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EDITORIAL

Tobacco and COVID-19: A position from Sociedade Portuguesa de Pneumologia

The impact of smoking on the transmission of the novel coronavirus SARS-CoV-2 and on the severity and mortality of COVID-19 is not yet fully understood. It is well established that tobacco consumption is an important risk factor for several chronic illnesses, such as respiratory and cardiovascular diseases, diabetes, cancer and others, and these patients are at greater risk for serious disease and death by COVID-19.[1,2]

Tobacco smoke has a known immunosuppressive effect, making smokers more vulnerable to infection. Biochemical analysis of induced sputum in healthy smokers has shown a higher ratio of CD4+/CD8+ T cells and a lower rate of T CD8+ lymphocytes, whose activity is crucial to the rapid resolution of acute viral infections. This suggests a cell-mediated immune deficit and a greater susceptibility to viral infections.[3] Smoking (and vaping) also increase epithelial permeability and cause oxidative stress and inflammation responses, leading to more susceptibility to viral and bacterial infections.[4]

Previous studies have demonstrated that smokers have a 34% higher probability of influenza-like illness compared to non-smokers, a five-fold increase in risk of laboratory-confirmed influenza and a higher risk of hospital admission.[5] They also have a higher mortality risk from other coronaviruses, as was seen in the previous outbreak of MERS-Cov (Middle Eastern Respiratory Syndrome).[6] This susceptibility probably includes the new coronavirus by additional mechanisms: Brake et al. have shown that smoking has the potential to up-regulate the angiotensin converting enzyme-2 receptor (ACE-2) in the respiratory epithelium, which is the receptor for both SARS-coronaviruses (SARS-CoV-1 and SARS-CoV-2) and for human coronavirus NL6384.[7] Besides smokers, this expression is also increased in patients with COPD, suggesting this group could be more susceptible to COVID-19 and turning this receptor into a potential therapeutic target.[8] Also Cai G. reported a higher expression of ACE-2 gene on samples from smokers compared to non-smokers[9] and Zhao et al. have shown that ACE-2 protein is expressed on the surface of a small population of type-2 pneumocytes, where genes regulating viral replication and transmission also have a high expression.[10]

Furthermore, the smokers' frequent and repeated hand-to-mouth contact represents a known infection pathway. Additionally, sharing tobacco products is associated with increased risk of transmission and the use of cigarettes, electronic cigarettes and waterpipes can contribute to SARS-Cov-2 dissemination through exhalation of aerosols that may contain the virus.[11] A recent study among teenagers and young adults showed that COVID-19 diagnosis was 5 times more likely among ever-users of e-cigarettes only (95% CI: 1.82–13.96), 7 times more likely among ever-dual-users (95% CI: 1.98–24.55) and 6,8 times more likely among past 30-day dual-users (95% CI: 2.40–19.55).[12]

Despite being scarce and sometimes contradictory, the scientific evidence available suggests an association between smoking and severity of COVID-19. A systematic review by Vardavas and Nikatara evaluated outcomes of 5 Chinese studies and using data published by Guan et al.,[13] estimated a 1,4 higher risk for severe COVID-19 presentation in smokers compared to non-smokers and a 2,4 higher risk of intensive care admission, mechanical ventilation or death.[14] The multivariate logistic regression analysis of another study by Liu et al.[15] showed that smoking history represents a 14 times greater risk of disease progression (OR: 14.28; IC95%:1.58–25.0; p = 0.018).[14,15]

A meta-analysis by Patanavanich and Glantz including 19 studies with 11,590 COVID-19 patients established a significant association between smoking and progression of COVID-19 (OR 1.91, 95% [CI] 1.42–2.59, p = 0.001), and suggested that quality limitations in some studies may actually underestimate this effect.[16]

A recent review paper including 8 systematic reviews or meta-analysis revealed growing evidence on the association between smoking status and COVID-19 severity and poor clinical outcomes. [17] This is also the conclusion of the WHO panel of experts, stating on May 11th that ''smokers are at higher risk of developing severe disease and death''.[18]

Although linked to severity of the disease and death, it is difficult to assess if smokers are at higher risk of contract-

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ing SARS-Cov-2 infection. Observations in different cohorts of relatively low rates of smokers among patients may be related to poor quality of records or lack of smoking status reports; well-designed population studies, controlled for other risk factors, are needed to address this question.[19,20]

WHO also warned researchers to ''be cautious about amplifying unproven claims that tobacco or nicotine could reduce the risk of COVID-19'', in view of recent non-peer reviewed studies with allegations that nicotine or tobacco might have a protective effect, due to low rates of smokers in COVID-19 patients.[18,21,22] These publications make claims with serious public health implications, with a complete lack of good evidence to support them and with unacceptable ethical conflicts, including one of the authors having been financed by the tobacco industry.[23] Although some studies point out biologically plausible pathways through which nicotine may impact SARS-CoV-2, the clinical significance of these is entirely unclear and there is no evidence to support the use of nicotine replacement therapy in COVID-19.[24]

It is important to note that there is a clear lack of good quality information concerning smoking status in most studies, challenging the investigation of the relation between tobacco and COVID-19. A recent living review and meta-analysis[25] found that only 26% of 256 studies reported current, former and never smoking status, and a high proportion did not distinguish between missing data and never smokers.

Beyond all well-known benefits, it is highly likely that smoking cessation can help reduce the transmission and severity of COVID-19 in the community, so reducing tobacco and related products should be part of pandemic control measures.

Taking into account what has been said above, smoking cessation programs should be a priority, especially in this Pandemic phase. Carbon monoxide (CO) measurement in the exhaled breath is a useful tool in smoking cessation programs; however, without specific disposable filters, adequate disposable mouthpieces and proper personal protective equipment,[26] it should not be used in clinical practice during Covid-19 pandemic.

With this in mind, the Portuguese Pulmonology Society has issued recommendations addressing tobacco use during the pandemic.[27] In the present text we update these recommendations, urging health authorities and policy-makers to:

1 Record smoking history in all COVID-19 patients.
2 Promote smoking cessation programs for patients and health care workers, including CO analysis only with adequate protective measures.
3 Facilitate the use of nicotine replacement therapy by health care workers who smoke, during work shifts.
4 Warn against sharing any tobacco products.
5 Warn smokers to only smoke in isolated, designated areas with ventilation.
6 Prioritize smokers as a risk group for infection.
7 Promote smoking cessation in the community.
8 Further advance tobacco control measures, such as raising taxes, smoke-free laws, publicity and marketing bans, including alternative tobacco products.

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Conflicts of interest

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EDITORIAL

Tuberculosis and its future in the COVID-19 era: The *Pulmonology* series 2021

In spite of on-going continued effort and COVID-19, TB remains a major cause of preventable morbidity and mortality and public health priority.[1]

Pulmonology tuberculosis (TB) 2018 series was very successful and highly cited,[2–10] contributing to the journal's Impact Factor (which increased from 2.096 to 2.778, and moving it into the second quartile of Respiratory Medicine journals) (Table 1). The topics covered ranged from state-of-the-art review on new points of care diagnostic tests,[4] to the new drugs pipeline,[5] while discussing important clinical issues like management of TB in children[7] or how to manage comorbidities and social determinant of TB.[8]

COVID-19 has created an unprecedented situation affecting everybody's life (restricting social activities, travelling, attendance at school and educational activities, etc.), damaging economies (increasing poverty, lowering countries' GDP, which are core determinants of TB) and overwhelming healthcare systems.[1,11,12] Recently Global Tuberculosis Network (GTN) studies have shown the devastating impact of COVID-19 on TB Programmes and activities,[12–16] and WHO has warned that previous estimates of mortality decline for TB will be reversed by COVID-19 in the absence of rapid and effective support to health programmes and TB services.[1]

As a contribution to the global fight against TB, *Pulmonology* has planned a 2021 TB series focusing on important priorities to be published in conjunction with World TB day. The choice of topics and the global perspective will be ensured by involving TB officers of the European Respiratory Society (ERS) and the Global TB Network (GTN) and contributors from experts all over the world.

We asked the GTN to report on the outcomes of their cohort of patients treated with the new TB drugs (bedaquiline and delamanid, alone or in combination). A previous global report on adverse events was published in 2019[17]; the prospective update of the cohort (project works like an ongoing register) allows researchers to report on a variety of outcomes (sputum smear and culture conversion as well as time to bacteriological conversion) on one of the largest available datasets, to date it includes more than 850 patients from 29 countries. The global nature of the cohort involved will ensure generalizability and cross fertilisation.

A second contribution will report on a potential interaction between TB and COVID-19, reviewing what has been published so far and covering both clinical and public health perspectives, proposing the next steps to better understand this new '*cursed duet*'.[18]

The third paper will discuss hospital admission criteria for TB patients, based on the analysis of available data (including data of duration of hospitalization from the ongoing global TB/COVID study[18] and will include recommendations on the precautions required to minimise airborne transmission in healthcare settings during COVID. The document will have a consensus component to ensure a wide view, as recently performed by the GTN.[15,19]

It is well known that HIV co-infection, diabetes mellitus, malnutrition, tobacco use and/or alcoholism may increase the risk of progressing to TB disease. It has also been shown that settings with the highest TB incidence rates are also those with higher incidence of HIV infection, incarceration, household overcrowding, unemployment, poor working conditions and migration. New risk factors may be on the horizon, relating to a possible direct or indirect effect of the COVID-19 pandemic (e.g. poverty, fear, lockdown, difficulty accessing health services etc.). The last article of the *Pulmonology* TB series will be a case study on a country's response (Portugal) within a global review of risk factors and social determinants of TB.

While calling on the scientific community, civil societies and all stakeholders involved to combine their efforts to reinforce the fight against TB, we hope the 2021 *Pulmonology* TB series will be useful for the cause and highlight further areas for cooperation.

https://doi.org/10.1016/j.pulmoe.2020.10.005

Table 1 Pulmonology tuberculosis series 2018: articles and citations.

First author	Title	Citations*
Duarte et al.[2]	Strengthening tuberculosis control to advance towards elimination: the 2018 Rev. Port. Pneumol. (RPP) TB Series.	1
Lopes et al.[3]	Tuberculosis in the news: how do Portuguese media cover TB.	0
García-Basteiro et al.[4]	Point of care diagnostics for tuberculosis.	28
Tiberi et al.[5]	New drugs and perspectives for new anti-tuberculosis regimens.	47
Rendon et al.[6]	Migration, TB control and elimination: whom to screen and treat.	9
Carvalho et al.[7]	Managing latent tuberculosis infection and tuberculosis in children.	7
Duarte et al.[8]	Tuberculosis, social determinants and co-morbidities (including HIV).	22
Chalmers et al.[9]	Non-tuberculous mycobacterial pulmonary infections.	8
D'Ambrosio et al.[10]	Team approach to manage difficult-to-treat TB cases: experiences in Europe and beyond.	9

* data from Scopus citation database.

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The authors have no conflicts of interest to declare.

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COMMENT

Retraction in the era of COVID-19 and its influence on evidence-based medicine: is science in jeopardy?

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In order to keep the scientific community well informed about the SARS-CoV-2 virus, a great number of articles have been published.[1] Up to July 14, 2020 a total of 31,360 documents were indexed on Pubmed, according to the LitCovid-NCBI.[2,3] The USA is the country with most articles published (5,033), followed by China (3,511) and Italy (2,590). The journals with most publications were: *BMJ* (BMJ Publishing Group Ltd.) (574), *Journal of Medical Virology* (John Wiley & Sons, Inc.) (317) and *The Lancet* (Elsevier) (230).

In this context, a search was carried out using the PubMed-Medline database on October 12, 2020 and using the following descriptors ''coronavirus disease-19 OR coronavirus disease OR corona virus OR COVID-19 OR COVID19 OR SARS-CoV-2'' and the following filters were applied in the data search: ''Retracted Publication, Retraction of Publication''. Retraction Watch was used to identify retracted articles in preprint services.

Table 1 shows the data related to retracted articles in Pubmed database and pre-print services [Bioxviv and medRxiv – preprint server operated by Cold Harbor Laboratory Spring].[4–25]

The first author's countries with most retraction were the USA and China with 3 articles, perhaps due to the large amount of publications from these countries. Also, a huge variety of SJR indicators was observed, ranging from low SJR indicator, such as *Annals of Clinical & Laboratory Science* (0.36) to those with the highest SJR indicator among medicine journals, such as *New England Journal of Medicine* (18.29) and *Lancet* (14.55). There were countless reasons for retraction, from duplicates and plagiarism to methodological issues and data misinterpretation. Duplication, ethical issues and plagiarism were more frequent in journals with low SJR indicator, whereas journals with high SJR indicator mostly reported methodological issues as the reason for retraction. The majority of the studies retracted were observational[4] followed by experimental.[3] A great variation was found in the study area, which included epidemiology, treatment, experimental and analysis.

The pre-peer-review databases presented the same amount of retractions as the journals, totaling 11 studies.[15–25] However, most of the reasons for retractions

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Table 1 Descriptive analysis of retracted studies in the PubMed-Medline® database.

Paper	First author	First author's Country	Reason for the retraction	Journal	SJR	Study type	Study area	Published online	Final publication	Retraction note	Objective	Main findings	Conclusions
Noninvasive versus invasive ventilation: one modality cannot fit all during COVID-19 outbreak[4]	Singh A	India	Plagiarism	Korean Journal of Anesthesiology	0.44	Letter to the editor	COVID-19 and noninvasive ventilation	Jul 08	Aug	Sep 14	To discuss the noninvasive ventilation in patients with COVID-19.	(i) To avoid intubation and, in this case, to reduce the risk of the mortality; (ii) The potential to generate aerosol and to transmit the SARS-CoV-2 virus using non-invasive ventilation has not been confirmed yet; (iii) There is a poor lung retractability in patients with COVID-19 because a massive alveolar damage was evident due to the release of inflammatory exudates in the alveoli and infiltrates in the interstitial, thus, leading to the development of acute respiratory distress syndrome; (iv) Non-invasive ventilation avoids the disadvantages associated with invasive ventilation.	A certain demographic profile of patients with COVID-19 and with acute respiratory distress syndrome (those with lesser comorbidities and younger) may benefit from noninvasive ventilation instead of intubation.
No deleterious effect of lockdown due to COVID-19 pandemic on glycemic control, measured by glucose monitoring, in adults with type 1 diabetes[5]	Beato-Víbora PI	Spain	Ethical issues	Diabetes Technology & Therapeutics	1.82	Observational	COVID-19 and diabetes mellitus	May 12	Ahead of print article	Aug	To evaluate the effect of COVD-19 lockdown on glycemia measures of patients with type 1 diabetes mellitus.	(i) Improvement was observed in 37% (n = 55) and deterioration in 16% (n = 23) of the patients for glycated hemoglobin during the lockdown period; (ii) During the lockdown, the continuous glucose monitoring (n = 68) increased in time from 70 to 180, from 61.2 ± 16.7 mg/dL to 64.1 ± 17.2 mg/dL and their estimated glycated hemoglobin decreased from 57 ± 12 mmol/L to 55 ± 12 mmol/L; (iii) Fast glucose monitoring users (n = 79) increased in time from 70 to 180, from 59.5 ± 15.4 mmol/L to 62.4 ± 15.7 mmol/L and estimated glycated hemoglobin from 57 ± 11 mmol/L to 54 ± 11 mmol/L.	COVID-19 lockdown was not negatively associated with altered glucose, by remote analysis of sensor data in patients diagnosed with type 1 diabetes mellitus.

Table 1 (*Continued*)

Paper	First author	First author's Country	Reason for the retraction	Journal	SJR	Study type	Study area	Published online	Final publication	Retraction note	Objective	Main findings	Conclusions
5G Technology and induction of coronavirus in skin cells[6]	Fioranelli M	Italy	Peer review manipulation	Journal of Biological Regulators and Homeostatic Agents.	0.4	Experimental (Hypothesis)	5G as an application in the construction of virus-like structures	Jul 16	Ahead of print article	Jul 16	To evaluate whether 5G millimeter waves may act favoring the production of Coronaviruses in biological cells.	The article described that, by decreasing the wavelength, waves emitted from towers in 5G could be more effective in evolutions of DNAs within cells.	It was proposed that a new generation mobile technology could play the main role in constructing several types of viruses, such as Coronaviruses within a cell.
Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis[7]	Mehra M	United States of America	The authors were unable to validate the veracity of the data described in the study.	Lancet	14.55	Observational	COVID-19 and Hydroxychloro-quine	May 22	Ahead of print article	Jun 5	To evaluate chloroquine or hydroxychloro-quine alone or associated with a macrolide for treatment of patients with COVID-19 using as main outcomes the occurrence of de-novo clinically significant ventricular arrhythmias and in-hospital mortality.	(i) Ventricular arrhythmias were more frequent in the treatment groups when compared with the control population; (ii) The treatment group presented a higher mortality when compared to the control population; (iii) Increase in hospital death was associated with age, body mass index, black race or Hispanic ethnicity, coronary artery disease, congestive heart failure, history of arrhythmia, diabetes, hypertension, hyperlipidemia, chronic pulmonary obstructive disease, being a current smoker, and immunosuppressed condition; (iv) Lower in-hospital mortality risk was associated with use of statin, female sex, ethnicity of Asian origin, use of angiotensin-converting enzyme inhibitors (but not angiotensin receptor blockers).	There were no benefits in-hospital mortality for the treatment of COVID-19 with hydroxychloro-quine or chloroquine (with or without a macrolide), instead, a higher risk of ventricular arrhythmias and greater hazard for in hospital death with COVID-19 was found.
SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion[8]	Wang X	China	Methodological issues	Cellular and Molecular Immunology	2.57	Experimental	Susceptibility of T lymphocytes to SARS-CoV-2 virus infection	Apr 7	Ahead of print article	Aug	To test the susceptibility of T lymphocytes to SARS-CoV-2 virus infection.	(i) SARS-CoV-2 virus may infect T cells through S protein-mediated membrane fusion; (ii) EK1 could inhibited the infection; (iii) Perhaps a different receptor may mediated the infection of T cells by SARS-CoV-2 virus, due to lower expression of angiotensin-converting enzyme 2 in T cells.	SARS-CoV-2 virus can infect T cells through S protein-mediated membrane fusion, and perhaps, through a different receptor, due to lower expression of angiotensin-converting enzyme 2 in T cells.

Table 1 (*Continued*)

Paper	First author	First author's Country	Reason for the retraction	Journal	SJR	Study type	Study area	Published online	Final publication	Retraction note	Objective	Main findings	Conclusions
A mechanistic analysis placental intravascular thrombus formation in COVID-19 patients[9]	Mulvey JJ	United States of America	Duplicate	Annals of Diagnostic Pathology	0.7	Observational	COVID-19 and gestations	Apr 25	Jun	Jun 22	To evaluate the placental pathology of full-term births to patients with COVID-19.	(i) The 5 cases enrolled showed fetal vascular malperfusion and thrombosis found within the chorionic plate and stem villi in larger vessels in the fetal circulation; (ii) A deposition might be present within the villi and perivillous areas and decidua similar to the normal placental controls; (iii) Frank thrombosis of fetal chorionic plate vessels occurred in 3 cases; also, in 2 cases larger vessel thrombosis was confined to the stem villi; (iv) Distal lesions in villi associated with the fetal malperfusion occurred in 2 cases (one case as foci of avascular villi and in another case villous stromal-vascular karyorrhexis); (v) The effects of thrombosis might result from the systematic effects of the virus, considering the rare identification of viral spike protein and viral RNA staining within the COVID-19 placentas.	It concluded that the vascular thrombosis without complement deposition can be a characteristic of the systemic nature of COVID-19's procoagulant effects unrelated to systemic complement activation.

Table 1 (*Continued*)

Paper	First author	First author's Country	Reason for the retraction	Journal	SJR	Study type	Study area	Published online	Final publication	Retraction note	Objective	Main findings	Conclusions
Clinical characteristics and blood test results in COVID-19 patients[10]	An XS	China	The authors identified errors in the laboratory data from patients with COVID-19. Also, the data was imputed in the statistical software.	Annals of Clinical & Laboratory Science	0.36	Observational	Epidemiology of the COVID-19	Apr	May	Jul	To evaluate blood test results and the clinical data from patients with COVID-19.	(i) 47 (73.4%) study participants were exposed to a confirmed source of COVID-19 transmission; (ii) The most common symptoms were fever (75%) and cough (76.6%); (iii) 28 (43.8%) patients with COVID-19 presented leukopenia, 10 (15.6%) lymphopenia, 47 (73.4%) elevated high-sensitivity C-reactive protein, 41 (64.1%) elevated erythrocyte sedimentation rate, and 30 (46.9%) had increased fibrinogen concentration; (iv) The counts of white blood cells and platelets, and the level of prealbumin increased significantly after treatment while aspartate aminotransferase, lactate dehydrogenase, and high-sensitivity C-reactive protein decreased; (v) Patients with COVID-19 who stayed more than 12 days in hospital presented higher body mass index and increased levels of aspartate aminotransferase, lactate dehydrogenase, fibrinogen, high-sensitivity C-reactive protein, and erythrocyte sedimentation rate.	Blood test results were associated with the clinical data and with the disease evolution in patients with COVID-19.
Cardiovascular disease, drug therapy, and mortality in COVID-19[11]	Mehra MR	United States of America	The authors were not granted access to the raw data to validate the findings.	New England Journal of Medicine	18.29	Observational	Cardiovascular disease and drug therapy in patients with COVID-19	May 1	Jun 18	Jun 25	To evaluate cardiovascular risk and drug therapy among hospitalized patients, as well as hospital deaths.	(i) Factors associated with in hospital death included age over 65 years, coronary artery disease, heart failure, cardiac arrhythmia, chronic obstructive pulmonary disease, current smoking; (ii) Angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers were not associated with in hospital death.	Patients with COVID-19 and cardiovascular disease had an increased risk of in hospital death; however, no association between in hospital death and use of Angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers was found.

Table 1 (*Continued*)

Paper	First author	First author's Country	Reason for the retraction	Journal	SJR	Study type	Study area	Published online	Final publication	Retraction note	Objective	Main findings	Conclusions
Effectiveness of surgical and cotton masks in blocking SARS-CoV-2[12]	Bae S	South of Korea	The authors did not recognize the concept of limit of detection for in-house reverse transcriptase polymerase chain reaction, which made some of the data unreliable and uninterpretable.	Annals of Internal Medicine	4.74	Experimental	Personal protective equipment	Apr 6	Jul 7	Jun 2	To associate the effectiveness of two types of masks (surgical and cotton masks) to filter the SARS-CoV-2 virus.	The median viral loads (log copies/mL) for SARS-CoV-2 virus were described for nasopharyngeal (5.66) samples, saliva (4.00) samples, after coughs without a mask (2.56), after coughs with a surgical mask (2.42), and coughs with a cotton mask (1.85).	Neither of the masks (surgical and cotton) was able to prevent the dissemination of SARS-CoV-2 virus to the environment and external mask surface.
Chinese medical staff request international medical assistance in fighting against COVID-19[13]	Zeng Y and Zeng Y	China	The account described therein was not a first-hand account.	Lancet Global Health	8.06	Correspondence	Health professional and medical support for COVID-19	Feb 24	Ahead of print article	Aug	To describe the urgent need for medical assistance to deal with COVID-19 in Wuhan, China.	The article described a physical and psychological demand to deal with COVID-19 in Wuhan, China. In addition, it reported that 1,716 Chinese medical workers were infected with SARS-CoV-2 virus and nine of them died.	There is an urgent need of medical staff support to deal with COVID-19 pandemic in Wuhan, China.
Chloroquine or hydroxychloro-quine for COVID-19: why might they be hazardous[14]	Funck-Brentano and Salem JE	France	The article is a comment for a previous retracted study, and it was republicated as "Retraction and republication: Cardiac toxicity of hydroxychloro-quine in COVID-19."	Lancet	14.55	Comment	COVID-19 and treatment	May 22	Ahead of print article	Jul 18	To discuss the findings and limitations of the ''Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis'' study.	The comment highlighted the main findings of the original study and discussed its limitations.	The comment demonstrated that more studies should be carried out to understand the relationship between death and ventricular tachycardia regarding the drug therapy to treat patients with COVID-19. The causes of deaths (i.e., arrhythmic vs non-arrhythmic) were not adjudicated in the study and should be better evaluated.
Uncanny similarity of unique inserts in the 2019-nCoV spike protein to HIV-1 gp120 and Gag[15]	Pradhan P	India	Withdrawn by the authors to revise its results	Bioxriv	-	Experimental	COVID-19 and HIV	Jan 31	Not applied	Feb 2	To compare the structure of HIV and SARS-CoV-2 virus	(i) 4 insertions are unique to SARS-CoV-2, and other coronaviruses do not present it; (ii) These 4 insertions are aligned with short segments with HIV-1 gp120 and Gag; (iii) S protein may have evolved from SARS-GZ02.	The authors evaluated a new evolutionary origin from SARS-CoV-2 virus, also, observed a similarity in the structure of HIV-1 and SARS-CoV-2 virus.
Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China[16]	Yang Y	China	The number of confirmed COVID-19 patients was 18 times higher than they predicted.	Medrxiv	-	Observational	Epidemiology of COVID-19 in China	Feb 11	Not applied	Feb 21	Data was not available	Data was not available	Data was not available

Table 1 (*Continued*)

Paper	First author	First author's Country	Reason for the retraction	Journal	SJR	Study type	Study area	Published online	Final publication	Retraction note	Objective	Main findings	Conclusions
Hydroxychloroquine plus azithromycin: a potential interest in reducing in-hospital morbidity due to COVID-19 pneumonia (HI-ZY-COVID)?[17]	Davido B	France	Controversy about Hydroxy-chloroquine and because the study was retrospective	Medrxiv	-	Data was not available	Treatment for COVID-19	May 11	Not applied	May 20	Data was not available	The data was not available	The data was not available
From SARS-CoV to Wuhan 2019-nCoV outbreak: similarity of early epidemic and prediction of future trends[18]	Chen Z	China	Submitted without the full consent of all authors	Bioxriv	-	Observational	Epidemiology and disease progression	Jan 25	Not applied	Jan 28	Comparison of COVID-19 pandemic and SARS	(i) Super spreader emerged early; (ii) SARS-COV-2 virus has a highly capability of human-to-human transmission; (iii) Medical staff was highly infected (iv) Discovery of human-to-human transmission in SARS-CoV-2 virus was late, compared do SARS-CoV virus; (v) The daily counts of COVID-19 cases were higher than the daily counts of SARS virus cases in 2003; (vi) Large-scale migration made the spread of disease favorable; (vii) The authors predicted that cumulative cases of SARS-CoV-2 virus might be 2 to 3 times the total of SARS; (viii) The infection peak will be in February.	The COVID-19 pandemic and SARS-CoV outbreaks were very similar, even though the Chinese government is taking very efficient decisions, the lack of awareness of the human-to-human transmission by the SARS-CoV-2 earlier, a super spreader may exist, contributes to the pandemic.
Analysis of ten microsecond simulation data of SARS-CoV-2 dimeric main protease[19]	Parves R	Bangladesh	Ethics violation	Biorxiv	-	Experimental	Bioinformatics	Apr 12	Not applied	Apr 16	The study carried out basic structural analysis, advanced flexibility and conformational analysis, for revealing out the regions and residues, which are mostly flexible and likely to be responsible for conformation of protease protein.	The authors were unable to understand the study findings and the techniques performed.	The authors were unable to understand the study's findings and the techniques performed.

Table 1 (*Continued*)

Paper	First author	First author's Country	Reason for the retraction	Journal	SJR	Study type	Study area	Published online	Final publication	Retraction note	Objective	Main findings	Conclusions
Computational analysis suggests putative intermediate animal hosts of the SARS-CoV-2[20]	Chu P	China	The authors want to perform an additional experiment to validate its results	Biorxiv	-	Experimental	Bioinformatics	Apr 05	Not applied	Apr 15	To evaluate the viral receptors binding with the host receptors	(i) SARS-CoV-2 virus showed the best binding with ACE2, when compared to SARS-CoV virus, RaTG13-CoV and Bat-CoV; (ii) RaTG13-CoV and Bat-CoV cannot bind efficiently into ACE2, compared with and SARS-CoV virus, which implicates in the existence of an intermediate host; (iii) Pangolin may not be the intermediate host for SARS-CoV-2 virus, in fact, tree shrew and ferret may be the intermediate hosts.	Tree shrew and ferret may be the intermediate hosts for SARS-CoV-2 virus, and not pangolins.
Mental health status and coping strategy of medical workers in China during the COVID-19 outbreak[21]	Siyu C	China	Authors withdrew it because they are performing more experiments to support their conclusion	Medrxiv	-	Data was not available	Clinical psychology and COVID-19	Feb 25	Not applied	Mar 07	Data was not available	Data was not available	Data was not available
Lung disease severity, coronary artery calcium, coronary inflammation and mortality in Coronavirus Disease 2019[22]	Gaibazzi N	Italy	The objectives of the study were not approved by the institutional review board	Medrxiv	-	Data was not available	Comorbidities and COVID-19	May 06	Not applied	Jun 20	Data was not available	Data was not available	Data was not available
Smoking prevalence is low in symptomatic patients admitted for COVID-19[23]	Gaibazzi N	Italy	The objectives of the study were not approved by the institutional review board	Medrxiv	-	Data was not available	Smoking and COVID-19	May 10	Not applied	Jun 13	Data was not available	Data was not available	Data was not available
Psychiatric predictors of COVID-19 outcomes in a skilled nursing facility cohort[24]	Cercy ST	USA	Privacy issues when conducting the retrospective chart review	Medrxiv	-	Data was not available	Psychiatry and COVID-19	May 26	Not applied	June 21	Data was not available	Data was not available	Data was not available
Treatment response to hydroxychloro-quine, lopinavir/ritonavir, and antibiotics for moderate COVID 19: a first report on the pharmacological outcomes from South Korea[25]	Kim SM	Republic of Korea	Controversy about Hydroxy-chloroquine and potential changes in results after peer review	Medrxiv	-	Data was not available	Treatment for COVID-19	May 18	Not applied	Jun 14	Data was not available	Data was not available	Data was not available

Bioxviv, pronounced b̈io-archiveïs a preprint server for biology and operated by Cold Harbor Laboratory Spring; medRxiv, pronounced m̈ed-archiveïs a preprint server for biology and operated by Cold Harbor Laboratory Spring; 2019-nCoV, new Coronavirus 2019; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SARS-Gz02, SARS coronavirus GZ02; COVID-19, coronavirus disease 2019; PubMed-Medline®, PubMed Medical Literature Analysis and Retrieval System Online; HI-ZY-COVID, Hydroxychloroquine plus azithromycin for COVID-19 treatment; HIV-1, Human immunodeficiency virus 1; Gag, Gag protein; Gp120, glycoprotein 120; SCImago Journal Rank indicator; SARS, severe acute respiratory syndrome; RATG-13-CoV, Bat Coronavirus RaTG13; Bat-Cov, Bat Coronavirus; ACE2, angiotensin-converting enzyme 2; USA, United States of America.

were related to ethical issues, including objectives of the studies not being approved by the institutional review board (IRB), absence of consent from all the authors and lack of experiments to confirm the results. Most of the reasons for retractions in these databases might have been prevented by the reviewers' careful analysis, which could have contributed to a more accurate paper.

Retraction should be avoided by using the maximum number of tools available, such as plagiarism identification by computational software and by improving the efficacy of the peer-review process.[26] Also, researchers should be more cautious when submitting data for publication, in order to avoid the problems related to data analysis or ethical issues, such as lack of authorization by the IRB. However, in several studies, it was not possible to determine the tenuous threshold between honest mistake and bad faith due to the author's desire to publish in high impact factor journals. Perhaps, retractions in high impact factor journals are more noticeable due to the greater number of readers, contrasting with low impact factor journals, where retraction is not as evident and does not cause as much ''fuss'' as in high impact journals.

Misconduct in science can cause serious consequences for society, health policy and other matters. During the COVID-19 pandemic the best example was the publication of the article entitled ''Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis''.[7] The article demonsrated no benefits on in-hospital mortality for COVID-19 treatment with hydroxychloroquine or chloroquine (with or without a macrolide), instead, a higher risk of ventricular arrhythmias and greater hazard for in-hospital death was found. The study was based on observational data from an analytics company known as ''Surgisphere''. No author evaluated the data included in the article and they were unable to access the full data to perform the statistical analysis. Following the publication, several groups identified database errors and the study was retracted. WHO denied that hydroxychloroquine or chloroquine had value in the treatment of COVID-19, based on its findings. The consequence of this retraction was discontinuation by the WHO and hydroxychloroquine, or chloroquine, were reallocated as drugs in test. Moreover, the Lancet changed its publication protocol and policy following this tragic episode.

To avoid publication of articles like the one in the Lancet, it is crucial to identify problematic articles, and it should not be totally the responsibility of the journal editorial staff and/or reviewers and/or tools; it is mainly up to the integrity and the ethics of the researcher who conducted the study. For example, the Brazilian government advocated in favor of the drug use and several governmental attitudes during the COVID-19 pandemic were contrary to the WHO recommendation. Following the retraction of that paper,[7] the Government and some citizens openly criticized the WHO as to the credibility of their recommendations.

The COVID-19 pandemic was associated with a high index of publication ''paperdemic''[27] and it favored the high level of retractions, including journals with the highest SJR and credibility in health science. Retractions can have consequences for health policies, mainly public ones, and can result in the rejection of evidence-based medicine by the government, like the Brazilian government and its hydroxychloroquine or chloroquine passion.

Conflicts of interest

The authors have no conflicts of interest to declare.

All authors have approved the manuscript and agreed with its submission to the journal. Also, all authors wrote and revised the manuscript.

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COMMENT

Tidal volume and helmet: Is the never ending story coming to an end?

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Noninvasive ventilation (NIV) has been increasingly used in acute care setting with various indications[1–3,4] but its use in patients with acute hypoxemic respiratory failure (AHRF) is controversial.[5,6,7]

Although spontaneous patient activity during mechanical ventilation (MV) may reduce the likelihood of ventilation-perfusion mismatch, especially in dependent regions, close to the diaphragm, high transmural vascular and transpulmonary pressure swing may worsen vascular leakage and increase tidal volume (V_t), leading to self-inflicted lung injury (SILI).[8] From the clinical side, expiratory V_t of 6 mL/kg used in invasive MV during lung protective ventilation[1] is almost impossible to achieve in most of the patients receiving NIV for AHRF. This is particularly important in de novo AHRF patients undergoing NIV,[1,2] since large expiratory V_t may be generated[9,10] in assisted pressure controlled modes by the ventilator pressure and by the respiratory muscles.

In this setting, reliable monitoring of V_t and unintentional leaks is of the utmost importance. When using an intensive care unit (ICU) ventilator driven by high pressures in the double limb configuration, leaks are computed as the difference between inspired and expired V_t. As a consequence, the amount of V_t that the patient gets is usually quantified as expiratory V_t.

However, some points need to be clarified:

1) One characteristic of unintentional leaks is that they are dynamic, which means they can abruptly change during the inspiratory or expiratory phase of the respiratory cycle (even cycle by cycle). Therefore, expiratory V_t measurements using masks may cause concern, because measurements may become unreliable, unstable and difficult to continuously monitor {Carteaux:201dg}, where there may be unintentional expiratory leaks[11];
2) Although there is a strong belief that preset V_t is equal to the real delivered V_t, in volume controlled mode using ICU ventilator driven by high pressures, on study found that V_t indicated by the ventilator was lower than the delivered V_t, with a difference that was often greater than 10% of the preset V_t.[12] This is also true during pressure controlled mode using NIV, where the direct measurement of flow (and its integration over the time, namely V_t) by the pneumotachograph inside the ventilator, needs to be corrected for the compressible volume. This is the amount of gas which is compressed in the cir-

Abbreviations: AHRF, acute hypoxemic respiratory failure; CPAP, continuous positive airway pressure; ICU, intensive care unit; ILC, intentional leak single-limb vented circuit; IMV, invasive mechanical ventilation; MV, mechanical ventilation; NIV, noninvasive ventilation; SILI, self-inflicted lung injury; TDV, turbine driven NIV ventilator; V_t, tidal volume.

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Table 1 Differences in tidal volumes measured by turbine driven ventilator and lung simulator at different levels of PEEP in the bench study.

Simulated condition	(TDV-LS)PEEP 5 cmH2O	(TDV-LS) PEEP 8 cmH2O	(TDV-LS) PEEP 10cmH2O	(TDV-LS) PEEP 12 cmH2O	p Value
Restrictive	61 (3)°+§	104.4 (1.3)*+§	1.1 (1.6)*°§	−11.9 (1.9)*°+	<0.001

Data reported from Ref. 17. Data are expressed in ml and reported as mean (±SD). PEEP: positive end expiratory pressure; TDV: turbine driven ventilator; LS: lung simulator; (TDV-LS): difference between VT measurements by turbine driven ventilator and lung simulator. *Different from 5; °different from 8, +different from 10, §different from 12.

cuit and in the mask (the greater the internal volume of the mask the higher the compressible volume) for each cmH_2O of pressure delivered by the ventilator during inspiration. Although most of ICU ventilators are usually equipped with algorithms to calculate and compensate for the compressible volume of the circuit,[13] they do not compensate for the mask internal volume or compliance;

Many companies manufacture dedicated turbine driven NIV ventilators (TDV) with a high pressure O_2 inlet to preset a given FiO_2 and an intentional leak single-limb vented circuit (ILC),[11] where V_t is not measured but estimated.[14] Although this circuit configuration is extensively used, the accuracy of V_t estimate depends on many factors, including the pressure decrease across the limb, especially where there are high unintentional leaks. This is the reason why some ventilators use a mathematical algorithm to calculate this pressure drop or they still measure pressure close to the mask. Finally, the V_t and leakage estimation in the presence of random leaks remains a challenge when using ILC.[1,14] However, V_t estimation has been found to have around 15% when compared to the real measured V_t in restrictive disorders. This means that, when 500 ml of volume are generated, estimates may be around ± 75 ml, a bias not significantly different from the one measured by many pneumotachographs inside the ventilator.[14]

They may also allow better patient-ventilator synchrony than ICU pressure driven ventilators, even when coupled with their NIV algorithms.[15] Accuracy in estimating leakage is also crucial to improve patient-ventilator synchrony, especially when pneumatic (flow) trigger systems are used. Most of these systems automatically change their sensitivity level according to leakage estimates to avoid trigger asynchronies (autotriggering or ineffective efforts).

Another important concern during NIV in de novo AHRF is that, compared to IMV, it cannot often be used continuously on a daily basis. Although the use of total face mask may increase patient's tolerance and compliance to NIV and decrease unintentional leaks, the likelihood of maintaining patients under NIV with a mask round the clock for days is remote.

An alternative interface is the helmet, which consists of a transparent hood covering the patient's whole head with a soft collar neck seal.[16] It is kept in place by two armpit belts or by an annular extendable plastic ring positioned under an inflatable cushion that eliminates the need for armpits straps.[16] Helmet NIV resulted in higher levels of positive end expiratory pressure (PEEP) and a lower intubation rate in patients with AHRF in a single randomized controlled trial.[16] This study suggests that the helmet may allow more time on NIV, at higher PEEP, compared to mask NIV, possibly resulting in a lower rate of endotracheal intubation. However, although interesting in term of comfort and in avoiding skin breakdown, the helmet has restrictions in measuring V_t due to its mechanical properties.[16]

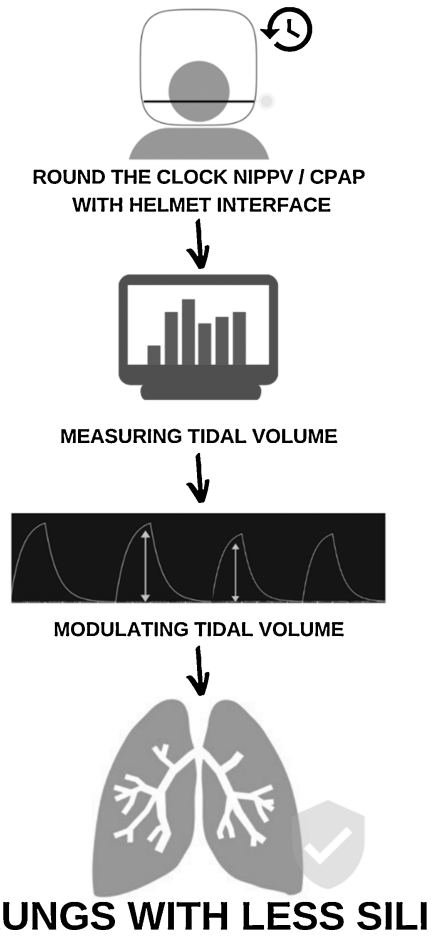

Figure 1 Modulating tidal volume in NIPPV/CPAP spontaneous breathing patients can reduce SILI.
Mechanism of reducing SILI through measuring and modulating Vt during round the clock cycles of mechanical ventilation with helmet interface.
CPAP: Continuous positive airway pressure; NIPPV: Noninvasive positive pressure ventilation; SILI: Self-induced lung injury.

We recently tested the hypothesis[17] that TDV coupled with a single limb ILC, setting intentional leak location at the helmet expiratory port,[18] would provide patient's V_t estimates. This configuration allows using the helmet even in

continuous positive airway pressure (CPAP) mode without additional rebreathing,[18] as in ICU ventilator in double limb configuration.[19] Results of the bench simulation in restrictive conditions (Table 1[17]) show that we could potentially use helmet NIV knowing V_t. Besides, differences in V_t between TDV and lung simulator remained stable across different tested leak flows.

This feasibility bench and human study demonstrated that estimating V_t during helmet NIV seems to be feasible and accurate in restrictive conditions. Although there are now questions about use of NIV in AHRF, the possibility of continuous noninvasive support for patients, knowing V_t, even in CPAP mode, could open new scenarios (Fig. 1), especially in ''difficult-to-treat'' hypoxemic patients, such as in major burns[20] or in the immunocompromised.[21] Further clinical studies are required to verify this method.

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None.

Authors' contribution

AC, MI, ML, CG conceived the content, wrote the manuscript and approved the last version.

Declarations of interests

AC has a patent pending N° 102019000020532 related to the content of this manuscript; MI declare to have no competing interests; ML received fees for lectures and consultancies from Breas, Philips and Resmed not related to the resent work; CG received fees for lectures or consultancies from Philips, Resmed, Vivisol, Air Liquide not related to the present work, and has a patent pending N° 102019000020532 related to the content of this manuscript.

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ORIGINAL ARTICLE

Evaluating the massive underreporting and undertesting of COVID-19 cases in multiple global epicenters

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Spread

Abstract
Background: With continuous global COVID-19 outbreak, differing case numbers and mortality rates are observed. While actual case numbers appear vague, mortality numbers related to COVID-19 seem more precise. In this study, we used the mortality rate as the main indicator to evaluate the extent of underreporting and underdetection of COVID-19 cases.
Methods: We have analyzed all available data provided by the World Health Organization on the development of international COVID-19 cases and mortality numbers on March 17th, 2020. A crude case-fatality risk (cCFR) and adjusted case-fatality risk (aCFR) was calculated for China, South Korea, Japan, Italy, France, Spain, Germany, Iran and the United States. Additionally, a fold-change (FC) was derived for each country.
Results: The highest aCFR and FC were detected for Spain. Based on their FC values, an extremely high number of undetected COVID-19 cases was displayed in France, the United States, Italy and Spain. For these countries, our findings indicate a detection rate of only 1–2% of total actual COVID-19 cases.
Conclusions: Due to limited testing capacities, mortality numbers may serve as a better indicator for COVID-19 case spread in many countries. Our data indicate that countries like France, Italy, the United States, Iran and Spain have extremely high numbers of undetected and underreported cases. Differences in testing availability and capacity, containment as well as overall health care and medical infrastructure result in significantly different mortality rates and COVID-19 case numbers for each respective country.

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Introduction

Amid the current COVID-19 pandemic, a continuous rise in mortality rates has been observed. At the same time, concerns have been voiced that COVID-19 testing has been insufficient and that many countries either lack testing kits and infrastructure, fear associated expenses or that cultural factors may impede virus' detection.[1–4] Once patients are hospitalized, their symptoms are described as flu-like, and their condition often deteriorates and results in death. Prior to a death occurrence, testing is often performed to rule out or confirm a COVID-19 related death. While some countries exhibit such restrictive approaches, others have implemented various measures to contain the virus e.g. social distancing, self-quarantine and lockdown. These measures can also potentially influence the testing procedure. Therefore, to get a better understanding of the spread of the virus in each country, this study compares total reported case numbers for each respective country with total COVID-19 related death numbers. If COVID-19 related mortality remains relatively constant within a certain margin, then this may give a much better estimate of virus spread than the case numbers reported. This study, therefore, aims to assess the extent of COVID-19 undertesting and underreporting based on reported and estimated mortality per case in multiple global epicenters, including China, South Korea, Japan, Italy, France, Spain, Germany, Iran and the United States.[5,6]

Materials and methods

Data sources

Confirmed COVID-19 cases

The total number of confirmed COVID-19 cases and related deaths for Asia (China, South Korea, Japan), Europe (Italy, France, Spain, Germany), Iran and the United States were sourced from the COVID-19 situation reports made publicly available by the World Health Organization (WHO) on January 20th, 2020. The present study used data reported by the WHO on March 3rd, 2020 and March 17th, 2020 (Fig. 1).[7]

Outcome measures and statistical analysis

Case-fatality risks of COVID-19

The crude case-fatality risk (cCFR) of COVID-19 infections on March 17th, 2020 was calculated by dividing the total number of deaths on March 17th, 2020 by the total number of confirmed cases on March 17th, 2020 for each respective country.[8–10] However, it is important to note that deceased patients were typically infected 14 days prior to death occurrence.[11] Therefore, we must consider the time lag between infection and death when calculating an adjusted CFR. For this purpose, we compared the total reported death numbers with confirmed COVID-19 cases tested 14 days prior.

Thus, adjusted CFR (aCFR) for each country at date **t**, accounting for time lags to death, was calculated as follows (Fig. 1)[6]:

$$\mathrm{aCFR}_t\,(\mathrm{country}) = \frac{\mathrm{total\ \ deaths}_t\,(\mathrm{country})}{\mathrm{total\ \ confirmed\ \ cases}_{t-14\,\mathrm{days}}(\mathrm{country})}$$

Total number of COVID-19 cases, crude case-fatality risks (cCFR) and adjusted case-fatality risks (aCFR)

Total COVID-19 cases at date *t* were calculated using the cCFR for each respective country according to the equations below:

$$\mathrm{cCFR\text{-}adjusted\ \ total\ \ cases}_t\,(\mathrm{country}) = \mathrm{total\ \ reported\ \ cases}_t\,(\mathrm{country}) \cdot \frac{\mathrm{cCFR}_t\,(\mathrm{country})}{\mathrm{cCFR}_t\,(\mathrm{country\ \ with\ \ the\ \ lowest\ \ cCFR})}$$

On March 17th, 2020, the cCFR for Germany was the lowest among all investigated countries in the study (0.22%;95% CI: 0.13%–0.37%). This number was used as a benchmark to calculate total COVID-19 cases in other countries. However, the calculated cCFR was not adjusted to the previously described 14-day shift. Adjusted total COVID-19 cases at date *t* were also calculated. For this purpose, we used the aCFR value for Germany and South Korea. South Korea had the lowest aCFR with 1.68% (95% confidence interval, (CI): 1.36%–2.09%). aCFR values of both countries were used as a benchmark to calculate adjusted total COVID-19 cases in other countries:

$$\mathrm{aCFR\text{-}adjusted\ \ total\ \ cases}_t\,(\mathrm{country}) = \mathrm{total\ \ reported\ \ cases}_t\,(\mathrm{country}) \cdot \frac{\mathrm{aCFR}_t\,(\mathrm{country})}{\mathrm{aCFR}_t\,(\mathrm{country\ \ with\ \ the\ \ lowest\ \ aCFR})}$$

The Wilson score interval method was used to calculate cCFR and aCFR at a 95% CI.[5,6] To assess the extent of underreporting and undertesting, we compared adjusted total cases to total reported cases in all countries. This number presents the demonstrated fold change for these countries. Of all countries, the aCFR of South Korea was the lowest on March 17th, 2020 and thus, it was used to calculate the adjusted total COVID-19 cases for the other investigated countries:

$$\mathrm{Fold\ \ change}_t\,(\mathrm{country}) = \frac{\mathrm{adjusted\ \ total\ \ cases}_t\,(\mathrm{country})}{\mathrm{total\ \ reported\ \ cases}_t\,(\mathrm{country})}$$

All statistical analyses were performed using IBM SPSS Statistics (SPSS Inc., version 25).

Results

COVID-19 case-fatality risks

Crude case-fatality

Crude case-fatality risks (cCFR) vary between 0.22% and 8.95%. Countries can be grouped into 3 distinct cohorts according to cCFR values of 1% (cohort 1), 1%–3% (cohort

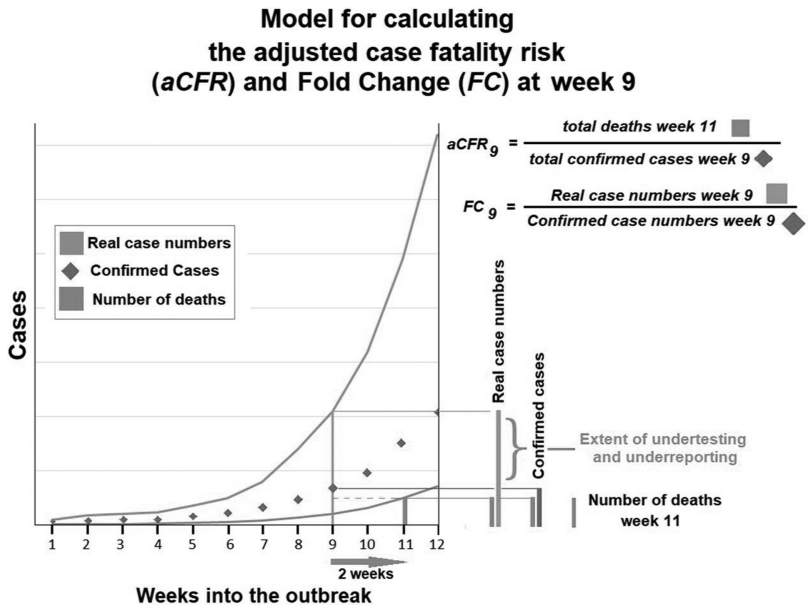

Figure 1 Model demonstrating adjusted case fatality risk and fold change at week 9 of the COVID-19 outbreak. Case fatality risk may surpass 100% if death tolls are higher than confirmed cases 14 days prior.

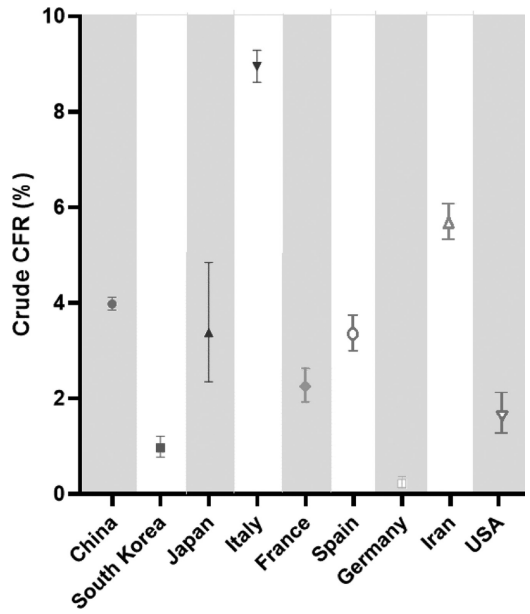

Figure 2 The Crude Case-fatality risk (cCFR) of major global COVID-19 epicenters (in percent); cCFR varies with numbers >2% (South Korea and US) and <8% (Italy). cCFR values are presented at a 95% CI.

Table 1 Crude case-fatality risk (cCFR) values in percent (%).

Cohorts	cCFR value	95% CI
Cohort 1		
South Korea	0.97	0.78–1.21
Germany	0.22	0.13–0.37
Cohort 2		
France	2.25	1.92–2.64
United States	1.66	1.28–2.13
Cohort 3		
China	3.98	3.85–4.12
Japan	3.38	2.35–4.84
Italy	8.95	8.62–9.29
Spain	3.36	3.01–3.75
Iran	5.69	5.33–6.07

2) and above 3% (cohort 3). South Korea and Germany are in cohort 1, with rates of 0.97% and 0.22%, respectively.

The second cohort displays a higher cCFR (1%–3%) and includes countries like France (2.25%) and the United States (1.66%). Finally, the third cohort shows the highest cCFR values and ranges from 3.38% to 8.95%. cCFR values are demonstrated in Fig. 2 and summarized in Table 1 with corresponding 95% CI values.

Time adjusted case-fatality risks (aCFR)

After adjusting the case-fatality risks (aCFR) for a median time lag of 14 days from first symptom onset to death occurrence, we see an increase in numbers from cCFR to aCFR. This increase is significant for all countries. The mean additive increase from cCFR to aCFR was +68% points. Investigated countries are again divided into three distinct cohorts according to aCFR values: aCFR < 10% (cohort 1), 10–50% (cohort 2), >50% (cohort 3). The first cohort includes South Korea, China and Germany with aCFR values of 1.68%, 4.02% and 8.28%, respectively. The second cohort only includes Japan with aCFR at 10.45%. The third cohort is the largest and its values range from 56.83% to 271.05% (see Fig. 3 and Table 2).

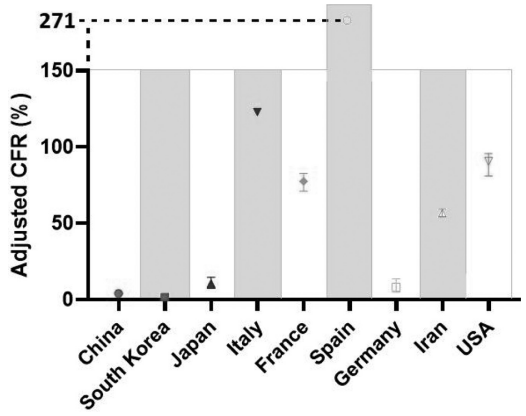

Figure 3 Adjusted Case-fatality risk (aCFR) of major global COVID-19 epicenters (in percent); aCFR varies substantially with numbers <10% (Germany and South Korea) and >200%, even exiting the scale (see Spain). aCFR is presented at a 95% CI which is negligible due to the size of the scale.

Estimating total COVID-19 cases and crude case-fatality risks (cCFR)

When estimating the real total amount of COVID-19 cases using the cCFR value of Germany as the standard, a considerable increase in COVID-19 case numbers compared to total reported cases is observed. Based on these calculations, we estimated the following numbers for investigated countries. All data is presented as reported vs. estimated cases in Table 3 (Fig. 4).

Adjusting numbers to aCFR of Germany and South Korea

Total COVID-19 cases were again estimated based on aCFR for Germany and South Korea. Doing so, we observed that estimated numbers were lower than when cCFR was used. This is true for all investigated countries (Fig. 5).

Table 2 Time adjusted case-fatality risks (aCFR) values in percent (%).

Cohorts	aCFR value	95% CI
Cohort 1		
South Korea	1.68	1.36–2.09
China	4.02	3.89–4.16
Germany	8.28	4.90–13.65
Cohort 2		
Japan	10.45	7.33–14.69
Cohort 3		
Iran	56.83	54.31–59.31
France	77.49	71.06–82.83
United States	90.63	81.02–95.63
Italy	122.94	Not available
Spain	271.05	Not available

Table 3 Estimating total COVID-19 cases and crude case-fatality risks (cCFR).

Countries	Reported cases	Estimated cases
Asia		
China	8.1×10^4	1.5×10^6
South Korea	8.3×10^3	3.8×10^4
Japan	8.3×10^2	10^4
Europe and Iran		
Italy	2.8×10^4	1.2×10^6
France	6.6×10^3	6.8×10^4
Spain	9.2×10^3	1.4×10^5
Iran	1.5×10^4	4×10^5
United States		
United States	3.5×10^3	2.68×10^4

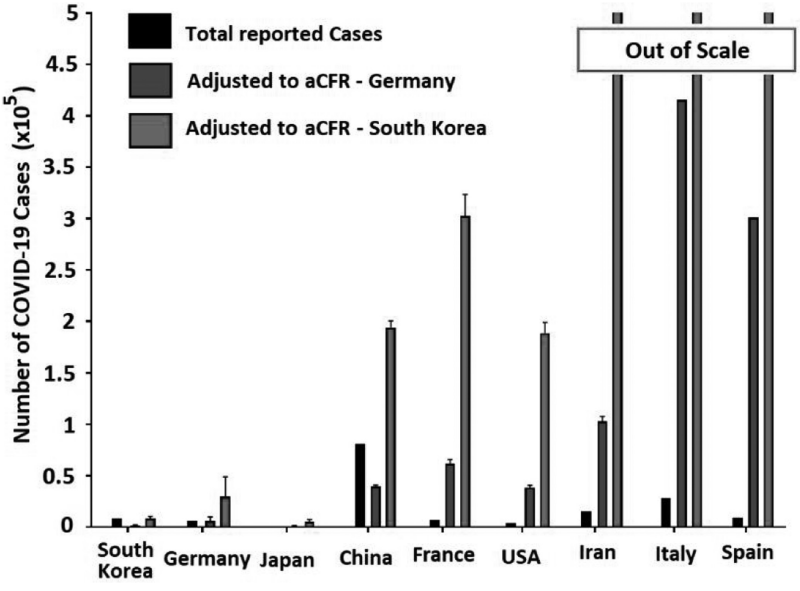

Figure 4 Reported (black) and estimated COVID-19 case numbers in global epicenters. Estimations were based on reported COVID-19 deaths and aCFR value for Germany (blue) and South Korea (red). Estimated case numbers for Iran, Italy and Spain exit the scale after adjusting to values from South Korean (aCFR).

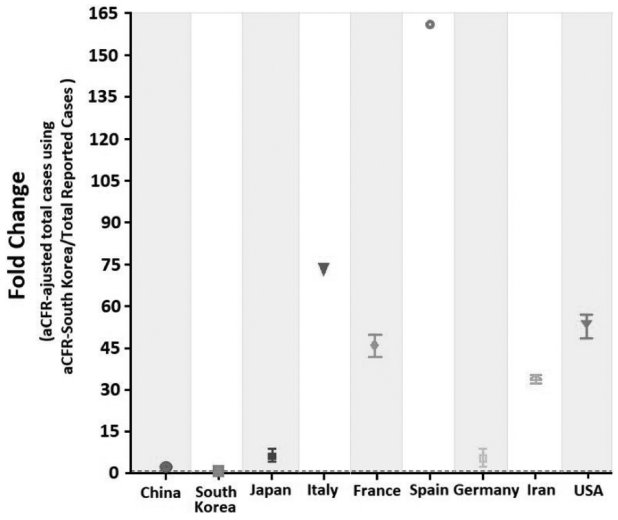

Figure 5 Estimating the extent of undertesting and underreporting of COVID-19 cases in each country. Fold change is highest for Spain, followed by Italy and the United States.

Estimation of underreporting and underdetecting demonstrated by fold change

Fold change as an indicator for underreporting and underdetecting displays a wide range of values between 5 until 161. The investigated countries can be grouped into 3 cohorts according to their fold change: 0–<5 (cohort 1), 5–10 (cohort 2) and >10 (cohort 3). The first cohort includes China (2.4) and Germany (4.9). The second cohort includes Japan (6.2). The third cohort includes

Iran (33.8), France (46), the United States (53.8), Italy (73) and Spain (161) (see Fig. 5).

Discussion

When analyzing reported death numbers, it becomes apparent that the quality of data on reported case numbers is very heterogenous. Calculated fold change indicates that in some emerging COVID-19 epicenters, (USA CF: 54, Italy: 57 and Spain CF: 161), less than 2 percent of COVID-19 cases were subjected to testing and consequently reported. This data is very concerning and points to extreme undertesting and underreporting. While these numbers may appear extraordinarily high for some epicenters, they may indicate a potentially overwhelmed and exhausted medical system or insufficient medical coverage. This lack of adequate medical services may further increase overall mortality. Impaired medical services can be assumed in countries like Italy, Spain and the United States with constant reports of overwhelmed medical facilities. Quality, quantity and capacity of healthcare systems substantially contribute to the successful management of hospitalized patients and can reduce mortality rates. However, it is very challenging to compare different healthcare systems with respect to COVID-19 mortality rates. While we know that healthcare plays a major role in this pandemic, it is not possible to quantify its effect on current mortality rates.

In fact, there is a wide range of factors that may play a significant role in total case numbers like extent, use and safety measures in public transportation, population density, access and quality of health system (quality and quantity/capacity), local temperature and humidity factors, cultural and religious practices, and how media presents the urgency of this immediate health threat. Our findings show that COVID-19 testing has been insufficient, and that many countries either lack testing resources, e.g. test kits and personnel, or fear associated costs. While CFR values for Germany and South Korea are probably close to actual mortality rates, this is not the case for most global epicenters in the third cohort.[12] Containment measures such as isolation, quarantine, lockdown and social distancing are highly effective[13,14] in reducing virus' spread, yet they should be utilized in a meaningful manner. At this point, it remains unclear whether curfew policies, as implemented in Italy, France and Spain, can potentially minimize the damage imposed by inadequate testing and insufficient follow-up of infected cases. Moreover, it further remains unclear how long a general unspecific curfew can be maintained. The repercussions of inadequate testing and follow-up of infected cases remain a key aspect in the fight against global COVID-19 spread. This is especially important because developing countries with immense populations such as India and Pakistan lack adequate testing infrastructure and may heavily depend on the efficacy of curfew measures. The quality of the provided data is one of the limitations of this study, since currently, different data sources on COVID-19 case numbers and deaths are available. Even though COVID-19 case numbers depend on testing efforts, and mortality rates depend on the local definition of a COVID-19 related deaths, there are still discrepancies in national reported cases numbers vs. WHO reported cases vs. case numbers provided by the Johns Hopkins University. Additionally, we increasingly observe retrospective corrections of COVID-19 related deaths in countries. Interestingly, we now receive reports of sudden increases in mortality numbers which are supposedly not COVID-19 related, yet no further explanation for this increase is provided. For most of these deaths, unspecific pneumonia is listed as the primary cause of death.

Conclusion

Our data support concerns about massively insufficient testing in many global COVID-19 epicenters compared to Germany and South Korea. If we assume that mortality rates are roughly stable, COVID-19 related mortality numbers might serve as a better indicator than case numbers to grasp the extent of COVID-19 spread. However, it is important to note that COVID-19 related mortalities typically occur 14 days after infection.

Ethics statement

No ethical approval was required for this study.

Author contribution

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Conflicts of interest

The authors have declared no conflicts of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Pharmacogenetics of advanced lung cancer: Predictive value of functional genetic polymorphism *AGXT* Pro11Leu in clinical outcome?

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KEYWORDS
Non-small cell lung cancer;
Single nucleotide polymorphism;
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Cohort study

Abstract
Introduction: AGXT gene codes for the enzyme alanine glyoxylate aminotransferase, which is involved in hepatic peroxisomal metabolism of platinum-based chemotherapeutic agents. The association of genetic variant *AGXT* rs34116584 on the clinical outcome and response to chemotherapy of patients with non-small cell lung cancer (NSCLC) remains to be established. Our aim was to evaluate the association of functional *AGXT* gene polymorphism in NSCLC progression, considering as primary and secondary endpoint, progression free survival (PFS) and overall survival (OS), respectively.
Methods: Genotyping of the*AGXT* rs34116584 genetic polymorphism was performed by mass spectrometry on 168 DNA samples from patients with NSCLC (stages IIIA-IVB). Univariate survival analysis included the study of Kaplan-Meier curves with the Log-Rank test, while Cox regression was used as a multivariate analysis.
Results: Multivariate analysis showed shorter PFS for T carriers [HR = 2.0, 95% CI, 1.4—3.0, p < 0.0001] and shorter OS [HR = 1.8, 95% CI, 1.1—3.0, p = 0.017] globally, as well as in a subgroup of patients (n = 144) treated with first line platinum-based chemotherapy [HR = 2.0, 95% CI, 1.3–3.1, p = 0.001] and [HR = 1.8, 95% CI, 1.1–3.1, p = 0.026], respectively.

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Conclusion: This polymorphism seems to have an impact on NSCLC progression, opening new perspectives for its inclusion as a pharmacogenetic predictor of response to platinum-based chemotherapy.

Introduction

Lung cancer is one of the most common malignancies worldwide and the most common cause of cancer deaths in the past few decades, with over one million subjects yearly diagnosed [1]. The 5-year survival rate is the lowest compared with other frequent malignancies [2]. Among all primary lung cancers, non-small cell lung cancer (NSCLC) represents approximately 85% of cases. The 5-year relative survival rate has been increasing over the last years, particularly due to progress in treatment over the years [3].

Although targeted therapies have redefined treatment options for patients with molecularly defined NSCLC (eg, epidermal growth factor receptor [*EGFR*]-mutant, anaplastic lymphoma kinase [*ALK*]-rearranged NSCLC), these therapies are ineffective in those whose tumours lack such genetic alterations, which comprise the majority of NSCLC patients [4].

Standard-of-care first-line chemotherapy for advanced NSCLC without actionable driver mutations or low expression of programmed death-ligand 1 (PD-L1) has historically been platinum-doublet, cisplatin or carboplatin, with or without maintenance therapy [5]. Despite its wide acceptance and use, platinum-based chemotherapy presents poor clinical outcomes and efficacy varies across patients. Currently, the combination of immune checkpoint inhibitors with chemotherapy in advanced driver mutation-negative NSCLC and tumour PD-L1 expression under 50%, has replaced the regimen of only platinum-based chemotherapy in first line treatment [6].

Beyond clinical and pathologic features, genetic variation is also considered a factor associated with treatment efficacy and prognosis [7]. Single-nucleotide polymorphisms (SNP), account for 90% of genetic polymorphisms, with some responsible for distinct molecular roles, contributing to inter-individual functional variability, correlating with relevant phenotypic variations in medicine [8]. The *AGXT* gene codes for the enzyme alanine glyoxylate aminotransferase, localized in hepatic peroxisomes, which is known to participate in glyoxylate detoxification [9]. Mutations in this gene have been reported to alter subcellular targeting and have been associated with type I primary hyperoxaluria [10]. A polymorphism in *AGXT* gene (rs34116584) is responsible for a C > T substitution at locus +32 that results in Pro-Leu substitution located at codon 11 of exon 1 [11]. The amino acid substitution at position 11 creates a conformational change that is related to decreased activity [11]. The polymorphism *AGXT* rs34116584 was shown to be associated with progression-free survival (PFS) in patients with metastatic colorectal cancer in response to oxaliplatin [12]. Here, we sought to evaluate whether this genetic variant was associated with clinical outcomes in NSCLC patients, under the platinum-based chemotherapy regimen.

Material and methods

Population

This study comprises a retrospective cohort of histologically confirmed NSCLC patients (n = 168), which were recruited between August 2017 and October 2018 from Coimbra University Hospital. Subjects with concomitant primary tumour in another organ were excluded. Clinical information was retrieved from clinical charts on pathological background, medications, stage, Eastern Cooperative Oncology Group performance status (ECOG PS), tumour mutational status, type of cancer treatment and disease progression/death. Targeted therapies were administered to carriers of genetic alterations in *EGFR* and *ALK*, whereas checkpoint inhibitors were used as salvage therapy. Information on chemotherapy-related febrile neutropenia (grade 3–4) in patients admitted to hospital stay was retrieved from clinical charts. The primary endpoint was progression-free survival (PFS) and the time-to-disease progression was calculated in months from the date of first line chemotherapy until the date of progression according to RECIST criteria. Overall survival (OS) was included as secondary endpoint, and the time-to-death was computed in months from the date of first line chemotherapy until the date of death/date of last visit. The research was reviewed and approved by the Coimbra University Hospital's Ethical Committee (ref. 0111/CES) and by the Portuguese National Committee for data protection (number 2588/2017). Informed consent was obtained from each participant in agreement with the Helsinki Declaration.

AGXT genetic polymorphism and genotyping

The single nucleotide polymorphism included in the present study (*AGXT* rs34116584) was selected after reviewing public databases, *in silico* analysis and review of scientific literature to identify this functional polymorphism with minor allele frequency above 1% [8,10,11]. Each patient donated a sample of blood (∼8 mL) for research, collected to EDTA-Vacutainer tubes, at the same time of blood collection for routine analytic follow-up. The collected blood was separated into plasma and buffy coat and stored at −80 °C until further analysis. DNA was isolated and purified from diluted buffy coats, using EZ1 BioRobot and EZ1 DNA Blood kit (QIAgen). *AGXT* rs34116584 was

genotyped using the Sequenom Mass ARRAY matrix-assisted laser desorption/ionization time-of-flight mass spectrometry platform (Sequenom, San Diego, CA, USA). Primers were designed using semi-automated Assay Design 3.1 Software (Sequenom).

Statistical analysis

Statistical analyses were performed on SPSS statistics software V.25.0 and *P* values below 0.05 were considered statistically significant. Continuous variables were depicted as average ± standard deviation or median (interquartile range) according to departure from normality using Shapiro-Wilk test. Additive (CC vs. CT vs. TT), recessive (CC/CT vs. TT) and dominant (CC vs. CT/TT) genetic models were stratified according to wild type allele C. The time-to-outcome for *AGXT* genotypes was tested using Kaplan-Meier curves and Log-rank test in univariate and Cox proportional hazard model for multivariate analyses. The univariate empirical analyses included *AGXT* genetic models as well as other clinicopathological covariates. A p-value <0.05 was used as criteria for inclusion of a clinical variable in the multivariate Cox regression analysis, whereas the genetic model to include was determined using the likelihood ratio. The estimates of sample size, power, and effect size (regression coefficient) for survival analyses that use Cox proportional hazards models were conducted using STATA 16.0. It also reports the number of events (failures) required to be observed in the study. Sample size and number of events were calculated assuming alpha = 0.05 and power>0.8. For both endpoints, the effect size was calculated from the resulting Hazard Ratio of AGXT variable in multivariate analysis. The minimal sample size for PFS was n = 62 with an estimated number of events of n = 50, whereas for OS, the calculated sample size was n = 173 and the estimated number of events n = 77.

Table 1 Clinical and oncological characteristics of the patients (N = 168).

Clinical Variables	
Age, Mean ± SD	64.8±10.7
Gender, N (%)	
Male	124 (73.8%)
Female	44 (26.2%)
Smoking history, N (%)	
No	31(18.5%)
Smoker	13 (7.7%)
Previous smoker	68 (40.5%)
pTNM 8th edition, N (%)	
IIIA	20 (11.9%)
IIIB	33 (19.6%)
IIIC	21 (12.5%)
IVA	65 (38.7%)
IVB	29 (17.3%)
ECOG performance status at diagnosis, N (%)	
0	39 (23.2%)
1	86 (51.2%)
2	39 (23.2%)
3	4 (2.4%)
4	0 (0%)
Histology, N (%)	
Adenocarcinoma	117 (69.9%)
Squamous cell carcinoma	42 (25.9%)
Adenosquamous	6 (3.6%)
Others	3 (1.8%)
First line systemic therapy, N (%)	
Platinum-based doublet chemotherapy	144 (85.7%)
Cisplatin	*121 (*84.0%
Carboplatin	*23 (*16.0%*)*
Targeted therapy	24 (14.3%)

Results

The clinicopathological characteristics of participating subjects are described in Table 1. The anatomical localization of distant metastases at diagnosis (n = 94) was distributed as pleura and lung (62.8%), extra-thoracic (29.8%) and multiple (7.4%). Regarding mutational status, we observed that 8.3% of patients (n = 14) had *EGFR* mutation (exon 19 deletions or exon 21 mutation), whereas 3.0% (n = 5) had rearrangements in the gene encoding anaplastic lymphocyte kinase. Platinum-based doublet chemotherapy was administered to 85.7% of NSCLC patients, most frequently the cisplatin combination. Adjuvant chemotherapy was administered in twelve patients. In a subgroup of patients with chronic renal disease (n = 24) the doublet chemotherapy with carboplatin was the first choice. Fifty-one patients underwent checkpoint inhibitors as second-, third- and fourth-line therapy. The median time-to-disease progression and the median time-to-death was 7.5 (CI 95%, 6.1–9.0) and 30.0 months (CI 95%, 16.9–43.2), respectively.

The *AGXT* rs34116584 genetic polymorphism distribution in this cohort of NSCLC patients was 71.7% C homozygous, 23.5% heterozygous and 4.8% T homozygous. Genotyping was successfully performed in 166 patients, with two missing genotyping. The median time-to-endpoint, hazard and survival univariate analyses of the empirical statistical procedure are depicted in Table 2. In the dominant genetic model, there was a significantly shorter PFS for T-allele carriers [5.4 months (CI 95% 4.3—6.4) versus 9.4 (CI 95%, 7.2—11.7), p < 0.0001] and a shorter OS [22.2 months (CI 95% 13.6—30.8) versus 43.6 months (20.3—66.9), p = 0.015] (Fig. 1). Notably, despite the *AGXT* rs34116584 T-carriers had shorter PFS than CC homozygous both in the subset of mutated (n = 14, p = 0.028) and wild-type (n = 154, p < 0.0001) *EGFR*, those *AGXT* carriers only presented shorter OS in wild-type (p = 0.022) but not for mutated EGFR (p = 0.692). Additionally, in a subset of patients with information on PD-L1 expression (n = 98, 33.7% without and 66.3% with PD-L1 expression ≥1%), Kaplan-Meier plots with Log-Rank tests showed that T-carriers had shorter time-to-progression independently of PD-L1 positivity (p = 0.010 and p = 0.040, respectively).

The statistically significant covariates from univariate analysis were included in a Cox proportional-hazards multivariate model. This data showed for *AGXT* T-carriers an increased risk for progression (HR = 2.0; 95% CI, 1.4—3.0; p < 0.0001) and for cancer-specific death (HR = 1.8; 95% CI, 1.1—3.0; p = 0.017), regardless of tumour size, distant metastasis at diagnosis, type of systemic therapy and type

Table 2 Univariate analyses of *AGXT* rs34116584 and clinical variables with time-to-progression and time-to-death.

	Progression-free survival			Overall survival	
	n	Median (95%CI)	P *	Median (95%CI)	P *
Age					
<65.4	86	7.2 (5.8-8.7)		43.6 (8.5-78.7)	
>65.4	82	8.6 (5.1-12.1)	0.541	23.6 (15.3-31.8)	0.078
Gender					
Male	124	7.2 (5.3-9.1)		28.1 (21.7-34.4)	
Female	44	8.9 (5.5-12.3)	0.547	82.5 (15.1-150.0)	0.102
Histology					
Adenocarcinoma	117	7.8 (5.7-9.9)		44.0 (18.6-69.4)	
Squamous cell		5.7 (4.4-7.0)		24.6 (17.0-32.2)	
Others *	429	9.5 (3.4-15.7)	0.201	31.3 (19.3-43.4)	0.069
T					
1	26	10.2 (4.1-16.3)		30.0 (14.1-46.0)	
2	46	9.4 (4.0-14.9)		67.4 (46.7-88.2)	
3	18	4.7 (1.4-8.1)		26.9 (19.5-34.3)	
4	78	5.5 (4.0-7.1)	**0.008**	25.4 (16.7-34.2)	**0.011**
N					
N0	13	9.0 (4.2-13.8)		–	
N1	18	7.1 (2.3-12.0)		82.5 (22.9-142.1)	
N2	34	9.5 (2.8-16.2)		26.9 (18.5-35.3)	
N3	103	6.6 (4.6-8.6)	0.151	31.3 (12.9-50.0)	0.790
M					
no	74	9.6 (5.2-14.0)		78.7 (53.0-104.4)	
yes	94	5.4 (4.5-6.2)	**0.003**	22.2 (17.3-27.1)	<0.0001
Type Therapy					
Surgery+CT	12	20.5 (0.0-49.2)		–	
CT	125	6.6 (4.9-8.2)		26.9 (21.0-33.0)	
CT+RT	31	8.9 (4.9-12.8)	**0.024**	34.9 (7.2-62.5)	0.188
ECOG PS					
Good (0-1)	125	8.0 (6.1-9.9)		44.0 (21.2-66.8)	
Poor (2-4)	43	5.4 (2.7-8.1)	0.171	12.9 (9.8-16.0)	**<0.0001**
Systemic Therapy					
Platinum based	144	6.2 (4.7-7.8)		28.1 (20.0-36.2)	
Target therapy	24	13.3 (0.2-26.3)	**0.005**	-	0.183
AGXT rs34116584					
Additive model					
CC	119	9.4 (7.2-11.7)		43.6 (20.3-66.9)	
CT	39	5.7 (5.0-6.4)		17.8 (10.0-25.7)	
TT	8	4.0 (3.4-4.6)	**<0.0001**	24.6 (21.9-27.2)	**0.009**
Dominant model					
CC	119	9.4 (7.2-11.7)		43.6 (20.3-66.9)	
CT/TT	47	5.4 (4.3-6.4)	**<0.0001**	22.2 (13.6-30.8)	**0.015**
Recessive model					
CC/CT	158	7.8 (6.3-9.2)		31.3 (16.7-45.9)	
TT	8	4.0 (3.4-4.6)	**0.025**	24.6 (21.9-27.2)	0.615

CT, chemotherapy; ECOG PS, ECOG performance status; OS, overall survival; PFS, progression-free survival; RT, radiotherapy. * Log-Rank test. ** others: pleomorphic, combined squamous and adenocarcinoma. 95%CI, 95% confidence interval.

of treatment modality (Table 3). To test the hypothesis that *AGXT* rs34116584 was associated with the response to platinum-based chemotherapy, the analysis was conducted in the group of patients treated with first line platinum-based doublet chemotherapy (n = 144). In this subgroup, there were no identifiable actionable driver mutations at the diagnosis. Univariate analysis showed longer PFS in C homozygous (median 8.6, CI 95%, 6.1–11.1 months) in comparison with T-carriers (median 5.1, CI 95%, 4.2–6.0 months) ($p < 0.0001$) (Fig. 1). Concordantly, the time-to-death was also longer in CC (median 34.9, CI 95%, 12.1–57.6 months) compared to T-carriers (median 19.8, CI 95%, 8.9–30.7 months) ($p = 0.037$) (Fig. 1). On multivariate analysis T-carriers had higher risk for disease progression (HR = 2.0, 95% CI, 1.3–3.1, $p = 0.001$) independently of relevant clinico-pathological covariates. In platinum-treated patients, those

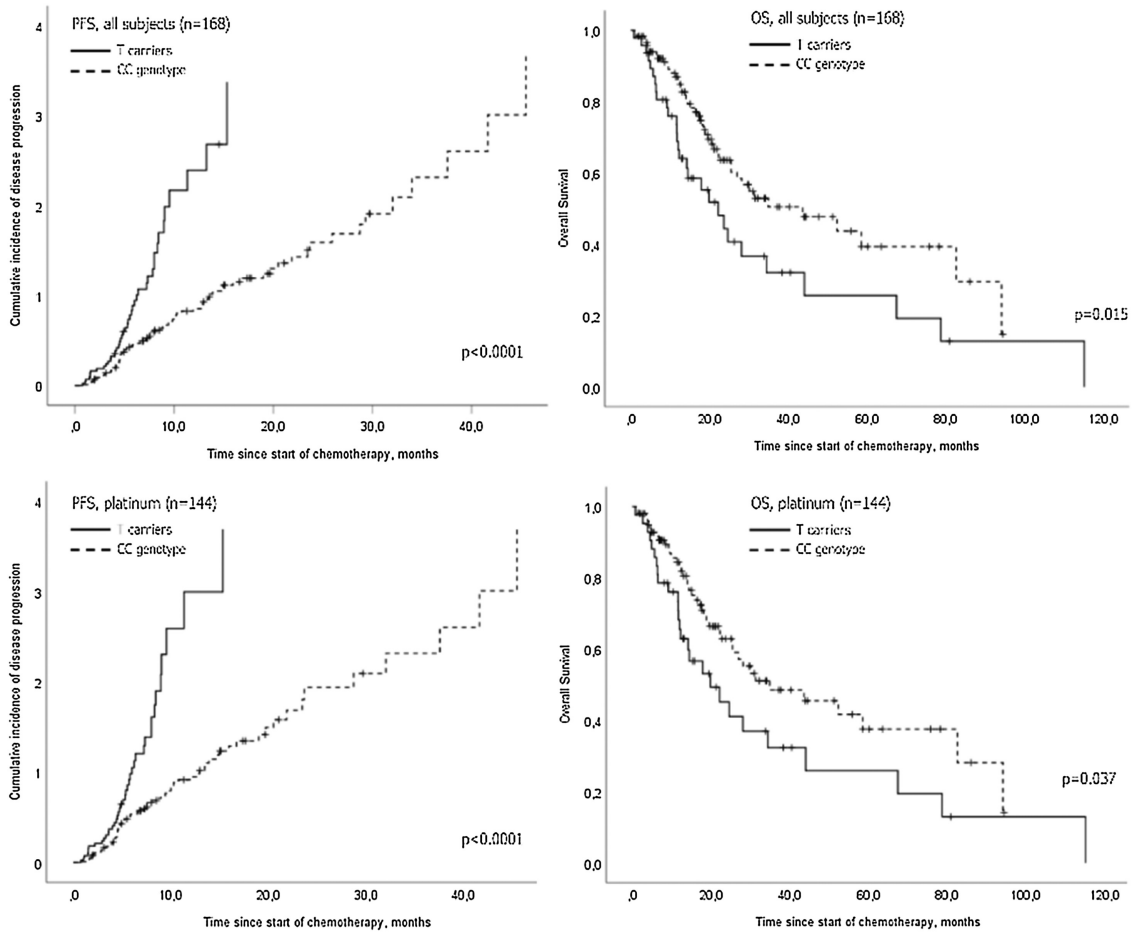

Fig. 1 Kaplan-Meier plots with Log-Rank tests for *AGXT* dominant genetic models in association with progression-free survival (PFS) and with overall survival (OS) for all NSCLC patients (n = 168) and those treated with platinum-based chemotherapy (n = 144).

with febrile neutropenia (n = 20) exhibited more frequently the T-allele compared to non-febrile neutropenia (35% versus 29%, respectively), despite the lack of association of the SNP with myelotoxicity (OR = 1.34, 95% CI, 0.49–3.64, p = 0.566).

Discussion

In the past, advances in genetic knowledge about lung cancer mutational landscape, together with development of targeted therapies, led to a paradigm shift in the treatment of NSCLC. Nevertheless, platinum-containing regimens remain the appropriate treatment for most patients [13]. Clinical management of resistance or toxicity to chemotherapy in NSCLC patients would benefit from the identification of predictive and prognostic molecular biomarkers, including functional genetic polymorphisms.

The *AGXT* gene, located in chromosome 2q37.3 region, encodes the alanine-glyoxylate aminotransferase, whose activity is largely confined to peroxisomes in the liver [14]. This enzyme catalyses the transamination between L-alanine and glyoxylate to produce pyruvate and glycine using pyridoxal 5′-phosphate as cofactor [15]. A missense genetic variant (*AGXT* rs34116584), with a proline-to-leucine substitution located at codon 11 of exon 1, occurs with a frequency of 15–20% in European and North American population [11]. This polymorphism was primarily studied in primary hyperoxaluria type I [16–18]. A recent report explored its role in cancer, showing an association with disease progression and death in metastatic colon cancer patients treated with oxaliplatin [12]. Reports are sparse concerning the association of this SNP with cancer and have never been explored in lung cancer patients.

Herein, the *AGXT*-rs34116584 genetic polymorphism was analysed in locally advanced/metastatic NSCLC patients, using as outcomes the PFS and OS. Multivariate analyses revealed an independent increased risk for disease progression and for death in *AGXT* rs34116584 T-carriers, after adjustment for tumour size, distant metastasis, ECOG PS, treatment modality or systemic therapy. Previous molecular *in vitro* studies showed that the C-to-T substitution results in an amino acid modification at position 11 and creates a conformational alteration that ultimately leads to a significant decrease in alanine-glyoxylate aminotransferaseś activity and subsequent accumulation of oxalate [19,20]. Both oxalate and glyoxylate generate reactive oxygen species (ROS) [21,22], which have been associated with increased mutational burden, tumour progression and dissemination [23]. Since T-allele carriers have higher levels of oxalate [24] and consequently are prone to increased ROS production, the

Table 3 Multivariate Cox regression including only the significant covariates after empirical analysis, for PFS and OS.

	Progression-free survival		Overall survival	
	HR (95%CI)	P	HR (95%CI)	P
cT (TNM)				
T1	Referent		Referent	
T2	1.6 (0.9-2.8)	0.131	0.6 (0.3-1.4)	0.278
T3	2.2 (1.1-4.6)	**0.026**	0.9 (0.4-2.2)	0.856
T4	2.1 (1.2-3.7)	**0.007**	1.6 (0.8-3.1)	0.159
Distant metastasis				
No	Referent		Referent	
Yes	1.6 (1.5-2.3)	**0.010**	2.1 (1.3-3.7)	**0.005**
Systemic Therapy				
Platinum	referent		–	
Target therapy	0.4 (0.2-0.8)	**0.003**	–	–
ECOG PS				
Good (0-1)	–		Referent	
Poor (2-4)	–	–	2.3 (1.4-3.7)	**0.001**
Type of therapy				
Surgery+CT	Referent		–	
CT	2.7 (1.1-6.7)	**0.026**	–	
CT+RT	2.8 (1.1-7.0)	**0.027**	–	–
AGXT rs34116584				
Dominant model				
CC	Referent		Referent	
CT/TT	2.0 (1.4-3.0)	**<0.0001**	1.8 (1.1-3.0)	**0.017**

CT, chemotherapy; ECOG PS, ECOG performance status; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; 95%CI, 95% confidence interval

worst prognosis described for TT/TC might be an oxidative stress-mediated deregulation induced by *AGXT* rs34116584 SNP. This effect might be exponentiated upon exposure to hypoxia and oxidative stress causing DNA damage, or during concomitant administration to cytotoxic therapies [25].

Furthermore, a significantly shorter time-to-disease progression was found for T-allele carriers independent of *EGFR* mutational status, although no relation was observed with OS for subjects with *EGFR* tumour mutation. These findings could be aligned with a minor clinical relevance for *AGXT* rs34116584 SNP in comparison to *EGFR* mutation status that impacts a longer-term endpoint. Notably, tyrosine kinase inhibitors (TKIs) improve survival in NSCLC patients with EGFR mutation [26], modifying the natural history of disease, and possibly impacting the association of the genetic polymorphism.

In patients under first line platinum-based doublets, we verified that T-allele carriers had shorter PFS and OS; regardless of tumour size, distant metastasis, ECOG PS and treatment modality. These well-established prognostic covariates, were shown to influence NSCLC clinical outcomes [27]. Here, the *AGXT* rs34116584 association with response to platinum-based chemotherapy remained significant, despite adjustment for these factors, suggesting that this SNP might add significant information to traditional clinical predictive and prognostic factors. The *AGXT* rs34116584 C > T substitution, induces a decrease of alanine-glyoxylate aminotransferase activity and is responsible for the mistargeting of the enzyme from the peroxisomes to the mitochondria, where the enzyme cannot work properly [10]. These changes were predicted to have significant effects in oxalate synthesis and excretion, and the deposition of insoluble calcium oxalate in the kidney and urinary tract [28], which could be associated with increased toxicity and lesser efficacy of platinum based chemotherapy.

Moreover, cisplatin causes a number of significant side effects including nausea and vomiting, neutropenia, ototoxicity, neurotoxicity, and renal function impairment [29]. Despite efforts to identify genetic predictors of the effectiveness and toxicity of cytotoxic therapies, up to now there are no robust data that can be used in clinical practice to guide the best subgroup of patients to receive cisplatin [29]. Although carboplatin induces nephrotoxicity to a lesser extent, it induces more myelotoxicity [30]. No association was found in our study for the *AGXT* rs34116584 SNP with febrile neutropenia, although the low number of subjects included in this analysis limits its conclusions.

To the best of our knowledge, this is the first report describing the prognostic impact of functional *AGXT* polymorphism in lung cancer patients. As such, further studies in larger independent populations are required to confirm these results. Despite inherent size limitations, in this study patients were recruited from a homogeneous cohort, the analysed SNP was selected based on functional biological relevance, and the study design and statistics accounted for important risk factors in NSCLC.

Conslusion

The functional impact of the *AGXT* rs34116584 SNP in decreasing the peroxisomal activity of the enzyme alanine

glyoxylate aminotransferase influence oxalate accumulation. This effect might have an influence in platinum metabolization, with impact on toxicity and tumour aggressiveness, being associated with worse prognosis. This polymorphism seems to have an impact on NSCLC progression, opening new perspectives for its inclusion as a biomarker or as a pharmacogenetic predictor of response to platinum-based chemotherapy.

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Ethics approval

This project has been reviewed and approved by Coimbra University Hospital's Ethical Committee (reference number 0111/CES; date of approval: 27th July 2017) and was also approved by the National Committee for data protection (number 2588/2017; date of approval: 6th March 2017).

Conflicts of interest

All authors declare that they have conflict of interest.

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ORIGINAL ARTICLE

Cost-effectiveness of omalizumab in real world uncontrolled allergic asthma patients

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KEYWORDS
Asthma;
Omalizumab;
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Abstract
Objective: To estimate the cost-effectiveness of omalizumab compared with standard of care in the treatment and control of severe persistent asthma, using the outcomes from the Portuguese subpopulation of the eXpeRience registry.
Methods: This was a pragmatic cost-effectiveness analysis based on real world data from the eXpeRience registry which recruited 62 patients with uncontrolled persistent allergic asthma from 20 participating centers in Portugal. Response to omalizumab treatment was measured prospectively up to 24 months by the physician's Global Evaluation of Treatment Effectiveness (GETE). Retrospective data on patients' clinical symptoms, asthma control, lung function, exacerbations, and healthcare utilization were available for up to 12 months before omalizumab initiation and served as the standard of care comparator. The number of exacerbations (severe and non-severe), the number of clinical episodes, the number of days absent from work and/or school, and GETE response to therapy were considered as effectiveness outcomes. Following a societal perspective, as cost indicators, both direct and indirect costs were considered. Direct costs relate to the cost of omalizumab, standard of care and clinical episodes (emergency room visits, hospitalizations, and unscheduled doctor visits). Indirect costs relate to the societal cost of work absenteeism. Unit costs for clinical episodes and drugs were taken from official sources within the Portuguese Health Authority. A univariate sensitivity analysis was performed.
Results: A rate of 1.5 exacerbations per patient-year was estimated following omalizumab treatment compared with 8.2 exacerbations per patient-year prior to omalizumab initiation, implying an 82.1% reduction in the incidence of exacerbations following omalizumab treatment relative to standard of care alone. A 54.1% reduction in GETE score was also observed in favor of omalizumab treatment. The mean cost per person-year was 3023€ in the 12 months of standard of care prior to omalizumab and 16,111€ in the period of treatment with omalizumab. The incremental cost-effectiveness ratios were 2244€/exacerbation avoided, and 1750€/unit decrease in GETE classification.

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Conclusion: Our results demonstrate that adding omalizumab to the treatment of patients with uncontrolled severe persistent asthma reduces the number of exacerbations, improving overall treatment effectiveness at an acceptable cost from a societal perspective.

Introduction

Asthma is one of the most common chronic non-communicable diseases in the world, affecting an estimated 339 million people of all ages as of 2016.[1] In Portugal, asthma affects about 6.8% of the population overall, 7.2% of the child/adolescent population (<18 years old), 6.3% of the young/middle-aged adult population (aged 18–65), and 8.0% of the older adult population (>65 years old).[2]

The emphasis of asthma management is on achieving and maintaining control of its clinical symptoms: wheezing, shortness of breath, coughing, and chest tightness. For the majority of patients, clinical control is typically achieved with the use of low to medium doses of inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABA). A proportion of patients is unable to achieve control despite treatment with high doses of ICS, LABA and, in some cases, even oral corticosteroids (OCS). This group of patients, defined as having severe persistent asthma, has been estimated to constitute 10–20% of all patients with asthma.[3] Compared to patients with non-severe persistent asthma, patients with severe persistent asthma are generally at increased risk of asthma exacerbations (severe onset of symptoms), negatively impacting normal daily activities and leading to increased healthcare use.[4–6]

A Portuguese prevalence-based cost-of illness study found that patients with uncontrolled asthma have a 2-times higher annual cost per patient (895€) compared to controlled patients (425€). The acute care usage cost domain (non-scheduled medical visits, emergency department visits, and hospitalizations) was found to be responsible for 62% of this increase.[7] In an Italian study, the total annual cost per patient with severe persistent asthma was estimated to be 3-fold higher than the cost for mild persistent asthma. For severe persistent asthma, indirect costs due to loss of paid workdays were found to contribute 55% to an estimated total annual per patient cost of 3328€, further including drug therapy, general practitioner and other physician visits, emergency room visits, and hospitalizations.[4]

A substantial proportion of patients with severe persistent asthma have allergic immunoglobulin E (IgE) mediated disease.[8] The first approved anti-IgE therapy for these patients is omalizumab, a humanized anti-IgE monoclonal antibody, indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma, characterised by frequent exacerbations despite daily use of high-dose ICS and LABA.[9]

Omalizumab as add-on to ICS-based therapy has been investigated extensively in randomized clinical trials (RCT) in children, adolescents, and adults with persistent allergic asthma. These RCT demonstrated that omalizumab is safe and effective in patients treated with omalizumab as compared to patients receiving placebo.[10–16]

These results have been confirmed in multiple observational studies.[17–21] The eXpeRience registry was a post-marketing, international, non-interventional, observational registry established to evaluate real-world effectiveness and safety of omalizumab.[18] Results for the 62 Portuguese patients enrolled in the eXpeRience registry have been discussed in detail.[20]

Although in the Portuguese subgroup of the eXpeRience registry omalizumab has also proven to be safe and effective,[20] to date, nothing is known about its cost-effectiveness from a Portuguese perspective. As such, the objective of this study was to determine the cost-effectiveness of omalizumab as add-on to ICS-based therapy for patients with severe persistent allergic asthma, based on the outcomes from the Portuguese subpopulation of the eXpeRience registry.[20]

Methods

Following the methodological guidelines for studies of economic evaluation of medicines in Portugal[22] in force at the time of the analysis, in this study the societal perspective was adopted. As time horizon, the observation period of each patient during the eXpeRience registry study was considered. On average, the observation period was 22 months, with a minimum follow-up time of 3.4 months and a maximum of 37 months (Table 1).

Study design and population

In Portugal, the eXpeRience registry recruited a total of 62 patients with uncontrolled persistent allergic asthma from 20 participating centers. Response to omalizumab treatment, as measured by the physician's Global Evaluation of Treatment Effectiveness (GETE) is available at approximately 16 weeks after initiation of omalizumab. Further data on patients' clinical symptoms, asthma control, lung function, exacerbations, and healthcare utilization are available retrospectively for up to 12 months before and prospectively at 16 weeks and possibly 8, 12, 18, and 24 months after omalizumab initiation.[17–21] Information on omalizumab and concomitant medication use is available only prospectively in the registry. We performed a pragmatic cost-effectiveness analysis based on data from the

Table 1 Summary of key model components.

Model component	Description/Assumption
Study population	Portuguese participants of eXpeRience registry[20]
Perspective	Societal
Time horizon	Duration of follow-up individual participants
Options to compare	Omalizumab plus standard of care Standard of care
Effectiveness outcomes	Number of exacerbations (severe and non-severe) Number of clinical episodes Number of days absent to work and/or school GETE response at 16 weeks
Cost of clinical episodes (€)	
Emergency room visit	150.73€[24]
Hospitalization	3378.08€[25,27]
Unscheduled doctor visit	93.35€[24]
Drugs (€)	
Omalizumab (75 mg/150 mg)	198.92€/385.09€[26]
Standard of care	Drug dependent[26]
Cost of absenteeism (€)	
Day of lost work	60.69€[28–30]
Sensitivity analysis (€)	
Asthma severity grade: 3	2768.82€
Asthma severity grade: 4	3987.34€
Respiratory system diagnosis with ventilator support 96+ hrs severity grade	13140.08€
Respiratory system diagnosis with ventilator support 96+ hrs severity grade	43767.75€
Unscheduled doctor visit - LL 95%CI	78.12€
Unscheduled doctor visit - UL 95%CI	108.57€
Emergency room visit - LL 95%CI	130.33€
Emergency room visit - UL 95%CI	171.13€
Cost to a firm of missed work - LL 95%CI: 25%	57.04€
Cost to a firm of missed work - UL 95%CI: 40%	63.89€

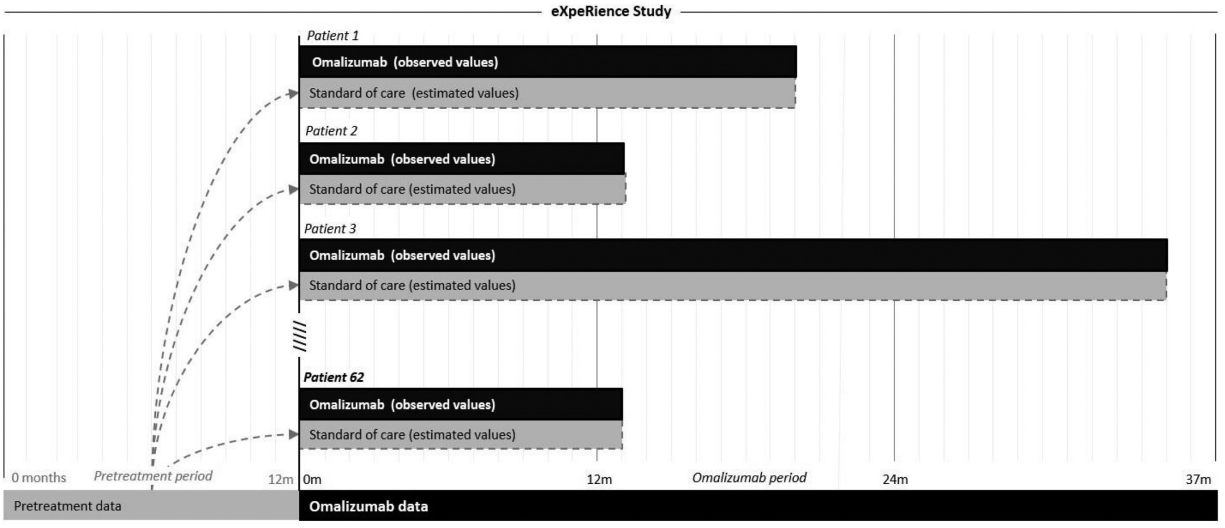

Figure 1 Scheme of pragmatic cost-effectiveness analysis of omalizumanb.

Portuguese registry participants, comparing the costs and effectiveness of two treatment alternatives for the management of severe allergic asthma: omalizumab plus standard of care and standard of care alone. A scheme representative of the analysis is presented in Fig. 1.

For the omalizumab plus standard of care treatment arm, the total number of exacerbations, clinical episodes (emergency room visits, hospitalizations, and unscheduled doctor visits), and days of absence (work and/or school) observed during the prospective phase of the study, as well as the

matching total amount of concomitant medication (standard of care), were available. The patient-year was calculated by the sum of observation time of each patient. GETE response was considered as observed after approximately 16 weeks of omalizumab initiation, considering a five-point scale: 1-excellent, 2-good, 3-moderate, 4-poor, and 5-worsening.[18]

For the standard of care treatment arm, to provide a term of comparison, corresponding retrospective data for each individual participant from the 12-month period before initiation of omalizumab was considered. During this period, patients were treated solely with standard of care. Retrospective data was extrapolated to a period equivalent to each participant's prospective period of the study.

As an example, consider a patient with 5 asthma exacerbations in the pre-omalizumab treatment period (12-months) and a 24-month omalizumab treatment period. In this study for the standard of care treatment arm, a period of 24 months with 10 exacerbations was considered (i.e., the estimated incidence rate in the pre-treatment period was 5 exacerbations/year and applying this rate to a period of time equivalent to the time period of the omalizumab arm, 24 months, gives 10 exacerbations). In a similar way to this example, the incidence rates, based on pre-treatment data, of the other indicators and applied to a period equivalent to the period of treatment with omalizumab were estimated by patient, for the standard of care treatment arm.

Since basal GETE does not exist, it was assumed that without any further change in treatment (e.g. continuing standard of care) the patientś health would worsen, so counterfactual GETE response on the standard of care at approximately 16 weeks was rated to be '5-worsening' for all participants.

In the absence of retrospective information on standard of care medication, concomitant medication recorded between baseline and the 16-week visit was conservatively used as a proxy.

Missing prospective data up to the final follow-up of each patient were imputed using a last observation carried forward (LOCF) approach, where deemed suitable. No data imputation was performed for retrospective missing data.

Effectiveness and cost outcomes

The number of exacerbations (severe and non-severe), the number of clinical episodes, the number of days absent from work and/or school, and GETE response to therapy were considered as effectiveness outcomes. As cost indicators, both direct and indirect costs were considered, costs are presented in euros, updated to 2017 values.[23] Direct costs relate to the cost of omalizumab, standard of care, and clinical episodes (emergency room visits, hospitalizations, and unscheduled doctor visits). Indirect costs relate to the societal cost of work absenteeism.

Unit costs for clinical episodes and drugs (Table 1) were taken from official sources within the Portuguese Health Authority.[24–26] The cost per hospitalization was determined as a weighted average of the costs of All Patient Refined Diagnosis Related Group numbers APR-DRG 141 (asthma, severity grades: 3 and 4) and APR-DRG 130 (respiratory system diagnosis with ventilator support 96+ hrs, severity grades: 1–4),[25] assuming that 7% of asthma related hospitalizations require mechanical ventilation.[27] Costs of emergency room visits and unscheduled doctor visits were obtained from the analytical accounting database for hospitals of the Portuguese National Health Service.[24] Drug costs were taken from the official drug retail price list.[26]

Table 2 Baseline characteristics of Portuguese patients (N = 62) in the eXpeRience registry.

	N/mean	%/sd
Female	43	69.4%
Age (years)	49.2	5.0
Duration of allergic asthma (years)	24.3	13.8
Daytime symptoms[a]	59	95.2%
Nocturnal symptoms/awakening[a]	51	82.3%
Limitations of activities[a]	55	88.7%
Need for reliever/rescue treatment[a]	57	91.9%
Uncontrolled asthma[b]	51	82.3%

sd – standard deviation.
[a] In the week prior to the visit.
[b] Patient's level of asthma control according to investigator assessment.

The indirect cost of a day of work absenteeism was based on the average monthly gross earnings of employees in Portugal 1097€ in 2015[28]), augmented by the employer contribution to Social Security (23.75%[29]) and the estimated cost to a firm of missed work (33%[30]).

Cost-effectiveness calculations

Final results are presented in terms of incremental cost-effectiveness ratios (ICER), representing the additional cost of obtaining one additional unit of effectiveness. Since no imputation of missing data was performed, the ICER related to each effectiveness outcome was calculated based only on participants for whom the necessary retrospective and prospective data was available to calculate the impact of omalizumab on both effectiveness and costs. For the GETE response to therapy, costs were calculated only up to the corresponding visit.

A univariate sensitivity analysis was performed for GETE response and cost parameters (hospitalization costs, emergency room visit costs, unscheduled doctor visit costs, and work absenteeism cost). For univariate sensitivity analysis of GETE was considered a baseline GETE response rated with 3 – ''moderate'' and 4 – ''poor'' instead of ''5-worsening'' for all participants. The different costs of hospitalization, varying according to the different severity grades of asthma and respiratory system diagnosis with ventilator support 96+ hrs and for the remind costs: emergency room visit costs, unscheduled doctor visit costs, and work absenteeism cost the sensitivity analysis was performed changing the costs according to the 95% confidence interval limits.

The analysis was performed with Microsoft Excel (2016).

Results

The Portuguese subpopulation of the eXpeRience registry enrolled 62 patients—69.4% of which were female—with a mean age of 49.2 years (Table 2). At baseline, the mean

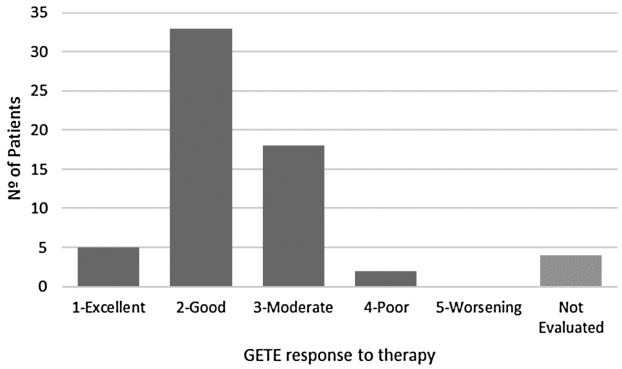

Figure 2 Distribution of GETE response to omalizumab plus standard of care for the Portuguese patients in the eXpeRience registry.

duration of allergic asthma was 24.3 years. According to investigator assessment, 82.3% of patients had uncontrolled asthma. Most patients were experiencing symptoms, limitations in activities, and the need for rescue treatment. The average duration of prospective observation of these patients was 22 months.[20]

Effectiveness

Retrospective and prospective information on exacerbations was available for a total of 58 patients (Table 3). Under omalizumab plus standard of care, 151 exacerbations occurred for a total follow-up of 103 patient-years, leading to a rate of 1.5 exacerbations per patient-year. Continuing the pre-omalizumab pattern of exacerbations, during the same total follow-up, would have led to an estimated 845 exacerbations under standard of care alone, corresponding to a rate of 8.2 exacerbations per patient-year. This implies an 82.1% reduction in the incidence of exacerbations for omalizumab plus standard of care as compared to standard of care alone. Similar results were obtained for the remaining event-related effectiveness outcomes (Table 3).

For GETE response to therapy, prospective data was available for 58 of the 62 patents (Fig. 2) after a median follow-up of 17 weeks. Considering the previously introduced five-point scale, average GETE response for omalizumab plus standard of care was estimated at 2.3, corresponding to a good-to-moderate response. With the counterfactual average GETE response on standard of care of '5-worsening' for all participants, this implies a 54.1% reduction in GETE-score.

Costs

For 54 Portuguese patients enrolled in the eXpeRience registry (Table 3), sufficient information on clinical episodes was available to estimate the impact of add-on therapy with omalizumab on direct costs. As can be seen from Table 4, over the considered time-horizon average 22 months, an estimated additional annual per-patient cost of 14,932€ due to omalizumab therapy is expected to be off-set by a saving of 1844€ in the remaining direct costs (85.3% of which due to avoided hospitalizations and emergency room visits). This leads to a net increase of 13,088€ in annual per-person direct costs.

The impact on indirect costs due to the introduction of omalizumab could only be estimated on the basis of 22 patients for whom data on work absenteeism was available (Table 3). Given the 72.3% reduction in missed days of work, for these patients, a reduction in indirect costs of 818€ per person-year was estimated (Table 5).

Cost effectiveness

As described earlier, ICERs were estimated only for patients for whom both the effectiveness outcome and a full cost estimation was possible.

Of the 58 patients for whom effectiveness estimates are available in terms of the number of exacerbations (Table 3), 5 patients were not included in the direct cost estimate due to a lack of information about clinical episodes. For the remaining 53 patients, cost-effectiveness results are presented in Table 6. Over an average follow-up of 1.8 years, a total of 559 exacerbations were estimated to have been avoided with omalizumab plus standard of care over standard of care alone. This comes to an estimated increase in total direct costs of 1,253,490€, resulting in an ICER of 2244€ per exacerbation avoided.

With the exception of GETE response to therapy, for the remaining effectiveness outcomes a similar analysis was performed (Table 6), leading to ICERs of 2592€ per clinical episode avoided (54 patients), 1058€ per day of work absenteeism avoided (21 patients), and 1096€ per day of school absenteeism avoided (5 patients). For work absenteeism, the only outcome for which indirect costs were considered, the increase in total costs of 475,273€ is the result of an increase of 502,538€ in total direct costs, off-set by a decrease in total indirect costs of 27,265€.

For GETE response to therapy, with costs calculated only up to the corresponding response evaluation visit, over an average follow-up of 19 weeks (0.4 years), treating patients with omalizumab plus standard of care as compared to standard of care alone is estimated to lead to an ICER of 1750€ per unit decrease in GETE classification.

Sensitivity analysis

The univariate sensitivity analysis shows that considering the different costs of hospitalization, the ICER varies between 2208€ and 2258€ per exacerbation avoided. Changing the cost of work absenteeism (cost per absent day) according to the 95% confidence interval limits, the ICER per avoided day of work absenteeism varies between 1055€ and 1062€ (Table 7). Finally, considering a GETE response rated with 3 – ''moderate'' and 4 – ''poor'' instead of ''5-worsening'' for all participants for the counterfactual standard of care generates ICER values of 7104€ and 2808€ per unit decrease in GETE classification, respectively (Table 8).

Discussion

Asthma is a chronic disease representing a major public health problem with evident socio-economic consequences

Table 3 Estimated effectiveness with omalizumab plus standard of care and standard of care alone for the Portuguese patients in the eXpeRience registry.

	Patients	Follow-up (PY)	Events	Rate (Events/PY)	Percentage reduction
Exacerbations					
SoC	58	103	845	8.2	
Omalizumab + SoC			151	1.5	82.1%
Clinical episodes					
SoC	54	98	593	6.1	
Omalizumab + SoC			100	1.0	83.1%
Work absenteeism					
SoC	22	37	688[a]	18.6	
Omalizumab + SoC			191[a]	5.2	72.3%
School absenteeism					
SoC	5	9	209[a]	22.9	
Omalizumab + SoC			60[a]	6.6	71.4%

SoC – standard of care; PY – person-years.
[a] Days.

Table 4 Estimated direct costs with omalizumab plus standard of care and standard of care alone for the Portuguese patients in the eXpeRience registry (based on 54 patients for which sufficient information on clinical episodes was available).

	Total cost (€)	ΔTotal cost (€)	Cost/PY (€)	ΔCost/PY (€)
Omalizumab cost				
SoC	0€		0€	
Omalizumab + SoC	1,456,780€	1,456,780€	14,932€	14,932€
Standard of care cost				
SoC	86,706€		889€	
Omalizumab + SoC	77,544€	−9162€	795€	−94€
Emergency room visits				
SoC	46,331€		475€	
Omalizumab + SoC	5058€	−41,272€	52€	−423€
Hospitalizations				
SoC	139,119€		1426€	
Omalizumab + SoC	27,025€	−112,094€	277€	−1149€
Unscheduled doctor visits				
SoC	22,779€		233€	
Omalizumab + SoC	5446€	−17,333€	56€	−178€
Total direct costs				
SoC	294,934€		3023€	
Omalizumab+SoC	1,571,853€	1,276,918€	16,111€	13,088€

SoC – standard of care; PY – person-years.

Table 5 Estimated indirect costs with omalizumab plus standard of care and standard of care alone for the Portuguese patients in the eXpeRience registry (based on 22 patients for which sufficient information on work absenteeism was available).

	Total cost (€)	ΔTotal cost (€)	Cost/PY (€)	ΔCost/PY (€)
Indirect cost				
SoC	41,743€		1131€	
Omalizumab+SoC	11,571€	−30,172€	314€	−818€

SoC – standard of care; PY – person-years.

in most developed countries.[4–6] The profile of complications and the intense need for differentiated health care in patients with severe persistent asthma results in costs three to four times higher than those of patients with less serious asthma.[5]

Clinical trials and observational studies have further demonstrated that patients treated with omalizumab plus

Table 6 Estimated incremental cost-effectiveness ratios for omalizumab plus standard of care as compared to standard of care alone for the Portuguese patients in the eXpeRience registry.

	Average follow-up (Years)	SoC	OML + SoC	Balance	ICER (€/evt. av.)
Exacerbations (N = 53)					
Events	1.8	704	145	−559	2244€
Costs (€)		292,533€	1,546,024€	1,253,490€	
Clinical episodes (N = 54)					
Events	1.8	593	100	−493	2592€
Costs (€)		294,934€	1,571,853€	1,276,918€	
Work absenteeism[a] (N = 21)					
Events	1.7	640	191	−449	1058€
Costs (€)		147,572€	622,845€	475,273€	
School absenteeism (N = 5)					
Events	1.8	209	60	−149	1096€
Costs (€)		10,402€	174,029€	163,628€	
GETE[b] (N = 52)					
Score	0.4	260	122	−138	1750€
Costs (€)		58,068€	299,596€	241,528€	

OML – omalizumab; SoC – standard of care; evt. av. – event avoided.
[a] Includes both direct and indirect costs.
[b] Time horizon up to the GETE response visit only.

standard of care have a reduction of asthma exacerbations, fewer clinical episodes and present less days of work and school absenteeism than patients treated with standard of care alone.[17–21] Savings in both direct and indirect costs, however, are likely to be off-set by an increase in drug costs due to the add-on nature of omalizumab therapy.

The present health economic evaluation considers as primary source for effectiveness data and resource consumption associated with the management of severe allergic asthma with omalizumab, data from the 62 Portuguese participants of the eXpeRience registry.[20] In health economic evaluation, the inclusion of real-world data has the potential to provide policy makers with a more relevant and realistic picture of costs and effects in daily practice than an RCT based evaluation.[31]

Our results are comparable to those presented in other cost-effectiveness studies on omalizumab therapy for severe asthma in real clinical practice.[32–34] In a study based on 79 Spanish patients receiving omalizumab for 10 months, a reduction of 7.75 in number of exacerbations with emergency room visits in 10 months was found.[33] Another Spanish study, based on 71 patients receiving omalizumab for 12 months, found a reduction of 7.72 in annual exacerbations rate, including a reduction of 4.17 in exacerbations by year leading to either an emergency room visit or hospitalization.[34] This study further estimated an 11,483€ increase in annual direct costs, leading to an ICER of 1487€ per avoided exacerbation. A study of 23 Italian patients receiving omalizumab over an average follow-up of 10 months showed an annual reduction of 6.27 clinical episodes and 17.61 days of inactivity.[32]

In the eXpeRience registry, prior to omalizumab treatment, an average rate of 4.9 exacerbations per year was observed. During the omalizumab treatment phase of the study, after 12 months, this rate decreased by 80% to an average rate of 1 exacerbation per year. For the Portuguese subgroup of eXpeRience patients, prior to omalizumab treatment, an average rate of 8.2 exacerbations per year was observed, whereas after 12 months of omalizumab treatment, 1.5 exacerbations per year were observed, close to the 12-month rate of the overall eXpeRience registry population, despite a higher baseline exacerbation rate. Besides potential differences in treatment optimization and asthma control at registry entry between the different countries included in the eXpeRience registry, the higher number of exacerbations prior to omalizumab treatment in the Portuguese subgroup of the registry might be explained, in part, by the geographical location, with a long Atlantic coast and high levels of humidity, influencing the severity of the disease.[35–37]

Despite the advantages of the inclusion of Portuguese real-world data from the eXpeRience registry, our study is not without limitations. First, due to the lack of a comparator arm in the eXpeRience registry, a standard of care arm had to be simulated based on retrospective data on exacerbations, healthcare utilization, and absenteeism. Second, with an average follow-up of only 22 months, it was not possible to consider a lifetime time horizon, typically used when considering the health economic evaluation of therapies for chronic diseases. Third, since the Portuguese participants in the eXpeRience registry only responded to the mini-AQLQ questionnaire,[38] for which no conversion algorithm to EQ-5D utilities is available, it was not possible to incorporate health outcomes by means of the quality of life component. Fourth, indirect costs are based on limited data about the number of missed days of work and could not be stratified according to the type of job of patients, due to a lack of detailed information. Nevertheless, given the implications of the disease on work absenteeism, the analysis was performed. Fifth, as in the current analysis the results for the omalizumab treatment arm are ''as observed'' in the eXpeRience registry, no probabilistic sensitivity analysis can be performed on the outcomes taken directly from the registry. Last, given the pragmatic nature of the analysis, data impu-

Table 7 Univariate sensitivity analysis at costs parameters.

	Exacerbations		Clinical episodes		Work absenteeism		School absenteeism		GETE	
	Balance	ICER (€/evt. av.)	Balance	ICER (€/evt. av.)	Balance	ICER (€/evt. av.)	Balance	ICER (€/evt. av.)	Balance	ICER (€/evt. av.)
Base case	1,253,490€	2244€	1,276,918€	2592€	475,273€	1058€	163,628€	1096€	241,528€	1750€
Asthma severity grade: 3 - 2768.82€	1,273,707€	2280€	1,297,135€	2633€	479,650€	1068€	163,628€	1096€	245,103€	1776€
Asthma severity grade: 4 - 3987.34€	1,233,274€	2208€	1,256,701€	2551€	470,895€	1048€	163,628€	1096€	237,952€	1724€
Respiratory system diagnosis with ventilator support 96+ hrs severity grade: 1–3,140.08€	1,261,388€	2258€	1,284,816€	2608€	476,983€	1062€	163,628€	1096€	242,924€	1760€
Respiratory system diagnosis with ventilator support 96+ hrs severity grade: 4 - 3767.75€	1,240,560€	2221€	1,263,988€	2566€	472,473€	1052€	163,628€	1096€	239,241€	1734€
Unscheduled doctor visit (LL 95%CI) - 78.12€	1,256,258€	2249€	1,279,745€	2597€	476,019€	1060€	163,858€	1098€	242,004€	1754€
Unscheduled doctor visit (UL 95%CI) - 108.57€	1,250,723€	2239€	1,274,092€	2586€	474,526€	1056€	163,397€	1095€	241,051€	1747€
Emergency room visit (LL 95%CI) - 130.33€	1,259,076€	2254€	1,282,503€	2603€	477,765€	1064€	163,933€	1098€	242,536€	1758€
Emergency room visit (UL 95%CI) - 171.13€	1,247,905€	2234€	1,271,333€	2580€	472,781€	1052€	163,322€	1094€	240,519€	1743€
Cost to a firm of missed work (LL 95%CI: 25%) - 57.04€	1,253,490€	2244€	1,276,918€	2592€	476,913€	1062€	163,628€	1096€	241,528€	1750€
Cost to a firm of missed work (UL 95%CI: 40%) - 63.89€	1,253,490€	2244€	1,276,918€	2592€	473,838€	1055€	163,628€	1096€	241,528€	1750€

SoC – Standard of care; evt. av. – event avoided.

Table 8 Univariate sensitivity analysis for GETE response.

	Base case GETE Score SoC: 5		GETE Score SoC: 4		GETE Score SoC: 3	
	Balance	ICER (€/evt. av.)	Balance	ICER (€/evt. av.)	Balance	ICER (€/evt. av.)
GETE Score	−138	1750€	−86	2808€	−34	7104€
Costs (€)	241,528€		241,528€		241,528€	

SoC – Standard of care; evt. av. – event avoided; GETE scale: 3 – ''moderate'', 4 – ''poor'' and 5 – ''worsening''.

tation methods for retrospective missing data (e.g.: Mutiple Imputation by Chained Equations[39] and others[40–42] were not considered.

In conclusion, the evidence produced in this study demonstrates that adding omalizumab to the treatment of patients with uncontrolled severe persistent asthma reduces the number of exacerbations, improving overall treatment effectiveness at an acceptable cost from a societal perspective.

Conflict of interests

AA: Declares collaborating and receiving fees from AstraZeneca, GlaxoSmithKline, Novartis, Laboratórios TEVA, Mundipharma, and Roche, through either participation in advisory board or consultancy meetings or congress symposia.

MPB: Speaker and Chair of symposia by invitation from Novartis Pharma AG. Scientific adviser of Diater.

BV: No conflict of interest.

SR: No conflict of interest.

JF: No conflict of interest.

Declaration of financial/other relationships

Co-authors SR, BV, and JF are employees of EXIGO, a consulting company that provides services to several pharmaceutical companies, including Novartis Farma SA and Novartis Pharma AG, and received funding to complete this analysis.

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ORIGINAL ARTICLE

Evaluation of reproducible and transparent research practices in pulmonology

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Reproducibility of results;
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Abstract
Background: Study reproducibility is valuable for validating or refuting results. Provision of reproducibility indicators, such as materials, protocols, and raw data in a study improve its potential for reproduction. Efforts to reproduce noteworthy studies in the biomedical sciences have resulted in an overwhelming majority of them being found to be unreplicable, causing concern for the integrity of research in other fields, including medical specialties. Here, we analyzed the reproducibility of studies in the field of pulmonology.
Methods: 500 pulmonology articles were randomly selected from an initial PubMed search for data extraction. Two authors scoured these articles for reproducibility indicators including materials, protocols, raw data, analysis scripts, inclusion in systematic reviews, and citations by replication studies as well as other factors of research transparency including open accessibility, funding source and competing interest disclosures, and study preregistration.
Findings: Few publications included statements regarding materials (10%), protocols (1%), data (15%), and analysis script (0%) availability. Less than 10% indicated preregistration. More than half of the publications analyzed failed to provide a funding statement. Conversely, 63% of the publications were open access and 73% included a conflict of interest statement.
Interpretation: Overall, our study indicates pulmonology research is currently lacking in efforts to increase replicability. Future studies should focus on providing sufficient information regarding materials, protocols, raw data, and analysis scripts, among other indicators, for the sake of clinical decisions that depend on replicable or refutable results from the primary literature.

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Key messages

What is the key question?

Are practices to improve study replicability and transparency being applied in pulmonology research?

What is the bottom line?

Current research in pulmonology is lacking in efforts to improve study replicability.

Why read on?

Study replicability is a fundamental aspect of the scientific method and practices to ensure this should be improved upon for the betterment of research that could eventually lead to clinical decisions.

Introduction

Reproducibility—the ability to duplicate a study's results using the same materials and methods as the original investigator—is central to the scientific method.[1] Study reproducibility establishes confidence in the efficacy of therapies, while results that contradict original findings may lead to overturning previous standards. Herrera-Perez et al. recently evaluated 396 medical reversals in which suboptimal clinical practices were overturned when randomized controlled trials yielded results contrary to current practices.[2] Given the evolving nature of evidence-based patient care, studies must be conducted in a way that fosters reproducibility and transparency. Further, materials, protocols, analysis scripts, and patient data must be made available to enable verification.

Efforts supporting reproducibility are becoming more widespread owing to the open science movement. In 2013, the Center for Open Science was established to ''increase the openness, integrity, and reproducibility of scientific research''.[3] The center sponsored two large-scale reproducibility efforts: a series of 100 replication attempts in psychology and a series of 50 landmark cancer biology study replication attempts. In the first, investigators successfully reproduced only 39% of the original study findings.[4] In the second, efforts were halted after only 18 replications because of lack of information and materials from authors, insufficient funding, and insufficient time to perform all the experiments.[5] The center also created the Open Science Framework, a repository in which authors may deposit study protocols, participant data, analysis scripts, and other materials needed for study reproduction. More recently, the center created Transparency and Openness Promotion Guidelines, which include eight transparency standards and provides guidance for funders and journals, and initiated the use of badges for journals that adopt reproducible practices.

Current estimates of study reproducibility are alarming. In the biomedical sciences, reproducibility rates may be as low as 25%.[6] One survey of 1576 scientists found that 90% of respondents believed science was experiencing a reproducibility crisis; 70% reported not being able to reproduce another investigator's findings, and more than half reported an inability to reproduce their own findings.[7] The picture is even less clear in the clinical sciences. Ioannidis found that of 49 highly cited original research publications, seven were refuted by newer studies, and seven suggested higher efficacy than follow-up results; only 22 were successfully replicated.[8] The National Institutes of Health and the National Science Foundation have responded to this crisis by taking measures to ensure that studies funded by tax dollars are more reproducible. However, little is known about the extent to which reproducibility practices are used in clinical research.

In this study, we evaluated reproducible and transparent research practices in the pulmonology literature.[11] Our goals were (i) to determine areas of strength and weakness in current use of reproducible and transparent research practices and (ii) to establish a baseline for subsequent investigations of the pulmonology literature.

Methods

This observational study employed a cross-sectional design. We used the methodology of Hardwicke et al.,[11] with modifications. In reporting this study, we follow the guidelines for meta-epidemiological methodology research[9] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[10] This study did not satisfy the regulatory definition for human subjects research as specified in the Code of Federal Regulations and therefore was not subject to institutional review board oversight. We have listed our protocol, materials, and data on Open Science Framework (https://osf.io/n4yh5/).

Journal and publication selection

The National Library of Medicine catalog was searched by DT using the subject terms tag ''Pulmonary Medicine[ST]'' to identify pulmonary medicine journals on May 29, 2019. To meet inclusion criteria, journals had to be published in English and be MEDLINE indexed. We obtained the electronic ISSN (or linking ISSN) for each journal in the NLM catalog meeting inclusion criteria. Using these ISSNs, we formulated a search string and searched PubMed on May 31, 2019, to locate publications published between January 1, 2014, to December 31, 2018. We then randomly selected 500 publications for data extraction using Excel's random number function (https://osf.io/zxjd9/). We used OpenEpi version 3.0 to conduct a power analysis to estimate sample size. Data availability was the primary outcome due to its importance for study reproducibility.[9] The population size of studies published in MEDLINE-indexed journals from which we selected our random sample was 299,255 with a hypothesized frequency of 18.5% for the factor in the population (which was based upon data obtained by Hardwicke et al.[11]); a confidence limit of 5%; and a design factor of 1. Based on these assumptions, our study would require a sample size of 232. To allow for the attrition of publications that would not meet inclusion criteria, we randomly sampled a total of 500 publications. Previous investigations, upon which this study is based, have included random samples of 250 publications in the social sciences and 150 publications in the biomedical sciences.

Extraction training

Prior to data extraction, two investigators (JN, CS) underwent training to ensure inter-rater reliability. The training

included an in-person session to review the study design, protocol, Google form, and location of the extracted data elements in two publications. The investigators were next provided with three additional publications from which to extract data. Afterward, the pair reconciled differences by discussion. This training session was recorded and deposited online for reference (https://osf.io/tf7nw/). Prior to extracting data from all 500 publications, the two investigators extracted data from the first 10, followed by a final consensus meeting. Data extraction for the remaining 490 publications followed, and a final consensus meeting was held to resolve disagreements. A third author (DT) was available for adjudication, if necessary.

Data extraction

The two investigators extracted data from the 500 publications in a duplicate and blinded fashion. A pilot-tested Google form was created from Hardwicke et al.,[11] with additions (see Table 1 for a description of the indicators of reproducibility and transparency). This form prompted coders to identify whether a study had important information that needed to be reproducible (https://osf.io/3nfa5/). The extracted data varied by study design. Studies without empirical data (e.g., editorials, commentaries [without reanalysis], simulations, news, reviews, and poems) had only the publication characteristics, conflict of interest statement, financial disclosure statement, funding sources, and open access availability. Non-Empirical studies do not have the expectation of being reproduced, and as such do not contain the indicators used for this study. Empirical studies included clinical trials, cohort, case series, secondary analysis, chart review, and cross-sectional. We catalogued the most recent year and 5-year impact factor of the publishing journals. Finally, we expanded the funding options to include university, hospital, public, private/industry, or nonprofit. In order to look more in-depth at areas of pulmonology research, the journal and sub-specialty of each empirical study was analyzed.

Verification of Open Access Status of publications

We used Open Access Button (http://www.openaccessbutton.org) to identify publications as being publicly available. Both the journal title and DOI were used in the search to mitigate chances of missing an article. If Open Access Button could not locate an article, we searched Google and PubMed to confirm open access status.

Publication citations included in research synthesis and replication

For empirical studies, Web of Science was used to identify whether the publication was replicated in other studies and had been included in systematic reviews and/or meta-analyses. To accomplish these tasks, two investigators (CS, JN) inspected the titles, abstracts, and introductions of all publications in which the reference study was cited. This process was conducted in a duplicate, blinded fashion.

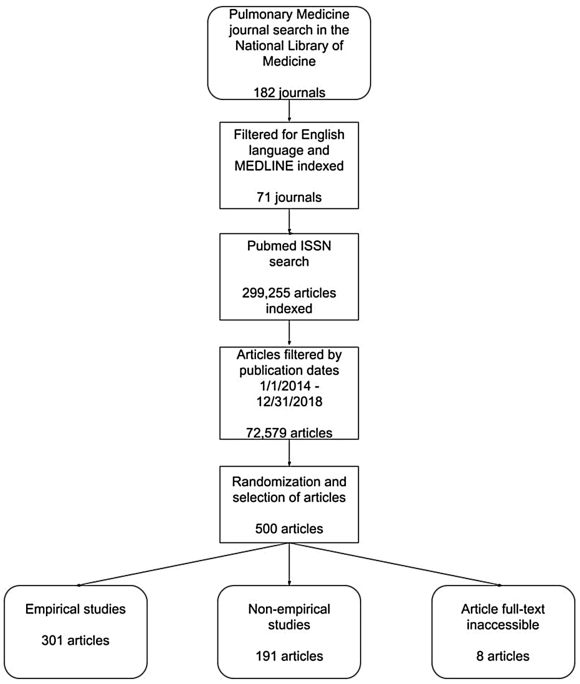

Figure 1 Article selection and filtering process.

Data analysis

We used Microsoft Excel to calculate descriptive statistics and 95% confidence intervals (95% CIs). The Wilson's Score for binomial proportions was used to create confidence intervals in this study.[12]

Role of the funding source

This study was funded through the 2019 Presidential Research Fellowship Mentor – Mentee Program at Oklahoma State University Center for Health Sciences. The funding source had no role in the study design, collection, analysis, interpretation of the data, writing of the manuscript, or decision to submit for publication.

Results

Study selection and article accessibility

Our PubMed search identified 299,255 publications. Limiting our search to articles published from January 1, 2014, to December 31, 2018, yielded 72,579 publications, from which 500 were randomly selected. Of these 500 publications, 312 were open access and 180 were behind a paywall. Eight publications could not be accessed by investigators and were thus excluded, leaving 492 for further analysis (Fig. 1). Characteristics of the included publications can be found in Table 2.

Availability of reproducibility indicators

Fig. 2 depicts an overview of our study results. A total of 238 empirical studies (excluding 56 case studies/case

Table 1 Indicators of reproducibility.

Reproducibility indicator	Number of studies	Role in producing transparent and reproducible science
Articles		
Availability of article (paywall or public access)	All (n = 500)	Widely accessible articles increase transparency
Funding		
Statement of funding sources	All included studies (n = 492)	Disclosure of possible sources of bias
Conflict of interest		
Statement of competing interests	All included studies (n = 492)	Disclosure of possible sources of bias
Evidence synthesis		
Citations in systematic reviews or meta-analyses	Empirical studies excluding systematic reviews and meta-analyses (n = 294)	Evidence of similar studies being conducted
Protocols		
Availability statement, and if available, what aspects of the study are included	Empirical studies excluding case studies (n = 245)	Availability of methods and analysis needed to replicate study
Materials		
Availability statement, retrieval method, and accessibility	Empirical studies excluding case studies and systematic reviews/meta-analysis (n = 238)	Defines exact materials needed to reproduce study
Raw data		
Availability statement, retrieval method, accessibility, comprehensibility, and content	Empirical studies excluding case studies (n = 245)	Provision of data collected in the study to allow for independent verification
Analysis scripts		
Availability statement, retrieval method, and accessibility	Empirical studies excluding case studies (n = 245)	Provision of scripts used to analyze data
Preregistration		
Availability statement, retrieval method, accessibility, and content	Empirical studies excluding case studies (n = 245)	Publicly accessible study protocol
Replication study		
Is the study replicating another study, or has another study replicated the study in question	Empirical studies excluding case studies (n = 245)	Evidence of replicability of the study

Bold values signifies to increase contrast between entries.

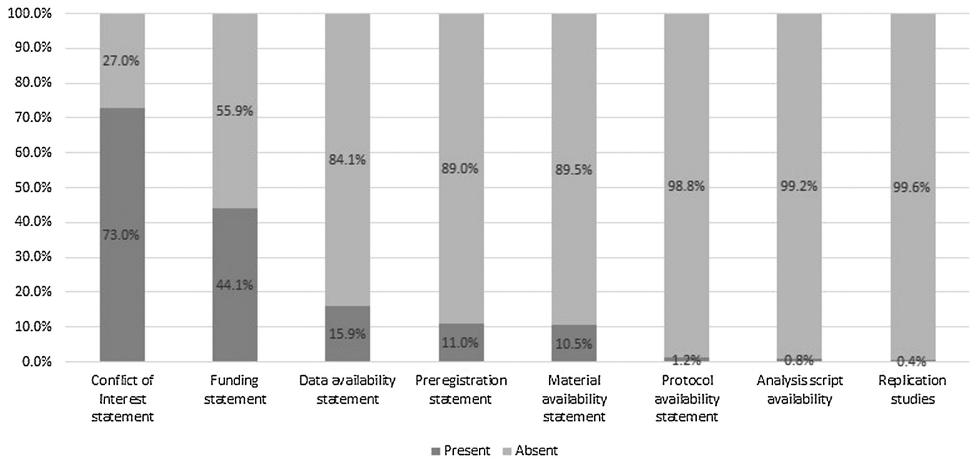

Figure 2 Proportion of studies with reproducibility indicators.

Table 2 Indicators of reproducibility in pulmonology studies.

Characteristics		N (%)	95% CI
Funding N = 492	University	8 (1.6)	0.5—2.7
	Hospital	5 (1.0)	0.1—1.9
	Public	65 (13.2)	10.2—16.2
	Private/industry	33 (6.7)	4.5—8.9
	Non-profit	11 (2.2)	0.9—3.5
	No statement listed	275 (55.9)	51.5—60.2
	Multiple sources	41 (8.3)	5.9—10.8
	Self-funded	1 (0.2)	0—0.6
	No funding received	53 10.8)	8.0—13.5
Conflict of interest statement N = 492	Statement, one or more conflicts of interest	98 (19.9)	16.4—23.4
	Statement, no conflict of interest	261 (53.2)	48.8—57.5
	No conflict of interest statement	132 (26.9)	23.0—30.8
	Statement inaccessible	1 (0.2)	0—0.6
Data availability N = 245	Statement, some data are available	37 (15.1)	12.9—18.2
	Statement, data are not available	2 (0.8)	0—1.6
	No data availability statement	206 (84.1)	80.8—87.3
Material availability N = 238	Statement, some materials are available	24 (10.1)	7.4—12.7
	Statement, materials are not available	1 (0.4)	0—1.0
	No materials availability statement	213 (89.5)	86.8—92.2
Protocol availability N = 245	Full protocol	3 (1.2)	0.3—2.2
	No protocol	242 (98.8)	97.8—99.7
Analysis scripts N = 245	Statement, some analysis scripts are available	2 (0.8)	0—1.6
	Statement, analysis scripts are not available	0	0
	No analysis script availability statement	243 (99.2)	98.4—100
Replication studies N = 245	Novel study	244 (99.6)	99.0—100
	Replication	1 (0.4)	0—1.0
Cited by systematic review or meta-analysis N = 294	No citations	259 (88.1)	85.3—90.9
	A single citation	20 (6.8)	4.6—9.0
	One to five citations	14 (4.8)	2.9—6.6
	Greater than five citations	1 (.0.3)	0—0.8
	Excluded in SR or MA	1 (0.3)	0—0.8
Preregistration N = 245	Statement present, preregistered	23 (9.4)	6.8—11.9
	Statement present, not pre−registered	4 (1.6)	0.5—2.7
	No preregistration statement	218 (89.0)	86.2—91.7
Frequency of reproducibility indicators in selected studies N = 301	Number of indicators present in study		
	0	49 (16.3)	—
	1	119 (39.5)	—
	2—5	133 (44.2)	—
	6—8	0	—
Open access N = 492	Found via open access button	215 (43.7	39.4—48.0
	Yes-found article via other means	97 (19.7)	16.2—23.2
	Could not access through paywall	180 (36.6)	32.4—40.8

series, six meta-analyses, and one systematic review) were evaluated for material availability. The majority of studies offered no statement regarding availability of materials ($n = 213$; 89.50% [95% CI, 86.81%–92.18%]). Twenty-four studies (10.08% [7.44%–12.72%]) had a clear statement regarding the availability of study materials. One study (0.42% [0%–0.99%]) included an explicit statement that the materials were not publicly available. Eighteen of the 24 materials files were accessible; the remaining six either led to a broken URL link or a pay-walled request form.

A total of 245 empirical studies (excluding 56 case studies/case series) were assessed for availability of protocols, raw data, and analysis scripts. Three studies provided access to a protocol (1.22% [0.26%–2.19%]). Data availability statements were more common, with 37 studies (15.10% [11.96%–18.24%]) including a statement that at least par-

tial data were available. Analysis scripts were found in two studies (0.82% [0.03%–1.61%]). More information on these metrics is presented in Supplemental Table 1 & 2.

Study preregistration

A total of 245 empirical studies (excluding 56 case studies/case series) were searched for a statement regarding study preregistration. Few studies included statements: 23 (9.39% [6.83%–11.94%]) declared preregistration, while four (1.63% [0.52%–2.74%]) explicitly disclosed that they were not preregistered. More information on preregistration is presented in Supplemental Table 1.

Study replication and citation analysis

Of 245 empirical studies analyzed, only one (0.41% [0%–0.97%]) reported replication of the methods of a previously published study. No studies were cited by a replication study. A total of 294 of the 301 empirical studies (excluding six meta-analyses and one systematic review) were evaluated to determine whether any had been included in a systematic review or meta-analysis. Twenty studies (6.80% [4.60%–9.01%]) were cited once in a systematic review or meta-analysis, 14 studies (4.76% [2.90%–6.63%]) were cited in two to five systematic reviews or meta-analyses, and one study (0.34% [0%–0.85%]) was cited in more than five systematic reviews or meta-analyses. One study (0.34% [0%–0.85%]) was explicitly excluded from a systematic review.

Conflict of interest and funding disclosures

All 492 publications were assessed for their inclusion of a conflict of interest statement and/or a funding statement. A majority ($n = 359$; 73.08%) included a conflict of interest statement, with 261 declaring no competing interests (53.16% [48.78%–57.53%]). More than half of the publications failed to provide a funding statement ($n = 275$; 55.89%; Table 2). In publications with a funding statement, public funding was the most common source ($n = 65$; 13.21%).

Journal and sub-specialty characteristics

The total number of studies sampled from each journal is listed in Table 3 with the average number of reproducibility indicators with it. All 58 journals had at least one publication with empirical data and *The Annals of Thoracic Surgery* had the most with 33. The subspecialties of pulmonology are listed in Table 4 with the number of publications and average reproducibility indicators. Notable subjects were 102 in interventional pulmonology, 66 in obstructive lung disease, and 57 in critical care medicine. Publications over pulmonary hypertension averaged the most reproducibility indicators at 2.

Table 3 Number of studies per pulmonology subspecialty and mean number of reproducibility indicators.

Pulmonology subspecialty	Number of studies	Mean number of reproducibility indicators
Interventional pulmonology	102	0.98
Tobacco treatment	3	1
Lung transplantation	8	1.13
Sarcoidosis	4	1.25
Neuromuscular disease	3	1.33
Cystic fibrosis	9	1.44
Critical care medicine	57	1.47
Lung cancer	27	1.52
Obstructive lung disease	66	1.76
Interstitial lung disease	9	1.78
Sleep medicine	9	1.89
Pulmonary hypertension	4	2

Discussion

In this cross-sectional review of pulmonology publications, a substantial majority failed to provide materials, participant data, or analysis scripts. Many were not preregistered and few had an available protocol. Reproducibility has been viewed as an increasingly troublesome area of study methodology.[13] Recent attempts at reproducing preclinical[14,15] and clinical studies have found that only 25%–61% of studies may be successfully reproduced.[6,16] Within the field of critical care medicine, a recent publication found that only 42% of randomized trials contained a reproduction attempt with half of those reporting inconsistent results compared to the original.[17] Many factors contribute to limited study reproducibility, including poor (or limited) reporting of study methodology, prevalence of exaggerated statements, and limited training on experimental design in higher education.[18] In an effort to limit printed pages and increase readability, journals may request that authors abridge methods sections.[19] Here, we briefly comment on selected indicators to present a balanced view of the perspectives of those in favor of reproducibility and transparency and those who resist enacting such changes.

First, data sharing allows for the independent verification of study results or reuse of that data for subsequent analyses. Two sets of principles exist. The first, known as FAIR, outlines mechanisms for findability, accessibility, interoperability, and reusability. FAIR principles are intended to apply to study data as well as the algorithms, tools, and workflows that led to the data. FAIR advocates that data be accessible to the right people, in the right way, and at the right time.[20] A second set of principles relate to making data available to the public for access, use, and share without licenses, copyrights, or patents.[21] While we advocate for data sharing, we recognize that it is a complex issue. First, the process for making data available for others' use requires skills. Further, the process, which includes the construction of data dictionaries and data curation, is time consuming. Furthermore, concerns exist with regard to unrestricted access to data facilitating a culture of ''research parasites,'' a term coined by Drazen and Longo[22] that suggests that secondary researchers might exploit primary research data for publication. Drazen and Longo also cautioned that secondary authors might not understand the decisions made when defi-

Table 4 Number of studies per journal and mean number of reproducibility indicators.

Journal title	Number of studies	Mean number of reproducibility indicators
Journal of cardiothoracic and vascular anesthesia	12	0.25
The annals of thoracic surgery	33	0.33
Respiration; international review of thoracic diseases	3	0.67
Respirology	3	0.67
The thoracic and cardiovascular surgeon	7	0.86
Respiratory investigation	1	1
Annals of thoracic and cardiovascular surgery	4	1
Canadian respiratory journal	2	1
Seminars in thoracic and cardiovascular surgery	1	1
Jornal Brasileiro de pneumologia	2	1
Journal of thoracic imaging	1	1
Respiratory care	3	1
Current allergy and asthma reports	1	1
European respiratory review	1	1
General thoracic and cardiovascular surgery	2	1
Journal of bronchology & interventional pulmonology	6	1.17
Annals of the American thoracic society	12	1.7
Respiratory physiology & neurobiology	4	1.25
Thoracic cancer	4	1.25
The journal of heart and lung transplantation	4	1.25
Heart, lung & circulation	7	1.29
The European respiratory journal	7	1.29
Lung	3	1.33
Pulmonary pharmacology & therapeutics	3	1.33
Journal of cystic fibrosis	6	1.33
American journal of physiology. lung cellular and molecular physiology	3	1.33
Interactive cardiovascular and thoracic surgery	8	1.38
The journal of thoracic and cardiovascular surgery	13	1.385
The clinical respiratory journal	5	1.4
Tuberculosis (Edinburgh, Scotland)	5	1.4
Journal of breath research	5	1.4
Experimental lung research	2	1.5
The journal of asthma	4	1.5
Clinical lung cancer	2	1.5
The international journal of tuberculosis and lung disease	5	1.6
Respiratory medicine	5	1.6
Chest	5	1.6
European journal of cardio-thoracic surgery	9	1.67
Thorax	7	1.71
Journal of cardiothoracic surgery	4	1.75
Respiratory research	9	1.78
Annals of allergy, asthma & immunology	10	1.8
American journal of respiratory and critical care medicine	5	1.8
Asian cardiovascular & thoracic annals	8	2
Journal of cardiopulmonary rehabilitation and prevention	1	2
Heart & lung : the journal of critical care	1	2
Sleep & breathing	7	2
Allergy and asthma proceedings	4	2
Chronic respiratory disease	2	2
International journal of chronic obstructive pulmonary disease	10	2
Multimedia manual of cardiothoracic surgery	1	2
The Lancet. Respiratory medicine	4	2
Pediatric pulmonology	8	2.13
Journal of aerosol medicine and pulmonary drug delivery	5	2.2

Table 4 (*Continued*)

Journal title	Number of studies	Mean number of reproducibility indicators
BMC pulmonary medicine	4	2.25
Journal of thoracic oncology	5	2.8
NPJ primary care respiratory medicine	1	3
COPD	2	3.5

ning parameters of the original investigations. Finally, the sensitive nature of some data causes concern among researchers.

Second, preregistering a study requires authors to provide their preliminary protocol, materials, and analysis plan in a publicly available website. The most common websites used by authors are ClinicalTrials.gov and the International Clinical Trial Registry Platform hosted by the World Health Organization. These registries improve the reliability and transparency of published findings by preventing selective reporting of results, preventing unnecessary duplication of studies, and providing relevant material to patients that may enroll in such trials.[23] The Food and Drug Administration (FDA) Amendments Act and the International Committee of Medical Journal Editors (ICMJE) have both required registration of clinical trials prior to initiation of a study.[24,25] Selective reporting bias, which includes demoting primary endpoints, omitting endpoints, or upgrading secondary endpoints in favor of statistical significance, may be especially pervasive and problematic. Numerous studies across several fields of medicine have evaluated the extent and magnitude of the problem.[26–28] The consequences of selective reporting bias and manipulation of endpoints may compromise clinical decision making. Another issue—*p*-hacking—occurs when researchers repeatedly analyze study data until they achieve statistically significant results. Preregistration of protocols and statistical analysis plans can be used to fact check published papers to ensure that any alterations made in the interim were made for good reason.

Third, transparency related to study funding and financial conflicts of interest should be emphasized. In a previous study, we found that one-third of the authors of pivotal oncology trials underlying FDA drug approvals failed to adequately disclose personal payments from the drug sponsor.[29] Recent news accounts of a prominent breast cancer researcher who failed to disclose financial relationships with pharmaceutical companies in dozens of publications has heightened awareness of the pervasiveness of this issue.[30] The ICMJE considers willful nondisclosure of financial interests to be a form of research misconduct.[31] It is critical that the public be able to adequately evaluate financial relationships of the authors of the published studies in order to evaluate the likelihood of biased results and conclusions.

Several changes are needed to establish a culture of reproducibility and transparency. First, increased awareness of and training about these issues are needed. The National Institutes of Health has funded researchers to produce training and materials, which are available on the Rigor and Reproducibility Initiative website,[32] but more remains to be done. Strong mentorship is necessary to encourage trainees to adopt and incorporate reproducible research practices. Research on mentorship programs has found that trainees who have mentors report greater satisfaction with time allocation at work and increased academic self-efficacy compared with trainees without a mentor.[33] Conversely, poor mentorship can reinforce poor research practices among junior researchers, such as altering data to produce positive results or changing how results are reported.[34] Other research stakeholders must be involved as well. Although many journals recommend the use of reporting guidelines for various study designs, such as CONSORT and PRISMA, evidence suggests that these guidelines are not followed by authors or enforced by journals.[35] When journals enforce adherence to reporting guidelines, the completeness of reporting is improved.[36] Detractors of reporting guidelines are concerned that certain checklists (CONSORT, STROBE, STARD) will be used to judge research quality rather than improve writing clarity, that editors and peer reviewers will fail to enforce these guidelines, and that insufficient research exists to evaluate the outcomes from applying these guidelines.[37] We analyzed *COPD*, *NPJ Primary Care Respiratory Medicine*, and *Journal of Thoracic Oncology* from our sample as the top three journals for containing reproducibility indicators in their publications. These journals have explicit instructions for authors to provide things such as materials/protocols such that independent researchers may recreate the study or raw data to confirm calculations.[38–40] Although reproducibility may be an emerging topic, these recommendations appear to be encouraging authors to include more thorough and complete research.

Our study has both strengths and limitations. We randomly sampled a large number of pulmonology journals containing various types of publications to generalize our findings across the specialty. Our study design also used rigorous training sessions and a standardized protocol to increase the reliability of our results. In particular, our data extraction process, which involved blinded and duplicate extraction by two investigators, is the gold standard systematic review methodology and is recommended by the Cochrane Collaboration.[41] We have made all study materials available for public review to enhance the reproducibility of this study. Regarding limitations, our inclusion criteria for journals (i.e., published in English and MEDLINE indexed) potentially removed journals that contained more lax recommendations regarding indicators of reproducibility and transparency. Furthermore, although we obtained a random sample of publications for analysis, our sample may not have been representative of all pulmonology publications.

Our results should be interpreted in light of these strengths and limitations.

In conclusion, our study of the pulmonology literature found that reproducible and transparent research practices are not being incorporated into research. Sharing of study artifacts, in particular, needs improvement. The pulmonology research community should seek to establish norms of reproducible and transparent research practices.

Author contributions

DJT, MV: Substantial contributions to the conception and design of the work. CAS, JN, DJT: Acquisition, analysis, and interpretation of data for the work. CAS, JN, DJT, TEH, JP, KC, MV: Drafted the work and revised it critically for important intellectual content. MV: Final approval of the version submitted for publication. CAS: Accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgment

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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.2020.07.001.

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REVIEW

''Tricks and tips for home mechanical ventilation'' Home mechanical ventilation: set-up and monitoring protocols

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Abstract In this part of the review series ''Tricks and tips for home mechanical ventilation'', we will discuss the evidence with regard to the place and manner of home mechanical ventilation initiation and follow-up. Outsourcing more and more of this chronic care to the home situation is a big challenge for the future: especially for the home situation, monitoring has to be non-invasive, reliable and easy to use, data security needs to be ensured, signals need to be integrated and preferably automatically processed and algorithms need to be developed based on clinically relevant outcomes.

Introduction

In the Netherlands, home mechanical ventilation (HMV) was founded 60 years ago.[1] The first patient transferred home while remaining dependent on mechanical ventilation in 1960 was a patient who survived poliomyelitis anterior acuta.[2] Home non-invasive mechanical ventilation (NIV) has emerged since the mid-1980s for patients with chronic respiratory failure. In the past decades, indications have evolved and the number of patients on HMV has increased. Recent data from Switzerland have shown an increase in home NIV prevalence from 15.1 to 37.9 per 100.000 with an increase in especially chronic obstructive pulmonary disease (COPD) patients and patients with Obesity Hypoventilation Syndrome (OHS).[3] Worth noting is the very variable practice between countries, both with regard to numbers as well as underlying diseases.[4] Nowadays, most patients on home mechanical ventilation are ventilated non-invasively.[4] With an increase in patients with pre-existing chronic respiratory failure to be initiated electively on HMV, the place of HMV set-up has changed from set-up exclusively in the ICU to nowadays an increasing tendency for home set-up.

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The key to successful therapy is a careful set-up and titration of ventilatory support. Hospital admission was for a long time considered necessary to set-up HMV. Also, in some countries, patients are admitted to hospital to titrate HMV during follow-up.[5] However, with increasing patient numbers and limited health care resources usually needed for acute care services, hospital admission for elective HMV initiation and titration has become less justifiable, if it is clear that other home-based protocols are at least non-inferior. In this review we will discuss the evidence with regard to the place and manner of HMV initiation and follow-up. Outsourcing more and more of this chronic care to the home situation is a big challenge for the future: especially for the home situation, monitoring has to be non-invasive, reliable and easy to use, data security needs to be ensured, signals need to be integrated and preferably automatically processed; algorithms need to be developed based on clinically relevant outcomes (Fig. 1).

Before HMV is started

Irrespective of the place of set-up, once HMV is started, therapeutic goals should be clear and communicated with the patient. A thorough analysis of the patient's motivation, goals, home situation including available support of family members, medical history and current medical situation is warranted. While HMV is usually titrated on reduction in arterial carbon dioxide ($PaCO_2$) levels, as a surrogate marker of ventilatory efficacy, patient wishes usually extend beyond gas exchange improvement. Independently of the underlying disease, patients suffer from symptoms of nocturnal hypoventilation, such as sleeping badly, frequent awakenings, morning headaches, tiredness and loss of vigilance.[6] On the other hand, expectations of HMV are different in various underlying diseases. While for patients with thoracic restrictive diseases (TRD) and particularly more slowly progressive neuromuscular diseases (NMD), such as M. Duchenne, the initiation of HMV has been shown to increase live expectancy dramatically,[6] for patients with rapidly progressive NMD such as amyotrophic lateral sclerosis (ALS) and COPD, improvement of symptoms and health-related quality of life (HRQoL) might be the most important goal, as these are progressive diseases and improvement in survival has been shown less convincingly.

Furthermore, a thorough analysis of comorbidities is needed. Especially in patients with concomitant cardiac failure, caution is needed as high ventilatory pressures might increase intrathoracic pressure, might reduce right ventricle preload and thus cardiac output. However, the effect of mechanical ventilation on cardiac functioning is a complex interplay between potential negative

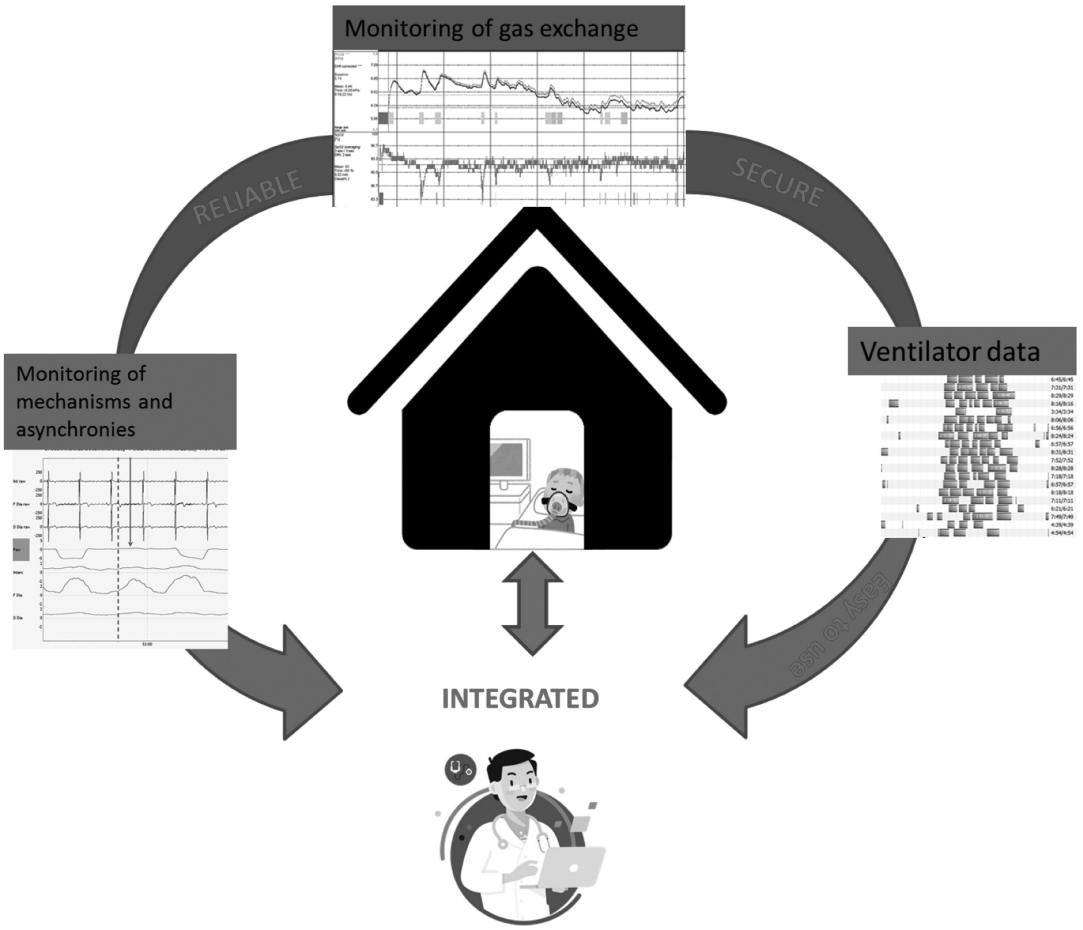

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Figure 1 Graphical representation of remote monitoring of long-term HMV; intended to show some of the most commonly used monitoring methods, but not all those available. Cartoons are taken from: https://www.cleanpng.com/. Red-outs are own resources.

and positive effects, depends on the patient's underlying condition, the applied ventilatory settings and compensatory mechanisms.[7,8] Therefore, the exact net effect is unpredictable[9] and it is advisable to monitor these patients more carefully during HMV set-up (for example by continuous or repeated blood pressure measurements).

Where to start

In many countries, HMV is still initiated in the hospital,[5] albeit there is no consensus on exactly how and where it should be organized: the places where it is done (i.e. pulmonary ward, respiratory care unit, intensive care unit) vary considerably, as do the costs. With increasing prevalence of HMV, this will place a huge burden on the health care system. Furthermore, patients with severe disability in daily living often prefer to stay at home where they have organized their care instead of being transferred to a rather stressful hospital environment.

In the last decade, several trials have emerged showing that home initiation of NIV in patients with neuromuscular diseases, restrictive thoracic disease and COPD is non-inferior to in-hospital initiation with a reduction of >50% of the costs.[10–13] It has to be noted that strict remote monitoring of ventilator data and gas exchange and daily remote or direct ''live'' support during the initiation period was offered in these trials. The recently presented results from the OPIP multicenter trial showed that in Obesity-Hypoventilation patients, NIV initiation at home with an auto-adjust mode without further monitoring and support was not cost-effective as patients initiated at home had far more healthcare contacts afterwards compared to patients initiated by a nurse-led overnight NIV titration in hospital.[14,15]

In daily practice, the strict protocol of home monitoring and daily remote assistance that was used in the recent positive trials, might not be possible in all centers, depending on the structure of the healthcare system and HMV team, reassurance possibilities for home care and local distances from the center to the patient. Secondly, the success of changes to remote HMV are dependent on not only technical possibilities but also on technical reliability and ease of use. Thirdly, privacy issues of data transfer need to be secured. Extending the ability to monitor at home with a reliable, solid, but easy to use independent home telemonitoring module or in-built ventilator module with telemonitoring capabilities would be a significant improvement in the care of today's and future patients on chronic NIV. Some ventilator manufacturers are developing these integrated modules for transcutaneous gas exchange monitoring, although it general use is limited by the fact that each manufacturer has developed his own software and platforms, and thus users (caregivers and patients) have to adapt to these differences when switching to a different ventilator.

What to monitor (at home and in the hospital)

Gas exchange

There is no consensus on how to initiate and titrate long-term home ventilation. To assure effective nocturnal ventilation, at least gas exchange should be monitored. Monitoring of daytime gas exchange as a reflection of nocturnal gas exchange may be useful. However, it has been shown that with a daytime $PaCO_2$ <6.0 kPa (<45 mmHg), up to 26% of the cases of (milder) nocturnal hypoventilation might be missed.[16] Also, in patients with a limited ventilatory capacity, daytime $PaCO_2$ may rise again after patients are disconnected from their ventilator. This thus does not reflect insufficient ventilatory support per se but merely reflects a too limited capacity to sustain benefits during the day. For these reasons, to judge ventilatory support, it is preferable to monitor also nocturnal gas exchange.

Pulse oximetry is a simple, easy way to detect oxygen desaturation. However, the specificity of the detection of nocturnal desaturation as a marker of nocturnal respiratory events is low and not reliable when patients use supplemental oxygen.[17] Nocturnal carbon dioxide measurements are therefore needed to monitor alveolar ventilation. The 'gold standard' to measure this is to retrieve repeated samples of arterial blood via an arterial line. However, arterial cannulation is uncomfortable, expensive and demands continuous monitoring in the hospital by trained personnel, in most hospitals only available in high care units. Early morning sampling of $PaCO_2$ is also less appropriate, since this is always after arousal and a period of spontaneous awake breathing. Capillary blood gas analysis is an alternative for arterial blood gases, but is still invasive, not appropriate for home monitoring and cannot be measured continuously during the night. Also, for capillary measurements it is known that arterial oxygen levels are underestimated when considering capillary levels compared to gold standard arterial levels, especially in hypoxemic patients,[18] with fingertip samples showing even more deterioration compared to ear lobe sampling.[19]

A noninvasive way to assess PCO_2 continuously is by measuring peak expired carbon dioxide tension ($PetCO_2$) or transcutaneous carbon dioxide tension ($PtcCO_2$). An advantage of continuous monitoring is that trends and thus also the effect of mechanical ventilation can be directly observed. While measuring $PetCO_2$ is not a reliable measurement for $PaCO_2$ in patients with a huge amount of dead space ventilation, such as in COPD,[20] $PtcCO_2$ values are comparable to arterial (gold standard) values, and can be used for the purpose of alveolar ventilation monitoring.[21,22] Therefore, we suggest using nocturnal $PtcCO_2$ to monitor HI-NIV gas exchange goals, both during the initiation period as well as during patient follow-up.

Ventilator data monitoring

Many ventilatory devices contain sensors and built-in software that provide information about compliance, settings, and estimated values of tidal volume, leaks, breathing frequency, minute ventilation, percentage of breaths triggered by the patient, and the apnea-hypopnea index (AHI) over an extended period. These parameters can help identify abnormal nocturnal events, and in some cases, the causes of these events. However, important concerns have been raised regarding variables recorded by ventilatory devices: 1) are they reliable and 2) are they clinically relevant, i.e. does monitoring of these variables lead to improved outcomes?[23]

Objective data on hours of ventilator use provide important information. On the one hand, a threshold numbers of hours of daily use is probably necessary to obtain clinical benefits.[24] A recent study in a large group of patients on HMV showed that less than 4 h usage per day was associated with worse survival.[25] Furthermore, interrupted patterns of ventilation or an overall decreased use may indicate inappropriate settings, adverse effects or patient discomfort. On the other hand, increasing use over time may also predict deterioration.[26,27] Thus daily use monitoring from ventilator hardware is reliable and seems to be of clinical use.

Data on tidal volume, leaks, breathing frequency and apnea/hypopnea index (AHI) are estimated parameters and when interpreting these data one should be aware of the drawbacks. First, reliability of these measures is limited. Tidal volume estimates are influenced by leaks, as with a single limb circuit with expiratory leak port—which is almost always used with NIV—expiratory volumes cannot be measured. Most noninvasive ventilators tend to underestimate the tidal volume delivered, especially with high IPAP levels and significant leaks.[28] Furthermore, the clinical relevance of measuring these parameters has not been thoroughly investigated. The question is whether data depicted by the ventilator relate to ventilatory efficacy with regard to improvement in gas exchange, improvement in health-related quality of Life (HRQoL) and symptoms and patient comfort.

In conclusion, compliance data should be used especially during follow-up of patients using HI-NIV. Other data provided by the ventilator may be of value, however, the usefulness, reliability and validity of most parameters require further evaluation.

Extended monitoring

In some difficult to ventilate patients, more extended monitoring might be necessary, ranging from performing additional poly(somno)graphies to quantify sleep quality and nocturnal sleep related events to sophisticated methods to quantify patient-ventilator (a)synchrony, lung mechanics and patient effort.

Poly(somno)graphy

When initiating long-term HMV, a sleep study can be considered a) before initiation to detect (concomitant) sleep-related breathing disorders (apnea's/hypopnea's), b) during initiation to adjust ventilator settings and c) during follow-up in patients in whom goals are not met.

Before starting a patient with chronic respiratory failure on long-term HMV, a poly(somno)graphy might be useful in patients in whom obstructive or central events or other sleep related problems are suspected. Especially in patients with OHS, concomitant obstructive sleep apnea (OSA) may direct the choice of therapy to continuous positive airway pressure (CPAP) instead of bilevel positive airway pressure (BiPAP), as studies have shown that both short- and long-term outcomes are comparable.[29–31] However, also in other patient groups, such as COPD,[32] Myotonic Dystrophy[33] but also Amyotrophic Lateral Sclerosis,[34] obstructive and central sleep related events are prevalent. In those patients, if chronic respiratory failure is accompanied by concomitant sleep apnea, it is unknown which mode (CPAP or BiPAP) is preferred. In practice, this will depend on the severity of both, symptoms and patient preferences and goals.

During initiation of chronic ventilatory support, in some hospitals, polysomnography (PSG) is used as standard manner to adjust ventilatory settings.[35,36] Although with PSG, sleep quality, respiratory events, patient-ventilator asynchrony, can be detected, PSG is expensive, complex and not available in all centers/settings. Furthermore, at least in COPD/OHS, it has been shown that PSG-adjusted NIV does not lead to more improvement in gas exchange compared to nurse led titration based on ventilator data and transcutaneous measurements of gas exchange.[37] Despite these findings, we hypothesize that PSG might have a role in the titration and follow-up of HMV in patients who are difficult to initiate on NIV, in whom concomitant sleep related disturbances are noticed and in patients in whom goals are not met. Further research is needed to detect those parameters/disturbances that affect clinical outcomes and automatic algorithms based on those parameters which can be used to change ventilatory settings.

Patient-ventilator (a)synchrony, lung mechanics and patient effort

Monitoring and trying to adjust for patient-ventilatory asynchrony (PVA) is very common with acute mechanical ventilation in the intensive care unit.[38] However, with long-term home NIV, its value is still unknown, also because description and quantification of PVA is not standardized. Monitoring PVA helps to identify abnormal respiratory asynchronous events during the night. However, monitoring PVA is complex and it is controversial whether in long-term HMV this leads to improved clinical outcomes. A recent pilot proof-of-concept clinical trial showed a trend toward greater improvements in daytime $PaCO_2$, HRQoL and sleep quality when using simple gas exchange monitoring compared to advanced monitoring.[37] Moreover, it was shown that the presence of PVAs do not necessarily affect outcomes in patients with CHRF.[39] Conversely, Adler et al. showed that actively titrating NIV to minimize PVA and sleep-disordered breathing decreased morning dyspnea and increased patient-comfort.[40]

There are multiple methods available to monitor PVA non-invasively. Theoretically these methods can also be used at home, but in clinical practice, are still quite difficult to perform and have a high chance of technical errors in the unsupervised situation. A method propagated by the SomnoNIV group is the use of visual analysis of polygraphic (PG) tracings of chest and abdominal movement to detect patient effort and compare this with pressure and flow tracings from an external pneumotachograph.[41] However, this method is quite complex, time-consuming and expensive, and in many centers only feasible when a sleep analysis is needed anyway. Furthermore, the tracings of chest and abdominal movement are not the gold standard to detect patient effort. In this respect, a more precise method to detect PVA might be to compare pressure waveforms with the patients' own respiratory activity measured with electromyography (EMG).[39,42] An example of surface EMG combined with air-

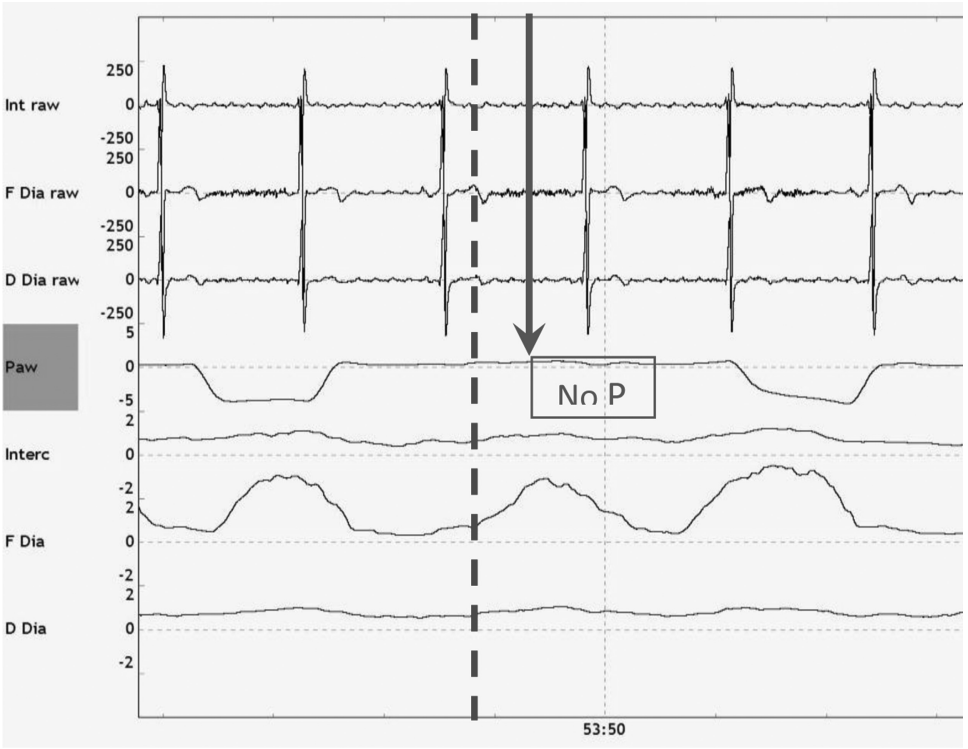

Figure 2 A tracing of a EMG recording of the diaphragm and intercostal muscles combined with a pressure tracing derived from an external pneumotachograph. At the place of the arrow diaphragm activity is observed without a pressure wave, so an ineffective effort occurs.

ways pressure to detect an ineffective effort is shown in Fig. 2. For both methods, the processing of the signals and detection of methods still requires a lot of time and effort; the development of reliable automatic methods to detect relevant events would be very welcome.

The available knowledge about the effect of long-term NIV on lung mechanics and physiology and respiratory muscle functioning and mechanics is limited. Some smaller trials from Belgium showed that NIV in COPD can improve ventilation-perfusion matching.[43] This knowledge gap is a pity as more insight in working mechanics might lead to better patient selection and a better funded approach towards the optimal settings. However, for long-term home NIV we need non-invasive monitoring methods suitable for the awake, moving patient in the home situation.

In conclusion, the more advanced monitoring described above is still an area of research. Methods need to be developed further to enable reliable home monitoring and automatic processing of signals and research has to show its eventual clinical value.

Follow-up of HMV

Follow-up of HMV patients is a black box; there are no evidence based guidelines describing how and how often ventilatory support should be monitored. Moreover, follow-up frequency might differ between patient groups; patients in rapidly changing conditions (children) or patients with a rapidly progressive disease (ALS/COPD) might need more frequent follow-up compared to the slower or non-progressive diseases. Furthermore, there is no consensus about which minimal set of parameters should be monitored. Finally, also in the follow-up of patients, telemedicine might bring attractive alternatives.

The number of studies on the use of follow-up telemonitoring in patients on HMV is limited. Furthermore, telemonitoring/tele-medicine is a very broad concept; the exact way (what is monitored, how often, which equipment is used, which actions are taken upon monitored data) largely influences the eventual results and benefits. Vitacca et al. enrolled 240 patients with chronic respiratory failure due to different underlying diseases in a study investigating tele-assistance composed of remote oxygen saturation monitoring and scheduled and unscheduled tele-consultations.[44] Sixty-two percent of the patients used home ventilation (43% NIV; 20% invasive mechanical ventilation). They showed that the number of hospitalizations per month was significantly fewer in the tele-assistance group and in COPD there were fewer acute exacerbations as compared to the standard care group. The tele-assistance team received mean 4.2 pulse oximeter reports per months and the number of requested calls (0.5/month) on top of the scheduled calls (2.42/ month) per patient per month was relatively low. Of note, of the 351 patient screened for the study, 111 patients (56% COPD) were excluded because of reduced cognitive status, insufficient family cultural requisites and lack of home prerequisite for tele-assistance. Chatwin et al. randomised 39 patients with severe COPD on LTOT or NIV (84%) to a rather extensive telemonitoring of physiological parameters and symptoms or to standard care, but failed to show benefit in terms of time to hospital readmission or HRQoL

during a 6-month time period.[45] In this study the number of home visits increased as well as the admission rate for acute exacerbations. Of note, the patients in this study seemed to be much more worried by their tele-monitoring, as the number of telephone consultations and alerts due to SpO2 was high (29 consultations per months and 187 alerts per month). This controversy between studies highlights the fact that the content of the tele-monitoring intervention (what is measured; how frequently) greatly influences the results; while sufficient monitoring might improve outcomes probably over- extensive monitoring without a self-management plan might only reduce patient self-efficacy.

While the above discussed studies monitored among others oxygen saturation and symptoms, in patients on HMV it is also possible to remotely monitor ventilator data, like compliance, tidal volume, breathing frequency etc. Studies have been performed focusing on the potential of predicting exacerbations prematurely by machine readouts through tele-monitoring.[26,27] This seems an intriguing objective, as these studies did show a reduction in hospital readmissions and severe exacerbations.

Crucial to the success of the use of telemonitoring in follow-up of patient on HMV is the development of a good system and good algorithm to pick up the right physiological changes/parameters that really predict worse outcomes. Furthermore, this algorithm should lead to correct actions of the patients and/or caregivers. Further studies are needed to show the benefit with regard to patient-related outcomes and costs. In the future, telemonitoring follow-up might lead to personalized treatment, selecting patients that need more or other care earlier than planned or on the other hand, avoid unnecessary care in patient who do fine on their own.

Conflicts of interest

Marieke Duiverman has no conflicts of interest for this manuscript.

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REVIEW ARTICLE

Tuberculosis and COVID-19 interaction: A review of biological, clinical and public health effects

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Abstract Evidence is accumulating on the interaction between tuberculosis (TB) and COVID-19.

The aim of the present review is to report the available evidence on the interaction between these two infections. Differences and similarities of TB and COVID-19, their immunological features, diagnostics, epidemiological and clinical characteristics and public health implications are discussed. The key published documents and guidelines on the topic have been reviewed.

Based on the immunological mechanism involved, a shared dysregulation of immune responses in COVID-19 and TB has been found, suggesting a dual risk posed by co-infection worsening COVID-19 severity and favouring TB disease progression.

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The available evidence on clinical aspects suggests that COVID-19 happens regardless of TB occurrence either before, during or after an active TB diagnosis. More evidence is required to determine if COVID-19 may reactivate or worsen active TB disease. The role of sequeale and the need for further rehabilitation must be further studied

Similarly, the potential role of drugs prescribed during the initial phase to treat COVID-19 and their interaction with anti-TB drugs require caution. Regarding risk of morbidity and mortality, several risk scores for COVID-19 and independent risk factors for TB have been identified: including, among others, age, poverty, malnutrition and co-morbidities (HIV co-infection, diabetes, etc.). Additional evidence is expected to be provided by the ongoing global TB/COVID-19 study.

Introduction

The year 2020 will probably be remembered as the 'COVID-19 (coronavirus disease) year'. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for this pandemic emerged in January/February, having originated from China in late 2019.[1–3] Although COVID-19 continues to dominate both the scientific literature and the media, other communicable diseases including tuberculosis (TB) should not be neglected.[4]

Much has been written on the potential interactions between COVID-19 and tuberculosis (TB) following the World Health Organisation (WHO) declaration of COVID-19 as a Public Health Emergency of International Concern,[5] initially based on assumptions, modelling[6–8] and scientific evidence.[9–13]

The view of the WHO,[7] and the specialized scientific press and newspapers[14,15] is that an important consequence of the COVID-19 pandemic would be a worsening of the TB epidemic globally, for a variety of reasons, such as additional pressures on health systems by COVID-19 resulting in weakening of the National TB programmes[16] and the potential biological effects of the interaction of the two infections, recalling the concept of 'cursed duet' which in the past was used for TB and HIV.[17]

The aim of the present review is to describe the available evidence on the interaction between COVID-19 and TB, starting from differences and similarities, proceeding to describe immunological features, diagnostic implications, epidemiological and clinical characteristics (including impact on mortality) and public health implications (impact on health services).

Methods

We made a rapid and non-systematic search of the literature using the key-words 'COVID-19', 'tuberculosis', 'immunology', ''diagnosis', 'prevention', 'treatment', 'infection control', 'workplace' to identify a minimum set of references from an electronic database (PUBMED), existing guidelines on TB and COVID-19, airborne diseases, and grey literature. This review belongs to the Pulmonology TB series 2021.[18]

Differences and similarities between COVID-19 and TB

Recent literature comparing,[19–26] COVID-19 and TB are summarised with key similarities and differences in Table 1.

The main difference is that TB is curable, while definite evidence on effective anti-viral agents or other drugs for COVID-19 is still lacking.[35,36]

Research on new and effective vaccines is ongoing for both diseases: vaccination for COVID-19 has now started while for TB several candidates are under evaluation to replace the old BCG.[37]

Both COVID-19 and TB have the capacity to stress health systems, they are airborne transmissible diseases, can be diagnosed rapidly (although implementation of rapid testing is not yet available in all settings), they cause stigma and need public awareness and cooperation to allow prevention, diagnosis and treatment to be effective. Although surveillance is able to report on TB and viral diseases separately, in the vast majority of countries the information on COVID-19 is still incomplete and information on TB do not contain many clinical and immunological parameters, which would be useful to better understand the interaction between the two diseases. Moreover COVID-19 pandemic has led to a significant fall in TB notifications.[9]

In terms of funding, although health systems can be considered relatively underfunded even in resource rich countries (a debate is ongoing in these countries on the adequacy of prevention services and on the needed number of intensive care unit beds) human and economic resources for TB are historically sub-optimal at the global level, while resources have been rapidly mobilised against COVID-19 following the wave(s) of the emergency.[19,20,38]

A long story of prevention and control exists for TB, with the development of: a) national TB control programmes and b) prevention, diagnosis and treatment policies and guidelines in almost all countries of the world (although they are not always correctly implemented). On the COVID-19 side, the policy guidance is under continuous development, following the growing evidence available with the first and subsequent waves.

Table 1 Differences and similarities between tuberculosis and COVID-19.

Specific aspect	COVID-19	TB	Comment
Human exposure	Recent (months)	Ancient (millennia)	COVID-19 was first identified in Wuhan, China in December 2019 and is believed to have likely originated in bats, although the precise origination remains unknown. TB in humans can be traced back to 9000 years ago in Atlit Yam, a city off the coast of Israel. On March 24, 1882, Dr. Robert Koch announced the discovery of *Mycobacterium tuberculosis*, the bacteria that causes tuberculosis (TB),[27]
Epidemiology	Significant burden	Significant burden	Both diseases pose a significant burden. For TB, there are roughly 1.8 billion people infected globally. Additionally, approximately 10 million new cases and 1.5 million deaths annually occur from tuberculosis.[7] For COVID-19, there are roughly 56.1 million cases and 1.34 million deaths globally as of November 18th, 2020[28]
Transmission	Droplet transmission of SARS-CoV-2.	Droplet transmission of *M. tuberculosis* bacterium.	COVID-19 may also be transmitted via surface contamination, possibly the fecal-oral route, and there may be some aerosol transmission. Transmission occurring from asymptomatic individuals may be less for TB than COVID-19.
Symptoms	– Fever or chills	– Coughing with mucus or blood	COVID-19 poses an additional challenge given that a proportion of spread is from asymptomatic individuals.
	– Cough, shortness of breath or difficulty breathing	– Coughing that lasts more than 2 months	
	– Fatigue and headache	– Chest pain	
	– Muscle or body aches	– Loss of appetite	
	New loss of taste or smell	– Weight loss	
	– Sore throat, congestion, or runny nose	Chills, fever, or night sweats	
	– Nausea, vomiting, or diarrhea	– Fatigue	
Comorbidities Increasing Vulnerability	– Cancer	– Cancer	For both diseases, the comorbidities leading to increased vulnerability of the patients are similar.
	– Chronic Kidney Disease	– Chronic Lung Diseases	
	– Chronic Lung Diseases	– Smoking	
	– Obesity	– Alcohol Use Disorders	
	– Heart Conditions	Depression	
	– Sickle Cell Disease	– HIV	
	– Immunocompromised State	– Immunocompromised State	
	– Type 2 Diabetes Mellitus	– Type 2 Diabetes Mellitus	

Table 1 (*Continued*)

Specific aspect	COVID-19	TB	Comment
Availability of effective vaccine	No (studies ongoing, expected early 2021)	Yes (old BCG vaccine; new candidate vaccines under study)	For tuberculosis, the Bacille Calmette-Guérin (BCG) vaccine is available for newborns and infants and recommended in high TB incidence settings. However, the effectiveness of the BCG vaccine is significantly lower for adults and elderly populations. For COVID-19, vaccine trials are currently ongoing. There appears to be a lack of data regarding the effectiveness of potential COVID-19 vaccines in elderly or immunocompromised individuals.
Other preventive measure	Yes (infection control with hand washing, social distancing, cough etiquette, contact tracing of infected individuals, lock-downs, curfews)	Yes (infection control with administrative, environmental and personal protection measures; contact tracing and treatment of infected individuals)	For COVID-19, personal protection equipment and maintaining physical distance are even more critical given the asymptomatic spread. While mitigation measures (curfews, closing businesses) are not used for TB, they have been necessary to combat COVID-19 in many countries, due to failure of containment measures and rapid community transmission. For both diseases, contact tracing and investigation at the onset is crucial, before community transmission becomes entrenched.
Availability of rapid diagnostics	Yes	Yes	For both diseases, screening symptoms include cough, fever, shortness of breath and nucleic acid amplification tests (NAAT) are recommended as the first test. For TB, sputum tests are used and chest radiography can identify active TB in patients. COVID-19 diagnostic tests use naso or oro-pharyngeal swabs and the use of saliva or sputum is currently being studied.
Availability of cure	No (studies ongoing, support measures used including oxygen and ventilation)	Yes	TB has established curative treatment regimens that include the administration of first line drugs such as rifampicin, isoniazid, ethambutol and pyrazinamide. Drug regiments can be completed at home with regular follow-up visits to the hospital. For COVID-19, trials are currently ongoing and only limited treatments are currently available, including the administration of remdesivir and dexamethasone in severe cases. Approximately 5% experience severe symptoms necessitating intensive care and invasive mechanical ventilation and ~20% are hospitalized.[29]

Table 1 (*Continued*)

Specific aspect	COVID-19	TB	Comment
Limitations of Current Treatments	Trials are currently ongoing and little is known about potential limitations due to lack of treatment options.	There is an increase in limitations due to the rise of resistant strains to rifampicin and isoniazid (MDR) and with additional resistances (XDR).	For TB, there are significant negative adverse events of medication leading to higher rates of non-compliance or early termination of the treatment plan. Additionally, treatment durations are lengthy and can last from 6 months to 2 years. For COVID-19, treatment duration is currently unknown due to the lack of available treatment plans. There are some compassionate use treatment options available to temporarily treat symptoms, however, no direct antiviral treatment is available.
Agreed-upon case-definition	Yes (still under development)	Yes (well established)	The case definition and associated criteria for COVID-19 classification continues to be updated and the latest interim case definition was approved on August 5th, 2020 by the CDC.[30] For tb, the case definition has been well established by the CDC since 2009[31] WHO has regularly update the full set of definitions to manage TB.[7]
Potentiality for stigma	Yes	Yes	The stigma of tuberculosis is a perceived risk of transmission from TB-infected individuals to susceptible community members. Additionally, TB is often stigmatized because of its associations with HIV, poverty, low social class, and malnutrition. For Covid-19, numerous forms of stigma and discrimination have been reported, including xenophobia directed at people thought to be responsible for bringing COVID-19 into countries, attacks on health-care workers and verbal and physical abuse towards people who have recovered from COVID-19.
Policy development	Rapid	Slow	Risk communication and rapid implementation of travel policies and quarantine restrictions are a large part of the COVID-19 mitigation efforts. While policy development for TB has been slow, countries have been working to adopt and implement national TB strategies and programs, however, a large gap between policy and practice continues to exist due to financial and human resource constraints.

Table 1 (*Continued*)

Specific aspect	COVID-19	TB	Comment
Resource mobilisation	Rapid	Slow	For Covid-19, resource mobilisation has occurred rapidly and through effective multi-sectoral engagement. Resource mobilisation for tuberculosis has been slow and there continues to be an annual funding deficit for TB research and development of more than $1.6 billion, a shortfall that is exacerbated by a lack of market incentives within the pharmaceutical industry.[32]
Economic impact	Huge (rapid)	Huge (slow)	The economic burden of TB between 2006 and 2015 for twenty-two high-burden countries is estimated be about $3.4 trillion.[33] In May 2020, the Asian Development Bank announced that the COVID-19 pandemic could cost the global economy between $5.8 and $8.8 trillion.[34]
Stress on health systems	Huge (rapid)	Huge (slow)	The Covid-19 pandemic put health systems under immense pressure and often stretches hospitals and healthcare providers beyond capacity due to lack of infrastructure and equipment (hospital beds, ventilators) and staff and skills (overworked healthcare workers, lack of intubation skills). An increase in tuberculosis cases in high-burden counties puts additional pressure on already resource strained health systems that are already facing additional epidemics such as HIV. Additionally, new and existing health systems across the globe need to adapt to the rise of resistant forms of tuberculosis to provide better and affordable care.
Availability of data	Incomplete	Simple and historically complete	TB is a slow-moving epidemic and quarterly data is available at the national level. Due to the rapid spread, COVID-19 requires daily data updates, which is often incomplete or inaccurate. Availability and accessibility of surveillance data is crucial for both TB and COVID-19 responses to follow and respond quickly to the hot spots.

COVID-19: coronavirus disease; TB: tuberculosis; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; BCG: Bacille Calmette-Guérin; NAAT: nucleic acid amplification tests; MDR: multi-drug resistant; XDR: extensively drug-resistant; CDC: Centers for Disease Control and Prevention.

Biological interactions

COVID-19 is a communicable disease caused by SARS-CoV-2, a member of the beta Coronaviridae family, which also includes SARS-CoV-1 (severe acute respiratory syndrome coronavirus 1) and MERS-CoV (Middle East respiratory syndrome coronavirus).[39] The SARS-CoV-2 genome is up to 80% similar to SARS-CoV-1 and 50% similar to MERS-CoV.[39,40] The coronavirus spike (S) glycoprotein, common to all these viruses, belongs to the class-I viral fusion proteins and upregulates and engages angiotensin-converting enzyme 2 (ACE2) as the entry receptor into humans.[41,42] However, not all people exposed to SARS-CoV-2 are infected and not all infected patients develop severe respiratory illness.[3] Accumulating evidence indicates that COVID-19 can be roughly divided into three stages: *stage 1*, an asymptomatic incubation period with or without detectable virus; *stage 2*, non-severe symptomatic period with the presence of virus; *stage 3*, severe respiratory symptomatic stage with high viral load[43] and important immune response with subsequent deterioration of the lung damage, respiratory failure (that may require invasive-mechanical ventilation) and multi-organ dysfunction.[44–47] (Fig. 1

It has been shown that a broad and coordinated SARS-CoV-2 antigen-specific adaptive immune responses (ADIMs) among CD4, CD8 and B cells are associated with lower COVID-19 disease severity, while absent or minimal adaptive immunity is associated with more severe COVID-19 disease. In particular SARS-CoV-2-specific CD4 + T cells are associated with protective immune responses.[48] Significant redundancy or compensation may exist between the protective actions of neutralizing antibodies, SARS-CoV-2-specific CD4 T cells, and SARS-CoV-2-specific CD8 T cells.[48]

CD4 + T lymphocytes are rapidly activated to become pathogenic T helper (Th) 1 cells and generate granulocyte-macrophage colony stimulating factor (GM-CSF). The cytokine environment induces CD14+CD16+ monocytes with high expression of IL-6 and accelerates inflammation. Also, over-activation of T cells, manifested by the increase in Th17 and high cytotoxicity of CD8 + T cells in the peripheral blood of a patient with severe COVID-19, have been reported.[49] Although the pathophysiology of SARS-CoV-2 is not yet fully understood, it seems there are similarities with that of SARS-CoV-1.[50]

Certain therapeutic interventions are under evaluation for the incubation and early stages of SARS-CoV-2 infection; these include convalescent plasma, pegylated IFNa (Interferon alpha), zinc, vitamin B3 and/or specific antivirals like remdesivir and Regeneron's casirivimab/imdevimab antibody cocktail and bamlanivimab (Eli Lilly), some of which have already US Food and Drug Administration Emergency Authorization.[51–53] However, the treatment with hydroxychloroquine and lopinvir/ritonavir has not been significantly associated with differences in hospital mortality.[54,55]

For patients with severe COVID-19, mostly immunosuppressive therapeutic options have been proposed, with dexamethasone being recommended for use and others currently being evaluated including HAS2 (Hyaluronan Synthase 2) inhibitors as well as activated MSCs (mesenchymal stromal /stem cells).[44,56,57] (Fig. 1). Lung and tissue damage, which can occur with hypoxia even in TB,[58] have also been described as sequelae to COVID-19 infection,[59] as well as thrombosis and pulmonary emboli.[47]

Although viral respiratory infections and TB impair the host's immune responses little evidence is available about co-infection of SARS-CoV-2 and *Mycobacterium tuberculosis*. TB status might play a role in the development of COVID-19 infection and exacerbation of the course of the disease for the co-infected population considering cases studied in China and India[60] and the evidence provided by a study performed on a systematic transcriptomic evaluation of immune signatures associated with COVID-19 clinical severity and the spectrum of asymptomatic and symptomatic TB.[17] In particular the results of this study performed on the transcriptomic evaluation of whole blood (WB), peripheral blood mononuclear cell (PBMC) and bronchoalveolar lavage fluid (BALF) signatures suggest that subclinical and active TB (ATB) increase the risk of severe COVID-19 disease, due to increased abundance of circulating myeloid subpopulations which are also found in the lungs of severe COVID-19 patients.[17] The increased IFN production and the type I and III IFN responses signatures are significantly upregulated in severe disease in both COVID-19[61] and TB[62] and may lead to disease progression and severe/fatal outcomes. COVID-19 may therefore pose the biggest threat to ending the TB epidemic.[6]

Also, the use of immunosuppressive drugs in severe and critical COVID-19 patients, although done for a limited period of time, may result in increased likelihood of active TB caused by reactivation or new infection of *M. tuberculosis*[63,64] even in post-pandemic times.

Diagnostic tests

A range of diagnostic tests is available for both TB and COVID-19. For both pathogens, nucleic acid detection tests, and antigen-based tests are available while culture-based and smear methods apply to *Mycobacterium tuberculosis* and serology for SARS-CoV-2 (Table 2).

The WHO has described the ASSURED criteria (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users), relevant to both *Mycobacterium tuberculosis* and SARS-Cov-2, to identify the most appropriate diagnostic tests for most settings.[77] However, a key limitation to all available tests, independent of the pathogen, is the inability to promptly declare if the pathogen is viable and infectious[78] For SARS-CoV-2, the virus requires live eukaryotic cells to replicate, with a minimum turn-arou.nd-time of one week to determine viability. For *Mycobacterium tuberculosis*, culture results to determine viability require a minimum of 6 weeks. Even in this age of state-of-the-art technology, rapid information on the state of infectiousness of these two pathogens remains elusive. An interesting experimental approach to evaluate SARS-CoV2-specific response in the whole blood has been recently reported[79,80]. It describes that SARS-CoV2-specific response is detectable in the whole blood and is present during the acute phase[79] as well as in the convalescents.[80]

Table 2 Diagnostic tests for *M. tuberculosis* and SARS-CoV-2.

Pathogen	*Mycobacterium tuberculosis*				SARS-CoV-2		
Diagnostic method	Culture	Smear microscopy	NAAT	Antigen-based test	NAAT	Antigen-based test	Serology
Example of test	BD BACTEC MGIT, solid culture	ZN stain/ AR stain	Xpert MTB/RIF Ultra assay	Loopamp MTBC detection kit	PCR/RT-PCR	See FDA website[65]	See FDA website[65]
Sensitivity	Gold standard	Up to 84%[66]	Up to 91%[67]	64-80%[68]	Up to 98% for nasopharyngeal swab [69] Up to 91% for saliva[69]	84.0% - 97.6%[70]	Varying[71]
Specificity	Gold standard	98-99%[66]	Up to 100%[67]	95-99%[68]	Gold standard	100%[70]	Varying[71]
Rapidness (time to result)	1—2 weeks (liquid) 3—8 weeks (solid)	$\leq$ 1 day[72]	< 2 h[73]	60 min[68]	Ranges from 15 min to >2 days[70]	15 min[70]	< 30 min – few hours[71]
Sample preparation	Multiple steps	Multiple steps	Three steps	Multiple steps	Multiple steps	Minimal to none	Multiple steps
Equipment	Culture incubator, biosafety cabinet	Microscope	GeneXpert instrument	Heating block	Thermal cycler, heating block	Digital telecom-munication	ELISA kit and microplate reader, or lateral flow assay strip
Deliverable (minimum laboratory level)	Intermediate	Peripheral	Peripheral	Peripheral	Intermediate	Peripheral/POC	POC - Intermediate
Affordability	US$ 1.63-45.96[74]	ZN: US$ 1.16—2.54 AR: 1.08-1.64[74]	US$ 9.98[75]	US$ 6.04[78]	$1.21-$4.39/sample in reagent costs for saliva[76] Instrument charges vary	< US $20	US $20—100

AR, Auramine-rhodamine; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; POC, point-of-care; RT-PCR, real-time polymerase chain reaction; TB-LAMP, tuberculosis loop-mediated isothermal amplification;; ZN, Ziehl-Neelsen.

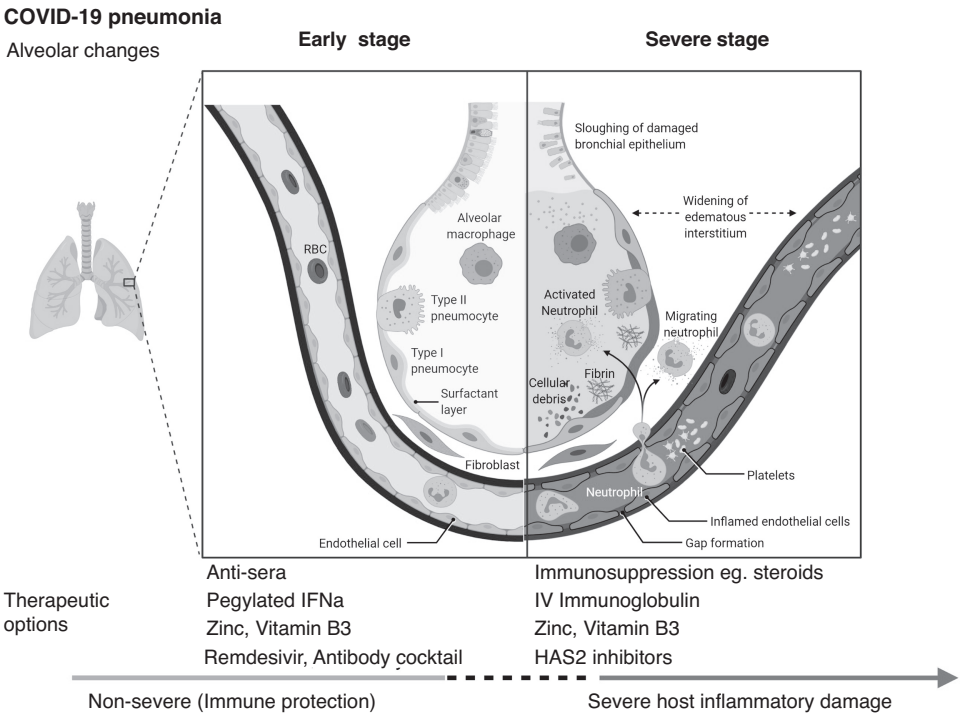

Fig. 1 Schematic representation of the progression of COVID-19 infection and potential adjuvant interventions. IFNa: Interferon alpha; IV: Intravenous; HAS2: Hyaluronan Synthase 2. Created with BioRender.com.

Epidemiological and clinical presentation of COVID-19 with TB infection

In a first meta-analysis of six studies from China on a few patients,[81] the TB prevalence among COVID-19 patients ranged between 0.47 to 4.47%. The TB prevalence was higher among patients with severe COVID-19 than in non-severe ones (1.47%, 10/680 vs 0.59%, 10/1703; OR: 2.1; P = 0.24).

In a cohort from eight countries (Belgium, Brazil, France, Italy, Russia, Singapore, Spain and Switzerland)[11] TB and COVID-19 were studied in 49 patients during the initial wave of the pandemic. TB was diagnosed before COVID-19 in 26 patients (53.0%), COVID-19 was diagnosed before TB in 14 ones (28.5%) while the diagnosis was concomitant in 9 patients (18.3%) (within the same week). Forty-two patients (85.7%) had active TB while 7 (14.3%) suffered post-cure TB sequelae. The authors concluded the following:

1) COVID-19 can occur before, simultaneously or after the diagnosis of TB;
2) The role of COVID-19 in boosting the development of active TB is yet to be established;
3) The role of TB sequelae in COVID-19 evolution is also unclear, potentially being a risk factor for worsening outcomes;
4) Further studies are needed to enable analysis of interactions and determinants of outcomes in patients with both diseases.

These findings have been confirmed by a similar study conducted in India.[82]

In an interesting clinical study conducted in a reference TB centre in Northern Italy, the Sondalo Hospital,[13] detection of Sars-Cov2 was made in 20 patients (the majority being young migrants without co-morbidities) following nosocomial transmission. All patients received hydroxychloroquine and no antiviral drug was administered, with oxygen administered to 4 patients at admission and 3 during their hospital stay. A single elderly patient with advanced pulmonary TB and cachexia developed COVID-19 pneumonia and died 6 days after admission. The other 19 patients had a good clinical outcome. TB lesions at chest radiography did not worsen and only 4 patients had signs of newly developed pneumonia.

The data reported suggest the following:

1 Low rate of clinical and radiological deterioration may be associated to young age of most patients, low frequency of co-morbidities, good quality of healthcare service
2 Impact of COVID-19 on active TB appears to be manageable with proper care. Rigorous infection control and personal protection devices are crucial to prevent the risk of in-hospital transmission.[83]

Prognosis and mortality resulting from COVID-19 and TB interaction

In the meta-analysis mentioned above[81] the risk of TB death was 1.4 times higher in COVID-19 patients. The findings of a

recent study[12] on 69 patients from 8 countries suggest the following:

1) The case fatality rate in the overall cohort was 11.6% (8/69); 14.3% (7/49) in the 8 countries study[11] and 5% (1/20, the single old patient with comorbidities) in the Sondalo Hospital study.[13]
2) Mortality is likely to occur in elderly patients with co-morbidities;
3) TB might not be a major determinant of mortality;
4) Migrants experienced lower mortality, probably due to their younger age and lower number of co-morbidities. However, the authors commented that in patients with severe TB and/or with a disease caused by resistant strains of *Mycobacterium tuberculosis*, a higher mortality rate can be expected also in younger individuals.

In a recent modelling study based on data from the Philippines,[84] the risk of death in TB patients co-infected with COVID-19 was 2.17 times higher than in non COVID-19 ones, with a shorter time-to-death. The risk of recovery in these patients was 25% lower than in non COVID-19 ones, with longer time-to-recovery.

A study from South Africa[85] showed that while HIV-TB co-infection doubled the risk of death of TB patients compared to HIV-uninfected individuals, TB (both drug-susceptible and drug resistant) increased the hazard of COVID-19 death of 2.7. A lower increase (1.51) was reported in those with previous TB.

A global study on TB and COVID patients, coordinated by the Global Tuberculosis Network (GTN) and supported by the World Health Organization (WHO) is going on at present to improve the description of the interaction between the two diseases. As of October 13th 2020, 36 Countries/Regions joined the global study, with 132 Centres from 27 Countries/Regions having already provided data for 597 individual patients.[86] The primary objective of the study is to describe the characteristics of patients with COVID-19 and TB (current or past), including diagnostic tests and prescribed therapies. The secondary objectives are: 1. To evaluate the logistic and organizational feasibility of a global repository for patients with COVID-19 and TB and 2) to describe the clinical outcomes (outcomes of COVID-19 disease, as well as interim and final treatment outcomes of TB patients).[86]

The GTN suggested several priority research questions to be answered with this global a study and others ones.

They include:

1 Does COVID-19 increase the risk of developing TB disease in individuals with TB infection?
2 What is the COVID-19 attributable risk on TB mortality?
3 What are the other determinants of mortality in TB—COVID-19 co-infected patients?
4 Is BCG vaccination protective for COVID-19?[87]
5 Do TB/COVID-19 co-infected patients require different management? (or in other words, which additional services are needed for these patients?)
6 What impact will COVID-19 have on TB services over the coming years, considering also the increasing effects of its second wave?
7 Are patients with post-TB sequelae a higher risk group for COVID? Do they suffer increased mortality or delayed cure? Do these patients require specific rehabilitation services?

According to recent studies, a high proportion of cases with post-TB treatment sequelae suffer from lung function impairment and poor Quality of Life (QoL). Preliminary data suggest that pulmonary rehabilitation is effective in patients with a previous history of TB.[88–91]

In addition, it has been well described that severe acute respiratory syndrome is the dominant finding of the acute phase of COVID-19 infection whilst functional impairment of patients surviving the COVID-19 acute phase has been poorly described. Recent studies suggested that early, post-hospitalization rehabilitative interventions should be recommended.[92–94]

Impact of the COVID-19 pandemic on TB services

Few studies are available on the potential interaction of COVID-19 on the TB health services.[9,15]

The GTN global study[9] evaluated patient attendances in TB health care units in 33 centres from 16 countries comparing the volume of TB-related healthcare activities in the first 4 months of the COVID-19 pandemic (January–April 2020) to the same period in 2019.[9] The majority of the centres experienced reductions during their national lockdowns in the first 4 months of 2020, in TB-related hospital discharges, of newly diagnosed cases of active TB, of the total active TB outpatient visits, and of the new latent TB infections diagnosed (and related outpatient visits). In some centres, personnel initially attributed for TB service provision were re-prioritised to COVID-19. In addition, the decreased attendance to TB clinics was associated with patient fear of exposure to COVID-19 in the community or with disruptions of the services or struggle in accessing health services during lockdown. Conversely, national lockdowns favoured the increased use of telemedicine. In the TB centres surveyed in Australia, Russia, India, and the United Kingdom, telehealth service use increased.

A study carried out in Sierra Leone[10] compared the number of patients assessed for presumptive TB and the number of those confirmed sputum smear positive in the first 4 months of 2020 with the number of cases reported in 2018 and 2019. The results show a significant drop of confirmed TB cases. Furthermore, the number of presumptive TB decreased in March/April 2020, with no treatment supervised nor cases of TB/COVID-19 coinfection or childhood TB detected in April 2020. The study shows the indirect impact of COVID-19 on TB care in a low-resource high TB-burden setting. The study suggests that Africa needs economic and technology support to strengthen its response to COVID-19 pandemic. Otherwise, all results achieved in recent years in the fight against TB may be lost.

Similar findings have been observed in Brazil,[95] China,[96] India,[7,97] Iran,[98] Nigeria[99] and United States (migrants).[100] A similar experience was reported on children in South Africa.[101] In Korea, on the contrary, the impact of COVID-19 on the performances of the TB private sector project (PPM) was not observed.[102] Repeat lockdowns of varying degrees

are reported in countries which have recurrent COVID-19 waves, and severe consequences to TB services are therefore expected.[26]

Conclusions

COVID-19 causes a spectrum of host immunological responses with asymptomatic individuals to severe cytokine-storm events that may be fatal. Immunosuppression including steroids used to treat COVID-19 may in future result in TB reactivation. Gold standard diagnostic tests for COVID-19 are PCR, and culture-based methods for TB, but an ideal point-of-care tests that can promptly inform if an individual is actively infectious with TB remains elusive.

COVID-19 can occur at any time during a patient's TB journey, with worse outcomes for patients affected by active pulmonary TB disease. More evidence is needed to understand the potential of COVID-19 to favor reactivation of an exisiting TB infection. The aspecific signs and symptoms common to COVID-19 and TB may facilitate a rapid access to imaging services (chest radiography and/or computerized tomography) which may manifest signs of a pre-existing TB.

Avaliable data is insuffcient to understand the potential effect of COVID-19 on the TB patients' treatment outcome,[11,12,86] as in existing series the majority of these patients are still undergoing treatment.

Based on the information available so far, the main determinants of mortality for COVID-19 are age and co-morbidities, including HIV co-infection, poverty, diabetes and malnutrition, all of these also have an impact on TB mortality.

We need higher quality prospective studies to really answer the main research questions raised. In the meantime patients who had or have active TB especially people living with HIV co-infection should do their upmost to avoid getting COVID-19 and should be offered suitable vaccination when possible.

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LETTER TO THE EDITOR

Current practices of non-invasive respiratory therapies in COVID-19 patients in Portugal — A survey based in the abstracts of the 36th Congress of the Portuguese Society of Pulmonology

Non-invasive respiratory therapies (NIRT) have become paramount interventions in the management of COVID-19 induced acute respiratory failure.[1] Recent data from the world's largest database[2] suggests that 20% of patients with COVID-19 were admitted at some point of their illness into an intensive care unit (ICU) or high dependency unit (HDU). Non-invasive ventilation is applied in 15% of cases while High-flow nasal cannula in 14%.

The Portuguese Society of Pulmonology published back in 26th March recommendations on the use of NIRT in COVID-19.[3] However it is not known how NIRT are currently being applied in Portugal.

The 36th Congress of the Portuguese Society of Pulmonology took place 12–14th November 2020. Analyzing the published abstracts,[4] we retrieved 9 describing the experience of treating patients with COVID-19 related acute respiratory failure who were admitted to 7 public hospitals between March and August 2020. Total number of patients studied was 1594 from 1 Hospital in the North of Portugal, 2 in the centre and 4 in Lisbon region. Mean age was 69 years and only three series reported mean PaO2:FiO2 ratios.

All except one Hospital (from the centre of Portugal) reported NIRT usage. Mean NIRT use was 16.3% (minimum 5% in an infectious disease department to 48.4% in a Pulmonology Department). Only 3 Hospitals reported ventilation modes; with two favoring CPAP (usage of 53.9% and 87.8% of NIRT) and one favoring Bi-Level (usage of 97. 4% of NIRT). Only two reports (one from a Hospital in the Northern region and one from Lisbon) described the pressure levels used. Two hospitals (from Lisbon region) reported use of High Flow Nasal cannula (in 3% and 4% of all the admitted patients). Only 3 Hospitals reported success rates of NIRT, with a mean of 59% (from only 23% in the hospital that used Bi-Level mode to 78% in the hospital that preferentially used CPAP).

In only one Hospital was the Pulmonology Department the frontline service to support patients with COVID-19 and acute respiratory failure. This had the highest NIRT success rate.

These results suggest that current practices involving NIRT in COVID-19 in Portugal are really heterogeneous, with limited descriptions of the interventions and outcomes.

There should be a National Audit to monitor use of NIRT in the real world and the Pulmonology specialty should be the driver, pushing for an increased number of Respiratory Intermediate care Units with the right protocols and equipoise.

Conflicts of interest

The author has no conflicts of interest to declare.

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Effects of prone and lateral position in non-intubated patients with 2019 Novel Coronavirus (COVID-19) pneumonia

To the Editor:

Mechanical ventilation in the prone position is a validated strategy of invasive ventilator support in the treatment of acute respiratory distress syndrome (ARDS).[1] Given its beneficial effects, there has been some research into the use of prone positioning also in non-intubated patients with ARDS[2,3] and in patients with COVID-19 to avoid intubation,[4,5] but few studies[2,3,6,7] have assessed its efficacy and possible effects during SARS Cov-2 pandemic.[8–13] The use of standard oxygen and High Flow Nasal Cannula (HFNC) in refractory hypoxemia due to SARS CoV-2 is controversial and many International Guidelines, while suggesting a brief trial, raise concerns about the potential risk of unduly delayed intubation. We describe the physiological changes and clinical outcome of three patients suffering from severe Acute Respiratory Failure (ARF) due to COVID-19 undergoing trials using semi-recumbent, prone and lateral position during standard oxygen and HFNC. All patients tested positive on reverse transcription-polymerase chain reaction (RT-PCR) on throat swabs; comorbidities and administered drugs are reported in Table 1.

A 74 year-old woman was admitted on March 19th, after 10 days of fever. On the 24th she was transferred to our Respiratory Intensive Care Unit (RICU) due to worsening of her respiratory conditions. On arrival, she was haemodynamically stable, her respiratory rate was 18/min in a reservoir oxygen mask at 15 l/min; ABG testing showed a severe impairment of gas exchange (PaO2/FiO2 87; PaO2 69 mmHg, PaCO2 33 mmHg, pH 7.49, HCO3- 27,8 mmol/L). We initiated non-invasive ventilation (NIV) with helmet interface (PSV: PS 22 cmH2O, PEEP 10 cmH2O, FiO2 80%), without improvement of gas exchange (PaO2/FiO2 80). A high resolution CT-scan (HRCT) showed bilateral consolidations with ground-glass opacities (GGO), mainly in the posterior dependent zones. Based on this radiological picture we pronated the patient whilst administering oxygen-therapy with reservoir mask. An almost immediate increase of SpO2 was observed (Fig. 1). At 2 h the PaO2/FiO2 had increased to 203 mmHg and this trend was maintained after 12 h of prone positioning (Table 1). She improved slowly with a schedule of pronation of two sessions lasting 6 h throughout the day and overnight and was discharged home on April 29th.

The second case was a 71-year-old man, admitted to the Emergency Department (ED) with fever and progressively worsening dry cough for one week. On admission, ABG showed ARF (PaO2/FiO2 261, PaO2 55 mmHg, PaCO2 31 mmHg, pH 7.45, HCO3-24 mmol/l). Clinical conditions and gas exchange rapidly worsened (ABG 48 h after admission: PaO2/FiO2 186, PaO2 65 mmHg, PaCO2 33 mmHg, pH 7.43, HCO3- 25,6 mmol/L) and on day 6 since admission he was referred to our RICU, where HFNC therapy was set (Flow 50 L/min, FiO2 50%). The HRCT scan showed parenchymal involvement of the left lung, with relative sparing of the right one. A spontaneous breathing trial was performed placing the patient on the right lateral decubitus during HFNC therapy. Respiratory rate rapidly decreased (from 22 to 16 breaths/min) and ABG showed a significant improvement of oxygenation (P/F ratio of 202 and 211 after 2 and 12 h respectively) (Table 1). Therefore, we scheduled at least two sessions lasting 6 h of lateral position throughout the day and overnight. He was transferred to the ward 8 days after ICU admission and discharged at home after 28 days.

The last patient was admitted to the ED after 6 days of fever, asthenia and dyspnoea. On admission, ABG was normal, but lung ultrasound documented signs suggestive of interstitial-alveolar pneumonia and a HRCT confirmed bilateral GGO associated with initial peripheral consolidations. The patient's condition deteriorated and she was transferred to our RICU, where HFNC therapy was started (Flow 45 L/min, FiO2 60%). A novel CT scan showed a relative sparing of the left lung, therefore she was placed in left lateral decubitus. Changes in oxygenation as well as in respiratory pattern are summarized in Table 1. Two sessions lasting 6 h of lateral position throughout the day and overnight determined a stable improvement of gas exchange and prevented mechanical ventilation. She was discharged home after 21 days from hospital admission.

Our findings indicate that this strategy is feasible and a useful option in the management of acute respiratory failure due to this disease. In fact, patient recumbency in accordance with imaging to adjust V/Q was associated with a significant improvement of oxygenation and breathing pattern, with good tolerance. In addition, we found no significant hemodynamic adverse effects. The physiologic rationale for prone positioning and lateral decubitus in non-intubated patients is strong: firstly, redistribution of V/Q ratio due to the gravity-induced increase of blood flow to spared regions of the lung, which becom better ventilated[14]; secondly, lung recruitment of previously dependent regions occurs as ''oedema'' flows away from anti gravitational alveoli.[14] Similarly, positioning patients with unilateral pleuro-parenchimal disease with the normal lung down, especially in the absence of pleural pain, can affect gas exchange.[15,16] Thirdly, the increase in oxygenation should also ameliorate hypoxemic vasoconstriction, reducing pulmonary vascular resistance and improving right ventricular function.[17] In addition, in the prone position we may obtain a relief from the weight of the mediastinum and a decrease in overdistension of the healthy areas, thanks to the distribution of trans-pulmonary pressure. In fact, recruitment of the dorsal lung, which has a higher degree of perfusion in either position, reduces shunt.[18,19] A retrospective study including 15 patients showed a beneficial effect of prone position during NIV in patients with severe ARF due to pneumonia.[2] Recently, Ding[3] reported a reduction in intubation rate in patients with moderate to severe ARDS when treated with combined prone positioning and NIV or HFNC.

Recent studies[8–13] showed that prone positioning may improve gas exchange in COVID-19 patients during oxygen therapy and non invasive support (HFNC or NIV). However, no information about the radiological pattern has been provided. In contrast, our cases showed that the distribution of parenchymal lesions could be a valid criterion to select patient for spontaneously breathing trial in prone positioning and lateral decubitus. Chest x-ray could be useful to support diagnosis, especially during Sars-cov 2 pandemic: sensitivity values range from 57% to 89%.[20] However,

Table 1 Demographic, clinical characteristics, laboratory and CT-scan findings at respiratory intensive care unit admission, drugs, ABGs.

	Patient 1	Patient 2	Patient 3
Demographics			
Age-yr	74	71	70
Sex	Female	Male	Female
Initial findings			
Medical history	Dyslipidemia, hypothyroidism, carotid atheroma	Hypertension, deep venous thrombosis	Hypercholesterolemia and hypertension
Symptoms at disease onset	Fever	Fever, cough	Fever, asthenia, dyspnoea
Pharmacological treatment			
(dosages are shown for drugs initiated during RICU stay)	Hydroxychloroquine, piperacillin-tazobactam, azithromycin, enoxaparin, tocilizumab 162 mg x2 s.c., methylprednisolone 1,6 mg/kg	Hydroxychloroquine, enoxaparin, ceftriaxone, tocilizumab 162 mg x2 s.c., methylprednisolone 1 mg/kg	Hydroxychloroquine, azithromycin, enoxaparin, ceftriaxone, tocilizumab, methylprednisolone
Imaging features			
Thoracic HRCT scan	GGO, bilateral pulmonary infiltrates, mainly in the posterior dependent zones	GGO and consolidations prevalent on the left lug	GGO and pulmonary infiltrates prevalent on the right lung
Days from Hospital admission to prone/lateral decubitus	6	11	8

[10pt]

Table 1 (*Continued*)

ABGs	Patient 1			Patient 2			Patient 3		
	PRE	During NIV	PP/LD after 12h	PRE	During HFNC	During PP/LD	PRE	During HFNC	During PP/LD
pH	7,49	7,48	7,47	7,42	7,45	7,43	7.48	7,49	7,45
PaCO2 (mmHg)	32	31	35	42	39	40	33	30	35
PaO2 (mmHg)	66	62	162	80	76	80	62	70	109
PaO2/FiO2	83	80	203	160	158	211	115	116	205
HCO_{3-} (mmol/L)	26	26	27	27	27	26	26	26	25
Vital Parameters									
	PRE	PP/LD after 2h	After 12h	PRE	PP/LD after 2h	After 12h	PRE	PP/LD after 2h	After 12h
RR (breaths per minute)	25	20	26	22	16	18	21	22	20
Heart rate (bpm)	87	72	80	74	60	65	68	64	65
Mean Arterial Pressure (mmHg)	97	113	107	108	97	103	88	87	96

RICU, Respiratory Intensive Care Unit; GGO, ground-glass opacities; s.c., sub cutaneous; NIV, non invasive mechanical ventilation; HFNC, High Flow Nasal Cannula; PP, prone position; LD, lateral decubitus.

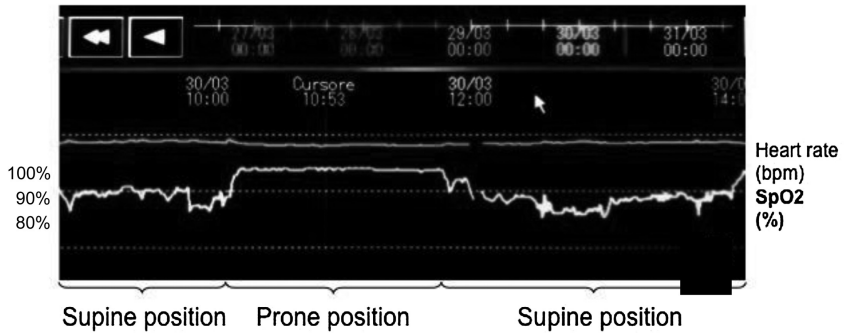

Figure 1 Pulse oximetry pleth waveform of the same patient during supine and prone position.

Chest-x-ray can not detect spared lung areas: exclusive dorsal lung areas involvement can not be detected without latero-lateral projection, not usually performed in critical setting, requiring orthostatic posture. As observed by Marini,[4] COVID-19 pneumonia appears to include an important vascular insult that potentially mandates a different approach from that usually applied for ARDS. Our patients, despite very poor oxygenation and extensive parenchymal lesions, recovered without needing either NIV or intubation, and such a result would not, probably, have been possible in a ''traditional'' ARDS. All healthcare workers exposed used personal protective equipment (PPE).[21] Interestingly, in all 3 cases reported we observed that PaCO2 did not change, indicating that the change in PaO2 was not a consequence of a change in alveolar ventilation, supporting the theory of a beneficial effect on V/Q ratio. However, we do not recommend delaying intubation or attempting this approach in a setting without intensive monitoring, which is necessary to quickly upgrade ventilatory support in non-responders.

To conclude, we have demonstrated that preferential decubitus on the least affected areas of the lung, either in prone or lateral position, in awake and spontaneously breathing, non-intubated patients with ARF due to COVID-19 pneumonia is feasible, well tolerated and is associated with a significant benefit on oxygenation. Further studies are warranted to confirm our results.

Declaration of interests

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

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Wearing of medical mask over the high-flow nasal cannula for safer oxygen therapy in the COVID-19 era

To the Editor

The emergence of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and its associated respiratory disease, coronavirus disease 2019 (COVID-19), has imposed social and medical burdens worldwide. Up to 12% of patients with SARS-CoV-2 infection required intensive care unit admission. Among them, 60-70% had acute hypoxic respiratory failure.[1]

High-flow nasal cannula (HFNC) oxygen therapy is the generally prescribed respiratory therapy for acute hypoxic respiratory failure. This therapy might help limit the need for invasive mechanical ventilation (IMV) and prevent the occurrence of associated adverse events such as ventilator-associated pneumonia in COVID-19 patients.[2] However, administration of HFNC oxygen therapy in COVID-19 patients remains controversial, owing to uncertainties regarding the potential risk of viral transmission to healthcare workers, as this therapy is considered as an aerosol-generating procedure.[3] Indeed, IMV can be selected when low-flow oxygen therapy through a nasal canula fails and a shortage of ventilators is a medical and social problem in regions particularly hard-hit by this pandemic. Therefore, a safe and effective respiratory management for COVID-19 patients should be urgently established.

Recent practical recommendations for COVID-19 patients indicate the use of a medical mask over the HFNC device to limit particle dispersion due to exhaled gas flow.[4,5] These recommendations are partially supported by two previous experimental studies that indirectly examined exhaled breath by visualizing airflow movement using smoke[6] and computational fluid dynamic (CFD) simulation.[7] However, to the best of our knowledge, there is no direct evidence that this strategy could reduce the risk of SARS-CoV-2 transmission to healthcare workers in clinical settings due to the technical difficulty in direct visualization of particle dispersion. Here we present an experimental trial with a novel fine particle visualization system, which allowed evaluating whether particle dispersion from coughing while on HFNC oxygen could be suppressed by an appropriately placed medical mask.

We ran six scenarios with a healthy volunteer with nasal cannula at 3 L/min and 21% fraction of inspired oxygen (room air) delivered at 40 L/min 37°C via HFNC (AIRVO™ 2 device with an Optiflow™ nasal interface [Fisher & Paykel, Auckland, New Zealand]). The volunteer was in a sitting position (seat height: 45 cm), and the evaluation was performed with and without wearing a standard medical mask. Particle dispersion was visualized by a video camera set at 29.97 frames per second (Eye Scope). This system used a light emitting diode (wavelength 400-410 nm; Parallel Eye D), which permitted a visualization of particle $\geq$1 μm in diameter. Images obtained were reconstructed as videos using commercial software (Particle Eye). Equipment described above depended on Shin Nippon Air Technologies (Tokyo, Japan).

First, we identified exhaled particles dispersed from coughing in the absence of either nasal cannula, HFNC, or a mask, which reached a horizontal distance of 57 cm (Fig. 1A and supplemental video A). Second, exhaled particles were dispersed from coughing in a similar fashion when using nasal cannula (Fig. 1B and supplemental video B) and HFNC (Fig. 1C and supplemental video C), which reached a horizontal distance of 62 cm and 59 cm, respectively. Notably, when the volunteer wore a standard medical mask, no exhaled particles were detected from coughing either without (Fig. 1D and supplemental video D) or with concurrent nasal cannula (Fig. 1E and supplemental video E) or HFNC therapy (Fig. 1F and supplemental video F).

Abbreviations: CFD, computational fluid dynamic; COVID-19, coronavirus disease 2019; HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

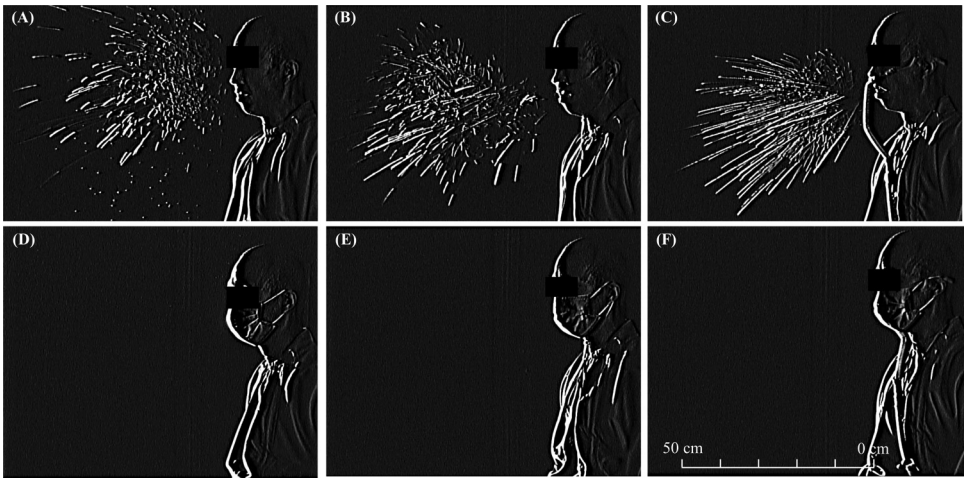

Figure 1 Photographs of droplet dispersion after cough when not utilizing (A) and utilizing supplemental oxygen via nasal cannula (B) and HFNC (C) and with an appropriately placed medical mask when not utilizing (D) and utilizing supplemental oxygen delivered by nasal cannula (E) and HFNC (F).
HFNC = high-flow nasal cannula.

This report substantially increases our understanding on the droplet dispersion risk during HFNC therapy. Wearing a medical mask over HFNC device almost completely suppressed particle dispersion induced by coughing. Our findings are first direct evidence that wearing a medical mask will be a useful manner in administering HFNC oxygen therapy and strongly support the recommendation as described above. Moreover, the present direct visualization of the suppressive effect of the medical mask *in vivo* further extends a previous CFD simulation by Leonard et al. who showed that the hypothetical medical mask captured 83.2% of particles (0.1-100 μm) during high-velocity nasal insufflation at 40 L/min.[7]

Despite the advanced technology, we and Leonard et al. could not visualize or simulate particles of <0.1 μm. Whether these small particles (aerosols) could be sources of transmission of SARS-CoV-2, remains unclear. Further studies are needed to evaluate whether HFNC oxygen therapy could increase risk of SARS-CoV-2 transmission to healthcare workers and whether wearing a medical mask under HFNC oxygen therapy could reduce this risk in clinical settings.

The visual evidence presented here should be shared with all care-givers wearing personal protective equipment to encourage the use of HFNC oxygen therapy for managing hypoxic COVID-19 patients. Hopefully, this method helps overcome this disastrous pandemic situation worldwide.

Conflict of interest

Satoshi Hamada reports grants from Teijin Pharma, outside the submitted work.

Financial conflicts

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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.2020.10.009.

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COVID-19 does not stop good practice in smoking cessation: Safe use of CO analyzer for smokers in the Covid era

Smoking has been proven to be an important risk factor for disease severity and worse outcomes in Covid-19, the disease caused by SARS-CoV-2.[1]

The World Health Organization (WHO) recommends not smoking in order to reduce the risk of harm caused by the disease and warns against reports that tobacco or nicotine could benefit Covid-19 as they do not provide sufficient evidence for this statement.[2] In our practice at the Antismoking Center of the National Cancer Institute of Milan, the smoker's assessment has proved particularly useful, in particular, for this purpose, we use carbon monoxide (CO) measure in the exhaled breath.

Starting from June 2020 it was possible, keeping the distance between patients and the use of personal protection devices, to resume the activity of the antismoking center, but the Covid-19 situation has posed non-emergency labs with the question of how to proceed with clinical tests safely while avoiding virus transmission among patients[3]; so, we addressed the problem of safe CO measurement.

The level of carboxyhemoglobin in the blood can be determined by measuring the exhaled CO through an instrument that provides the CO value in parts per million (ppm). This type of measurement is then configured as an extremely useful tool in smoking cessation assessment, to enhance motivation to quit and for follow-up of smoking cessation programs.

One of the major company for CO analyzers is Bedfont Scientific Ltd with its main product ''Smokerlyzer™'', a portable instrument with research and education aims. The model we have available in our antismoking centre is a Micro+ Smokerlyzer™ model purchased in 2012. It is composed of the electronic device (Fig. 1a), the fitting provided with an antibacterial filter (Fig. 1b) which lasts 30 days and the disposable mouthpieces (Fig. 1c). For the latest models Bedfont has produced disposable antibacterial filters, but our model is not compatible.

To safely use the CO analyzer, we thought of substituting the fitting with an antibacterial filter with a new one, specially created (Fig. 1d). This fitting, designed with the help of our clinical engineering department, was made of a plastic polymer and printed via a 3D printer. The size of the fitting (section and length) was calculated to make minimum modifications in order not to change significantly the

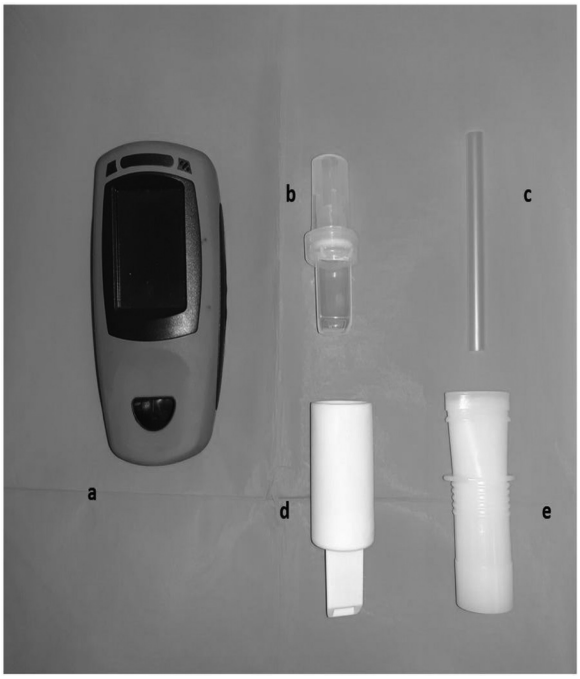

Figure 1 Smokerlyzer's components: electronic device (a); original fitting (b); disposable mouthpieces (c); fitting specially created (d); disposable spirometry mouthpieces (e).

flow rate and the volume of air entering the device; in this way it is possible to avoid alterations related to the detection and calibration of the instrument. It does not contain any filters and it can be washed and disinfected after each use. The fitting has been molded to allow the attachment of disposable mouthpieces that we usually use for the execution of spirometries (Fig. 1e). This mouthpiece contains an electrostatic and certified mechanical filter that removes bacteria and viruses at an efficiency rate of >99%, thus reducing risks of cross contamination during testing. Through this solution we can guarantee the use of a single filter for each patient.

The safety of this measurement must be guaranteed not only for patients but also healthcare professionals. The use of appropriate personal protective equipment (PPE) is of pivotal importance for the healthcare workers involved in the care of patients with viral infections, such as the current pandemic, Covid-19.[4] In collaboration with Health and Safety Protection Unit, considering that this procedure provides for the emission of exhaled breath, we have reviewed it: workers must carry out the procedure with Covid-19 personal PPE and, as further precaution, the patient is asked to plug his or her nose with disposable forceps so that there is no exhalation from the nasal cavities during the procedure.

Due to the risk of Covid-19 transmission, it was impossible for us to test the CO analyzer for correct measurement of exhaled CO for smokers with and without modified fitting, but during the first period of the modified device use, we verified that the detector has not undergone alterations in the measurement of the CO concentration. In fact, we used the device during our checks among smoking patients and we detected values compatible with the self-reported smoking status.

The completely new situation that arose during the period of the Covid-19 pandemic, characterized by social isolation, physical distancing, possible loss of employment and prolonged lockdown, is highly stressful and therefore predisposing people to find refuge in addictive substance, and among these, tobacco.[5]

Therefore, smokers and ex-smokers are at greater risk of worsening their health condition by smoke dependence due to the pandemic; furthermore, smoking does not only constitute individual damage: the lockdown has forced many people to stay at home, increasing indoor smoking and therefore the possibility of exposing family and neighbors to secondhand smoke[6]; in addition, cigarette smoke has been identified as a possible vehicle for the Covid-19 virus as droplets are more easily released into the environment while smoking.[7] In addition some studies[5] have even indicated that the pandemic has increased the possibility of people wanting to quit smoking.

All these considerations suggest the importance of promoting smoking cessation during the Covid-19 pandemic. In the future it will be necessary not to interrupt the antismoking services, including the measurement of CO safe for patients.

Conflicts of interest

The authors have no Conflicts of interest to declare.

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Results from phase II, open-label study of anti-tumoral activity of first-line erlotinib in advanced/metastatic NSCLC patients with EGFR activating mutations, in Portugal: The MuTAR study

Dear Editor,

Non-small cell lung cancer (NSCLC) is the most common cause of cancer death worldwide, with low survival (6–12 months and overall 5-year survival 5–10%), mostly because it is usually diagnosed in advanced stages.[1]

In NSCLC, the most common epidermal growth factor receptor (EGFR) mutations are exon 19 and exon 21, highly associated with sensitivity to tyrosine kinase inhibitors (TKI).[2] EGFR mutations are more common in non-smokers, women, adenocarcinomas and Asians patients.[1] Erlotinib is an orally active and potent TKI[3] indicated for first-line and maintenance treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations.

This study (NCT01260181) was a phase II, non-randomized, open-label study to evaluate the anti-tumoral activity of erlotinib in patients with locally advanced or metastatic NSCLC with EGFR activating mutations. It was designed to evaluate the efficacy of erlotinib first-line treatment–as a single daily oral dose of 150 mg, until disease progression or unacceptable toxicity, death or withdrawal of consent–evaluated by complete or partial objective response rate (ORR) in Portugal.

This event-driven study was set up in 9 hospitals from January 2011 (start of recruitment period) to September 2017 (last safety follow-up visit).

There were 216 patients screened, 30 were enrolled, positive for exon 19 (40.0%) and/or exon 21 mutations (60.0%). Twenty-nine (96.7%) completed the treatment. At the end one patient was alive.

Patients' mean age was 66.3 ± 9.21 years, 80% were female. Most were non-smokers (76.7%) with 20 pack-year smoking history. Median disease duration was 1 month (0–32 months) and histology for 96.7% of patients was adenocarcinoma. TNM classification was mostly stage IV (1 patient stage IIIB). Fifty percent of patients had bone metastatic disease and 80% another metastasis location. Two hundred and sixteen comorbidities have been reported and all patients had at least one. At screening, all patients had ECOG performance status 0 (20.0%), 1 (66.7%) or 2 (13.3%).

Efficacy results showed an ORR of 63.3% (95% CI: 46.1%–80.6%), in intention-to-treat, and 75.0% (95% CI: 50.1%–99.5%), in *per-protocol* population. The stable disease was the best overall response for the anti-tumoral activity in 30.0% of patients and progressive disease was the best overall response in 3.3%. The best overall response is summarized in Table 1.

Median progression-free survival (PFS) was 10 months (95% CI: 7.8–15.8), and median overall survival was 20.8 months (95% CI: 14–31.2). The median duration of response was 10.4 months (95% CI: 8–15.8). For exon 19 patients, the median PFS was 14.4 months (95% CI: 4.2–41.8) and for exon 21 9.8 months (95% CI: 3.8–13.5).

Table 1 Best overall response (RECIST v1.1 criteria) for the study populations.

ITT population	Total (n = 30)
Best overall response, n (%)	
Complete response	0
Partial response	19 (63.3%)
Stable disease	9 (30.0%)
Progressive disease	1 (3.3%)
Inevaluable	0
Not available/not accessed	1 (3.3%)
Total	30
Objective response rate,[a] n (%),95%CI	19 (63.3%), [46.1%, 80.6%]
PP population	**Total (n = 12)**
Best overall response, n (%)	
Complete response	0
Partial response	9 (75.0%)
Stable disease	3 (25.0%)
Progressive disease	0
Not evaluable	0
Not available/not accessed	0
Total	12
Objective response rate,[a] n (%), 95%CI	9 (75.0%), [50.1%, 99.5%]

Note: For the 7 patients without information of overall response at the end of the study visit, best overall response was obtained according to the information from the study treatment visits available.
95%CI: 95% confidence interval; ITT: intention to treat; PP: per protocol.
[a] Objective response rate: patients with complete or partial response.

Safety profile was as expected, with 341 adverse events reported by 29 patients. The most common AEs were rash acneiform (63.3% of patients) and diarrhea (50.0%) (Table 2). From these, 49.0% were at least remotely related to treatment. More than 65% of AEs were recovered/resolved while more than one third were not recovered/not resolved, and 3 (0.9%) were fatal. There were 10 SAEs experienced by 8 patients (26.7%), 5 of them were at least remotely related to study drug (diarrhea, gastrointestinal disorders, pelvic infection, skin and subcutaneous tissue disorders and vascular disorders). One AE (interstitial lung disease) was of special interest.

There were 4 deaths in the study, one due to pneumonia (not related to the study drug), one due to intestinal perforation (possibly related to the study drug), one unexplained (not related to the study drug) and the other due to progressive disease. At the end of study 51.9% of the patients had a subsequent therapy for NSCLC.

In our study, erlotinib has shown results similar to other published clinical trials in first-line treatment.[4,5] In EURTAC study of first-line erlotinib versus standard IV chemotherapy, PFS was significantly longer in erlotinib-treated patients (10.4 months) than chemotherapy patients (5.1 months). Another phase-II study[4] in Caucasians reinforced erlotinib as a first-line treatment of choice, with median PFS of 11

Table 2 Incidence of AEs and SAEs in the safety population.

	Total (n = 30)
Patients with at least 1 adverse event (≥20%), n (%)	29 (96.7%)
Rash acneiform	19 (63.3%)
Diarrhea	15 (50.0%)
Anorexia	8 (26.7%)
Rash maculo-papular	8 (26.7%)
Respiratory, thoracic and mediastinal disorders	8 (26.7%)
Fatigue	7 (23.3%)
Paronychia	7 (23.3%)
Skin and subcutaneous tissue disorders	7 (23.3%)
Upper respiratory infection	7 (23.3%)
Constipation	6 (20.0%)
Eye disorders	6 (20.0%)
Gastrointestinal disorders	6 (20.0%)
Patients with AEs with remote, possible or probable relationship with study drug (≥20%), n (%)	28 (93.3%)
Rash acneiform	18 (60.0%)
Diarrhea	15 (50.0%)
Maculopapular rash	8 (26.7%)
Paronychia	7 (23.3%)
Skin and subcutaneous tissue disorders - Other, specify	7 (23.3%)
Patients with at least one serious adverse event, n (%)	8 (26.7%)
Depression	1 (3.3%)
Diarrhea	1 (3.3%)
Fracture	1 (3.3%)
Gastrointestinal disorders	1 (3.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3.3%)
Pelvic infection	1 (3.3%)
Renal and urinary disorders	1 (3.3%)
Respiratory, thoracic and mediastinal disorders	1 (3.3%)
Skin and subcutaneous tissue disorders	1 (3.3%)
Vascular disorders	1 (3.3%)
Patients with SAEs with remote, possible or probable relationship with study drug, n (%)	4 (13.3%)
Diarrhea	1 (3.3%)
Gastrointestinal disorders - Other, specify	1 (3.3%)
Pelvic infection	1 (3.3%)
Skin and subcutaneous tissue disorders - Other, specify	1 (3.3%)
Vascular disorders - Other, specify	1 (3.3%)
Deaths	4

months, clinical benefit rate of 81% and median OS of 23 months, in line with our results.

In BELIEF study,[6] of erlotinib 150 mg/day + intravenous bevacizumab 15 mg/kg/21 days, PFS was 13.2 months. In another double-blind, phase 3 trial in untreated patients with advanced NSCLC, EGFR mutation-positive for exon 19/21, assigned to osimertinib 80 mg/day or standard EGFR-TKI (gefitinib 250 mg od/erlotinib 150 mg/day), median PFS was 10.2 months with standard EGFR-TKIs and 18.9 months with osimertinib, with similar safety profile. The first-line bevacizumab + erlotinib versus erlotinib alone (BEVERLY study) is still waiting for results.

Safety profile was according to previous published clinical trials,[3,4,6,7] with rash and diarrhea being the most commonly reported, at mild/moderate intensity.

In conclusion, erlotinib has shown to be effective and well tolerated in Portuguese NSCLC EGFR mutated patients, with locally advanced or metastatic stages. Our findings support erlotinib to be considered as first-line therapy option for locally advanced or metastatic NSCLC with EGFR-activating mutation in Portugal.

Authors contributions

Fernando Barata contributed to the conception and design of the study.

Fernando Barata, Henrique Queiroga, Encarnação Teixeira, Teresa Almodovar, Marta Soares, Barbara Parente, Juan Carlos Mellidez, Paula Alves contributed to acquisition of data.

Fernando Barata, Ana Antunes contributed to analysis and interpretation of data.

Fernando Barata, Ana Antunes contributed to drafting the article.

Fernando Barata, Henrique Queiroga, Encarnação Teixeira, Teresa Almodovar, Marta Soares, Barbara Parente, Juan Carlos Mellidez, Paula Alves, Ana Antunes contributed to revising the article critically for important intellectual content.

All the authors contributed to the final approval of the version to be submitted.

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Conflict of interests

The authors, F. Barata, H. Queiroga, E. Teixeira, T. Almodovar, M. Soares, B. Parente, J.C. Mellidez, P. Alves, declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

A. Antunes declares herself to be employee of Roche Farmacêutica Química which can be perceived an competing interest.

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Value of rebiopsy in advanced Epidermal Growth Factor Receptor mutated Non-Small Cell Lung Cancer: Real-world data

Letter to the Editor

Acquisition of Epidermal Growth Factor Receptor (EGFR) mutation resistance (mainly T790M) to EGFR tyrosine kinase inhibitors (TKI) occurs in about half of Non-Small Cell Lung Cancer (NSCLC) patients treated with TKI.[1] Mutational status is important to guide therapy.[2,3] Pirker stated that while tissue biopsy is currently the main source for molecular analyses, liquid biopsies will gain importance for diagnosis and disease monitoring in the future.[4] The aim of this study was to analyse the value of liquid and tissue rebiopsy for evaluation of EGFR mutational status in a real-world setting.[5,6]

We carried out a retrospective identification of patients tested for EGFR mutation at a Portuguese cancer center between January 2015 and October 2019. We collected clinical data from patients with advanced EGFR mutation NSCLC. Descriptive statistic was used to analyse patients' characteristics.

Of the 824 patients that were evaluated for EGFR mutation, 160 (19%) had EGFR-mutant NSCLC.

Table 1 Rebiopsy sites and T90M detection success rate.

1st rebiopsy site	Number of biopsies	T790M +
Tissue biopsy/cytology	**25**	**11 (44%)**
Bronchial tissue	13	8 (62%)
Pleural fluid	8	3 (38%)
Cerebrospinal fluid	2	0
Bronchial secretions	1	0
Thoracic Lymph node	1	0
Liquid biopsy	**25**	**6 (24%)**
2nd/3rd rebiopsy site	Number of biopsies	T790M+
Tissue biopsy/cytology	**9**	**1 (11%)**
Bronchial tissue	4	0
Pleural fluid	3	0
Brain	1	1 (100%)
Bone	1	0
Liquid biopsy	**25**	**4 (16%)**

Eighty-five of 160 patients (53%) had advanced disease (11 patients with stage III, 65 patients with stage IV and 9 patients presented a relapsing NSCLC). All neoplasms were adenocarcinomas due to a selection bias of our institution (only adenocarcinmomas are tested for EGFR mutation. The median age at diagnosis was 69 years old [range: 39–95] and 66% of patients were female. History of tobacco use was reported as 42%.

The most common EGFR mutation was exon 19 deletion (del19) (33 patients) followed by L858R point mutation on exon 21 (24 patients) and del19 plus de novo T790M mutation (7 patients). Other uncommon mutations identified were L858R plus T790M, G719X on exon 18, del19 plus insertion of 20 and S7681 on exon 20 plus L858R.

Sixty-nine of 85 patients (81%) received EGFR-TKI and 46 patients (67%) developed disease progression on TKI. All 46 patients were submitted to a first (1st) rebiopsy, corresponding to a total of 50 rebiopsies: 25liquid biopsies and 25 tissue biopsies/cytologies (some patients had both). Eighteen patients underwent a second and third (2nd/3rd) rebiopsy, corresponding to a total of 34 rebiopsies: 25 liquid biopsies and 9 tissue biopsies/cytologies.

The most common sampling method was liquid biopsy both for 1st (50%) and 2nd/3rd rebiopsies (74%). Bronchial tissue was the most common site for tissue biopsy/cytology followed by pleural fluid both in 1st and 2nd/3rd rebiopsies. Less common sites were cerebrospinal fluid, thoracic lymph nodes and bronchial secretions for 1st rebiopsy and brain and bone for 2nd/3rd rebiopsies.

We analysed the proportion of T790M mutation identified for each rebiopsy site as shown in Table 1.

In 1st rebiopsy, bronchial tissue was the site where T790M mutation was most frequently identified (62%), followed by pleural fluid (38%) and liquid biopsies (24%). No T790M mutation was identified in other sites, corresponding to a T790M mutation detection rate of 44% for 1st tissue rebiopsy

In 2nd/3rd rebiopsy, T790M mutation was identified in the only brain biopsy performed and in 16% of the liquid biopsies. No T790M mutation was identified in other sites, meaning the detection rate for T90M mutation 2nd/3rd tissue rebiopsies was only 11%.

As shown in Fig. 1, 16 of 46 patients (35%) undergoing a 1st rebiopsy harbored a T790M mutation. Among the 30 remaining patients, 12 did not repeat biopsy and 18 were submitted to a 2nd/3rd biopsy. Five of those 18 patients (28%) were submitted to 2nd/3rd biopsies harbored a T790M mutation.

Furthermore, 18 of 46 patients undergoing rebiopsy presented exclusive intrathoracic disease. In this setting, T790M mutation was detected in 5 of 40 all rebiopsies (13%).

In patients with exclusive intrathoracic disease, liquid biopsy failed to identify T790M mutation, regardless of the number of rebiopsies. However, out of those 20 negative liquid biopsies, one had a positive matched tissue biopsy/cytology. T790M mutation was identified in 5 of 20 tissue rebiopsies/citologies performed (25%).

Among 28 patients with extrathoracic disease, T790M mutation was detected in 17 of 44 rebiopsies performed (39%). T790M mutation was found in 10 of 30 liquid biopsies (33%) and in 10 of 14 tissue biopsies/citologies (50%).

The overall survival was higher among patients submitted to rebiopsy [28.9 months (95%CI 21.2–35.0)] than among those were not [18.6 months (95%CI 9.87-NR)]. Although the increase of 10 months in overall survival was not statistically significant ($p = 0.3116$), this lack of significance might be related with the small number of our cohort. Additionally, we may consider that this tendency towards overall survival benefit could be related with a better performance status of the rebiopsied patients (fit to receive treatment). Also, we can hypothesize that rebiopsy might guide the physician to choose the best treatment, which would l lead to a better overall survival.

Our results suggest that 2nd/3rd biopsies are worth performing, as the proportion of patients with mutation identified is still significant and have a clinical impact in therapeutic choices and prognosis.[7]

T790M mutation is less identified in patients with exclusive intrathoracic disease. Liquid biopsy might not add value in this setting but tissue biopsy/cytology must be considered.

In extrathoracic disease, a higher proportion of T90M mutation was identified both in tissue biopsy/cytology and liquid biopsy. Although tissue biopsy/cytology was better than liquid biopsy, it is more difficult to perform and more invasive.

Furthermore *EGFR* mutant patients undergoing rebiopsy can present different resistance mechanisms, which reflects intratumoral and intertumoral heterogeneity, as well as dynamic changes in the relative populations of resistant clones over time.[8]

Despite the retrospective single center nature and small sample of our study, it is the first to present rebiopsy data of EGFR mutated NSCLC patients in Portugal and it is in line with other similar studies.[9,10] Eun Kyong Goag et al. also reported a sample with a similar prevalence of EGFR mutations, with 561% in exon 19 del 34,1% in L858R or L861Q (compared with 47,8% of del19 and 34,8% in L858R in our sample) and the T790M mutation was identified in 43.9% patients with exon 19 del as the most significant factor affecting T790M mutation development (hazard ratio: 6.875, $P = 0.014$). Similarly, our detection rate of T790M was 44% after the first tissue rebiopsy and the T790M mutation was detected in 50% of patients with an initial del19 mutation

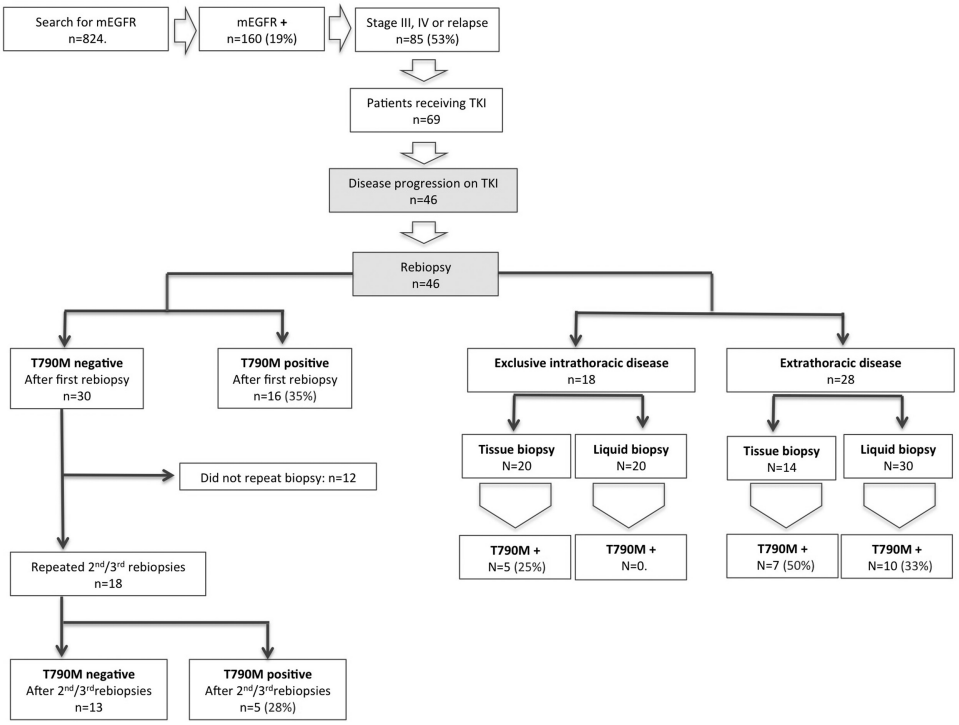

Fig. 1 Study flow chart.
Abbreviations: n: number of patients; N: number of biopsies.

(compared with 65% in Goag's study) and in 26% of patients with and an initial L858R mutation (vs. 21,5%).[9] Similarly in another Japanese study, the T790M mutation was also more frequent with an exon 19 deletion mutation (63%) than in those with a L858R mutation (38%) (p = 0.035).[10] Prospective, multicenter studies are needed to validate these findings.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Secondary organizing pneumonia after Varicella-Zoster virus infection: a rare association

Dear Editor,

Organizing pneumonia (OP) is a histologic pattern of the lungs' response to a wide variety of insults, including infectious, non-infectious, or no apparent reason (cryptogenic).[1,2] It is usually a great mimicker showing a wide variety of signs, symptoms, and high-resolution computed tomography (HRCT) findings, which makes it a frequent differential diagnosis. The usual distribution in the HRCT is patchy, peribronchiolar with the presence of numerous buds of granulation tissue within alveoli, often involving alveolar ducts and small airways; areas of consolidation are also the characteristics of organizing pneumonia.[2] Anatomopathological study is needed for final diagnosis.[1,3,4] Although duration and initial symptoms depend on the underlying aetiology, OP usually presents with a several-month history of non-productive cough, low-grade fever, malaise, and shortness of breath. It is mostly seen in patients with pulmonary infection, drug reactions, transplantation, collagen vascular disease, granulomatosis with polyangiitis, after toxic-fume inhalation, e-cigarettes usage and, rarely, lung cancer of unknown primary site.[1,5,6] When the underlying cause is not found, it is idiopathic and then called cryptogenic. Among the pulmonary infections, OP could be present after a bacterial, fungal, mycobacterial or even viral infection. Response to therapy is dependent on the treatment of the underlying cause but, usually, there is a good response to corticosteroid therapy with a good prognosis.[3,4]

We report a case of a 35-year-old male, smoker of 15 packs per year, who went to the emergency department with pruriginous cutaneous eruption. Physical examination revealed vesicular cutaneous lesions, and on pulmonary auscultation a reduction of vesicular murmur and crepitations on the left hemithorax. Analysis identified respiratory failure, thrombocytopenia, hepatic dysfunction, and elevation of inflammatory parameters (C-Reactive Protein = 9.73 mg/dL (Normal < 0.5 mg/dL) with normal procalcitonin). The chest radiograph revealed bilateral opacities with air bronchogram (Fig. 1A). After the identification of epidemiological context for varicella-zoster infection (son with chickenpox), patient was admitted to hospital stay with the diagnosis of pneumonia due to Varicella-Zoster virus and medicated with intravenous acyclovir and levofloxacin for 7 days. A good clinical, analytical, and imaging response was observed (Fig. 1B). During the hospitalization, a thoracic computed tomography (CT) scan was done, showing multiple small nodules scattered in the pulmonary parenchyma, some forming small conglomerates and surrounding ground glass. They presented bilateral distribution, but predominantly in the lower lobes. The largest conglomerate measured was 15 mm in diameter and was located in the lower-left lobe. (Fig. 1C). The patient was discharged asymptomatic.

After one year, the patient returned to the emergency department with fever, odynophagia, cough, and haemoptysis, showing no changes in physical examination or blood analysis. The following thoracic CT revealed a micronodular pattern with mostly calcified nodules. In the lower right lobe, a dense 19 mm nodule with ground-glass pattern and, juxtaposed to this, other calcified 19 mm and 5.8 mm nodules were found. There was a growth of the previously reported lesion in the lower-left lobe, which measured 21 mm. (Fig. 2A).

Blood and sputum culture were negative and bronchoalveolar lavage showed no changes. CT guided biopsy of the lower left lobe lesion was performed, with anatomopathological exam revealing focal lesions of organizing pneumonia with foamy macrophages in intralveolar localization (Fig. 2B). After the exclusion of other causes of organizing pneumonia and considering the previous diagnosis of varicella-zoster pneumonia, this cause was assumed. Corticosteroid therapy was started with an initial dose of oral prednisolone of 30 mg (0,5 mg/kg) daily for 6 months. Symptoms and imaging gradually improved and, after 1 year, clinical or imaging recurrence was not observed (Fig. 2C).

The present report describes a case of OP associated with varicella-zoster infection. Hypersensitivity pneumonitis (HP) could have a very similar clinical presentation such as fever, cough, and ground glass consolidations on CT and has a high incidence among Portuguese population in contact with birds, mould, cork or isocyanates.[7] However, besides an identifiable exposure history, imaging changes are usually upper lobe predominant. Despite the usually good prognosis with response to antigen avoidance, some chronic forms, mainly fibrotic, could have the same prognosis as idiopathic pulmonary fibrosis.[8] As previously stated, OP is an histological pattern associated with a variety of disorders,[1,4] however, OP is rare after viral infections. There are a few cases reported of influenza

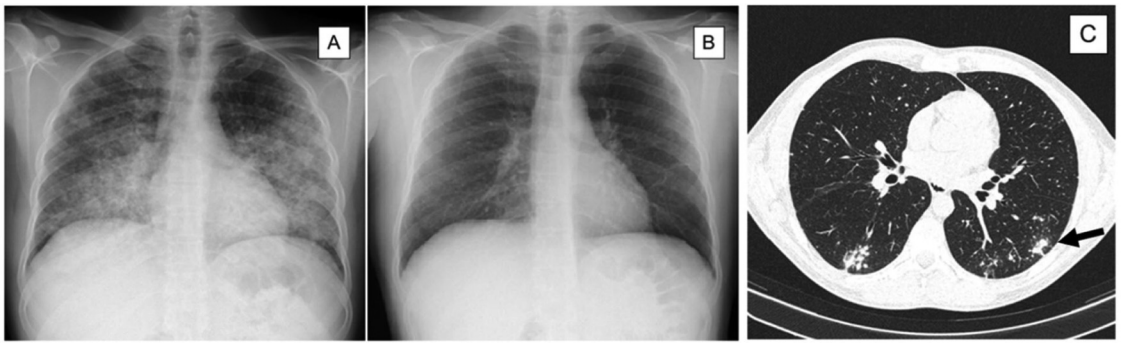

Figure 1 Imaging evolution of Varicella-Zoster pneumonia.
Posteroanterior chest radiograph evolution during Varicella-Zoster Pneumonia. A) On admission with bilateral opacities with air bronchogram. B) On discharge day showing almost complete resolution of the previously described lesions.
Thoracic computed tomography. C) On final days of hospitalization by varicella-zoster pneumonia showing multiple small nodules scattered in the pulmonary parenchyma, some forming small conglomerates, and surrounding ground glass with bilateral distribution, but predominantly in the lower lobes. The largest conglomerate measuring 15 mm in the lower left lobe (arrow).

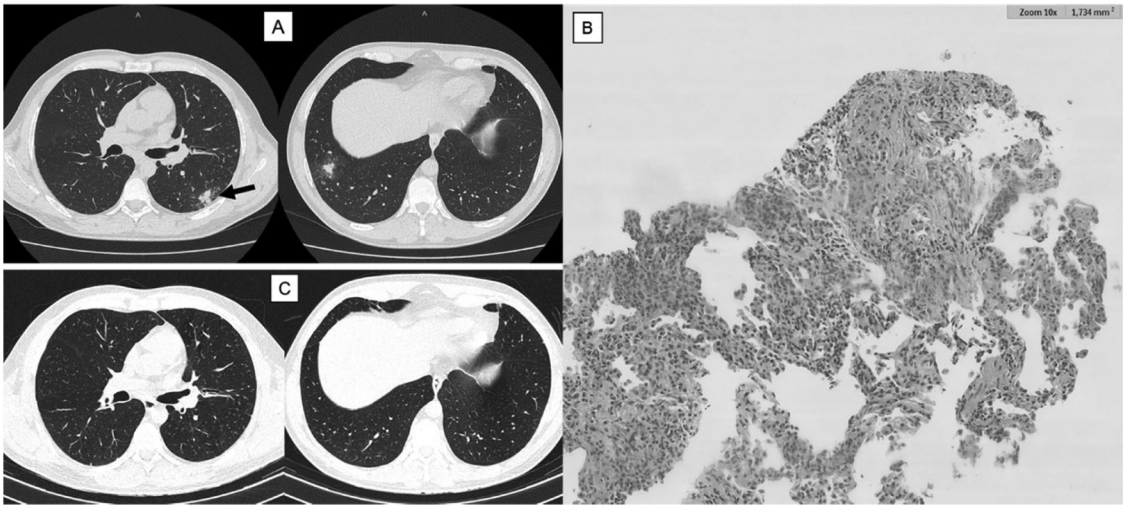

Figure 2 Imaging evolution and histology of Organizing Pneumonia secondary to Varicella-Zoster infection.
Thoracic computed tomography (CT). A) One year after varicella-zoster infection showing a micronodular pattern with mostly calcified nodules. In the lower right lobe, a dense 19 mm nodule with ground-glass pattern and, juxtaposed to this, other two calcified nodules. Growth of the previously reported lesion in the lower-left lobe, measuring 21 mm (arrow). **CT guided biopsy of the lower left lobe lesion.** B) Anatomopathological exam showing focal lesions of organizing pneumonia with foamy macrophages in intralveolar localization. **Thoracic CT.** C) One year after corticosteroid treatment maintaining micronodular pattern with calcified nodules, but with complete resolution of the previously described lesions.

association,[5] while the association with varicella-zoster is even rarer. The few cases reported of OP after varicella-zoster infection occurred in patients with known risk factors for varicella-zoster infection, such as cigarette smoking, pregnancy, immunosuppression and male sex.[9,10] Early diagnosis and treatment contribute to a favourable prognosis. We acknowledge the need for the physicians' awareness of the secondary OP after varicella-zoster infection, even if the disease had previously been cured.

Patient's consent

Patient's informed consent was obtained.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Daytime non-invasive ventilatory support via intermittent abdominal pressure for a patient with Pompe disease

To the editor:

Late onset Pompe disease (LOPD) is a glycogen storage disorder characterised by progressive skeletal and respiratory (i.e. diaphragmatic) muscle weakness and ventilatory pump failure (VPF).[1] Enzyme replacement therapy (ERT) can prolong survival.[2] Noninvasive ventilation (NIV) is often used with low bi-level positive airway pressure (PAP) which may be inadequate for optimal respiratory muscle rest and ventilator support. Higher pressure support (PS) of 14 cm H2O or more often called Noninvasive ventilatory support (NVS) needs to be used. While NIV can improve gas exchange, sleep, and quality of life (QOL) for mild cases, only increased pressures can be used for continuous support to prolong survival.[3] Both NIV and NVS can be provided during sleep via different interfaces. The nasal mask or mouth-piece is better during daytime. Intermittent abdominal pressure ventilator (IAPV) can also provide daytime support. It consists of an air-sack inside a corset inflated by a ventilator. The sack compresses the abdomen to raise the diaphragm and to increase tidal volumes.[4,5] IAPV use by LOPD patients has not yet been described, and we aimed to report its feasibility in this study.

Case Study: A 22-year-old male university student, diagnosed with LOPD at age two, began bi-weekly ERT at age 11. The ERT was adjusted over the years based on his body weight. At age 13 he began nocturnal CPAP for obstructive sleep apnoea (OSA). Within two years, due to hypercapnia, he was transitioned to NIV, and since then continued with limited follow-up. Settings: inspiratory (I)PAP 12, expiratory (E)PAP 4 cm H2O, respiratory rate 14/min which he presented to us using in 2019. During our first visit, he had severe scoliosis, emaciation (BMI 12.8 kg/m^2), and recent onset of hyper-somnolence and morning headaches. Pulmonary function testing (PFT), arterial blood gases (ABG), and polysomnography (PSG) using NIV data are in Table 1. His QoL was assessed by the McGill Questionnaire.[6] Over the previous 30 days mean nocturnal use was 9 h with average Vt 350 mL with 85% of the breaths triggered. Then, IPAP

Table 1 Baseline characteristics.

	Baseline (T0)
SB	
pH	7.41
pCO2 (mmHg)	51
pO2 (mmHg)	87
HCO3- (mmHg)	32,3
BE (mol/l)	6.7
SNIP (cmH2O)	30
PEF (L/min)	250
SVC (L, %)	1,10 (20)
FVC (L, %)	1,10 (21)
FEV1 (L, %)	1 (22)
NIV	
AHI	11,4
TST90 (%)	0

SB, spontaneous breathing; BE, base excess; SNIP, sniff nasal inspiratory pressure; PEF, peak expiratory flow; SVC, slow vital capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; NIV, Non-invasive ventilation; AHI, apnea-hypopnea index; TST90, total sleep time with oxyhemoglobin saturation below 90%.

Table 2 Settings of the two respiratory support ventilators, and data results.

	T1				T2				T3			
Bilevel night settings Ipap/Epap	12/4				16/4				20/4			
ABG	SB		IAPV (1 h)		SB		IAPV (1 h)		SB		IAPV (1 h)	
pH	7.40		7.47		7.43		7.45		7.40		7.42	
pCO2	51		39		50		44		44		41	
pO2	85		94		89		97		90		97	
HCO3-	31.6		28.4		33.2		30.6		27.3		26.6	
BE	6.8		4.7		8.9		6.6		2		1.9	
IAPV settings	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Frequency (cpm)	25.2	29.8	15	15	24.7	32.4	14.9	14.9	24.5	26,9	14	15
Inspiratory Volume (mL)	360	420	580	670	340	496	580	674	380	507	542	830
Expiratory Volume (mL)	340	400	510	655	323	470	512	679	388	512	564	845
PIF (lpm)	34	38	44	59	34	43.9	41.5	53	34	35.6	48	51
PEF (lpm)	25	37.7	34	38	30.6	37.4	43.5	54.4	32	37	46	54
McGill QoL												
- *Physical well-being*	4				5				5			
- *Physical symptoms*	8				9				9			
- *Psychological symptoms*	8.75				8.75				8.75			
- *Existential well-being*	4.6				6.5				7.5			
- *Support*	7				8				6.5			

Legend: T1, 2, 3, Time 1, 2, 3 of follow up. ABG, ambient air arterial blood gas analysis; SB, spontaneous breathing; IAPV, intermittent abdominal pressure ventilator; PIF, Peak inspiratory Flow; PEF, Peak inspiratory Flow; QoL, quality of life.

was gradually increased to 16 (i.e. PS of 12 cm H2O).[2] This resulted in 600 mL tidal volumes which he was happy to continue.

One month later, he continued 12 cm PS NIV for a mean 10 h per night, had an apnea-hypopnea index of 0.7, and average Vt 500 mL with 96% of breaths triggered. However, daytime dyspnea and fatigue continued, and despite a trial with the same ventilator he was not inclined to use mouthpiece, or NIV via nasal mask at university or socially. Diurnal hypercapnia persisted so the IAPV was introduced with a belt pressure (PBelt) of 50 cm H2O (LUNA DS, Dima Italia Inc., Bologna, Italy). His symptoms cleared, ABG, and tidal volumes improved (Table 2). Transcutaneous CO2 (TCO2) averaged 45 mmHg during IAPV use and 51 mmHg during nocturnal NIV. He was instructed to increase PS to NVS settings of IPAP 18, EPAP 4 cm H2O. Delivered volumes increased up to 750 mL. He also combined used the IAPV about 4 h during daytime.

At 3 month follow-up he reported reduction of morning headaches and sleepiness. The ABG and QoL improved, while PFT and PSG remained stable. Given the residual hypercapnia we further increased IPAP to 20 cm H2O. Six 6 months later (T3), 24-h mean TCO2 was 38.9 during IAPV, and 44 mmHg during NVS, and ABG and QOL further improved (Table 2).

This case demonstrates both diurnal and nocturnal blood gas improvements by increasing typical NIV settings to NVS settings. However, with advancing weakness, diurnal hypercapnia can persist or return. For this, IAPV use was practical and effective for this LOPD patient who was not compliant with diurnal NVS. Indeed, NVS has become the cornerstone of daytime support for VPF. It normalizes ABG, and continuous dependence on it has prolonged the lives of some post-polio patients by over 66 years, Duchenne muscular dystrophy patients by 30 years, and spinal muscular atrophy type 1 by 25 years so far, without resort to tracheotomy.[3] Varying interfaces helps avoid excessive skin pressure, mouth and upper airway dryness, mucus impaction, social interaction and eating difficulties.[3,5,7] Daytime IAPV facilitates activities of daily living to improve QoL, especially for patients unwilling to use daytime NVS.[4]

There are several advantages to the IAPV: no facial interfaces, increased cough flows and tidal volumes, improved speech duration, and it is simple to don and wear. Disadvantages include: regurgitation after meals, need to be seated, and cannot be used in a bath or shower.[4,5]

In conclusion, in this young LOPD patient IAPV normalized alveolar ventilation, tidal volumes, gas exchange, and relieved daytime symptoms to improve QoL in both his physical and existential well-being. It also avoided NVS side effects for the combined IAPV use. Further studies are warranted to broaden its application.

Conflicts of interest

The authors have no conflicts of interest to declare.

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CORRESPONDENCE

Does alcohol consumption really affect the outcome of nontuberculous mycobacterial infections?

Dear Editor,

I read with great interest the article by Jacob et al., entitled ''The effect of alcohol consumption in the treatment of nontuberculous mycobacteria.''[1] Little is known about the relationship between alcohol consumption and nontuberculous mycobacterial (NTM) infections, and the result of this article will add insights into the exacerbating factors for this disease. However, it seems early to decide that alcohol consumption is a risk factor for worsening NTM infections.

This study did not refer to some important risk factors for developing NTM infections: the use of immunosuppressants, and the history of solid organ or hematopoietic stem cell transplantations (Table 1).[2,3] Besides, it seems crucial to refer to the history of liver diseases. Although cirrhosis is not an established risk factor for developing NTM infections, the liver function is important in selecting the treatment regimen because of the hepatic toxicity of rifampicin and isoniazid.[3]

The factors I mentioned above were not included in the analysis in the article by Jacob et al. So, it seems premature to think that alcohol consumption is the risk factor for worsening NTM infections.

Table 1 The classic factors for developing and worsening NTM infections; NTM: nontuberculous mycobacterial; TNF-α: tumor necrosis factor alpha; INF-γ: interferon gamma.

The risk factors for NTM infections
Acquired immunodeficiency syndrome
Cancer chemotherapy
Carcinoma
Chronic azithromycin use
Immunosuppressants such as TNF-α inhibitors
INF-γ receptor deficiencies, and auto-antibodies to INF-γ
Inhaled antibiotics
Oral and inhaled steroid therapy
Peritoneal dialysis
Proton pump inhibitors
Signal transducer and activator of transcription 1 deficiency
Transplant recipients
Underlying lung diseases

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PHOTO

Idiopathic pleuroparenchymal fibroelastosis presenting in recurrent pneumothorax and bilateral pleural effusion: A case report

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Idiopathic pleuroparenchymal fibroelastosis (IPPFE) is widely recognized as a specific entity belonging to idiopathic interstitial pneumonia[1] and is usually characterized with progressive exertional dyspnea and pneumothorax.[2] There are no previous reports of an IPPFE case with recurrent pneumothorax and bilateral pleural effusion.

Here, we reported an unusual IPPFE case with recurrent pneumothorax with bilateral pleural effusion. A case of a 28-year-old female, non-smoker was initially admitted to our hospital due to dry cough and progressively worsening dyspnea. High resolution computed tomography (HRCT) revealed pneumothorax in the right upper zone and consolidation in the bilateral upper zone (Fig A–D). Biopsy of right upper lobe and right pleura revealed obvious fibrosis and elastosis in thickening pleura and subpleural parenchyma, which were in keeping with IPPFE (Fig E–H). 5 months later, the patient was re-admitted for progressive hypoxaemia and respiratory distress (Fig I–L). Imaging showed bilateral apical pleural thickening with concurrent bilateral pleural effusion. Following antibiotics therapy and oxygen therapy for a week, she was discharged after the return of stable vital signs. However, she suffered from gradually worsened wheezing and died on the 120th day after discharge from the hospital.

In conclusion, IPPFE should be considered if a case presents with bilateral pleurae thickening and subpleural parenchymal lesions with an upper lobe predominance. Elastin fiber stain should be performed routinely in patients with the clinical and radiological features of IPPFE, if biopsy specimen can be obtained. Pleural effusion may implicate disease progression and poor prognosis.

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the Ethics Committee of Tianjin Chest Hospital. Written informed consent was obtained from individual.

Consent to publication

Written informed consent has been obtained from the relative of the participant, who is approved the publication of the manuscript with anonymity.

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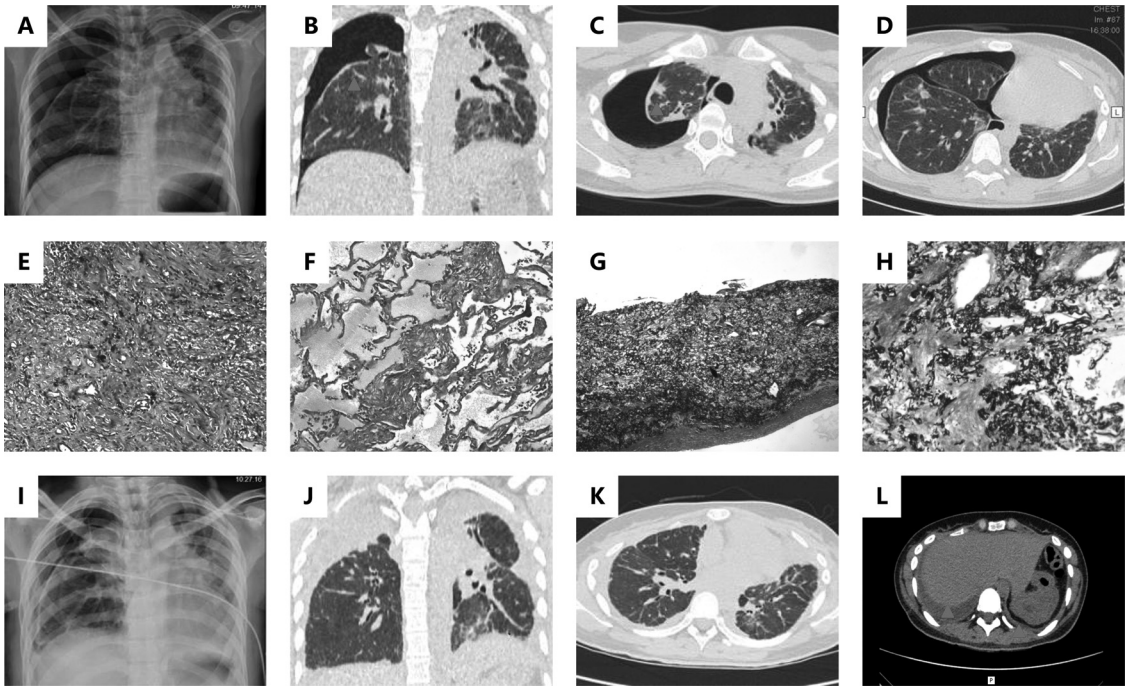

Figure (A) Chest radiograph shows pneumothorax on the right side; High resolution computed tomography (HRCT) coronal (B) and axial (C) show pneumothorax on the right side, bilateral pleurae thickening and subpleural parenchymal consolidation (red arrow); (D) HRCT shows that the fibrosis and consolidation are scanty of the lower lobes. (E) Section of pleurae biopsy (H&E stain ×100) shows the thickened pleura; (F) Masson's trichrome stain (×100) demonstrates dense fibrosis in subpleural lung parenchyma; (G) Elastic Van Gieson (EVG) stain (×100) highlights excessive elastin fibers deposition in pleura; (H) EVG stain (×100) reveals subpleural lung parenchyma. (I) Chest radiograph shows peumothorax on the left side; (J) HRCT coronal plane shows progressive bilateral pleurae thickening; (K) HRCT axial plane exhibits increasing linear and patchy opacities in the lower lobe; (L) HRCT exhibits bilateral pleural effusion (red arrow).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Authors' contributions

YXZ and YCL input into the concept and design of the study. LY, HM and YZ analyzed imaging data. YXZ, LY, YCL analyzed the medical file and wrote the manuscript. All authors have read, revised the manuscript and approved the final version.

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