatments. As discussed by the authors in the context of tocilizumab and exemplified also by the hydroxychloroquine landslide,[3] experimental drugs are not always harmless, particularly when indiscriminately used. Patient safety should always be prioritized, which is why experimental drugs must be administered within the framework of registered RCTs that are accompanied by appropriate monitoring and regulation.

Research methodology may have also contributed to the negative findings of the above-mentioned RCTs. One example of a potential determinant of outcome in relation to treatment is the timing of administration in respect to the clinical phase of the disease.[4] Another is the treatment dose. Case mix may also have diluted the results; there may be sub-populations of COVID-19 patients who do actually benefit from receiving tocilizumab. Hopefully the full reports of the COVACTA and EMBACTA trials will shed some light on these questions and more. These analyses combined with additional data from the interventional tocilizumab arm of the RECOVERY trial (www.recoverytrial.net) may yet change our perspective on this drug. To summarize, although oft repeated, the following rhetoric is simply the truth: more (high quality) research is urgently needed.

Authors' contribution

AC, MI, SE conceived the content, drafted the manuscript and approved the final version for publication.

Funding

None.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Kow CS, Hasan SS. Interleukin-6 blockade with tocilizumab in COVID-19: Does it live up to its hype? Pulmonology. 2020, http://dx.doi.org/10.1016/j.pulmoe.2020.10.004.
2. Cortegiani A, Ippolito M, Greco M, Granone V, Protti A, Gregoretti C, et al. Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review. Pulmonology. 2020, http://dx.doi.org/10.1016/j.pulmoe.2020.07.003. Jul 20:S2531-0437(20)30153-7.
3. Cortegiani A, Ippolito M, Ingoglia G, Iozzo P, Giarratano A, Einav S. Update I. A systematic review on the efficacy and safety of chloroquine/hydroxychloroquine for COVID-19. J Crit Care. 2020;59:176–90, http://dx.doi.org/10.1016/j.jcrc.2020.06.019.
4. Furlow B. COVACTA trial raises questions about tocilizumab's benefit in COVID-19. Lancet Rheumatol. 2020;2(10), e592.

A. Cortegiani[a,b,*], M. Ippolito[a], S. Einav[c]

[a] *Department of Surgical, Oncological and Oral Science (Di.Chir.On.S.), University of Palermo, Italy*
[b] *Department of Anesthesia, Intensive Care and Emergency, Policlinico Paolo Giaccone, University of Palermo, Palermo, Italy*
[c] *Intensive Care Unit of the Shaare Zedek Medical Medical Centre, Hebrew University Faculty of Medicine, Jerusalem, Israel*

* Corresponding author at: Department of Surgical, Oncological and Oral Science (Di.Chir.On.S.), University of Palermo, Italy.
E-mail address: andrea.cortegiani@unipa.it (A. Cortegiani).

8 October 2020

https://doi.org/10.1016/j.pulmoe.2020.10.003

Spontaneous pneumomediastinum: Beyond the risky diving

To the Editor:

We read with great interest the letter from Cascais-Costa et al.[1] on the risk of developing pneumomediastinum as a result of diving. The authors reviewed the medical condition along with its primary risk factors. Hyperventilation due to psychological stress is one cause that is scarcely referenced in the medical literature. We introduce a case of a patient with a leptosomal phenotype body who presents a spontaneous pneumomediastinum resulting from an anxiety crisis.

Spontaneuos pneumomediastinum (SP) is an uncommon condition where air gets trapped in the mediastinum without trauma associated. The most common factors are emesis, cough or Valsava maneuvers. Other trigger situations are asthma exacerbation, barotrauma, use of illicit drugs or tracheobronchial/esophageal rupture.[2] Psychological stress with consequent altered breathing pattern are reported as a cause of SP.[3] Psychiatric diseases such anorexia nervosa or anxiety attacks, have also been shown to cause SP. This could be related to the intentional vomiting or the previously mentioned alterations in the ventilatory pattern. This generates an increase in intrathoracic pressure causing alveolar rupture, which then releases air from the peribronchial spaces to the mediastinum.[4] Similar to pneumothorax cases, those who have a leptosomic clinical phenotype with tall and thin body and are also young and predominantly male are considered to have several of the predisposing risk factors that are associated with the appearance of SP. This is due to the structure of the thoracic tissues.[5] In some cases, pneumothorax or pneumoperitoneum may appear as a pneumomediastinum complication. Usually, if no surgical interventions are needed, treatment consists of relieving symptoms and conservative management with radiological follow up.

A 34 years-old male patient, nonsmoker with other toxic habits, medical history or respiratory pathologies, was admitted to emergency room with 12 h-history of pharyngeal, cervical and thoracic oppressive pain that got worse with body movements. No fever, coughing attacks, vomiting, great efforts, Valsalva maneuvers or other findings were present. Upon admission his BMI was 19 kg/m^2. Patient expressed feeling increased levels of psychological stress resulting from job issues that arouse due to the pandemic. Patient displayed cyclic episodes of short breathing and hyperventilation patterns. His blood pressure was 145/75 mmHg, respiratory rate was 24 beats/min and oxygen saturation of 96% at room air. On examination, palpable crepitus at the neck area and upper torso were detected. There were no relevant findings on laboratories studies. Thorax radiography revealed air presence in the left paratracheal structures with no indication of a pneumothorax. Subsequent CT cervical scan showed air located in vascular, prevertebral and perivisceral spaces (figure A black arrows), which extended from the skull base to the thorax. CT thorax scan revealed air in prevascular space, supra-aortic trunks, trachea, great vessels and peribronchovascular area (Macklin effect – figure B black arrow-) to the latero-cervical region. Subcutaneous emphysema was in the supraclavicular spaces. These findings are consistent with spontaneous pneumomediastinum affecting the cervical region. Tracheobronchial and esophageal rupture were ruled out by a bronchoscopy and barium esophagography. Subsequent to the thoracic surgical evaluation, no surgical intervention was needed. After 48 h with an improved follow up, patient was discharged with good outcomes.

In conclusion, this case demonstrates that a patient with leptosomic body phenotype who is experiencing increased levels of stress could be at risk of developing a spontaneous pneumomediastinum.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Cascais-Costa C, Teixeira G, Andrade L. Risky diving. Pulmonology. 2020;26:174–6.
2. Dirweesh A, Alvarez C, Khan M, Christmas D. Spontaneous pneumomediastinum in a healthy young female: a case report and literature review. Respir Med Case Rep. 2017;20:129–32.
3. Kribs A, Lang-Roth R, Bohm GB. Class test stress as an unusual cause of spontaneous pneumomediastinum in a 14-year-old girl. Pediatr Emerg Care. 2009;25:401–2.
4. Golpe Gómez R, Mateos Colino A, Docasar Bertolo L, Miguélez Vara C. Spontaneous pneumomediastinum associated with anxiety state. An Med Interna. 2002;19:378–9.
5. Jougon JB, Ballester M, Delcambre F, Mac Bride T, Dromer CE, Velly JF. Assessment of spontaneous pneumomediastinum: experience with 12 patients. Ann Thorac Surg. 2003;75:1711–4.

Jordi Juanola-Pla[a,d,*], Mireia Carmona-Tomàss[b], Sonia Casals-Vila[c]

[a] *Pulmonology Department, Hospital de Mataró, Consorci Sanitari del Maresme, Mataró, Barcelona, Spain*
[b] *Family medicine Department, CAP Cirera Molins, Mataró, Consorci Sanitari del Maresme, Mataró, Barcelona, Spain*
[c] *Radiology Department, Hospital de Mataró, Consorci Sanitari del Maresme, Mataró, Barcelona, Spain*

[d] *High School of Health sciences Tecnocampus Mataró-Maresme, Pompeu Fabra University, Barcelona, Spain*

* Corresponding author.
E-mail address: jjuanola@csdm.cat (J. Juanola-Pla).

https://doi.org/10.1016/j.pulmoe.2020.07.004

Wearing masks and the fight against the novel coronavirus (COVID-19)

Correspondence:

We read with great interest the article by Ippolito et al.[1] in which the authors summarized the use of medical masks in the viral outbreaks like the COVID-19. They pointed out that wearing medical masks and respirators are critical in the personal protection for the healthcare workers, especially in virus breakouts such as COVID-19. They also expressed their concerns about the worldwide mask supplies running out. As their study compared different features of medical masks and respirators, the essential role of wearing masks for both inward and outward protection (protecting the wearer from the environment and the opposite) was emphasized. Apart from the inward and outward protection that wearing the mask provides, the indirect effect of wearing masks during epidemics can also be of great importance.

As COVID-19 is present in saliva,[2] wearing the medical mask stops the transmission of this disease in droplets and aerosols. As patients may be asymptomatic and the reactivation of this disease is possible,[3,4] wearing masks by asymptomatic individuals is strongly recommended. In addition to the direct mechanisms of preventing the spread of the virus, which is the main function of medical masks in viral infections, the other way that wearing the medical masks helps the healthcare systems to combat such epidemics is by decreasing the workload of the healthcare systems and facilitating detection of the new cases.

In COVID-19 outbreak, the symptoms of the disease are cough, fever, fatigue, diarrhea, headache, sputum production, haemoptysis, dyspnoea and lymphopenia.[5] These symptoms are common among other types of influenza and bacterial common cold. Wearing masks will also prevent those types of infections caused by other types of pathogens which are communicable with aerosols and droplets. If all the individuals in a community wear masks, the number of cases referred to the hospitals presenting COVID-19 like symptoms decreases. In other words, the work load of the medical system decreases. So, the real cases of COVID-19 can be screened out of all other types of influenza and common cold comparatively easily. By referring fewer people to the clinics and hospitals, the chance of the contamination of new patients while visiting the hospitals and clinics also deceases. This strategy might help countries to fight against the outbreak of COVID-19.

Funding

The authors declare that no funding was received for this paper.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

None.

References

1. Ippolito M, Vitale F, Accurso G, Iozzo P, Gregoretti C, Giarratano A, et al. Medical masks and Respirators for the Protection of Healthcare Workers from SARS-CoV-2 and other viruses. Pulmonology. 2020. S2531-0437(20)30088-X. https://doi.org/10.1016/j.pulmoe.2020.04.009.
2. Alizargar J, Etemadi Sh M, Aghamohammadi M, Hatefi S. Saliva samples as an alternative for novel coronavirus (COVID-19) diagnosis. Journal of the Formosan Medical Association. 2020, http://dx.doi.org/10.1016/j.jfma.2020.04.030. In press.
3. Alizargar J. Risk of reactivation or reinfection of novel coronavirus (COVID-19). Journal of the Formosan Medical Association. 2020, http://dx.doi.org/10.1016/j.jfma.2020.04.013. In press.
4. Aghamohammadi M, Alizargar J, Hsieh N-C, S-FV Wu. Prophylactic anticoagulant therapy for reducing the risk of stroke and other thrombotic events in COVID-19 patients. Journal of the Formosan Medical Association. 2020, http://dx.doi.org/10.1016/j.jfma.2020.05.005. In press.
5. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433, http://dx.doi.org/10.1016/j.jaut.2020.102433.

Javad Alizargar*

Research Center for Healthcare Industry Innovation, National Taipei University of Nursing and Health Sciences, Taipei City 112, Taiwan

* Corresponding author.
E-mail address: jaz.tmu@gmail.com

9 May 2020

https://doi.org/10.1016/j.pulmoe.2020.05.011