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EDITORIAL

Investigating the response to COVID-19 and understanding severe TB cases: The 2022 Pulmonology TB series

Some discoveries in prevention, diagnosis and treatment of tuberculosis (TB) and subsequent implementation led to speed-up of progress towards the modern management of this disease, which in 2020 still killed 1.5 million people and caused suffering to another 8.5 million, of whom 3.3 million were women and 1.1 million children.[1]

It is important to remember we fight an ancient foe. The agent responsible for the "white plague", discovered by Robert Koch, was presented in Berlin on 24th March 1882, nowadays known as World TB Day.[2] We also remember other important discoveries, which among many others included the introduction of X-rays (Wilhelm Conrad Röntgen, 1985), of the Bacillus Calmette-Guérin (BCG) vaccination with an attenuated strain of *Mycobacterium bovis* (which Albert Calmette and Camille Guérin- introduced into clinical practice in 1921) and of treatment with streptomycin (William H. Feldman and Horton Corwin Hinshaw- first case treated with the new drug in 1944).

Pulmonology was in the frontline of the fight against TB with its TB series published in 2018[3—11] and in 2021,[12—14] the latter focused on the COVID-19 pandemic and its relationship with TB. TB is essentially one of the main 'victims' of the COVID-19 pandemic, for several reasons including the direct interaction between the two diseases in terms of morbidity and mortality,[12,15—19] the shifting of specialised staff from TB services to manage the COVID-19 emergency and the effects of fear on patients and staff, the impact of lockdown/social distancing measures and the re-organization of health services among others.[20—24]

Importantly, the further perspective of this deadly interaction, including the potential risk of developing post-TB and post-COVID-19 sequelae hampering the quality of life and requiring rehabilitation services must be considered.[12,25—29]

The topic of the 2022 World TB day is "Invest to end TB. Save lives".[30]

Pulmonology is happy to contribute to the fight against TB by publishing three relevant articles, which complete what was done in previous years, by covering the area of health services organization and management of severe cases of TB.

The first article of the series by Rodrigues et al. is aimed at investigating how infection control norms and standards were applied during the different waves of the COVID-19 pandemic in the out-patient centers in Portugal and globally, and how these centers, which are responsible for diagnosis, treatment, screening and prevention of TB responded during the pandemic.[31] The study is comprehensive and representative, and offers the possibility of reflecting on the need for health services to adapt in order to prevent further transmission of COVID-19 (but also of TB) while continuing to manage and control TB to prevent a future resurgence and increased mortality from the disease, a scenario which the World Health Organization has forecasted.[1]

An area that is still poorly understood is how to optimize management of severe cases of TB with or without COVID-19, admitted to an Intensive Care Unit (ICU), given their challenging management and poor prognosis.[32]

Pulmonology has previously published an interesting contribution from developing countries to create a simple score to predict which patients are likely to deteriorate and die rapidly if not transferred to ICU.[33]

The second paper of the Pulmonology TB series 2022 is a systematic review by Galvin et al. which investigated 529 articles in the literature to raise important questions on the topic.[34] The study identified an average mortality rate exceeding 50% among the severe TB patients admitted to ICU, ranging from 29% to 95%. In addition, the study demonstrated that mortality in high TB prevalence/limited-resource settings is 23.4% higher than in low TB prevalence ones. Interestingly, the existing severity scores investigated underestimate the actual mortality. Other significant findings of the study are that acute respiratory failure is the

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leading cause of admission to ICU and that negative predictors of outcome exist, including hospital-acquired infections, the need for mechanical ventilation and vasopressors, delay in anti-TB treatment, more than one organ failure and worse severity scores.

Still on the same page, an original study based on an extensive data set of 448 patients from 9 countries in Europe, Latin America and Asia investigated the characteristics of the severe TB patients admitted to ICU, including the cause of admission (the most frequent being intubation) and the description of their clinical management and outcome (in press). Interestingly, about half of the patients initiated anti-TB treatment in the ICU. The study findings indicate that a substantial proportion of patients had malabsorption necessitating intravenously administered anti TB drugs. The study demonstrated a positive correlation between the predictive scores and the patients' mortality in terms of prognosis. The probability of treatment success was significantly associated with a longer duration of intravenous anti-TB treatment.

This is the most extensive study on the topic so far, its strengths being also in its global representativeness.

We hope this contribution of Pulmonology to the World TB Day and the fight against the White Plague will be appreciated by our readers and that the findings of these three studies will help to end TB in the COVID-19 pandemic era.

Declaration of Competing Interest

None.

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EDITORIAL

Multidimensional approach to obstructive sleep apnea

More than a billion individuals worldwide suffer from an excess of sleep-disordered breathing, with obstructive sleep apnea (OSA) undoubtedly being the most common form.[1] Due to its extraordinarily high prevalence[1] and negative health consequences,[2-4] OSA is now considered an evident public health problem, especially in those countries where overweight or obesity (the main risk factors for OSA) are also a common conditions.[1] In most pulmonology departments (and, of course, sleep Units), OSA is the most frequently assessed disease. The health costs caused by OSA (especially in its severe or untreated forms) are three times that of an individual without OSA, while more than 80% of cases remain undiagnosed.[5]

Two of the main characteristics of OSA are its complexity (no single variable is capable of capturing its severity or prognosis, and its origin may involve different pathophysiological mechanisms (endotypes), some with possible therapeutic consequences),[6-8] and its heterogeneity[9,10] (various forms of presentation and clinical phenotypes, which sometimes complicate the suspected diagnosis). Although the guidelines for clinical practice often recommend individualizing cases when establishing a diagnosis and treatment of OSA (according to the presence or absence of a set of variables),[11] the truth is that in routine clinical practice only two of these variables are usually used to both make a diagnosis and propose a therapeutic regimen: the apnea-hypopnea index (AHI) per hour of sleep and the value of the Epworth Sleepiness Scale (ESS) as a subjective measure of daytime hypersomnia.[12] Various studies have cast doubts, however, on the diagnostic value and severity grading of these two variables in OSA, as well as their relevance for therapeutic decisions and even a prognosis.[13,14] Furthermore, the correlation between the two variables is low in most cases.[15] **Table 1** shows some of the limitations of each measure.

Moving beyond AHI or ESS, however, other variables closely related to OSA have been shown to be of significant value in an assessment of the disease's impact: these include some nocturnal oximetric measures with or without obesity,[16,17] some comorbidities and cardiovascular risk factors and the individual's baseline quality of life. For example, recent studies have shown how the hypoxic burden (nocturnal desaturation related to respiratory events during sleep) has a greater prognostic capacity than the AHI for future cardiovascular risk.[18] Moreover, measurement of the nocturnal changes in heart rate as a surrogate for the sympathetic activation produced by apneas and hypopneas has also proven to be of prognostic value.[19]

To date, however, there are no validated multidimensional scores for OSA that groups together a limited number of important easy-to-measure variables on a weighted basis and serves to better approximate the severity or prognosis of OSA and its overall impact on an individual. In our opinion, one interesting approach would be that adopted by some authors for COPD[20] or bronchiectasis,[21] although this remains to be validated. According to this approach,[6] at least three dimensions of OSA should be assessed: 1. Severity (using simple polygraphic variables (software already available), which, in addition to the AHI, would introduce the hypoxic burden, the baseline oxygen measure and at least one nocturnal continuous hypoxia measure as a surrogate for cardiopulmonary diseases or obesity with nocturnal impact on oxygen saturation); 2. Disease activity, which could easily be measured by nocturnal variability in heart rate (as a surrogate for sympathetic activation) or the control of blood pressure levels,[22] until the emergence of new well-validated biomarkers (especially cardiovascular, pro-inflammatory and metabolic biomarkers),[23,24] and 3; The impact of the disease on the patient (assessed via the ESS, although ideally a simple quality-of-life questionnaire could be developed to include hypersomnia as only one of the dimensions, alongside others with a personal or socially related impact and an assessment of psychological/neurocognitive disorders such as depression). Obviously, this new multidimensional score should be validated (and eventually modified) not only in middle-aged men (as has traditionally, and erroneously, been the case in most studies on OSA) but also in women and the elderly. It should also be validated as a measure of the overall severity of the disease and its prognostic value, especially on the cardiovascular front (together with other important variables in this respect, such as cardiovascular risk factors, including obesity, and previous cardiovascular disease); it should be integrated in the telemedicine

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Table 1 Disadvantages of the Apnea Hypopnea Index and the Epworth Scale for the diagnosis, assessment of severity, treatment and prognosis of sleep apnea.

Apnea Hypopnea Index	Epworth Scale
Night-to-night variability	It is a subjective measure
High variability of hypopnea definition	Not specific (many causes of hypersomnia not due to OSA)
Limited implication of oximetric parameters	Little correlation between the response of the patient and their partner
Arbitrary cut-off points	Cut-off points not well defined
Prognostic value not proven	Impact of comorbidities and drugs
It depends on other variables such as position, comorbidities and treatments	Little correlation with objective measures of hypersomnia
Changes with age and gender in physiological terms	High intra- and inter-individual variability
Fails to reflect some important physiologic derangements resulting from respiratory events.	Not validated for some important groups, such as women and the elderly
Lack of information about the depth and the duration of ventilatory disturbances	It does not measure quality of life
Asumption that apneas and hypopneas are equal in their biologica effect	Geographical variability
No dependent of sleep-stage	Debatable prognostic value

management of the patient[25-27] (the rapid development of telemedicine is probably one of the few positive things that the sleep community has obtained from the COVID-19 pandemic situation),[28] and finally, it should be validated with respect to response to treatment (since all the variables that comprise this score are potentially modifiable with treatment). It is true that some measures of interest, such as sleep fragmentation, analytical biomarker values and the measurement of more complex pathophysiological variables, would not enter this score, but there is a crucial need for maximum simplicity in order to enhance the generalization of its use, given the epidemiological relevance of the disease.

Ultimately, although our proposal may be just one of the many (better or worse) that may appear, what seems certain is that we cannot continue to exclusively link the severity of OSA, and the therapeutic decisions on this disease, to variables that present as many limitations as the AHI and the ESS values. We must be aware that, in the world of progress towards precision medicine and personalized treatment, OSA lags behind other respiratory diseases and that the scientific sleep community should focus its efforts on reversing this situation as soon as possible.

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COMMENT

Unvaccinated COVID-19 patients in the ICU: Views from both sides of the barrier

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It is widely held by the scientific community that a substantial percentage of the population would need to be immune against the COVID-19 virus if we are to succeed in bringing the pandemic under control, and the safest way to achieve that objective is through a judicious, mass vaccination strategy. Within less than a year from the beginning of the COVID-19 pandemic, the collective, international efforts of the scientific community and some pharmaceutical companies have led to the development and approval of several COVID-19 vaccines. At the time of writing, numerous clinical trials have confirmed the favorable safety profile of these vaccines,[1] and more than 4.51 billion individuals worldwide, equal to about 58.8 percent of the world population, have been vaccinated against the virus.[2]

Notwithstanding the available evidence and the overriding consensus among medical scientists about the importance and safety of COVID-19 vaccines, vaccine hesitancy, defined as "the delay in acceptance or refusal of vaccines despite availability of vaccine services",[3] has become a growing challenge for public health authorities and seems to be leading to a sub-optimal vaccination coverage in high income countries.[4] The reasons underlying COVID-19 vaccine acceptance or hesitancy in the general population are unquestionably complex and not completely understood. Some of the most important factors influencing vaccine acceptance are linked to trust in science and in the information provided by health care workers and institutions, risk perception of the COVID-19 infection, and perceived vaccine safety and efficacy. Vaccination hesitancy seems to be linked to concerns about the side effects and safety of the vaccines, to the fact that they were developed in such a short period of time, and to skepticism about the benefits of this particular vaccine or of all vaccinations in general. Vaccine acceptance/hesitancy also seems to be associated with age, ethnicity, educational and income levels and marital status.[5-7]

In order to improve the success of COVID-19 vaccine programmes, a coordinated, evidence-based education, communication, and behavioral intervention strategy has been recently proposed, including automated reminder systems with online resources, presumptive language by health-care providers, and addressing logistical barriers to access through onsite vaccination.[8]

Fit, relatively young unvaccinated people account for up to 75% of subjects with COVID-19 currently being admitted to Intensive Care Units (ICUs)[9]: those patients unnecessarily reduce ICU bed availability and inescapably increase front-line healthcare professionals' risk of infection. Inevitably, ICU workers may feel anger or frustration as they care for patients who could have prevented their serious health complications requiring specialized care simply by being vaccinated at the opportune time. Given these considerations, any reasonable person is prompted to wonder: were these patients unaware of the danger of refusing vaccine? Were they victims of medical misinformation? Do they change their minds/attitude about vaccination after their harrowing experience in the ICU?

In the hopes of learning more about the real reason/s behind vaccination resistance, those of us working in the

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Table 1 Participants' demographic, educational and employment characteristics, and main reasons for refusing to get COVID-19 vaccine.

Patients (N°)	68
Age (yrs), median (range)	58 (36-91)
Gender (M,F)	49/19
Educational status	
○ Has a high school diploma or less	14
○ Took some college classes or is a college graduate	44
○ Has a graduate degree	10
Employment status	
○ Employed	38
○ Unemployed	30
Main reasons for refusing COVID-19 vaccine	
1. Unaware that it was important to get the vaccine	24
2. Concern about the efficacy of the vaccine	5
3. Concern about the side effects and safety of the vaccine:	
○ Concern due to allergic reactions in the past	8
○ An acquaintance suffered from side-effects	10
○ According to some relatives/friends, the vaccine is dangerous	13
4. Convinced that COVID-19 does not exist, it was invented or a way to make money	8
If you could take the vaccine now, would you?	
○ Yes	51
○ No	11
○ Undecided	6

SARS-CoV-2 Respiratory ICU (RICU) of the Padova University Hospital designed a simple ad-hoc questionnaire for our patients based on a literature review of barriers to vaccination uptake.[5-7,10] The questionnaire was administered by trained medical professionals (i.e., physicians, residents, and nurses) to the patients at the time they were discharged from the RICU. Out of 145 patients admitted to our RICU for severe COVID-19 from September 1st to December 15th 2021, 101 (70.1%) were unvaccinated; 68 of these agreed to fill out the questionnaire; these results (unpublished data) are outlined in Table 1.

An analysis of the patients' answers suggests that vaccine refusal was driven by three main reasons: a) a lack of knowledge about the importance of receiving the vaccine against COVID-19; b) concerns about the safety of the vaccination; and c) a mixture of skepticism about orthodox medical interventions and adherence to conspiracy theories. As few individuals are untouched by the experience of requiring ICU care,[11] we were expecting to see that practically all of our unvaccinated COVID-19 patients had changed their minds about the vaccine. Instead, our results demonstrated that *even after* their RICU experience, a significant proportion (11/68, 16.2%) *still* rejected vaccination.

What can we conclude from the results of our questionnaire? First, despite the efforts of international and national institutions and world-renowned scientific experts, patients still appear to be misinformed regarding the importance of COVID-19 vaccination. Second, some seem to be exceedingly worried about the vaccine's side effects, in particular they seem to fear severe allergic reactions. We would all agree that these are a more relevant barrier to vaccination than wild conspiracy theories. Third, the fact that after a frightening experience in ICU some patients are *still* displaying anti-vaccination attitudes could suggest that there are strong psychological barriers behind their decision.

In conclusion, although irrational arguments explain the decisions of a minority of unvaccinated patients, misinformation and lack of knowledge as well as fear appear to be the most common reasons leading to vaccination refusal in patients requiring ICU admission. Intensive care professionals need to bear this in mind to overcome frustration and not to run out of compassion for their unvaccinated patients.

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ORIGINAL ARTICLE

Point-of-care COVID-19 antigen testing in German emergency rooms — a cost-benefit analysis

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Real-time reverse transcriptase polymerase chain reaction (RT-PCR);
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COVID-19

Abstract
Background: The current COVID-19 pandemic is causing significant morbidity and death worldwide and produces significant socio-economic losses.
Objective: To assess the cost—benefit relation of implementing point-of-care COVID-19 antigen testing (POCT) in emergency rooms (ER) of German hospitals.
Methods: A deterministic decision-analytic model simulated the incremental costs of using the Sofia® SARS Antigen FIA test compared to those of using clinical judgement alone to confirm or exclude COVID-19 in adult patients in German ER, prior to hospitalization. Direct and indirect costs, with and without subsequent RT-PCR confirmation, were evaluated from the hospital perspective.
Results: With respect to ER patients, in base-case analysis, considering a COVID-19 prevalence of 15.6% and a hospitalization rate among COVID-19 suspects of 10.1%, POCT testing reduces average costs of hospitalized patients by €213 per tested patient if nasopharyngeal swabs of patients suspected to have COVID-19 are also sent to external labs for RT-PCR testing.

In probabilistic sensitivity analysis, under all reasonable assumptions, implementing the Sofia® SARS Antigen FIA saves on average about €210 as compared to applying the clinical-judgement-only strategy. The major part of cost savings, €159 or 75.9%, is due to the POC test's high specificity resulting in a 21-fold lower proportion of unnecessary bed blocking at the first day of hospitalization.

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Conclusions: Using highly specific rapid COVID-19 tests in COVID-19 suspects at German ER, despite of their sub-optimal sensitivity, may significantly reduce hospital expenditure.

Introduction

The severe acute respiratory syndrome COVID-19, caused by coronavirus 2 (SARS-CoV-2), first appeared in December 2019 in Wuhan, China, with an accumulation of pneumonia and has since spread across the globe.[1] Clinical features of the disease, known as COVID-19, include fever, headache, and cough, but more severe symptoms such as shortness of breath and respiratory failure have also been reported.[2] As of April 30, 2021, around 151 million cases and more than 3.2 million deaths have been registered in 210 countries and territories worldwide.[3]

The rapid escalation of the situation caused the World Health Organization to declare a pandemic on March 11, 2020.[4] Since then, the continued human-to-human transmission of SARS-CoV-2 has created tremendous challenges for healthcare systems and public health laboratories. Accurate and rapid identification of those infected with SARS-CoV-2 is therefore key to immediate clinical care and to containing the spread of the virus. The current reference test used to establish SARS-CoV infection worldwide is the real-time reverse transcriptase polymerase chain reaction (RT-PCR). These assays have nearly perfect sensitivity and specificity and are therefore well suited as "gold standard" for the diagnosis of clinically ill patients. However, utilization of RT-PCT tests for immediate COVID-19 in hospitals raises substantial challenges: As they require RNA extraction, are dependent on availability of PCR reagents and have a relatively long turnaround time, RT-PCR tests are often performed in batches in clinical laboratories outside the hospital, necessitating specimen transport. Therefore, they usually require a time-lag of one day before the report of the test result becomes available. In Germany currently 71.5% of all hospitals have eliminated their in-house laboratories.[5] Thus, to ensure the correct diagnosis, nasopharyngeal swabs or other respiratory specimen of patients suspected of having COVID-19 must usually be sent to external labs for centralized RT-PCR testing.

In contrast, lateral flow assay (LFA) SARS-CoV-2 antigen tests can be performed at point of care, provide results within 15—30 min and are inexpensive. Numerous SARS-CoV-2 POC antigen tests are currently available, offering the potential for rapid identification of those individuals in the emergency setting who are not only infected, but infectious and are therefore at greatest risk of spreading the infection. For methodological reasons, the detection limit for SARS—CoV—2 RNA material out of clinical samples tested by RT—PCR is always lower than the detection limit for SARS—Cov—2 antigen. Whilst RT-PCR results may still show positive signals for up to several weeks after reaching peak cycle threshold (Ct) values, the detectability of even the best performing antigen test deteriorates with decreasing viral load.[6] However, if patients visit ER before the end of the first weeks of symptoms when pharyngeal virus shedding is very high and infected individuals are likely to be most infectious, sensitivity of high-quality antigen tests is only slightly reduced and can help to filter out the infectious persons.[7] Consequently, POCT may help to prevent the hospital — if COVID-19 suspects have to be hospitalized due to the severity of symptoms - from isolating such patients and blocking a second bed in the patients´ rooms at the hospital ward unnecessarily.

Furthermore, rapid assessment of infectious COVID-19 is highly relevant to the management of scarce economic resources also for another reason. Since 1 January 2004, hospital costs in Germany are based on the German diagnosis-related groups (G-DRG) system, which assigns each COVID-19 case to the category E79C). This imposes a fixed "base rate" of payment for 13 days of treatment. If the hospital treatment exceeds the so-called "mean length of stay", i.e., 6.9 days (as calculated mathematically by the DRG Institute for Hospital Reimbursement (InEK) using case-related data from its contracted hospitals[8]), then the G-DRG rate paid as reimbursement by the statutory health insurance (SHI) usually does not cover the costs incurred by the hospital. Accordingly, when treating COVID-19 patients covered by the SHI, hospitals should try to keep the duration of hospital stays as short as possible.[9]

According to the most recent guidelines of the German Robert Koch Institute (RKI) isolation of an immunocompetent patient can be stopped and discharge be started only if - although viral load on swabs decreases as symptoms resolve[10] - at least 14 days have passed since the onset of the first symptoms, a lasting improvement in the acute COVID-19 symptoms has been present for $>$ 48 h and a RT-PCR (preferable recommended) or an antigen test is negative.[11] Again, as the negative result of a POCT test is usually available one day earlier than that of the RT-PCR costs may be saved from the hospital's perspective by a respectively earlier discharge. The aim of our calculations was to examine whether routine implementation of POCT in COVID-19 suspects visiting an ER leads to directly measurable economic advantages from the hospital perspective, taking as an example the Sofia® SARS Antigen FIA test under the assumption that all nasopharyngeal swabs of COVID-19 suspects are sent to external labs for RT-PCR testing. Using its performance characteristics, we compared the economic outcomes to those that occurred when conventional clinical judgement alone was used to confirm or exclude SARS-CoV-2 in patients deemed to have a combination of symptoms so serious as to warrant hospitalization. The hypothetical savings would come about thanks to earlier patient classification, in anticipation of a RT-PCR result, available only one day later.

Materials and methods

Test system

The Sofia® SARS Antigen Fluorescent Immunoassay (FIA) is a point-of-care system based on lateral flow technology that

uses monoclonal antibodies labelled with Europium as a fluorescent tag. The assay uses SARS CoV-2 specific epitopes of the nucleocapsid protein as target. The tip of a nasal or nasopharyngeal swab is dispensed in a solution that disrupt the viral membrane in order to inactivate the virus and to release the nucleocapsid protein into the solution for subsequent detection with the assay. After pipetting of 120 μl of the solution by a fixed-volume pipette, its contents will be dispensed into the sample well of a cassette and inserted into the Sofia® analyzer. The analyzer performs incubation, then measurement of the fluorescent signal, and calculates the qualitative result using assay specific algorithms. The final result is available in 15 min.

Model approach

Our model is parametrized by data on sensitivity and specificity of the Sofia® SARS Antigen FIA compared to the conventional clinical approach. With respect to POCT, two scenarios are considered: In the first, all COVID-19 patients coming to the ER of a hospital during the current COVID-19 pandemic are tested with the Sofia, after using a nasopharyngeal swab. Depending on the severity of symptoms, a patient is hospitalized or discharged from the ER. In case of hospitalization, the patient is isolated from the moment of presumptive diagnosis, given a positive Sofia test result, upon resolution of fever and respiratory symptoms, but in any case at least for 14 days after first onset of symptoms. Given the high specificity, but only moderate sensitivity of the Sofia (98.9% and 80.0%,[12] see in Online Supplement for details), additional RT-PCR testing of the patient's samples is always required in patients whose test is scored negative. As RT-PCR testing in an external laboratory, where the patients' samples have to be sent in addition, ideally has both a sensitivity and a specificity of up to 100%, this would clarify whether or not the disease is due to SARS-CoV-2 and also false negative Sofia results could be corrected. According to the current German guidelines, however, antigen test results in COVID-19 suspects must always be confirmed by RT-PCR, even positive antigen test results.[13]

Due to the increased risk of thromboembolism associated with COVID-19 disease, a course of antithrombotic prevention, using low molecular weight heparin at half the therapeutic dose, is immediately started in all COVID-19 suspects admitted to the hospital.[14]

In the alternative scenario (versus Sofia® SARS Antigen FIA), i.e.in the conventional clinical approach, the decision as to whether the present respiratory symptoms are caused by COVID-19 is made using symptom-based judgement, without rapid pre-testing. Thus, if hospitalization were required, the decision to isolate a COVID-19 suspect is only based on that clinical decision. In any case, a clinical sample in the form of a nasopharyngeal swab is taken from all COVID-19 suspects deemed to require hospitalization, to be sent out for RT-PCR testing.

If the patient is not to be hospitalized but discharged and sent home directly from the ER, SHI is charged for the costs of routine diagnostics (chest X-ray, routine laboratory values, physical examination, etc.) as well as the costs of POCT, the latter following the corresponding ambulatory doctors fee schedule, position number 32791.[15]

Thus, these patients are not considered in our analysis. If a COVID-19 suspect is ultimately hospitalized the costs of the Sofia testing have to paid by the hospital itself. In contrast, the costs of the externally performed RT-PCR that are directly billed to the hospital by the external laboratory are usually balanced by the reimbursement the hospital receives for performing a RT-PCR according to the German Hospital Finance Act (*Krankenhausfinanzierungsgesetz*, KHG).[16] Accordingly, initial RT-PCR testing, the swabs of which are taken in the ER, does not appear as a cost factor in our model.

Additional costs from the hospital perspective are the so called "opportunity costs" that might occur as long as a COVID-19 suspect is uneccesarily kept in isolation (see details below). This occurs in the cases of false-positive clinical judgement or a false-positive POCT. Under the premise that most COVID-19 patients are accommodated in a twin-bedded room and that hospital wards in Germany during COVID-19 pandemic are working at nearly full capacity, the economic losses caused by blocking the second bed are incurred by the hospital itself.

If a patient is isolated due to erroneous clinical judgement (no SARS-CoV-2 infection present) or false positive POCT, the isolation can be ended as soon as the report of the negative laboratory RT-PCR result is available the next day. It is assumed that the administration of low-molecular-weight heparin is continued until discharge if SARS-CoV-2 infection is confirmed by external PCR. In the case of a negative PCR result, that medication is dropped immediately. Thus, patients falsely suspected of having COVID-19, by whatever means, end up being isolated and receiving antithrombotic prevention for one day.

According to the current CDC guidelines,[17] no studies have yet found evidence that clinically recovered adults with persisting viral RNA have transmitted SARS-CoV-2 to others. This has led to the recommendation that discontinuing isolation prior to discharge should rely on a symptom-based rather than test-based strategy. The German RKI, however, requests not only that isolation in hospital should end no earlier than 14 days after onset of symptoms, it also requests a negative test result, preferably RT-PCR.[11] As the median duration of hospital stay in Germany is currently 10 days[18] it can be expected that, by performing a POCT, patients can be discharged one day earlier than forseen by the DRG, saving the assumed delay that external RT-PCR testing imposes. As the hospital receives a fixed DRG flat rate in any case, this would result in an economic benefit to the hospital.

Our model also takes into account the effects of COVID-19 transmission to unvaccinated health care workers by COVID-19 sufferers who have gone undetected and not been isolated, due to false clinical judgement or a false-negative POCT result. For this we have incorporated a secondary attack rate. Although data are insufficient to precisely define the duration of exposure time that constitutes a significant transmission risk, even exposure to an infected individual for less than 15 min over a 24-h period, especially during performance of an aerosol generating procedure, may be sufficient[19] for transmission to occur. The measured effect is sick days for hospital workers, the costs of which, under the German system, is borne by the hospital. For purposes of simplification, in our model only one health care worker is assigned to an unisolated patient, and the infection risk weighted by the probability of being effectively vaccinated.

In a modified approach we assume a positive POCT does not need confirmation by a RT-PCR. In this case those who

were tested false positive are isolated for the whole duration of hospitalization and intensified antithrombotic preventive therapy is offered unnecessarily.

Model structure

The decision tree simulates the outcomes of three management strategies in the ER of a German hospital in a hypothetical cohort of 1000 adult patients attending the ER with acute moderate-to-severe respiratory infection and suspicion of COVID-19. Costs from the hospital perspective were compared, as described above: (1) empiric clinical investigation with RT-PCR, but without POC antigen COVID-19 testing (POCT) and (2) POCT and mandatory RT-PCR testing, or (3) RT-PCR testing only when the POCT was negative, used to guide the decision as to whether a patient - if hospitalization is required due to signs of severe lower respiratory infection - requires strict isolation. As POCT for those patients who are sent home from ER is paid by the local KV and external RT-PCR is not required in such mild cases, the decision tree is restricted to patients due for hospitalization.

Total costs of outcomes were simulated for each study arm including (1) medical cost of POCT with the Sofia® SARS Antigen FIA which has been authorized for use by the German Paul-Ehrlich-Institut (PEI), the German Federal Institute for Vaccines and Biomedicines, (2) medical costs of external RT-PCR testing if performed prior to hospitalization, (3) opportunity costs due to blocking a twin-bed reimbursement for one day of hospital stay, (4) reimbursement per day of hospital stay within the fixed payment DRG period and (5) sick pay costs at the expense of the hospital if staff members are secondarily infected by hospitalized but unrecognized COVID-19 patients (Fig. 1).

We used TreeAge Software (TreeAge Inc. Williamstown MA, USA) for model building and analysis and examined our inputs over a wide range in sensitivity analyses to identify influential factors that would alter the base-case findings. Firstly, univariate sensitivity analysis was performed using all variables to examine the extent to which our calculations are affected by varying selected assumptions. Variation was done using either a) the lower and upper bounds of a parameter's standard deviation or b) those of its 95% confidence interval. Where these are not applicable, our model simply causes parameter values to vary by ± 20% of the base-case value according to international practice, unless stated otherwise.

Furthermore, and in order to capture the interactions between multiple inputs, we provide a probabilistic sensitivity analyses (PSA) by assigning an appropriate statistical (probability) distribution for all parameters, randomly drawn in a 2nd order Monte-Carlo simulation (n = 1000). All costs are reported in 2021 Euros (€).

Model input

The figures for the other epidemiological, labaraotoy and economic parameters are listed in Table 1; their origins are described in detail in the Online Supplement.

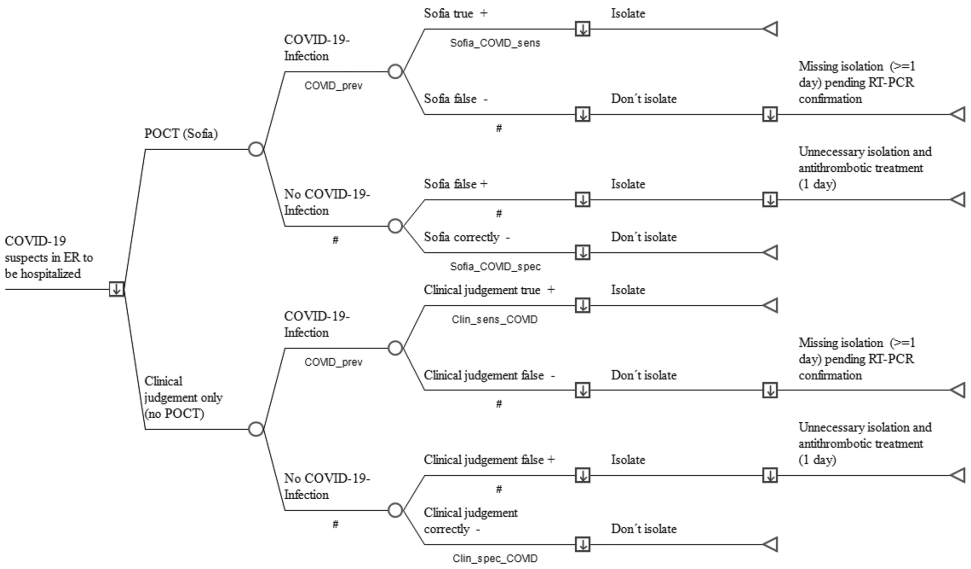

Fig. 1 Point-of-Care antigen testing (POCT) versus the conventional approach in COVID-19 suspects prior to hospitalization
Legend to Fig. 1:A decision node (square) indicates a choice facing the decision maker or the consequences of a decision. Branches from a chance node (circles) represent the possible outcomes of an event; terminal nodes (triangles) denote the endpoints of a scenario and are assigned the costs of a prior series of actions and events. The arrows in the decision notes pointing downwards demonstrate that the optimal path of the model is that with the lowest total cost. ER: Emergency room; POCT: Point-of-Care antigen testing; RT-PCR: Reverse Transcriptase-PCR; COVID_prev: Prevalence of COVID-19 [reference 3 (Supplement)], Sofia_COVID_sens: Real life sensitivity of Sofia test [reference 12 (Supplement)]: Sofia_Covid_spec: Real life specificity of Sofia testing [reference 12 (Supplement)]; Clin_sens_COVID: Sensitivity of diagnosing SARS-CoV-2 infection [reference 8 (Supplement)]; Clin_spec_COVID: Probability of correctly excluding SARS-CoV-2 [reference 8 (Supplement)].
#: Complementary probability (all probabilities of chance node's branches to sum to 1.0); +: positive; -: negative.

Table 1 Input for cost–benefit analysis.

Variables Category	Variable Name	Distribution *	Value (Base Case)	Relative Change (Range)	Reference
Prevalence of COVID-19	COVID_prev	PERT	0.156	0.079–0.412	[3 (Supplement)]
Additional revenue per day due earlier discharge	cRev_day_POCT	uniform	€323.91	±20% (€259.13–€388.69)	Calculated using data from the Institut für das Entgeltsystem im Krankenhaus (InEK) [20 (Supplement)]
Real life specificity of Sofia testing	Sofia_COVID_spec	uniform	0.989	95% CI (0.958–0.998)	[12 (Supplement)]
Opportunity costs due to blocking twin bed	cOpp_POCT	uniform	€690.92	±20% (€522.74–€829.1)	Calculated from InEK data [20 (Supplement)]
Probability of correctly excluding SARS-CoV-2	Clin_spec_COVID	PERT	0.683	95% CI (0.60–0.758)	[8 (Supplement)]
Sensitivity of diagnosing SARS-CoV-2 infection	Clin_sens_COVID	PERT	0.806	95% CI (0.729–869)	[8 (Supplement)]
Costs of enoxaparin per day	cAntithromb_day	uniform	€7.09	±20% (€5.67–€8.51)	Rote Liste [Red List] 2021
Costs of Sofia SARS-CoV FIA®	cSofia_COVID	uniform	€12	±20% (€9.6–€14.40)	As declared by manufacturer
Real life sensitivity of Sofia test	Sofia_COVID_sens	PERT	0.80	95% CI (0.644–0.909)	[12 (Supplement)]
Secondary cases due to one unknown COVI-19 case	*sec*_COVID	PERT	0.025	95% CI (0.013–0.05)	[17 (Supplement)]
Costs of productivity loss per day	cPL_day	uniform	€167.58	±20% (€134.06–€201.1)	Calculated from [27 (Supplement)]
Number of days of health care workers out of work due to COVID-19	sick_days	uniform	15	+12 (27)	[25 (Supplement)]
Probability that hospitalization is required	pHosp	PERT	0.1010	95% CI (0.097–0.1050)	[14 (Supplement)]
Costs of RT-PCR performed in external laboratory	cRT-PCR_ext	uniform	€42.74	+20% (€51.29)	Nationwide laboratory inquiry

* in probabilistic sensitivity analysis.

Table 2 Results of the base-case analysis (with and without confirmation by external RT-PCR).

Base-Case Analysis	Comparators	Mean Cost Per Patient (€)	Incremental Cost (€) *	Absolute Cost Savings (€)
a) with confirmation by external RT-PCR				
COVID-19 patients prior to hospitalisation	Sofia SARS Antigen FIA®	−20.36	0	−20.36
	Conventional approach	192.21	212.57	
b) without confirmation by external RT-PCR				
Base-Case Analysis	Comparators	Mean Cost Per Patient (€)	Incremental Cost (€)*	Absolute Cost Savings (€)
COVID-19 patients prior to hospitalisation	Sofia SARS Antigen FIA®	37.96	0	—
	Conventional approach	192.21	154.25	

* Incremental cost denotes the increase in total costs resulting from using the conventional approach alone versus POCT.

Results

In the base-case analysis, utilizing the Sofia® SARS Antigen FIA test in COVID-19 patients is on average €212.57 less costly per eventually hospitalized patient, compared to the conventional clinical approach (see Table 2a), although all POCT results, negatives as well as positives in the ER, will be re-checked by external PCR. Included in this amount is a cost saving of €20.36 in absolute terms per tested patient in favor of the hospital. The costs for the initial RT-PCR ordered by the ER are not considered here, since the incurred laboratory costs — in contrast to the POCT — are de facto reimbursed to the hospital at the expense of the SHI.

The amount of cost saving is, above all, dependent on the specificity of clinical judgement. Reducing the base case value of 68.3 to60.0% (worst case) results in a further cost savings of €48.90 on top of the €212.57, whilst an increase to 75.8% diminishes the saving by to €169.38. This is revealed by our univariate sensitivity analysis, in which all variables included in the decision analysis are changed between plausible extremes ranges (Table 3). Decreasing by 20% the opportunity costs of blocking a twin bed reduces the amount of cost saving by €43.19. The principal advantage of the Sofia® SARS Antigen FIA — namely of excluding a COVID-19 infection, with high specificity — is the third important component. However, even when assuming a decrease in specificity of the Sofia to the lower bound estimate of the 95% confidence interval, i.e. by 3.19% from the base case value of 98.9%, no reversion of the relative cost savings occurring by utilizing the Sofia takes place, the cost savings decrease only to €194.19.

An increasing number of COVID-19 cases in the ER, i.e. a higher level of prevalence, hardly influences the economic outcome. Even under worst-case assumptions, where 41.2% of all patients with respiratory symptoms reporting to an ER turn out to be COVID-19 cases, a cost saving of €207.15 in favor of the hospital remains. Also, when the revenue costs for one hospital day gained by early release of a COVID-19 patient thanks to a negative POCT are lowered by 20%, the cost savings are only reduced by €8.09. If the sensitivity of the Sofia decreases from 80% to 64.4%, the lower bound of its 95% confidence interval, savings are even less diminished (by €7.66). Variations of all other parameters do not or do only marginally change the absolute amount of expenditures in favor of the hospital.

A modified approach, where the positive result of POCT is not retested by RT-PCR, results only in relative, but not in absolute cost savings (€154.25, see Table 2b). Patients who tested false positive by POCT would have been isolated unnecessarily and received antithrombotic prevention on average for 10 days. During this period, no other patient could be admitted to the second bed in the two-bed room and thus opportunity costs for each single day would occur at the expense of the hospital. Although the specificity of the antigen test testing in the ER is very high, one of those falsely isolated non-COVID-19 patients would burden the hospital with additional costs of €6282. Although only 1.1% of the 84.4% hospitalized non-COVID-19 patients would be tested false positive, the approach without RT-PCR re-testing would on average lead to additional costs per falsely tested patient of €69.1 compared to the re-testing approach. Therefore, the approach with re-testing of POCT by RT-PCR is clearly favorable not only from the clinical but also economic point of view.

In probabilistic sensitivity analysis (PSA), i.e., under all reasonable assumptions, performing POCT on each patient prior to hospitalization reduces the costs that occur when COVID-19 suspects are isolated based only on the conventional clinical approach, by €209.91 (see Table 4). Of note, testing with Sofia® SARS Antigen FIA is constantly less expensive than the purely clinical approach and on average even less expensive than in base analysis, even when a RT-PCR test is used to confirm or deny the preceding POCT result one day later.

The major portion of this savings figure is due to the fact that in PSA, where the results are based on random-sampling and therefore differ from those of the univariate analysis, the proportion of initial unnecessary bed blocking was more than twenty-one-fold higher (25.9 vs 1.2%) with conventional clinical judgement than with the Sofia® SARS Antigen FIA. As this mistake can be corrected only 1 day later, when the result of the RT-PCR is available, the cost difference between the two strategies, with respect to opportunity costs - weighted by the proportion of 81.5% of patients who were not infected with SARS-CoV-2, is €159.24 in favor of the Sofia test. Although the sensitivity of the Sofia is minimally lower than that of the purely clinical approach, the earlier discharge by obtaining a negative POCT result one

Table 3 Tornado diagram* (Point-of-Care COIVD-19 antigen testing versus the conventional clinical approach).

Variable Name	Variable Description	Lowest value	Basecase value	Highest value	Saving (€) at lowest value	Saving (€) at highest value	Spread [T]	Risk%[¥]	Cum Risk%
Clin_spec_COVID	Probability of correctly excluding SARS-CoV-2	0.60	0.683	0.758	−261.47	−168.38	93.08	0.53	0.53
cOpp_POCT	Opportunity costs due to blocking twin bed	522.74	690.92	829.10	−169.13	−248.26	79.12	0.38	0.90
Sofia_COVID_spec	Real life specificity of Sofia testing	0.958	0.989	0.998	−194.19	−217.93	23.74	0.03	0.94
COVID_prev	Prevalence of SARS-CoV-2	0.079	0.156	0.412	−230.58	−207.15	23.43	0.03	0.97
cRev_day_POCT	Additional revenue per day due to POCT	259.13	323.91	388.69	−204.48	−220.65	16.17	0.02	0.99
Sofia_COVID_sens	Real life sensitivity of Sofia test	0.644	0.80	0.909	−204.91	−217.92	13.01	0.01	1.00
cSofia_COVID	Costs of Sofia test	9.60	12.00	14.40	−215.27	−209.87	5.40	0.00	1.00
cRT_PCR_ext	Costs of RT-PCR in external laboratory	42.74	42.74	51.29	−213.64	−212.57	1.07	0.00	1.00
Clin_sens_COVID	Sensitivity of diagnosing SARS-CoV-2 infection	0.729	0.806	0.869	−212.96	−212.09	0.87	0.00	1.00
cAntithromb_day	Costs of enaxaparin per day	5.67	7.09	8.51	−212.20	−212.94	0.73	0.00	1.00
*sec*_COVID	Secondary cases due to one unknown COVID-19 case	0.013	0.025	0.050	−212.61	−212.61	0.06	0.00	1.00
sick_days	Number of days of HCW out of work due to COVID-19	15.00	15.00	27.00	−212.57	−212.60	0.03	0.00	1.00
cPL_day	Costs of productivity loss per day	134.06	167.58	201.10	−212.56	−212.58	0.01	0.00	1.00
pVacc_eff_COVID_HCW	Probability of effectively vaccinated health care workers	0.6355	0.6360	0.6363	−212.57	−212.57	0.00	0.00	1.00
pHosp	Probability that hospitalization is required	0.097	0.1010	0.1050	−212.57	−212.57	0.00	0.00	1.00

[*] One-way sensitivity analyses of all model variables arranged in order, with the variable with the biggest impact at the top and the variable with the smallest impact at the bottom.
[¥] Risk%: This is a measure of how much of the total uncertainty is represented by the respective variable. The Risk% values sum to 1.0 across all the variables.
[T] Highest cost saving minus lowest cost saving in €.

Table 4 Results of the probabilistic sensitivity analysis (Monte Carlo Simulation).

Probabilistic Sensitivity Analysis	Comparators	Mean Cost Per Patient (€)	Standard Deviation (± SD)	Incremental Cost (€) *
COVID-19 patients prior to hospitalisation	Sofia® SARS Antigen FIA	−24.76	16.62	0
	Conventional approach	185.15	30.58	209.91

* Incremental cost denotes the increase in total costs resulting from using the conventional approach alone versus POCT.

day earlier that the result of the RT-PCR results in a cost saving of €50.57.

Discussion

Newer real-time POC tests such as the Sofia® SARS Antigen FIA, which can claim specificity of nearly 99%, come close to laboratory RT-PCR testing in their ability to very rapidly and reliably exclude the presence in a patient of transmissible COVID-19. Therefore, they offer the potential to avoid unnecessary isolation that occurs extensively under the conventional clinical approach. The COVID-19 situation, which forces snap clinical decisions, does not work in favor of the conventional approach. There have been complex attempts to better predict the presence of COVID-19 by creating artificial intelligence (AI) programs which process clinical data as well as imaging techniques. Xia et al.[20] describe that when considering 52 clinical and laboratory coefficients, e.g., disseminated intravascular coagulation, d-dimer, procalcitonin, enlarged lymph nodes or rhabdomyolysis together with CXR features, sensitivity increased to 94% and specificity to 75%. However, the complex information required is hardly available in the setting of an ER before deciding whether a possible COVID-19 patient should be hospitalized or not.

In real life studies, POCT with the Sofia to detect the COVID-19 virus in symptomatic patients shows sensitivity nearly identical to that of the empirical clinical approach. However, little information on the onset of symptoms among study participants was available to the researchers there, and an unknown percentage of the patients included may have been tested later than 7 days following the start of symptoms, when sensitivity of the antigen test is known to decrease, again due to decreasing viral load over time. This may at least partially explain the striking discrepancy of more than 15% between the values in the pivotal studies of the manufacturer and the few evaluation studies used for our economic analysis. Another cause may be inappropriate preanalytics, e.g., pipetting swab material into viral transport media rather than performing the POCT immediately as required by the manufacturer's operation procedures.

Nevertheless, the key to achieving the calculated cost saving of €209.91 per patient by implementing a POC antigen COVID-19 test from the hospital's perspective lies in the time lag between taking the swabs in the ER, which in most cases get sent to an external laboratory, and receiving the RT-PCR report one day later. Each time a patient is wrongly assumed to be suffering from a SARS-CoV-2 infection; hospital capacity is reduced, leading to corresponding revenue loss in terms of one day of opportunity costs for the hospital. Performing the Sofia test on the spot results in significantly fewer false assumptions made regarding the presence of COVID-19 patients and the rate of unnecessary bed blocking on the first day of hospitalization is twenty-one nine-fold lower when compared to the conventional clinical approach.

Thus, in PSA of our model, the routine implementation of a POCT for COVID-19 suspects being moved from the ER for admission to a German hospital ward is consistently less expensive than the conventional symptom-based judgement for which the RT-PCR testing results is available only after a delay of 1 day. Of note, this ranking is not dependent on changes in the prevalence of COVID-19 in such patients, as long as during the ongoing COVID-19 "third wave" the COVID-19 prevalence in ER patients does not exceed and remain above 41.2%. Of note, we did not consider the number of those patients with severe COVID-19 who needed respiratory support (oxygen with or without subsequent invasive mechanical ventilation) at the beginning of hospital stay. As the 28-day mortality of those patients may be reduced by administering anti-inflammatory treatment with dexamethasone,[21] a prompt and reliable diagnosis of SARS-CoV-2 in those patients is necessary. In their cost-effectiveness model, *Ricks* et al.[22] found that a POCT-led strategy averted more deaths and entailed lower costs than did RT-PCR testing, given that RT-PCR testing was performed in fewer than 85% of cases, with the remainder managed through clinical judgement alone ($140,000 versus $150,000 per death averted).

However, in contrast to our model, where a sensitivity of clinical judgement was estimated to be nearly the same as that of the POCT (80.6% versus 80.0%), the authors stipulated a broad range of uncertainty for the sensitivity of clinical judgement, starting with low 45% (range 45—99%), whilst sensitivity of POCT was *a priori* set at 80%.

Our study has some limitations that must be kept in mind when interpreting its results. As always, the general limitation of a single-center economic model that cannot depict the reality of utilization of bed capacity of every hospital deserves consideration, as does the local SARS-CoV-2 infection prevalence among exposed health care workers. Therefore, to validate our estimates, prospective cost studies, preferably with a multicenter study design, are required. Furthermore, our calculations refer only to hospitals that must send samples to an external laboratory for COVID-19 testing and wait for the report. Hospitals that have a laboratory department at their disposal that already conducts high quality RT-PCR tests whilst the patients are waiting in the ER, even during weekends and at night, will probably not benefit by COVID-19 POCT. It is important, however, that, although test results must be quickly provided, the cycle threshold (Ct) values, which inversely correlate with the number of virus present in the sample, must be reported so as to reliably indicate infectiousness of a COVID-19 suspect.

Conclusions

The utilization of the Sofia® SARS Antigen FIA test, as representative of high quality POC antigen tests, is likely to reduce hospital-related costs in cases of suspected COVID-19 in German emergency departments. As such, POCT can reduce costs from the hospital's perspective and allows resources to be allocated for other precautions. Prospective clinical studies should be undertaken to further evaluate its economic advantages in the immediate future.

Ethical considerations

Ethical approval was not necessary as only publicly available secondary data were used.

Conflicts of interest

R.D. received a fee for speaking at a microbiological congress supported by Quidel Inc.

A.N. declares no conflict of interest.

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ORIGINAL ARTICLE

Predictors of intubation in COVID-19 patients treated with out-of-ICU continuous positive airway pressure

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KEYWORDS
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Abstract
Background: As delayed intubation may worsen the outcome of coronavirus disease 2019 (COVID-19) patients treated with continuous positive airway pressure (CPAP), we sought to determine COVID-specific early predictors of CPAP failure.
Methods: In this observational retrospective multicentre study, we included all COVID-19 patients treated with out-of-ICU CPAP, candidates for intubation in case of CPAP failure. From these patients, we collected demographic and clinical data.

List of abbreviations: ABG, Arterial blood gas analysis; ARDS, Acute respiratory distress syndrome; ARF, Acute respiratory failure; CI, Confidence interval; CCI, Charlson Comorbidity Index; COVID-19, Coronavirus disease 2019; CPAP, Continuous positive airway pressure; FiO_2, Fraction of inspired oxygen; HFNC, High flow nasal cannula; ICU, Intensive care unit; LDH, Lactate dehydrogenase; MERS, Middle East respiratory syndrome; NIPPV, Noninvasive positive pressure ventilation; PaO_2, Arterial oxygen partial pressure; RR, Respiratory rate; SARS, Severe acute respiratory syndrome; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SpO_2, Peripheral oxygen saturation.

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Results: A total of 397 COVID-19 patients were treated with CPAP for respiratory failure, with the therapeutic goal of providing intubation in case of CPAP failure. Univariable analysis showed that, age, lactate dehydrogenase (LDH) and white cell counts were all significantly lower in patients with successful CPAP treatment compared to those failing it and undergoing subsequent intubation. The percentage changes between baseline and CPAP application in the ratio of partial pressure arterial oxygen (PaO_2) and fraction of inspired oxygen (FiO_2), PaO_2, respiratory rate and ROX index were higher in patients experiencing successful CPAP compared to those failing it. FiO_2 and male gender were also significantly associated with intubation. Multivariable analysis adjusting for age, gender, Charlson Comorbidity Index, percentage change in PaO_2/FiO_2 or PaO_2 and FiO_2 separately, lactate, white blood cell count, LDH and C-reactive protein levels led to an area under the curve of 0.818 and confirmed that age, LDH and percentage increase in PaO_2/FiO_2 are predictors of intubation.
Conclusions: In COVID-19 patients requiring CPAP, age, LDH and percentage change in PaO_2/FiO_2 after starting CPAP are predictors of intubation.

Background

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause a different spectrum of illnesses, ranging from asymptomatic infection to atypical acute respiratory distress syndrome in 4–16% of cases.[1,2] When hypoxemic acute respiratory failure (ARF) occurs, supplemental oxygen is the first-line medication. For ARF patients developing hypoxemia despite receiving conventional oxygen therapy, with no indications for invasive mechanical ventilation (IMV), international guidelines recommend the use of high flow nasal cannula (HFNC) instead of conventional oxygen therapy or noninvasive positive pressure ventilation (NPPV).[3] If HFNC is not available and there is no urgent indication for endotracheal intubation, current guidelines recommend a trial of NPPV with close monitoring and short-interval assessment for deterioration, even though this procedure is supported by very low-quality evidence.[3] Furthermore, in acute respiratory distress syndrome (ARDS) patients, the effectiveness of noninvasive continuous positive airway pressure (CPAP) remains largely undocumented.

The Italian Respiratory Society (SIP/IRS) and the Italian Thoracic Society (AIPO-ITS) have recently issued a clinical management algorithm for the treatment of COVID-19 patients requiring oxygen escalation through helmet CPAP. More recently, a multicentre observational study has shown that CPAP along with HFNC and NPPV can be readily applied outside of the ICU environment during COVID-19.[4] However, intubation after CPAP failure has been shown to occur in 22–25%[5] of patients, and other studies on noninvasive ventilation have reported that delayed intubation might worsen patient survival.[6] For this reason, the use of CPAP in COVID-19 patients is still under debate. Hence, the identification of early predictors of CPAP failure represents an urgent unmet clinical need.

In the present study, we identify for the first time early factors associated with intubation in COVID-19 patients treated with CPAP out-of-ICU and candidate for intubation in case of CPAP failure. This information may help clinical decision making in these challenging pandemic times.

Methods

Study design

The present study is a large multicentre, retrospective observational study performed from March 1st to April 15th, 2020, in six hospitals of Eastern Piedmont in Northern Italy. The participating hospitals were the following: ''Maggiore della Carità'', Novara, ''SS. Antonio Biagio e Cesare Arrigo'', Alessandria, ''S. Andrea'', Vercelli, ''VCO ASL'', Domodossola, ''Nuovo Ospedale degli Infermi'', Biella. The study was performed in accordance with the Declaration of Helsinki. The Ethics Committee approval was obtained for all the participating centres (CE 87/20, CE 112/20, CE 111/20, CE 110/20, ASO.RianGen.20.02, AslVC.RianGen.20.01).

Patient enrolment and data collection

Patients who met the following inclusion criteria were included in the study: 1) age $\geq$ 18 years; 2) hypoxemic ARF due to COVID-19 requiring out-of-ICU CPAP—*i.e.*, respiratory distress despite Venturi mask oxygen therapy and partial pressure of oxygen to inspiratory oxygen fraction below 200 mmHg; 3) full treatment therapeutic goal—*i.e.*, patients scheduled to receive intubation in the case of CPAP failure.

Exclusion criteria were: 1) intubation on the same day as that of CPAP initiation; 2) CPAP administered as prophylactic treatment after extubation, 3) do-not-intubate order, *i.e.*, when CPAP was ceiling of treatment.

The therapeutic goal of CPAP was collegially discussed in various multidisciplinary team meetings together with the patients and their families, taking into account comorbidities,[7] quality of life and patient preferences.

For all enrolled patients, we collected demographic characteristics and blood sample exams performed on

admission—*i.e.*, white blood cell count, lymphocytes count, creatinine, alanine transaminase, aspartate transaminase, lactate dehydrogenase (LDH), C-reactive protein, D-dimer, ferritin. We also recorded the values of arterial blood gas (ABG), respiratory rate and inspiratory oxygen fraction (FiO_2) delivered by a Venturi mask before and after 2–24 h of CPAP application. The ABG percentage change (△%) was calculated as follows: (parameter during CPAP - parameter during Venturi mask / parameter during Venturi mask) * 100. Charlson Comorbidity Index (CCI)[8] was computed on the first day of hospital admission. Intubation was defined as CPAP failure. The drugs administered during the hospital stay have been also registered.

Continuous positive airway pressure (CPAP) settings

As previously described,[6] CPAP was delivered through helmets (Intersurgical, Mirandola (MO), Italy; Dimar, Medolla, MO, Italy) through flowmeter (60—70 L/min) and face masks (Intersurgical, Mirandola, MO, Italy; Dimar, Medolla, MO, Italy; Fisher&Paykel, Auckland, New Zealand; ResMed, San Diego, CA, USA; Philips Respironics, Murrysville, PA, USA) *via* flowmeters or Boussignac systems (typically 30—70 L/min). FiO_2 was set by regulating oxygen and air flow. Antibacterial/viral filters were applied to the expiratory port. CPAP was started in all patients with respiratory distress despite oxygen therapy by Venturi mask up to FiO2 50% and a partial pressure of oxygen to inspiratory oxygen fraction below 200 mmHg, not necessitating immediate endotracheal intubation. Initial CPAP setting was between 10 and 12 cmH_2O, thereafter, CPAP pressure could be increased up to 15 cmH_2O or decreased, according to patient's needs, tolerance and any side-effects. PEEP and FiO_2 were set to obtain a SpO_2 between 92—96%, or 88–92% if the patient suffered of chronic pulmonary obstructive disease or severe restrictive diseases, as suggested by the Italian respiratory societies. CPAP was delivered on an as-needed basis. When respiratory parameters improved, CPAP support was gradually reduced with a progressive increase of CPAP time off until full discontinuation.

Respiratory intermediate care unit organization

As previously described,[6] respiratory intermediate care units were organized as follows. The nurse-to-patient ratio varied from a maximum of 1:6 both during day and night to a minimum of 1:8 and 1:12 during day and night, respectively. In three hospitals, the medical staff was mixed, including internists, pneumologists, emergency physicians, cardiologists and ICU physicians, while in the other three hospitals the medical team was the same as before COVID-19 pandemic, *i.e.*, internists. CPAP was predominantly prescribed by the anaesthesiologists involved in the COVID-19 ward team, and less commonly by pneumologists and emergency physicians, or by consulting ICU physicians. Mos physicians were already for CPAP use; those who were not received a specific rapid *ad-hoc* training. Ward monitoring included SpO_2, non-invasive blood pressure and ECG, applied continuously or at a defined time points depending on the severity of the patient. Blood gas analysis was performed when clinically relevant. Patients received daily visits from the consulting physician who prescribed CPAP if not continuously involved in the team.

Criteria for intubation

Physicians from the six ICU involved in the present study, stated they agreed and followed the criteria for intubation[9,10] *i.e.*, cardiac or respiratory arrest; inability to protect the airway; coma or psychomotor agitation; unmanageable secretions or uncontrolled vomiting; life-threatening arrhythmias or electrocardiographic signs of ischemia; hemodynamic instability defined as systolic arterial pressure <90 mmHg despite adequate filling or use of vasoactive agents; intolerance to all interfaces; dyspnea during CPAP, respiratory rate >30 breaths/min; peripheral oxygen saturation (SpO_2) below 92% during CPAP despite 60% FiO_2 and acidosis with a pH < 7.35.

Statistical analysis

Descriptive statistics were used to summarize the main demographic characteristics, and the results of laboratory findings of all patients were included in the study. Categorical variables were reported as absolute frequencies and percentages, while numerical variables were given as median and interquartile range (IQR). Univariable and multivariable Poisson regression model with robust standard error were performed to calculate the relative risks (RR) and the corresponding 95% confidence intervals (95% CI) of the association between the results of laboratory findings, clinical parameters, △% of the ABG values and risk of intubation. Given the high correlation between the △% of some ABG parameters, several multivariable models were performed to separately evaluate the role of these variables. The other variables (*i.e.*, age, gender, CCI, LDH, C-reactive protein, white blood cell and lymphocyte count) were included in all models. Estimates were further adjusted by study center. The C-index was used to assess the predictive ability of the multivariable models and its 95% CI based on 150 bootstrap samples was calculated as well. A secondary analysis was performed on the ABG values obtained during Venturi mask oxygen therapy and CPAP.

All hypothesis tests were two-tailed and a *P*-value of 0.05 was considered statistically significant. Statistical analysis was performed using SAS (version 9.4; SAS Institute Cary, NC, USA).

Results

From March 1st to April 15th, 2020, a total of 397 patients were enrolled in the study. Of these, 30 (7.6%) patients were excluded from the study as they had been intubated on the same day as that of CPAP initiation. Two-hundred-seventeen patients were successfully treated with CPAP, while 150 patients failed CPAP and were thus subjected to endotracheal intubation. Table 1 shows the distribution of demographic and clinical characteristics of the patients stratified by ''successful CPAP'' or ''failed CPAP'' as well as the *P*-value derived from the univariable models. Table 1 s

Table 1 Characteristics and variation of arterial blood gas parameters in patients with successful or failed CPAP.

	Successful CPAP *n* = 217	Failed CPAP *n* = 150	Missing values	*P* value
Demographic and clinical characteristics				
Age, years	65 (55−71)	68 (58−73)	0 (0)	0.005
Males, *n* (%)	148 (68)	120 (80)	0 (0)	0.010
Aspartate-aminotransferase, U/L	32 (24−52)	35 (24−53)	25 (7)	0.107
Alanine-aminotransferase, U/L	40 (27−53)	44 (32−65)	137 (37)	0.253
Charlson Comorbidity index	0 (0−1)	0 (0−2)	0 (0)	0.730
Lactate dehydrogenase, U/L	518 (360−675)	654 (486−922)	46 (13)	<0.001
C-reactive protein, mg/dL	10 (5−15)	13 (6−19)	18 (5)	0.274
Creatinine, mg/dL	0.88 (0.72−1.12)	1.01 (0.84−1.29)	3 (1)	0.383
White blood cell count, $\times 10^3/\mu L$	6.75 (5.11−8.91)	7.04 (5.17−10.00)	2 (0.5)	0.014
Lymphocyte count, $\times 10^3/\mu L$	0.84 (0.62−1.15)	0.8 (0.59−1.08)	5 (1)	0.397
Ferritin, ng/mL	1022.5 (538−1601)	1181.5 (771−1856)	196 (53)	0.056
D-Dimer, μgFEU/L	788 (469−1570)	1080 (596−2276)	230 (63)	0.107
Treatment, n (%)				
CPAP device				
Helmet	161 (77)	120 (85)	15	0.091
Mask	49 (23)	22 (16)	(4)	
CPAP, days	8 (5−12)	4 (2−6)	0 (0)	<0.001
Pharmacological treatment				
Hydroxychloroquine	182 (84)	135 (90)	0 (0)	0.092
Anti-retroviral	116 (54)	98 (65)	42 (11)	0.008
Tocilizumab	12 (6)	6 (4)	42 (11)	0.557
Enoxaparin	182 (84)	114 (76)	0 (0)	0.061
Corticosteroids	106 (49)	38 (25)	42 (11)	<0.001
△% ABG				
PaO_2	59% (10−155%)	19% (−4 to 62%)	48 (13)	0.007
SpO_2	4% (0−7%)	2% (−2 to 9%)	4 (1)	0.516
FiO_2	0% (−40 to 0%)	0% (−40 to 20%)	93 (25)	0.035
Lactate	−12% (−27 to 0%)	0% (−14 to 9%)	140 (38)	<0.001
Respiratory Rate	0% (−28 to 17%)	−7 (−27 to 20%)	105 (29)	0.562
PaO_2/FiO_2	87% (7−203%)	44 (−12 to 120%)	125 (34)	0.001
SpO_2/FiO_2	5% (−2 to 81%)	6 (−18 to 69%)	94 (26)	0.067
ROX index	19% (0−103%)	7 (−38 to 60%)	222 (60)	0.039

Values are reported as median (interquartile range) or number (percentage).
CPAP continuous positive airway pressure, *FEU* fibrinogen-equivalent unit, *n* number, ABG arterial blood gas, PaO_2 partial pressure of oxygen, SpO_2 oxygen saturation, FiO_2 inspired oxygen fraction.

shows the same data stratified by centre. Among demographic and clinical patients' characteristics, age (65 *vs.* 68 years, $P = 0.005$), gender (male 68% *vs.* 80%, $P = 0.010$), LDH (518 *vs.* 654 U/L, $P < 0.001$) and white blood cells (6.75 *vs.* 7.04 $\times 10^3/\mu L$, $P = 0.01$) resulted significantly different between successful and failed CPAP. Helmet was applied in 77% and 85% of CPAP successes and failures, respectively. Fifteen patients received CPAP trough both helmet and mask. CPAP duration was significantly different among CPAP successes and failures (8 *vs.* 4 days, $P < 0.0001$). Most patients received hydroxychloroquine and prophylactic enoxaparin. Noteworthy, steroids were administered more frequently in the CPAP success group (49% *vs.* 25%, $P < 0.0001$).

Among respiratory variables, $\triangle PaO_2$ (59% *vs.* 19%, $P = 0.007$), $\triangle FiO_2$ (0% *vs.* 0%, $P = 0.035$), △lactate (-12% *vs.* 0%, $P < 0.001$), $\triangle PaO_2/FiO_2$ (87 *vs.* 44%, $P = 0.001$), △ROX index (19 *vs.*7%, $P = 0.039$), resulted significantly different between CPAP success and failure. Table 2 reports ABG values obtained during Venturi mask oxygen therapy prior to CPAP initiation and those obtained at 2−24 h after CPAP, while Table 2s reports ABG values stratified by centres.

The values of PaO_2, SpO_2, lactate and RR, recorded during Venturi mask oxygen therapy, as well as those of PaO_2, SpO_2, FiO_2, lactate, RR, PaO_2/FiO_2 and SpO_2/FiO_2, measured during CPAP, resulted significantly associated with CPAP failure.

Multivariable analysis of both clinical data on admission and the △% ABG values between Venturi mask and CPAP, allowed us to develop 4 models (Table 3). The best models were those obtained by adjusting for age, gender, CCI, white blood cell and lymphocyte count, LDH and C-reactive protein levels, △lactate and either $\triangle PaO_2/FiO_2$ or $\triangle PaO_2$ and $\triangle FiO_2$, separately, both leading to an area under the curve of 0.818.

From the model analysis, we found that age (RR, 1.026; 95% CI, 1.009−1.044, model 3), gender (RR, 1.718; 95% CI, 1.094−2.699, model 3), LDH (RR, 1.001; 95%CI, 1.000−1.001, model 3), and PaO_2/FiO_2 (RR, 0.998; 95%CI, 0.996−0.999, model 3), were independent predictors of intubation.

Table 2 Detailed arterial blood gas parameters before and during CPAP in patients stratified by successful CPAP.

	Successful CPAP *n* = 217	Failed CPAP *n* = 150	Missing values	P value
ABG before CPAP				
PaO_2, mmHg	62 (54–75)	56 (45–72)	20 (5.45)	0.006
SpO_2, %	93 (90–96)	90 (84–95)	2 (0.54)	<0.001
FiO_2, %	50 (50–100)	50 (50–100)	83 (23)	0.751
Lactate, mmol/L	1.1 (0.8–1.4)	1.3 (1–1.9)	62 (17)	<0.001
Respiratory rate, breaths/min	26 (20–32)	26 (22–35)	127 (35)	0.037
PaO_2/FiO_2, mmHg	120 (75–160)	103 (69–152)	98 (27)	0.412
SpO_2/FiO_2, %	180 (96–194)	160 (95–196)	84 (23)	0.755
ROX index	6 (4–9)	7 (4–10)	206 (56)	0.854
ABG during CPAP				
PaO_2, mmHg	106 (76.05–167)	68(53.65–92.55)	38 (10.35)	<0.0001
SpO_2, %	98 (95–99)	94 (87.5–97)	2 (0.54)	0.0019
FiO_2, %	50 (50–60)	60 (50–60)	21 (5.72)	<0.0001
Lactate, mmol/L	1 (0.8–1.4)	1.3 (0.9–1.7)	89 (24.25)	0.0007
Respiratory Rate, breaths/min	24 (20–25)	25 (22–30)	130 (35.42)	<0.0001
PaO_2/FiO_2, mmHg	212 (145–332)	121(87–173)	50 (13.62)	<0.0001
SpO_2/FiO_2, %	192 (163–198)	158 (137–190)	21 (5.72)	<0.0001
ROX index	8 (7–10)	6 (5–7)	144 (39.24)	<0.0001

Values are reported as median (interquartile range) or number (percentage).
CPAP continuous positive airway pressure, *ABG* arterial blood gas, *n* number, PaO_2 partial pressure of oxygen, SpO_2 oxygen saturation, FiO_2 inspired oxygen fraction.

Table 3 Results from multivariable analysis according to different models.

	Model 1 RR (95%CI)	Model 2 RR (95%CI)	Model 3 RR (95%CI)	Model 4 RR (95%CI)
△% ABG				
PaO_2	0.997 (0.995–0.999)	Not entered	Not entered	Not entered
SpO_2	Not entered	0.989 (0.981–0.998)	Not entered	Not entered
FiO_2	1.003 (1.001–1.005)	1.002 (1.000–1.005)	Not entered	Not entered
Lactate	1.000 (0.997–1.003)	1.000 (0.997–1.003)	1.000 (0.997–1.003)	1.000 (0.997–1.003)
PaO_2/FiO_2	Not entered	Not entered	0.998 (0.996–0.999)	Not entered
SpO_2/FiO_2	Not entered	Not entered	Not entered	0.997 (0.995–1.000)
Demographic and clinical characteristics				
Age	1.026 (1.008–1.044)	1.025 (1.007–1.044)	1.026 (1.009–1.044)	1.025 (1.007–1.044)
Males *vs* Females	1.732 (1.088–2.757)	1.794 (1.124–2.864)	1.718 (1.094–2.699)	1.750 (1.117–2.742)
Charlson Comorbidity index	0.987 (0.896–1.087)	1.010 (0.916–1.114)	0.981 (0.894–1.077)	0.992 (0.905–1.087)
Lactate dehydrogenase	1.000 (1.000–1.001)	1.001 (1.000–1.001)	1.001 (1.000–1.001)	1.001 (1.000–1.001)
C-reactive protein	1.011 (0.990–1.033)	1.020 (0.999–1.042)	1.013 (0.991–1.035)	1.020 (0.999–1.042)
White blood cell count	1.014 (0.960–1.071)	1.005 (0.950–1.063)	1.014 (0.959–1.072)	1.004 (0.949–1.063)
Lymphocyte count	0.833 (0.594–1.167)	0.835 (0.545–1.281)	0.843 (0.613–1.159)	0.849 (0.565–1.274)
C-index (95%CI)	0.818 (0.771–0.906)	0.792 (0.769 – 0.883)	0.818 (0.753–0.883)	0.791 (0.775–0.897)

ABG arterial blood gas, PaO_2 partial pressure of oxygen, SpO_2 oxygen saturation, FiO_2 inspired oxygen fraction, *RR* relative risk, *CI* confidence interval. All models are adjusted by centre.

Discussion

Our study, comprising 367 COVID-19 positive patients treated with out-of-ICU CPAP due to hypoxemic ARF and candidate to intubation in case of CPAP failure, shows that gender, LDH on admission and percentage of increase in PaO_2/FiO_2 between Venturi mask and CPAP are independent predictors of CPAP failure once corrected for the major clinical variables—*i.e.*, age, CCI, white blood cell and lymphocyte count and C-reactive protein levels on admission.

A number of investigations seeking to find relevant outcome predictors among hospitalized patients with COVID-19 have shown that, on admission, increased D-dimer concentration[11] and neutrophil-to-lymphocyte ratio[12] as well as enhanced levels of C-reactive protein,[13] creatinine[13] and cardiac troponin I[14] are all associated with a higher risk of intubation. Similarly, a body mass index (BMI) $\geq$ 35 kg/m,[15] increasing age,[15] male sex,[15] comorbid status,[13] respiratory rate,[13] and SpO_2[13] have been shown to be independently associated with worse in-hospital outcomes.

To the best of our knowledge, there has only been one out-of-ICU study, performed in high-dependency units, evaluating some potential predictors associated with CPAP failure, defined as death or intubation, in CPAP-treated patients (n = 157).[5] The results of this study show that severity of pneumonia on admission and enhanced baseline IL-6 levels are both associated with death and intubation.[5] Of note, 41.4% of the patients included in that study had a do-not-intubate order.

Here, we report the first large multicenter study on predictors of intubation in out-of-ICU COVID-19 patients (n = 367) candidate for intubation in the case of CPAP failure. Among the clinical and laboratory characteristics considered, we show that male gender is associated with a higher risk of intubation, in good agreement with what reported by previous studies on COVID-19 patients admitted to hospital[16–18] or ICU.[19]

Our results identify LDH as a *bona fide* predictor of out-of-ICU CPAP failure. LDH is a ubiquitous intracellular enzyme, which catalyzes the interconversion of pyruvate and lactate, with concomitant interconversion of NADH and NAD^+. High LDH values, resulting from multiple organ injury and decreased oxygenation paralleled by upregulation of the glycolytic pathway,[20] have been associated with worse outcomes in patients with viral infections, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[21–24] In line with our findings, elevated LDH values have been recently shown to be associated with increased risk of severe COVID-19 pneumonia and mortality.[25]

A known predictor of intubation in NPPV-treated patients is PaO_2/FiO_2 < 200 mmHg, 1 h after NPPV initiation.[26] In our study, during Venturi mask oxygen therapy, the PaO_2/FiO_2 values were similar in both the ''failed CPAP'' and ''successful CPAP'' patient groups. In contrast, during CPAP therapy, those patients who failed had a median PaO_2/FiO_2 value of 121 mmHg, while those who succeeded had one above 200 mmHg.

In our study cohort, the intubation rate was 45%, also taking into account those patients (n = 30) excluded from the study because intubated on the same day CPAP was started. This intubation rate is similar to that observed in non-COVID-19 ARF patients treated with NPPV,[26] but almost twice as high as that reported by two large studies on CPAP-treated COVID-19 patients (25%[4] and 22%[5]), comprising both ''do-not-intubate'' and ''candidate for intubation'' patients. In the cohort of patients included in the study by Franco et al.,[4] the severity of hypoxemic ARF, as assessed by PaO_2/FiO_2 is lower than in our investigation, which might explain the lower rate of CPAP failure. In the study by Aliberti et al.,[5] when DNI patients are excluded, as in our study, the intubation rate increases up to 37%.

Finally, though beyond the aims of the present investigation, it is worth mentioning that droplets and large aerosols generated by all the respiratory therapies included CPAP in patients with COVID-19 may represent a risk factor for healthcare worker contamination despite using the recommended personal protection equipment.[27,28] In a multicentre observational study, in healthcare workers treating 670 consecutive patients with confirmed COVID-19 with CPAP, NPPV or HFNC, 11.4% tested positive for infection.[4] In our study, although we were not able to collect data on healthcare workers positive swabs, all strategies aimed at containing healthcare workers contamination *i.e.*, appropriate personal protection equipment and to minimize droplet spread from CPAP *i.e.*, minimize leaks, exhalation filter, have been undertaken.

One limitation of our study is that we were not able assess the predictive value of the respiratory rate and ROX index and of immune system activation markers (*e.g.*, ferritin, D-dimer) in our models due to the large number of missing data. We were also unable to record some other potential early predictors of intubation, such as ventilation-related markers (*e.g.*, expiratory tidal volume). Missing data cause weakness in detecting statistically significant association. Nonetheless, we found LDH and PaO_2/FiO_2 to be associated with higher intubation probability, which, assuming that what is missing is random, corroborates their value as outcome predictors. Evidence in medical treatment at the time the study was conducted, was not against hydroxychloroquine and not yet in favor of corticosteroids as subsequently. Therefore, our data need to be confirmed in patients treated differently. Lastly, ABG after CPAP was performed over a time period ranging from 2 to 24 h, which under normal circumstances may be considered a very long time span, but it was not regarded as such in our case because we were operating during the early phase of the COVID-19 pandemic.

Conclusions

Our results reveal that gender, LDH on hospital admission and percentage of increase in PaO_2/FiO_2 changing from Venturi mask to CPAP therapy are independent predictors of intubation in out-of-ICU CPAP-treated COVID-19 patients.

Authors' contributions

RV, NDV, FDC and GC, had the idea for and designed the study, had full access to all of the data in the study, took responsibility for the integrity of the data, contributed to the design of the study and to the interpretation of data for the work and drafted the paper. FBA and LS had the idea for and designed the study, had full access to all of the data in the study and, took the responsibility for the accuracy and the data analysis and drafted the paper. PN contributed to the design of the study and to the interpretation of data for the work and drafted the paper. FR, CP, CM, DC, CO, ES, LC, TC, MT, LG, MAM, GA, SB, MB, SBai, PB, SBa, VB, SC, FC, VD, LDC, MMae, MM, FMo, RP, MP, VR, DR, LV, and FV contributed to the acquisition, integrity and analysis of the data. FM contributed to the interpretation of data for the work. All authors 1) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; 2) revised the work critically for important intellectual content; and 3) gave final approval of the version to be published.

Competing interests

FR reports personal fees for lectures from Philips Respironics, outside the submitted work.

CO has a patent, No. 102016000114357, with royalties paid from Intersurgical SpA.

DC reports personal fees from Nestlé Healthcare nutrition, outside the submitted work.

FM received fees for lectures from GE Healthcare, Hamilton Medical, Seda Spa; consulting agreement between University of Pavia and Hamilton Medical.

PN reports personal fees from Intersurgical SpA, Resmed, Philips, Novartis, MSD, Getinge, Orion Pharma and non-financial support from Draeger, outside the submitted work. In addition, PN has a pending patent, No. 102020000008305, filed to the Università di Padova, and a patent, No. 102016000114357, with royalties paid from Intersurgical S.p.A.

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Authors request that names of the individual members of the COVID-19 Eastern Piedmont Network be searchable through their individual PubMed records.

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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.2020.12.010.

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ORIGINAL ARTICLE

Early awake proning in critical and severe COVID-19 patients undergoing noninvasive respiratory support: A retrospective multicenter cohort study

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Abbreviations: ARF, acute respiratory failure; NRS, non-invasive respiratory support; NIV, non-invasive mechanical ventilation; MV, mechanical ventilation; ETI, endotracheal intubation; ICU, Intensive Care Unit; HFNC, High Flow Nasal Cannulae; APACHE II, acute physiology and chronic health evaluation II score; SAPS II, simplified acute physiology score; SOFA, subsequent organ failure assessment; RR, respiratory rate; PEEP, positive end expiratory pressure; PSV, pressure support ventilation; CPAP, continuous positive airways pressure; Vt, tidal volume; HR, hazard ratio; OR, odds ratio.

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KEYWORDS
COVID-19;
Acute respiratory failure;
Non-invasive mechanical ventilation;
Prone position

Abstract:
Background/materials and methods: This retrospective cohort study was conducted in two teaching hospitals over a 3-month period (March 2010–June 2020) comparing severe and critical COVID-19 patients admitted to Respiratory Intensive Care Unit for non-invasive respiratory support (NRS) and subjected to awake prone position (PP) with those receiving standard care (SC). Primary outcome was endotracheal intubation (ETI) rate. In-hospital mortality, time to ETI, tracheostomy, length of RICU and hospital stay served as secondary outcomes. Risk factors associated to ETI among PP patients were also investigated.
Results: A total of 114 patients were included, 76 in the SC and 38 in the PP group. Unadjusted Kaplan–Meier estimates showed greater effect of PP compared to SC on ETI rate (HR = 0.45 95% CI [0.2—0.9], p = 0.02) even after adjustment for baseline confounders (HR = 0.59 95% CI [0.3—0.94], p = 0.03). After stratification according to non-invasive respiratory support, PP showed greater significant benefit for those on High Flow Nasal Cannulae (HR = 0.34 95% CI [0.12—0.84], p = 0.04). Compared to SC, PP patients also showed a favorable difference in terms of days free from respiratory support, length of RICU and hospital stay while mortality and tracheostomy rate were not significantly different.
Conclusions: Prone positioning in awake and spontaneously breathing Covid-19 patients is feasible and associated with a reduction of intubation rate, especially in those patients undergoing HFNC. Although our results are intriguing, further randomized controlled trials are needed to answer all the open questions remaining pending about the real efficacy of PP in this setting.

Background

The Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) pandemic infection has dramatically increased the number of patients admitted to hospital who developed pneumonia and acute respiratory failure (ARF) (COVID-19 disease) to be treated with non-invasive ventilatory support.[1,2] Although potentially beneficial and safe for trained healthcare operators,[3] non-invasive respiratory support (NRS) still presents high failure rates (27–90%),[1–6] particularly in patients complicating with acute respiratory distress syndrome (ARDS) (20–41%).[7,8] When ceiling of treatment is excluded, upgrade to endotracheal intubation (ETI) and mechanical ventilation (MV) may be required to assist these patients, rapidly saturating the availability of intensive care unit (ICU) beds and potentially leading to increased mortality.[6]

Innovative approaches such as awake prone position (PP) have been therefore considered to improve the performance of NIRS in COVID-19 pneumonia, in order to spare ICU resource utilization and to reduce mortality. The ultimate guidelines from the European Society of Intensive Care Medicine suggest using PP for at least 12 h in patients with COVID-19 and moderate to severe ARDS subjected to MV[9] with the aim of reducing lung ventilation/perfusion mismatching and shunt fraction and to improve hypoxemia.[10] Evidence from non-COVID19 ARDS patients have showed that due to gravitational effects and anatomical shape matching of the lung to the thoracic cavity, PP relieves the dependent lung regions from the compressive forces exerted by heart weight, improves lung aeration from dorsal to ventral areas, generates a more uniform strain distribution, and enhances lung perfusion.[11,12]

To date, small studies conducted in patients with ARF and assisted with non-invasive ventilation (NIV) or High Flow Nasal Cannulae (HFNC) showed that PP improves oxygenation and reduces the rate of ETI.[13,14] In non-intubated patients with COVID-19 pneumonia, preliminary findings demonstrated only physiological benefits (increase in oxygenation or a decrease in respiratory rate and/or dyspnea) following awake PP was associated to NRS.[15–22]

Although the available evidence is weak and mainly reports physiological advantages deriving from the PP strategy under MV, it might be arguable that at least a selected subset of spontaneously breathing COVID-19 patients are going to obtain significant clinical gains from PP. With this retrospective multicenter analysis we aimed at investigating the potential clinical benefits following early awake PP under NRS in a cohort of patients with severe and critical COVID-19 pneumonia.

Materials and methods

Study setting and design

This retrospective, multicenter observational cohort study was carried out in the Respiratory Intensive Care Units (RICUs) of the University Hospitals of Modena (Italy) and Bologna (Italy). The study has been approved by the regional Ethical Committee of Emilia Romagna (CE N. 453/2020 and 715/2020) and trial registered on *clinicaltrial.gov* (number: NCT04649658).

Patients selection and case definition

All patients aged 18 ≥ 80 year admitted to both RICUs for severe/critical COVID-19 pneumonia between March 1st and June 1st 2020 were selected. SARS-CoV2 infection was confirmed by PCR method with nasopharyngeal swab. COVID-19-related pneumonia was defined as severe by the presence of a respiratory rate (RR) ≥30 breaths per minute (bpm), peripheral blood oxygen saturation (SaO2) ≤93%, PaO2/FiO2 ratio <300 mmHg breathing room air, and lung infiltrates >50% of the lung filed early at admission,[23,24] and critical according to criteria of either WHO[25] and the National Health Commission of China[24] for COVID-19-induced ARDS which aligns with the Berlin Definition.[26]

Patients with endotracheal intubation (ETI) performed within the first 24-h from admission, ceiling of escalation, do not intubate (DNI) order as expressed by patient's will or upon clinical judgement, missing core data at medical record analysis (i.e. clinical characteristics at baseline, pronation data, type and time of ventilatory support, mortality, need for tracheostomy, length of RICU and hospital stay) were not considered for analysis.

Patients included were then divided into two groups: (1) those undergoing awake PP maneuvers (**PP**) in addition to standard care; (2) those performing standard care only (**SC**).

Standard care

Standard of care was in agreement with the Italian Society of Infectious Diseases' Guidelines (SIMIT)[27] and started shortly after admission. This included:

- oxygen supply and (NRS) to target SaO2 > 90%;
- hydroxychloroquine (400 mg bis in die (BID) on day 1 followed by 200 mg BID on days 2–5 eventually adjusted for creatinine clearance estimated by a chronic kidney disease algorithm);
- azithromycin (500 mg daily for 5 days) at physician's discretion when suspecting a bacterial respiratory superinfection;
- low molecular weight heparin for prophylaxis of deep vein thrombosis according to body weight and renal function unless counterndicated.

A proportion of patients received off-label treatment with Tocilizumab,[28,29] a recombinant humanized monoclonal antibody of the IgG1 class directed against both the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor. NRS were adopted using an inspiratory fraction of delivered oxygen (FiO2) increased up to a target transcutaneous oxyhemoglobin saturation >90%. Settings of each NRS have been adjusted by the attending physician based on the continuous monitoring of the cardiorespiratory parameters and included:

- Non-invasive ventilation (NIV) with patients connected through a conventional circuit with a sized oronasal mask (BluestarTM, KOO Medical Equipment, Shanghai, PRC) to a high-performance ventilator (GE Healthcare Engstrom CarestationTM, GE Healthcare, Finland or Mindray SynoVent E3, Mindray Medical, Italy) in pressure support pre-set mode. Positive end expiratory pressure (PEEP) was initially set at 8 cmH2O and subsequently fine-tuned according to clinical parameters and ventilator waveforms. Pressure support (PS) was set at 10 cmH2O, and then progressively modified, according to tidal volume, waveforms, and respiratory drive.
- High Flow Nasal Cannulae (HFNC) with patients connected to a high flow device (Optiflow™and AIRVO™, Fisher & PaykelHealthcare Ltd, Auckland, New Zealand) deliveredoxygen through different sized nasal cannulae. Flow delivery was initially set at 60 L/min and temperature at 37 °C then adjusted according to the patient's tolerance.
- Continuous Positive Airway Pressure (CPAP) with patients were connected through a helmet interface (Helmet Starmed, Intersurgical SpA, Mirandola, Italy) designed for pandemics. PEEP was initially set at 8 cmH2O and subsequently fine-tuned according to clinical parameter. This was obtained by connecting a blender system to the available oxygen source to achieve adequate FiO_2 levels.

Prone position treatment

Once admitted to RICU a non-randomly subset of patients enrolled was subjected to early awake PP in addition to the standard care. In particular, PP treatment was assigned to consecutive patients in the charge of two specific physicians when they were on duty at the RICUs (namely, RT in Modena and VC in Bologna), given their experience in pronation maneuvers. Patients assigned to all the other doctors were instead submitted to standard care. PP treatment was started soon after admission. Patients eligible for PP were aged 18–80 years and had been admitted to RICU with indication for NRS therapy, whereas exclusion criteria for pronation were those previously reported by Coppo et al.[19] Thos eligible were taught by RICU staff on how to achieve PP and then encouraged to maintain pronation for at least 3 -h before being helped back to supine in bed. However, they were free to resume their supine position or to maintain pronation at their own discretion. Number of daily PP sessions varied from a minimum of 1 to a maximum of 4 based on the physician's judgment and/or the patient's preference.

Covariate variables

Chart review, medical record, and archived data collection wereconductedin each center. The following variables were then inserted into an electronic database: demographics, relevant comorbidities, clinical characteristics (arterial blood gases-PaO2/PaCO2/pH, PaO2/FiO2 ratio, respiratory rate-RR, blood lactate level, dyspnea grade by BORG scale, mean arterial pressure-MAP), laboratory tests (blood count, renal function, C-reactive protein-CRP, procalcitonin-PCT, D-dimer) on admission, type and duration of required NRS, rate and time of ETI, mortality, need for tracheostomy, length of RICU and hospital stay. Radiographic appearance on available computed tomography (CT) scan performed on admission was assessed by an expert radiologist blinded to the study purpose. Radiographic presentation of COVID-19 lung involvement was classified according to the number of lobes involved, the presence of bilateral abnormalities, the

predominant distribution (diffuse, peripheral, patchy) and the main pattern (interstitial versus consolidative).

Outcome variables

Primary purpose was to evaluate the impact of awake PP on ETI rate in patients with severe and critical COVID-19 pneumonia admitted to RICU to be assisted with NRS. In both hospitals the decision as to whether proceed to ETI was taken according to the best clinical practice by the attending staff. Criteria for ETI included: (a) PaO2/FiO2 ratio unchanged or worsened despite use of NRS, (b) need to protect airways due to neurological deterioration or massive secretions, (c) hemodynamic instability or major electrocardiographic abnormalities, (d) unchanged or worsened dyspnea and persistence of respiratory distress despite NRS (i.e. RR > 35 bpm, gasping for air, psychomotor agitation requiring sedation, abdominal paradox). Secondary scope was to compare time to ETI, mortality, NRS-free-days (i.e. days spent without HFNC, NIV, CPAP, or invasive mechanical ventilation at 1-month), tracheostomy, length of RICU and hospital stay between PP and SC groups. Furthermore, potential risks (among the epidemiological, clinical and radiographic factors) associated to ETI were investigated in the PP group.

Statistical analysis

Sample size calculation was performed assuming an estimated ETI rate of 70% for the study cohort[1,30] and a presumed reduction by 40% in those receiving pronation (data derived from an exploratory analysis in 30 patients). Assuming $\alpha = 0.05$, power 80% and an enrollment ratio of 1:2 (proportion of patients subjected to pronation or to standard care, respectively) a sample of 93 patients was considered sufficient to confidently perform analysis on the primary outcome.

To test whether baseline covariates were balanced and did not significantly affect treatment a post-hoc propensity score was allocated. We ran logistic regression using prone position as the dependent variable with all baseline features as covariates. Propensity scores were obtained by calculating the fitted value from the logistic model for each patient and then comparing, showing that allocation to treatment was not significantly affected by baseline condition (Fig. S1, supplementary material). Baseline characteristics were compared in PP and SC groups; continuous variables were expressed as median and interquartile ranges (IQR) and compared by t test and Wilcoxon-Mann–Whitney test, whereas categorical variables were reported as numbers and percentages (%) and compared by χ^2 test or Fisher's exact test.

The time to ETI analysis was performed with participants' follow-up accrued from the date of admission until ETI. Time to ETI was compared using unweighted Kaplan–Meier curves and analyzed through a cumulative incidence function model using Fine-Grey competing risk model[31] with baseline fixed covariates considering mortality as competing risk. The effect of pronation on ETI was shown by means of unadjusted and adjusted hazard ratio (HR) with 95%CI. Age, PaO2/FIO2 ratio, pH value and respiratory rate were identified as 4 key confounders, and then used for adjustment. In order to test the hypothesis that the difference between groups might vary according to the type of NRS, we formally included an interaction term in the Fine-Grey regression model. Results were then showed after categorizing the population into two strata using categorical separation. The association of the two different treatments with pre-specified secondary outcomes was further carried out through Fisher's exact test and Wilcoxon–Mann–Whitney test.

In patients undergoing PP univariate and multivariate logistic regression were then performed to detect predictors of ETI among all of the available factors recorded at admission.

The time course of PaO_2/FiO_2 ratio before and after pronation according to ETI within the first 7 days from RICU admission was assessed through ANOVA analysis. Then a post-hoc Bonferroni-Dunn's multiple test was used to perform the pairwise comparison of means for each group.

A two-sided test of less than 0.05 was considered statistically significant. Statistics were performed using SPSS version 25.0 (IBM Corp.New York, NY, USA) and Graphpad prism version 8.0 (Graphpad Software, Inc. La Jolla, Ca, USA) unless otherwise indicated.

Results

Population

One-hundred-fourteen patients were included 1:2 in the analysis (38 PP: 76 SC) among all those patients diagnosed with severe and critical COVID-19 and referred to the two RICUs over the period considered. Study chart is shown in Fig. S2 (Supplementary material).

Epidemiological, clinical and respiratory characteristics are presented in Table 1. The vast majority of patients were male (70%) and more than a third of them presented ARDS (37%), while the median PaO2/FIO2 ratio was 149 (78–232) mmHg. Time from disease onset to admission was comparable between the two groups (median 8 [4–12] days for PP and 9 [4–13] for SC, p = 0.5).

Patients in the PP group came out significantly younger than in SC (61 VS 70 years old, p = 0.03), while no differences were observed in terms of severity scores, comorbidities and biochemical markers. PP patients showed a worse PaO2/FIO2 ratio, higher RR and pH value at baseline. No inter-groups difference was observed in the received standard treatment, in either drugs or NRS.

No adverse events were reported when proning maneuvers were applied to these patients.

Outcomes

Overall ETI rate was 32.5%; 7 (18%) and 30 (39.5%) patients were subjected to MV in PP and SC groups respectively. Time to ETI did not differ between groups (5 [3–5] days and 4 [3–5] days for PP and SC, p = 0.7). Unadjusted Kaplan–Meier estimates (supplementary Figure 3, *panel A*) and Cox regression analysis showed the beneficial effect of PP compared with SC on ETI (HR = 0.45 95CI [0.2—0.92], p = 0.02). After adjusting for the key confounders, results again confirmed the group difference (HR = 0.59 95CI [0.3—0.94], p = 0.04);

Table 1 General and clinical features of the study population presented as a whole and according to prone position manoeuvre.

Variable	Overall n = 114 (100)	Standard care (SC) n = 76 (67)	Prone position (PP) n = 38 (38)	p value
Age, years (IQR)	67 (32—80)	70 (33—80)	61 (32—75)	0.03
Male sex, n (%)	80 (70)	55 (73)	25 (66)	0.5
Smoker, n (%)	33 (29)	22 (29)	11 (29)	0.9
BMI, Kg/m^2	27.5 (19—37)	28 (20—37)	26 (19—36)	0.3
SAPS II, score (IQR)	25 (12—46)	25 (12—41)	27 (14—46)	0.4
APACHE II, score (IQR)	10 (4—22)	10 (4—20)	11 (4—22)	0.7
SOFA, score (IQR)	4 (2—7)	4 (2—6)	4 (2—7)	0.8
Time from disease onset to RICU admission, days (IQR)	9 (4—13)	9 (4—13)	8 (4—12)	0.5
ARDS, n (%)	42 (37)	30 (39)	12 (32)	0.6
Comorbidities				
Systemic hypertension, n (%)	92 (81)	60 (79)	32 (84)	0.6
COPD, n (%)	17 (15)	11 (15)	6 (16)	0.9
ILD, n (%)	3 (3)	2 (2)	1 (3)	0.9
Asthma, n (%)	3 (3)	2 (2)	1 (3)	0.9
Cancer, n (%)	12 (11)	8 (11)	4 (11)	0.9
Ischemic heart disease, n (%)	16 (14)	10 (13)	6 (16)	0.8
Type 2 diabetes, n (%)	22 (19)	14 (18)	8 (23)	0.6
Arrhythmia, n (%)	17 (15)	12 (16)	5 (13)	0.8
Renal failure, n (%)	10 (9)	8 (10)	2 (6)	0.7
Immunodeficiency, n (%)	10 (9)	6 (8)	4 (10)	0.9
Hepatitis, n (%)	8 (7)	4 (5)	4 (10)	0.4
Charlson index, score (IQR)	2 (0—9)	2 (0—9)	2 (0—8)	0.9
Symptoms on admission				
Fever, n (%)	110 (96)	74 (98)	36 (94)	0.3
Cough, n (%)	55 (48)	34 (45)	21 (55)	0.4
Dyspnea, n (%)	108 (95)	71 (94)	36 (94)	0.9
Fever + cough, n (%)	55 (48)	37 (48)	18 (48)	0.9
Fever + dyspnea, n (%)	106 (93)	70 (92)	36 (94)	0.9
Cough + dyspnea, n (%)	49 (40)	34 (45)	15 (39)	0.7
Fever + cough + dyspnea (%)	49 (40)	34 (45)	15 (39)	0.7
Physiological parameters on RICU admission				
Dyspnea, BORG scale score (IQR)	5 (1—10)	5 (1—10)	6 (2—10)	0.7
Kelly, score (IQR)	1 (1—2)	1 (1—2)	1 (1—2)	0.9
Body T, °C (IQR)	37.4 (36.0–39.6)	36.9 (36.0–39.2)	37.4 (36–39.6)	0.3
RR, bpm (IQR)	29 (15—45)	27 (15—40)	34 (18—46)	0.02
HR, bpm (IQR)	95 (50—140)	96 (51—125)	95 (50—140)	0.7
MAP, mmHg (IQR)	93 (77—113)	94 (85—113)	91 (77—103)	0.1
pH, value (IQR)	7.46 (7.30–7.58)	7.45 (7.30–7.56)	7.47 (7.31–7.58)	0.02
$PaCO_2$, mmHg (IQR)	32 (20–72)	32 (22–72)	32 (20–62)	0.3
PaO_2/FIO_2, mmHg (IQR)	149 (78–232)	153 (84–232)	141 (73–223)	0.03
HCO_3^-, mmol/L (IQR)	21 (19—28)	21.2 (20.8—28.3)	19.8 (18.7—27.6)	0.1
Lactate, mmol/L (IQR)	1.4 (1—2)	1.3 (1—2)	1.6 (1—2)	0.9
Non-invasive support				
HFNC, n (%)	69 (61)	46 (61)	23 (61)	0.9
CPAP, n (%)	25 (22)	16 (21)	9 (23)	0.9
NIV, n (%)	19 (17)	13 (17)	6 (16)	0.9
Pharmacological treatment				
Systemic steroids, n (%)	80 (70)	55 (73)	25 (66)	0.5
Hydroxychloroquine, n (%)	94 (82)	64 (84)	30 (79)	0.8
Azithromycin, n (%)	74 (65)	47 (62)	28 (71)	0.3
Heparin (Prophylactic dose), n (%)	57 (50)	35 (46)	22 (58)	0.3
Heparin (Treatment dose), n (%)	46 (40)	33 (43)	13 (34)	0.4
Lopinavir/ritonavir, n (%)	26 (23)	17 (22)	9 (24)	0.9
Darunavir/cobicistat, n (%)	24 (21)	18 (24)	5 (16)	0.2
Tocilizumab, n (%)	41 (36)	29 (38)	12 (32)	0.5
Laboratory tests				

Table 1 (*Continued*)

Variable	Overall n = 114 (100)	Standard care (SC) n = 76 (67)	Prone position (PP) n = 38 (38)	p value
White cells count, n*10^9/L (IQR)	7.4 (2.1–24.9)	7.5 (2.7–22.2)	6.8 (2.1–24.9)	0.5
Hemoglobin, g/L (IQR)	12.5 (5.1–17.4)	13.0 (5.1–17.4)	12.4 (7.3–15.4)	0.3
Lymphocytes, 10^9/L (IQR)	1.08 (0.06–20.0)	1.0 (0.1–12.0)	1.3 (0.1–20.0)	0.1
Platelets, 10^9/L (IQR)	210 (80–472)	220 (80–472)	179 (116–318)	0.4
C-Reactive Protein, mg/dL (IQR)	5.9 (0.1–36.4)	6.1 (0.2–35.4)	4.8 (0.1–36.4)	0.4
D-Dimer, μg/L (IQR)	2.16 (0.28–15.0)	1.89 (0.29–15.0)	3.90 (0.28–12.1)	0.1
Albumin, g/L (IQR)	32 (14–56)	31 (14–45)	32 (23–56)	0.1
LDH, U/L (IQR)	333 (144–982)	318 (144–964)	355 (179–982)	0.1
BUN, mg/dl (IQR)	35 (16–132)	35.5 (16.0–132.0)	32.5 (23.0–68.0)	0.3
Creatinine, mg/dl (IQR)	0.9 (0.3–4.7)	0.92 (0.6–4.7)	0.85 (0.27–2.02)	0.2

Data are presented as number and percentage for dichotomous values or median and interquartile range (IQR) for continuous values.
Abbreviations: IQR = inter quartile range; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; RR = respiratory rate; HR = heart rate; MAP = mean arterial pressure, ARDS = acute respiratory distress syndrome; APACHE II = acute physiology and chronic health evaluation II score; SAPS II = simplified acute physiology score; SOFA = subsequent organ failure assessment score, HFNC = high flow nasal cannula; CPAP = continuous positive airways pressure; NIV = non-invasive mechanical ventilation; LDH = lactic dehydrogenase; BUN = blood urea nitrogen.

Table 2 Hazard ratios from fitting a Fine-Grey regression model.

	Unadjusted and adjusted relative hazards of ETI			
	Unadjusted HR (95%CI)	p value	Adjusted* HR (95%CI)	p value
	All cases			
Standard care	1		1	
Prone position	0.45 (0.2—0.9)	0.02	0.59 (0.3—0.94)	0.03
	Stratum HFNC			
Standard care	1		1	
Prone position	0.26 (0.09—0.72)	0.03	0.34 (0.12—0.84)	0.04
	Stratum no HFNC			
Standard care	1		1	
Prone position	0.55 (0.2—1.3)	0.2	0.6 (0.6—1.81)	0.4
	Stratum NIV			
Standard care	1		1	
Prone position	0.76 (0.17—3.3)	0.7	0.86 (0.35—3.9)	0.8
	Stratum no NIV			
Standard care	1		1	
Prone position	0.38 (0.17—0.82)	0.03	0.43 (0.27—0.93)	0.04
	Stratum CPAP			
Standard care	1		1	
Prone position	0.59 (0.18—1.92)	0.3	0.81 (0.07—1.4)	0.2
	Stratum no CPAP			
Standard care	1		1	
Prone position	0.35 (0.15—0.79)	0.03	0.38 (0.2—0.81)	0.03

Data are presented as HR and 95% CI.
Abbreviations: HR = hazard ratio; CI = confidence interval; ETI = endotracheal intubation, HFNC = high flow nasal cannula; CPAP = continuous positive airways pressure; NIV = non-invasive mechanical ventilation.
* Adjusted for age, PaO_2/FIO_2, pH value and respiratory rate.

however, the stratified analyses showed that this difference varied according to the use of NRS even after adjusting confounders (Table 2).In particular, awake PP significantly reduced the risk of ETI in patients undergoing HFNC, but not NIV or CPAP.

Tracheostomy and mortality rate were similar (p = 0.4 and p = 0.4) between PP and SC; Kaplan–Meier curve analysis did not show any difference in 30-day survival between groups (Fig. S3, *panel B*). Number of days free from NRS was higher (20 and 15 days respectively, p = 0.03), and length of stay in

Table 3 Clinical outcomes of the study population presented as a whole and according to prone position manoeuvre.

Outcome	Cohort			OR	p-value
	Total n = 114	Standard care n = 76	Prone position n = 38		
30 days mortality, n (%)	22 (19)	17 (23)	5 (13)	0.5 (0.2—1.6)	0.4
Respiratory support free days at day 30, n (IQR)	17 (2—24)	15 (2—22)	20 (2—24)	–	0.03
Tracheostomy, n (%)	21 (18)	16 (21)	5 (13)	0.6 (0.2—1.8)	0.4
RICU stay, days (IQR)	13 (3—26)	15 (3—26)	10 (3—21)	–	0.02
Hospital stay days, n (%)	23 (3—45)	24 (3—45)	20 (3—41)	–	0.03

The data are presented as a numbers and percentage value for dichotomic variables and as median and interquartile ranges for continuous variables. The statistical significance was set for $p < 0.05$.
OR = odds ratio; IQR = interquartile range; RICU = respiratory intensive care unit.

RICU (10 vs 15 days, p = 0.02) and in hospital (20 vs 24 days, p = 0.03) were shorter in PP than in SC group at 30-day. See the overall results in Table 3.

Risk analysis in PP group

Table 4 reports the results derived from the univariate and the multivariate analysis in patients proned. In the univariate analysis, those patients proned and intubated were older, had a higher prevalence of ARDS, maintained awake proning for less time/day, showed greater perceived dyspnea, mainly received NIV, and displayed a diffuse distribution of lung CT scan abnormalities. In the multivariate analysis, less time spent when proning, presence of ARDS, use of NIV, and diffuse pattern at chest CT scan were factors independently associated with ETI.

Interestingly, the daily time course of average PaO2/FIO2 ratio before and after proning was considerably different in PP patients intubated compared with those who were not (see Fig. S4).

Discussion

In this retrospective, multicenter observational study, we investigated the effects of early awake proning in COVID-19 patients admitted to RICUs for noninvasive respiratory support, compared with standard management (SC).

The main study findings were: (1) PP prevents the need for intubation when compared to SC alone, even after adjustment for baseline confounders, (2) the reduction of ETI is particularly significant in subgroup undergoing HFNC compared with NIV or CPAP, and (3) the duration of positioning as well as the associated radiographic features consistently affect the efficacy of PP.

PP is a validated strategy in the treatment of ARDS patients, being recommended for more than 12 h/day in severe patients.[9,33] Several mechanisms might contribute to the benefit of PP including the lung recruitment of previously dependent regions from relief of compressive weight, the distribution of transpulmonary pressure (PTP), the better ventilation–perfusion (V/Q) matching and the amelioration of right ventricular function.[10]

Given its beneficial effects, some researches hypothesized the use of PP also in patients with hypoxemic acute respiratory failure who are breathing spontaneously.[13,14] Although, there is a strong physiological rationale for proning also in non-intubated patients, to date, there is still a paucity of high-quality evidence in this area.

Aside from case series and case reports, results from preliminary prospective studies in non-intubated COVID-19 patients have mostly demonstrated short-term physiological effects in terms of oxygenation improvement or a decrease in respiratory rate and/or dyspnea when awake PP is associated to NRS.[16–20] In a prospective study on 56 patients with SARS-CoV2 pneumonia treated with supplemental oxygen or NIV, Coppo et al.[21] showed that a trial of at least 3 h of awake PP was effective in improving PaO2/FIO2 ratio. Interestingly the increase in blood oxygenation was maintained after resupination in half of patients. Authors suggested that patients are more likely to respond to PP if procedure is performed early after hospital admission and in subjects with increased inflammatory biomarkers. No effect on clinical outcomes (i.e endotracheal intubation or mortality) was found.[21]

Given that patient assignment to PP treatment did not depend on the response to a preliminary prone position test, it is arguable that the PP group consisted of both responders and non-responders according to the definition of Coppo et al.[21] This might explain why patients whose average PaO2/FIO2 ratio benefited the most from PP had significant difference in the rate of intubation as compared to those who did not show any consistent improvement after proning. Moreover, intubated patients maintained prone position for less time/day compared to PP patients who did not undergo ETI (3 h vs 6 h respectively) whereas comparable values of baseline PCR and D-dimer suggest a similar disease severity and/or progression. It is worth noticing that, although not significant, systemic steroid usage was associated with unfavorable outcome in PP patients. Since evidence on the beneficial effect of steroids in patients with COVID-19 ARF has been emerging,[32] our results may sound contradictory. However, our data refer to a period (April–June 2020) when evidence was lacking and the use of steroids was left to physician judgment in terms of molecule, dosage, time to start treatment and duration, thus generating heterogenous schedules. Moreover, the limited number of patients and the unpowered analysis does not allow us to consider these results as significant.

Table 4 General and clinical features of the PP cohort according to ETI and associated risk.

Variable	No ETI n = 31 (82)	ETI n = 7 (18)	Univariate OR	95%CI	p value	Multivariate OR	95%CI	p value
Age, years (IQR)	60 (34–68)	70 (52–75)	1.8	1.4–7.9	0.03			
Male sex, n (%)	20 (65)	5 (71)	1.4	0.2–7.7	0.9			
Smoker, n (%)	9 (29)	2 (29)	1	0.2–5.5	0.9			
BMI, Kg/m^2	25.6 (19–31)	27.7 (22–35)	1.5	0.2–8.9	0.6			
SAPS II, score (IQR)	25 (12–40)	28 (14–46)	1.8	0.3–21	0.4			
APACHE II, score (IQR)	10 (4–21)	13 (4–22)	1.4	0.4–12	0.5			
SOFA, score (IQR)	4 (2–6)	4 (2–7)	1.2	0.1–15	0.8			
ARDS, n (%)	7 (23)	5 (71)	8.6	1.2–47	0.02	3	1.3–21	0.04
Time from disease onset to RICU admission, days (IQR)	8 (4–11)	8 (4–12)	1.1	0.2–8	0.8			
Prone position time/day, hours (IQR)	6 (1–12)	3 (1–5)	0.4	0.3–0.8	0.02	0.7	0.2–0.9	0.04
Comorbidities								
Systemic hypertension, n (%)	26 (84)	6 (86)	1.2	0.2–16	0.9			
COPD, n (%)	5 (16)	1 (14)	0.9	0.1–6.5	0.9			
ILD, n (%)	1 (4)	0 (0)	0.01	0–40	0.9			
Asthma, n (%)	1 (4)	0 (0)	0.01	0–40	0.9			
Cancer, n (%)	3 (10)	1 (14)	1.6	0.1–12	0.9			
Ischemic heart disease, n (%)	5 (16)	1 (14)	0.9	0.1–6.5	0.9			
Type 2 diabetes, n (%)	7 (23)	1 (14)	0.6	0.04–4.3	0.9			
Arrhythmia, n (%)	4 (12)	1 (14)	1.2	0.1–9.1	0.9			
Renal failure, n (%)	1 (3)	1 (14)	5	0.3–97	0.3			
Immunodeficiency, n (%)	3 (10)	1 (14)	1.6	0.1–12	0.9			
Hepatitis, n (%)	3 (10)	1 (14)	1.6	0.1–12	0.9			
Charlson index, score (IQR)	2 (0–8)	2 (0–8)	1	0.3–6	0.9			
Symptoms on admission								
Fever, n (%)	30 (97)	6 (86)	0.3	0.01–4.4	0.3			
Cough, n (%)	16 (52)	5 (71)	2.3	0.4–13	0.4			
Dyspnea, n (%)	30 (97)	6 (86)	0.3	0.01–4.4	0.4			
Fever + cough, n (%)	14 (45)	4 (57)	1.6	0.4–7.2	0.7			
Fever + dyspnea, n (%)	30 (97)	6 (86)	0.3	0.01–4.4	0.4			
Cough + dyspnea, n (%)	12 (39)	3 (43)	1.2	0.3–5.1	0.9			
Fever + cough + dyspnea (%)	12 (39)	3 (43)	1.2	0.3–5.1	0.9			
Physiological parameters on RICU admission								
Dyspnea, BORG scale score (IQR)	5 (2–8)	8 (6–10)	2.7	1.6–18	0.01			
Kelly, score (IQR)	1 (1–2)	1 (1–2)	0.9	0.01–24	0.9			
Body T, °C (IQR)	37.5 (36–39.3)	37 (35.7–39.6)	1.2	0.2–19	0.8			
RR, bpm (IQR)	34 (20–45)	32 (18–40)	0.7	0.3–11	0.6			
HR, bpm (IQR)	93 (50–136)	100 (60–140)	1.3	0.1–14	0.7			
MAP, mmHg (IQR)	90 (77–90)	93 (81–103)	1.1	0.01–10	0.9			
pH, value (IQR)	7.48 (7.34–7.58)	7.45 (7.31–7.51)	0.8	0.4–7.9	0.6			

Table 4 (*Continued*)

Variable	No ETI n = 31 (82)	ETI n = 7 (18)	Univariate OR	95%CI	p value	Multivariate OR	95%CI	p value
$PaCO_2$, mmHg (IQR)	31 (19–58)	34 (20–62)	1.3	0.4—11	0.5			
PaO_2/FIO_2, mmHg (IQR)	138 (75–210)	150 (84–226)	1.2	0.3—7.5	0.4			
HCO_3^-, mmol/L (IQR)	18.9 (18.7—26)	21.2 (19.5—27.6)	1.3	0.2—9.8	0.7			
Lactate, mmol/L (IQR)	1.6 (1—1.8)	2.1 (0.7—2.2)	1.5	0.4—14	0.4			
Non-invasive support								
HFNC, n (%)	22 (71)	1 (14)	0.1	0.01—0.6	0.01	0.3	0.04—0.6	0.02
CPAP, n (%)	7 (23)	2 (29)	1.4	0.2—7.2	0.9			
NIV, n (%)	2 (6)	4 (57)	19	2.6—117	0.01	4.5	1.5—41	0.03
Pharmacological treatment								
Systemic steroids, n (%)	19 (61)	6 (86)	3.8	0.5—47	0.4			
Hydroxychloroquine, n (%)	23 (74)	6 (86)	2.1	0.2—27	0.9			
Azithromycin, n (%)	22 (62)	6 (86)	2.5	0.3—31	0.6			
Heparin (Prophylactic dose), n (%)	18 (58)	4 (57)	0.9	0.2—4.3	0.9			
Heparin (Treatment dose), n (%)	10 (32)	3 (43)	1.5	0.3—6.8	0.7			
Lopinavir/ritonavir, n (%)	7 (23)	2 (29)	1.4	0.2—7.2	0.9			
Darunavir/cobicistat, n (%)	4 (24)	1 (16)	1.1	0.1—10	0.9			
Tocilizumab, n (%)	10 (32)	2 (29)	0.8	0.5	0.9			
CT Radiographic features*								
Lobes involved								
1	0 (0)	0 (0)	—	—	—			
2	0 (0)	0 (0)	—	—	—			
3	5 (21)	1 (17)	0.8	0.1—6.5	0.9			
4	10 (42)	2 (33)	0.7	0.1—3.8	0.9			
5	9 (38)	3 (50)	1.7	0.3—8.2	0.7			
Bilateral involvement	24 (100)	6 (100)	—	—	—			
Distribution								
Diffuse	4 (17)	4 (67)	10	1.5—60	0.03	8	1.3—45	0.04
Peripheral	2 (10)	1 (17)	1.8	0.1—18	0.9			
Patchy	18 (75)	1 (17)	0.1	0.1—0.53	0.02	0.3	0.1—0.6	0.02
Pattern								
Mainly interstitial	6 (25)	4 (67)	6	0.99—35	0.1			
Mainly consolidative	18 (75)	2 (33)	0.2	0.03-1	0.1			
Pulmonary embolism	11 (46)	4 (67)	2.4	0.4—14	0.7			
Laboratory tests								
White cells count, $n*10^9/L$ (IQR)	7.2 (4.6–24.9)	5.3 (2.1–20.1)	0.6	0.2—6.5	0.3			
Hemoglobin, g/L (IQR)	12 (7.3–14.4)	13.4 (8.3–15.4)	1.4	0.3—10	0.6			

(*Continued*)

Variable	No ETI n = 31 (82)	ETI n = 7 (18)	Univariate OR	95%CI	p value	Multivariate OR	95%CI	p value
Lymphocytes, 10^9/L (IQR)	1.5 (0.1–20.0)	0.9 (0.1–5.0)	0.7	0.1—12	0.8			
Platelets, 10^9/L (IQR)	175 (130–318)	154 (116–270)	0.5	0.1—7.2	0.7			
C-Reactive Protein, mg/dL (IQR)	4 (0.1–26)	6.7 (1.1–36.4)	2.5	0.8—22	0.1			
D-Dimer, μg/L (IQR)	3.4 (0.28–9)	4.9 (0.56–12.1)	2.1	0.6—18	0.3			
Albumin, g/L (IQR)	35 (23–56)	29 (23–56)	0.7	0.3—9.4	0.5			
LDH, U/L (IQR)	312 (179–982)	400 (210–1065)	1.4	0.5—5.4	0.6			
BUN, mg/dl (IQR)	35 (24–72.0)	27 (23–60)	0.6	0.1—11	0.8			
Creatinine, mg/dl (IQR)	0.89 (0.27–2.2)	1.2 (0.47–4.7)	1	1.3—7.6	0.6			

Data are presented as number and percentage for dichotomous values or median and interquartile range (IQR) for continuous values.
Abbreviations: IQR = inter quartile range; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; RR = respiratory rate; HR = heart rate; MAP = mean arterial pressure, ARDS = acute respiratory distress syndrome; APACHE II = acute physiology and chronic health evaluation II score; SAPS II = simplified acute physiology score; SOFA = subsequent organ failure assessment score, HFNC = high flow nasal cannula; CPAP = continuous positive airways pressure; NIV = non-invasive mechanical ventilation; LDH = lactic dehydrogenase; BUN = blood urea nitrogen.
* CT images available only for 30 patients.

After stratification according to NRS, the synergistic use of awake-PP and HFNC gave greater significant benefit to ETI reduction. These results are in contrast to a previous study[22] that demonstrated that the use of awake-PP did not reduce the intubation rate in 199 patients with COVID-19 ARF treated with HFNC and was associated with a delay in intubation. However, the 28-day mortality was not affected. Because homogenous lung aeration with PP[30] could result in reduced respiratory effort and lead to a lower incidence of intubation, we can speculate that a higher proportion of potentially recruitable lung takes place in early phases of ARDS compared with later phases. Interestingly, patients with NIV support did not experience significant benefit from PP. Maybe patients undergoing NIV were likely those with higher respiratory distress, thus presumably expressing a more extended and inhomogeneous lung involvement (i.e. advanced stages of ARDS). We can further suppose that NIV may reduce compliance to prone position maintenance over time. Conversely, in patients with lower level of distress who benefited from HFNC, prone position might result in a more homogeneous transpulmonary pressure distribution during spontaneous breathing, thus resulting in a less harmful lung stretch. Nonetheless, this speculation remains to be clarified to future studies.

We also found that patchy pattern on chest CT scan was independently associated with NRS failure. Endothelial injury is emerging as a central hallmark of COVID-19 pathogenesis. It has been demonstrated that the lungs of patients with COVID-19 display distinctive vascular features, consisting of severe endothelial injury associated with intracellular SARS-CoV-2 virus, widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries as well as significant new vessel growth (Pulmonary Vascular Endothelitis, Thrombosis, and Angiogenesis in Covid-19). All these findings can contribute to further deterioration in V/Q mismatch and lung tissue damage. Finally, in agreement with previously published studies,[16–22] we found that awake proning was safe, and no adverse events occurred in PP group.

This study has some limitations which need to be disclosed. First, the retrospective nature impairs the generalizability of our results. Second, the different standard operating procedures across the two centers can affect patient outcomes, such as mortality, number of days free from NRS or ICU stay. Patients were encouraged to maintain prone positioning for at least 3-h in both centers, however number of daily PP sessions was based on the physician's judgment and/or the patient's preference. At the same time, the decision as to whether proceed to ETI was taken by the attending staff, according to shared and well-defined ETI criteria. Notwithstanding, the presence of a control group and the identification of 4 key confounders (age, PaO2/FIO2 ratio, pH value and respiratory rate), used for analysis adjustment, could considerably mitigate these biases.

In conclusion, the description of our cohort provides further evidence that early proning in awake and spontaneously breathing Covid-19 patients is feasible and associated with a reduction of intubation rate, especially in those patients undergoing HFNC.

These intriguing results warrant further randomized controlled trials to answer all the pending questions about the real efficacy of PP in this setting.

Conflicts of interest

The authors have no conflicts of interest to declare.

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.2021.03.002.

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ORIGINAL ARTICLE

Smoking behavior and secondhand smoke exposure among university students in northern Portugal: Relations with knowledge on tobacco use and attitudes toward smoking

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Abstract
Objectives: To assess the prevalence of active smoking and secondhand smoke (SHS) exposure among college students in the north of Portugal, and analyze the relationship between knowledge about tobacco use and attitudes toward smoking.
Materials and methods: This a cross-sectional study with a representative sample of college students ($n = 840$) in one university in Portugal. A validated self-reported questionnaire was administered to a proportional stratified random sample during the academic year of 2018/2019. We evaluated associations between smoking status, SHS exposure, smokers peers, knowledge and attitudes toward smoking and sociodemographic variables.
Results: The results showed that 20.1% of the students surveyed were current smokers (7.3% occasional smokers, 2.9% regular smokers and 9.9% daily smokers). Most current smokers started smoking before the age of 17 (61.4%) and reported never having tried to quit smoking (59.7%). Only 34.4% of students reported (almost) not having been in enclosed spaces with smokers in the past 7 days. Exposure to SHS and having smoker friends contributes to the prevalence of tobacco use. In general, students showed favorable attitudes toward smoking, especially those who are smokers, have smoking friends and are more exposed to SHS. The level of knowledge about tobacco was moderate, with a higher number of correct responses by former smokers.

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Conclusions: These results suggests an urgent need for socio-educational programs for counseling on smoking cessation. In addition, is also strongly recommended that, throughout academic training, students develop personal and social skills for dealing with the tobacco epidemic.

Introduction

Tobacco use remains a serious public health problem as it is a major cause of preventable diseases and death,[1,2] or in other words, the most avoidable cause of death.[3] Furthermore, secondhand smoke (SHS) exposure increases morbidity and mortality from coronary heart disease, lung cancer, respiratory infections, and other illnesses. Despite (inter)national tobacco prevention policies, such as a ban on smoking in public places, increased taxes on tobacco products and social education about the harmful effects of smoking, the recognition of the severe health consequences of smoking has been a slow process.[4] While these types of policy interventions are only indirectly aimed at young adults, they demonstrate the positive effects of smoking bans in public spaces, being associated with reduced smoking progression, reduced consolidation of experimentation with regular smoking and increased smoking cessation among young adults.[5] This is particularly relevant in areas where alcohol is served, given the strong association between tobacco and alcohol consumption in this age group.[6]

Starting smoking early increases the risk of regular smoking, and early adulthood is often associated with increased cigarette smoking and the establishment of regular smoking habits.[7] The academic environment may constitute a context that favors tobacco use,[8] as well as initiation/experimentation[9] through the way it is socially accepted in this context (Nolen-Hoeksema, 2004). Several studies have shown an increase in the number of smokers on academic courses, both in the number of students who began to smoke regularly and in the number of cigarettes smoked daily.[10] For example, Tercyak, Rodriguez and Audrain-McGovern (2007)[11] found that 25% of those who reported never having smoked in high school started smoking a year later.

Given the impact at various levels of tobacco use and the initiation and increase of smoking among young adults, it is important to understand how knowledge and attitudes toward tobacco use relate to smoking behavior, as this understanding will enable the development of health education programs in higher education from a preventive and educational perspective. In scientific literature, several investigations have addressed the relationship between knowledge, attitudes and smoking habits in higher education.[12–14] These studies take into account the fact that university students are in the process of being educated and that in future, they will be agents of change, responsible for promoting healthy lifestyles.[15]

The purpose of this study was to assess the prevalence of active smoking and secondhand smoke exposure among college students in the north of Portugal and analyze the relationship between knowledge about tobacco use and attitudes toward smoking.

Materials and methods

Population and sample

For the 2018/2019 academic year, 5447 students were registered in the 1st and 3rd year of integrated bachelors and masters degrees, with a higher prevalence of girls attending this university. Excluded from the sample were courses related to health sciences, undergraduate or postgraduate masters who did not have classes in the 1st or 3rd year. We excluded courses in the area of health sciences because we considered that the health knowledge of these students could skew the results of the study.

The minimum sample size needed for this study was 592 students (margin of error = 5%, confidence level = 99%, and response distribution = 50%). For this purpose, a stratified probabilistic sampling of university students was performed according to the academic year and the scientific area of study. The different undergraduate and master's degrees were divided into scientific areas (as defined by the Foundation for Science and Technology): Social and Human Sciences, Judicial and Economic Sciences, Exact and Nature Sciences and Engineering Sciences.

In this cross-sectional study with a representative sample of college students ($n = 840$) in one university in Portugal, data were collected using a validated self-reported questionnaire without biochemical confirmation.

The sample consists of 464 incoming students (55.2%) and 376 final year students (44.8%). The scientific area of studies included, 302 (36.0%) students from the engineering sciences, 270 (32.1%) students from the social and human sciences, 136 (16.2%) students from the exact and natural sciences and 132 (15.7%) students in the area of law and economic sciences. Most of the students surveyed were female (55.4%, $n = 465$), not in an affective relationship (58.3%, $n = 486$), displaced from their usual residence (64.9%, $n = 537$), full-time student (88.8%, $n = 739$) and with a BMI corresponding to a normal weight (73.1%, $n = 599$). The average age of the sample was 20.78 years (SD = 4.221), with a range of 18–54 years, only 3% of students were 30 or older.

Instruments

Currently, there are several scientific instruments to monitor the prevalence of smoking among young adults, as the Youth Risk Behavior Surveillance System (YRBSS),[16]

the Behavioral Risk Factor Surveillance System (BRFSS),[17] the National Survey on Drug Use and Health[18] and the National Youth Tobacco Survey.[19] Nevertheless, the data to be collected by using any of these surveys did not fully meet the objectives of the intended investigation. Therefore, the development of the instruments present in this investigation was carried out in three stages: scale construction (1st stage); content validity (2nd stage); psychometric validity (3rd stage), according to the procedures defined by Bowling (1998).[20]

For the construction of the scale (1st stage) was carried out a systematic review of the literature[14] in order to identify the questions and items commonly used to assess knowledge, attitudes and smoking habits in higher education. Based on this review, an analytical matrix was created for each of the dimensions to be analyzed, and those with the same semantic similarities were eliminated.

For the content validity (2nd stage) we invited 10 PhD researchers from several Portuguese universities with recognized work in the area of Health Education in Higher Education and the feedback from 5 of the invited investigators and all proposed semantic changes were considered. Similarly, the instrument was applied to 12 university students, using the method ''thinking aloud''[20,21] to identify items that might be confusing, excluding less relevant or redundant items, and verify that pre-coded response options were sufficient. In order to obtain greater objectivity, the following scale was used as the criterion of clarity evaluation for each item: 1 - confused; 2 - unclear; 3 - clear. After suggested redrafting, the preliminary version of the questionnaire survey was presented to a sample of 32 students, not included in the final sample.

The questionnaire included sociodemographic variables (sex, age, scientific area of study, academic year, weight and height (to calculate BMI), have a affective relationship, professional situation e current residence) and specific questions related:

- Smoking status (''Do you currently smoke?'' Possible answers: I currently smoke daily (at least 1 cigarette per day); I currently smoke regularly (at least one cigarette a week, but not every day); I currently smoke occasionally (less than one cigarette per week); I don't smoke now, but I used to smoke daily (at least 1 cigarette a day); I don't smoke now, but I used to smoke occasionally (at least 1 cigarette per week); I never smoked. And for current smokers: ''How many cigarettes do you smoke per week? Or per day?''); first experience of smoking (''How old were you when you started smoking?''); cessation attempts (''Have you ever tried to quit smoking?'')
- Smoker peers (''How many of your friends smoke regularly?'';
- Secondhand smoke (SHS) exposure (''Throughout the week, how long are you in enclosed spaces with smokers?'');
- Tobacco use knowledge (TUK): 6-item scale with answer options - True, False, Don't Know (1. ''Smokers are more likely to get lung cancer than non-smokers''; 2. ''Smokers feel tired more easily than non-smokers''; 3. ''The heart of a smoker works harder because carbon monoxide stops the blood from carrying oxygen''; 4. ''The nicotine present in cigarettes lowers blood pressure''; 5. ''The nicotine present in cigarettes is a nervous system stimulant''; 6. ''Smokers are more likely to develop osteoporosis than non-smokers'');
- Attitudes toward smoking use (AtS): 3-items scale on a 5-point likert scale (1 – strongly disagree, 5 – fully agree) (1. ''Smoking helps one relax and reduces stress''; 2. ''Smoking helps one to think''; 3. ''Smoking helps control body weight'').

Procedure and statistical analysis

All the students who attended the selected courses were personally invited to participate. At the end of each randomly selected class, the objectives of this study were presented and after informed consent, students filled out the paper-pencil questionnaire, in the classroom context. The response rate was 96.2% (95% CI 94.8–97.6), 33 questionnaires were excluded as not answered or incorrectly filled out. So we invited 873 university students to participate in this study.

All ethical research procedures with humans referred to by Christensen et al. (2015)[22] were fulfilled and the study was approved by the University Ethics Committee.

Data were analyzed using the IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). For statistical analysis, we analyzed frequencies and contingency tables, performed Pearson's correlation, Chi-square test, independent *t*-test, and one-way variance (ANOVA) and Hochberg's GT2 multiple comparison procedures. A p value < 0.05 was considered as significant.

Multinomial regression model was developed including only variables with a significant bivariate association with smoking status. The nominal indicator of 'non smoker' was assigned as the reference category and all covariates were entered into the model simultaneously. Variables found not to contribute to the prediction of the dependent variable were excluded from the final model. A significance level of 0.05 was considered.

Tobacco use patterns were analyzed according to the classification: No-smoker (who never smoked – ''I never smoked''); Former smoker (who have smoked weekly – ''I don't smoke now, but I used to smoke occasionally (at least 1 cigarette per week)'' and daily – ''I don't smoke, but I used to smoke daily (at least 1 cigarette a day)'') and Current smoker (occasional smokers – ''I currently smoke occasionally (less than one cigarette per week)'', regular smokers – ''I currently smoke regularly (at least one cigarette a week, but not every day)'' and daily smokers – ''I currently smoke daily (at least 1 cigarette per day)'').

To the scale about knowledge the number of correct responses was added to give an overall knowledge score, and means calculated. This means that the higher the scale value, the higher the level of knowledge.

The attitude scale was subjected to Cronbach's alpha analysis in order to analyze its reliability,[20] and a good reliability index was obtained ($\alpha = .770$). In addition, inter-item correlations ranging from .674 to .387. Reading the results of this scale shows, the higher the average of the scale, the more negative the attitudes of university students toward tobacco consumption.

Table 1 Frequencies and Chi Square test for sociodemographic variables and smoking-related characteristics. Bold: statistical significance

		Smoking status						Chi Square test	
		No-smoker		Former smoker		Current smoker		χ^2	*p*
		f	%	*f*	%	*f*	%		
SHS exposure	Never or almost never	233	40.7	24	26.1	29	17.3	86.536	**.000**
	Few times	210	36.7	27	29.3	51	30.4		
	Sometimes	102	17.8	24	26.1	49	29.2		
	Most of the time	17	3.0	11	12.0	24	14.3		
	Almost Always or Always	10	1.7	5	6.5	15	8.9		
Smoker peers	None or almost none	107	18.8	8	8.5	11	6.7	114.594	**.000**
	Few	215	37.7	26	27.7	29	17.6		
	Some	211	37.0	34	36.2	70	42.4		
	Most	34	6.0	20	21.3	44	26.7		
	Almost all or all	3	0.5	6	6.4	11	6.7		
Year of frequency	1st year	329	39.2	58	6.9	77	9.2	8.260	**.016**
	3rd year	249	29.6	36	4.3	91	10.8		
Scientific area	Engineering sciences	217	25.8	28	3.3	57	6.8	20.103	**.003**
	Exact and natural sciences	95	11.3	13	1.5	28	3.3		
	Judicial and economic sciences	70	8.3	22	2.6	40	4.8		
	Social and human sciences	196	23.3	31	3.7	43	5.1		
Sex	Male	252	30.0	38	4.5	85	10.1	3.340	.188
	Female	326	38.8	56	6.7	83	9.9		
Age	<20	266	31.7	35	4.2	54	6.4	11.370	**.003**
	>=20	312	37.1	59	7.0	114	13.6		
Affective relationship	Yes	212	25.5	58	7.0	77	9.2	23.206	**.000**
	No	362	43.5	35	4.2	89	10.7		
Current residence	Displaced	182	22.0	31	3.7	78	9.4	12.942	**.002**
	Not displaced	389	47.0	60	7.2	88	10.6		
Professional situation	Full time student	527	63.3	73	8.8	139	16.7	23.984	**.000**
	Worker/Student	44	5.3	21	2.5	28	3.4		
BMI	Low weight	43	5.3	7	0.9	8	1.0	3.122	.538
	Normal weight	412	50.3	68	8.3	119	14.5		
	Overweight	107	13.1	16	2.0	39	4.8		

Results

The results showed that 68.8% of the students surveyed were non-smokers, 11.2% were former smokers and 20.1% were current smokers (7.3% occasional smokers, 2.9% regular smokers and 9.9% daily smokers). Regular and daily smokers consume on average 8.43 ($SD = 6.462$) cigarettes per week and 8.33 ($SD = 4.870$) cigarettes per day, respectively. Most current smokers started smoking aged under 17 (61.4%) and reported never having tried to quit smoking (59.7%). Only 34.4% of students reported (almost) never having been in enclosed spaces with smokers in the previous 7 days.

Tobacco use is positively correlated with smoker peers ($r_{sp} = .329$, $p < 0.01$) and with SHS exposure ($r_{sp} = .295$, $p < 0.01$), so, smokers tend to have more friends who smoke ($\chi^2(8) = 114{,}594$, $p = .000$) and are more exposed to SHS than former smokers and non-smokers ($\chi^2(8) = 86{,}536$, $p = .000$) (Table 1).

Smoking was significantly associated with sociodemographic characteristics such as which academic year, scientific area, age, being in an affective relationship, current residence, and professional situation. This means that there is a higher prevalence of smoking in: graduating students compared to the year first students ($\chi^2(2) = 8.260$, $p = .016$); students of the economics and law compared to the other scientific areas ($\chi^2(6) = 20.103$, $p = .003$); older students compared to the younger ones ($\chi^2(2) = 11.370$, $p = .003$); students who are in a relationship compared to those who are not ($\chi^2(2) = 23{,}206$, $p = .000$); students who moved away from home at the time of entering higher education compared to non-displaced students($\chi^2(2) = 12{,}942$, $p = .002$); student-workers compared to full-time students ($\chi^2(2) = 23{,}984$, $p = .000$) (Table 1). Note that no statistically significant differences were found in tobacco use according to sex or BMI of respondents.

In general, students showed favorable attitudes toward smoking, because the mean score 2.01 (SD = .924) showed that most respondents disagreed or strongly disagreed with the items of AtS. But, there were significant differences based on smoking status, smoker peers, SHS exposure, scientific area, sex and current residence, as shown in Table 2. Not surprisingly, smokers had more negative attitudes than

Table 2 Mean, one-way ANOVA and t-test for smoking characteristics, sociodemographic variables and attitudes toward smoking (AtS).

		AtS	ANOVA		Hochberg		
		Mean (SD)	*Z*	*p*			
Smoking status	Non-smoker	1.77 (.826)	85.886	**.000**	1.7653		
	Former smoker	2.21 (.795)				2.2138	
	Current smoker	2.72 (.918)					2.7186
Smoker peers	None or Almost none	1.70 (.768)	15.581	**.000**	1.6960		
	Few	1.90 (.866)			1.9019		
	Some	2.02 (.910)			2.0183		
	Most	2.50 (1.037)				2.4965	
	Almost All or All	2.77 (.925)				2.7667	
SHS exposure	Never or almost never	1.85 (.843)	7.298	**.000**	1.8470		
	Few times	1.98 (.942)			1.9801		
	Sometimes	2.11 (.937)			2.1085	2.1085	
	Most of the time	2.41 (.965)				2.4067	
	Almost Always or Always	2.48 (.973)				2.4839	
Scientific area	Engineering Sciences	2.15 (.903)	6.791	**.000**		2.1488	
	Exact and Natural Sciences	2.04 (.976)			2.0373	2.0373	
	Law and Economic Sciences	2.06 (.924)			2.0615	2.0615	
	Social and Human Sciences	1.81 (.891)			1.8075		
BMI	Low weight	1.91 (.956)	2.465	.086			
	Normal weight	1.98 (.880)					
	Overweight	2.15 (1.048)					
			t-student				
			t	*p*			
Acadmic year	1st year	1.96 (.907)	−1.677	.094			
	3rd year	2.07 (.942)					
Sex	Male	2.17 (.987)	4.478	**.000**			
	Female	1.88 (.849)					
Age	<20	1.94 (.886)	−1.908	.057			
	>=20	2.06 (.949)					
In relationship	Yes	2.02 (.961)	.233	.818			
	No	2.00 (.902)					
Current residence	Displaced	2.11 (.935)	2.516	**.012**			
	Not displaced	1.94 (.908)					
Professional situation	Full time student	2.00 (.919)	−.749	.454			
	Worker/Student	2.08 (.952)					
Total		2.01 (.924)					

those who had never smoked or stopped smoking ($F(2, 824) = 85.886$, $p = .000$). And students who report that most or almost all friends are smokers and are mostly or almost always exposed to SHS exhibit more negative attitudes than students with no, few or some smoker friends ($F(4, 811) = 15.581$, $p = .000$) and are never or rarely exposed to SHS ($F(4, 814) = 7.298$, $p = .000$), respectively.

Engineering sciences respondents showed more negative attitudes, while those in social and human sciences showed the most favorable attitudes ($F(3, 823) = 6.791$, $p = .000$). Girl respondents and students who lived at home had more favorable attitudes than boy respondents ($t(825) = 4.478$, $p = .000$) and students who had moved away from home ($t(813) = 2.516$, $p = .012$), respectively.

There were no significant differences by year of frequency, age, being in a relationship, IBM and professional situation.

Table 3 shows respondents' knowledge of tobacco use. The mean score was 3.11 ± 1.26 (out of 6) correct answers. There were no significant differences in knowledge scores because of smoker peers, SHS exposure, year of frequency, scientific area, age, being in a relationship, current residence or IBM. However, one-way ANOVA showed significant differences between TUK and smoking status. Respondents who had ceased smoking had a significantly higher mean knowledge score than those who still smoked and those who had never smoked ($F(2, 829) = 3.559$, $p = .029$). Furthermore, *t*-test showed significant differences between TUK and sex of respondents and current residence. That is means girls and displaced students had a lower level of knowledge than boys ($t(830) = 2.336$, $p = .020$) and students living at home ($t(822) = -2.334$, $p = .020$), respectively.

For the final model, we kept the variables that had a statistically significant effect on the logit probability of the

Table 3 Mean, one-way ANOVA and *t*-test for smoking characteristics, sociodemographic variables and tobacco use knowledge (TUK).

		TUK				
		Mean (SD)	ANOVA		Hochberg	
			Z	*p*		
Smoking status	No-smoker	3.04 (1.303)	3.559	**.029**	3.0384	
	Current smoker	3.20 (1.143)			3.2000	3.2000
	Former smoker	3.38 (1.219)				3.3830
Smoker peers	None or almost none	3.02 (1.362)	1.644	.161		
	Few	3.01 (1.263)				
	Some	3.16 (1.222)				
	Most	3.36 (1.268)				
	Almost all or all	3.15 (.875)				
SHS exposure	Never or almost never	3.04 (1.317)	1.356	.248		
	Seldom	3.18 (1.279)				
	Sometimes	3.00 (1.259)				
	Most of the time	3.31 (.899)				
	Almost always or always	3.35 (1.226)				
Scientific area	Engineering sciences	3.13 (1.224)	.309	.819		
	Exact and natural sciences	3.14 (1.141)				
	Law and economic sciences	3.15 (1.330)				
	Social and human sciences	3.05 (1.333)				
BMI	Low weight	2.93 (1.041)	.706	.494		
	Normal weight	3.14 (1.272)				
	Overweight	3.12 (1.282)				
			t-student			
			t	*p*		
Academic year	1st year	3.15 (1.273)	.982	.326		
	3rd year	3.06 (1.250)				
Sex	Male	3.22 (1.292)	2.336	**.020**		
	Female	3.02 (1.233)				
Age	<20	3.10 (1.213)	−.182	.855		
	>=20	3.12 (1.299)				
In relationship	Yes	3.17 (1.271)	1.165	.244		
	No	3.07 (1.245)				
Current residence	Away from home	3.14 (1.204)	.302	.763		
	Living at home	3.11 (1.280)				
Professional situation	Full time student	3.07 (1.258)	−2.334	**.020**		
	Worker/Student	3.40 (1.278)				
Total		3.11 (1.263)				

smoking status: AtS ($G^2(2) = 101.993$, $p = .000$); Smoker peers ($G^2(8) = 20.492$, $p = .009$); SHS exposure ($G^2(8) = 21.693$, $p = .006$); In relationship ($G^2(2) = 16.247$, $p = .000$); Professional situation ($G^2(2) = 14.410$, $p = .001$). The adjusted model was statistically significant ($G^2(22) = 257.946$, $p = .000$) and correctly predicted the status smoking 72.5% of the time (93.9% for non smokers).

Table 4 summarizes the results of the multinomial logistic regression for smoking status. The model made it possible to predict that: students who were less exposed to SHS were less likely to be smokers compared to non-smokers; students who had fewer smoking friends were less likely to be smokers and ex-smokers compared to non-smokers; being in a relationship compared to not being in a relationship increases the chances of being a former smoker in relation to a non-smoker; being a full-time student compared to student workers reduces the chances of being a former smoker by 67.7% and of being a smoker by 58.4%; students scoring higher on AtS were more likely to be a former smoker or current smoker than non-smoker.

Discussion

This study examined current smoking status, smoking history, cessation attempts and knowledge of tobacco use and attitudes toward smoking among students at one university in Portugal. Our data showed that 1 in 5 uni-

Table 4 Adjusted odds ratios (OR) and 95% confidence intervals (CI) from multinomial logistic regression model predicting former smoker and current smoker.

		Smoking Status			
		Former smoker[a]		Current smoker[a]	
		OR	(95% CI)	OR	(95% CI)
SHS exposure	Never or almost never	.324	(.087–1.210	.223*	(.069–.720)
	Seldom	.371	(.104–1.324)	.289*	(.094–.888)
	Sometimes	.537	(.149–1–928)	.488	(.158–1.504)
	Most of the time	1.304	(.310–5.486)	1.147	(.322–4.085)
	Almost Always or Always				
Smoker peers	None or Almost none	.116*	(.020–.655)	.152*	(.029–.785)
	Few	.125*	(.025–.617)	.118**	(.025–.551)
	Some	.143*	(.030–.688)	.221*	(.049–.995)
	Most	.262	(.052–1.329)	.413	(.089–1.929)
	Almost All or All				
In relationship	Yes	2.707***	(1.653–4.435)	1.388	(.908–2.122)
	No				
Professional situation	Full time student	.323***	(.171–.608)	.416**	(.225–.768)
	Worker/Student				
AtS		1.829***	(1.391–2.405)	3.096***	(2.430–3945)

OR: odds ratio; 95% CI: 95% confidence interval.
[a] Reference category: no-smoker.
* $p < .050$.
** $p < .010$.
*** $p < .001$.

versity students are smokers but that the prevalence of smoking in this university was lower than identified in other national[23–26] and international studies (Spain[10,27,28]; Greece[29]; Iran[30]; Australia[31]; Jordan[32]; Palestine[33]; Liban[34]; United Kingdom[35]; Italy[36]; Czech Republic[37]; Serbia[38]; Brazil[39]; Saudi Arabian[40]; Belgium[41]; Chile[42]; Poland[43]; Turkey[44]). Similarly, we found a high proportion of students who were former smokers (11.2%), considering that they are young adults and despite the fact that most current smokers (61.4%) started smoking before entering higher education.[10,45] This could be explained because before leaving home, there had been an aspect of parental control which was lost when entering higher education.[46] The prevalence of smoking increased with permanence in higher education, which corroborates scientific literature.[3,32,33,47,48] Consequently, older students included more smokers than younger students (13.6% versus 6.4%) and there were also statistically significant differences depending on the number of cigarettes consumed per day or per week. That is, older smokers smoke, on average, 12.10 (±7.340) cigarettes per week or 8.84 (±4.969) cigarettes per day, while younger smokers smoke, on average, 5.09 (±3.048) cigarettes per week or 5.09 (±2.468) cigarettes per day ($t = -2.909$, $p = .009$ and $t = -2.445$, $p = 0.17$, respectively).

A national study[49] showed that 37.2% of young people aged between 15 and 34 years old had used tobacco in the previous 30 days, meaning this prevalence was higher than verified in this study.

Unlike other national[24,26] and international studies[30,33,42,47,48,50–53] in which male students smoked more than female students, our study did not find any differences in smoking between the sex of respondents. This is consistent with a study conducted in 2004 at the same university.[54]

Most smokers reported never having attempted to quit smoking (59.7%), a very high percentage compared to other studies.[10] This indicates, efforts should be made to understand why students are reluctant to quit smoking.

The prevalence of SHS in closed public spaces is high, due to the fact that more than half of the students (65.6%) had been exposed to SHS in the previous week. Despite prohibitive smoking policies in enclosed public places, college students had a high level of exposure to SHS.[48,55,56] Furthermore, we found that smokers are more exposed to SHS than non-smokers.[57]

Most respondents (52.2%) reported that at least some of their friends were smokers, consistent with the literature, not forgetting that having smoking friends seems to influence tobacco use among university students.[30,38,40,45,50,51,53,58–60]

Regarding attitudes toward tobacco, we found that most students showed favorable attitudes toward smoking[31] but, as in other studies,[31,33] non-smokers demonstrated higher scores on positive attitudes than smokers and former smokers. The influence of smoking friends, exposure to SHS and being enrolled in engineering science courses seems to reduce positive attitudes toward tobacco use.

In terms of knowledge about tobacco use, several studies have shown that smokers have low levels of knowledge,[61] suggesting that increasing knowledge about the effects of smoking would decrease smoking rates during academic

courses.[47] In our study, there was a moderate level of knowledge about tobacco,[30,33,48] higher in students who had already quit smoking.[31,32]

Unlike other research findings, where girls were better informed than boys[31,32,62] or where there were no differences,[30] we found that boys were better informed than girls.[33]

It is also important to highlight the sociodemographic variable ''current residence'', because students who had left their familial home smoked more, knew less about the harmful consequences of smoking and showed more negative attitudes compared to students who had not changed their residence after entering higher education.

Finally, the limitation of this study should be noted. Restricting the study to a single university limits generalizability to the total population of university students in Portugal.

No data were collected concerning the smoking habits of parents/households and, although scientific studies state that children of smoking parents have a greater tendency to be smokers, this type of question did not fit within the scope of our study. One final limitation should be considered. Since the data were collected in 2018–2019, the use of e-cigarettes or ''heat-not-burn'' tobacco products are at least worth mentioning, especially looking at young people.

Conclusions

This study suggests an urgent need for higher education institutions to implement socio-educational programs to discourage tobacco use among university students. In addition, it is also highly recommended that during academic training students develop personal and social skills to deal with the tobacco epidemic.

Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Treatment interruption patterns and adverse events among patients on bedaquiline containing regimen under programmatic conditions in India

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Abstract
Background: The study aimed to analyze frequency and severity of adverse events (AEs) and other reasons for interruption of treatment and loss to follow up (LTFU) during first six months of treatment among tuberculosis patients on bedaquiline containing regimens.
Methods: This pilot exploratory observational study included 275 patients enrolled consecutively over two years who received bedaquiline containing regimen under programmatic conditions in India.
Results: Among 275 patients with median age of 25 years, 86 (31.3%) patients had at least one interruption with 122 total episodes of interruption. Among these 70 were temporary, 35 were permanent interruptions and 17 were LTFU. The AEs due to drugs were the commonest reason for interruption observed in 81.4% of temporary interruption group and 97.1% of permanent interruption group. Among a total 192 adverse event episodes, 49.5% were minor (grade 1–2) and 50.5% were serious (grade 3–5). Personal factors were the commonest reason for interruption observed in LTFU (94.1%) group. The most common temporarily interrupted drug was bedaquiline in 8.7% and permanently stopped drug was linezolid in 5% of patients.
Conclusions: Our study observed that drug related AEs are important risk factors associated with treatment interruptions in bedaquiline containing regimens. Bedaquiline is the most common temporarily interrupted drug due to AEs.

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Introduction

Tuberculosis (TB) is a major public health problem worldwide. As per Global TB report 2019, globally 10 million people developed TB disease and about a quarter of those cases were reported from India in 2018.[1] The proportion of cases who are infected with strains resistant to isoniazid and rifampicin, called multidrug-resistant tuberculosis (MDR-TB) among new and previously treated cases in India, were 2.8% and 14% respectively.[1]

Adherence to the long course of TB treatment is a complex, dynamic phenomenon with a wide range of factors impacting on treatment taking behavior.[2] However, an estimated 50% of patients on long term therapy for chronic diseases, including TB, are non-adherent.[3] Non-compliance leading to treatment interruption due to any reason may affect the outcome adversely.[4] Multiple number of drugs leading to adverse events (AEs) in drug resistance TB (DR-TB), patients' personal factors, TB programme related factors and environmental factors may be responsible for the interruptions and loss to follow up (LTFU) during the treatment period.[5]

Bedaquiline, is a novel drug recently approved for the treatment of tuberculosis. The addition of bedaquiline to an optimized background regimen (OBR) results in faster and significantly more culture conversions leading to higher successful outcome.[6] The information about interruptions and AEs, especially with newer drugs and drug combinations, in bedaquiline containing regimen is sparse.[7–9]

The study aimed to analyze the frequency and severity of AEs and other reasons for interruptions of treatment and loss to follow up (LTFU) during the first six months of treatment among TB patients on bedaquiline containing regimens under programmatic conditions in India.

Methods

Setting

This was a pilot exploratory observational study. All patients, who received bedaquiline containing regimen through conditional access under programmatic management of drug resistant tuberculosis (PMDT) at a tertiary center in northern India were enrolled prospectively, over a period of two years from October 2016 to October 2018.

Study population

The eligibility criteria for enrollment were adult patients with pulmonary DR-TB who required the addition of bedaquiline with/without other newer/repurposed drugs based on drug resistance pattern to construct an effective regimen as per recommendations of national programme for management of DR-TB.[10]

Ethical considerations

Ethical and research approval was obtained from Institutional Research and Ethical Committee (office letter no. NITRD/PGEC/2018/6624 letter no. NITRD/RC/2018/5742 respectively).

Definitions

In this study, missed doses of all drugs or part of regimen (one or more drugs) was considered as interruption. The interruption was further classified into:

1 Temporary – If drug/drugs were restarted after interruption; temporary interruption was further classified as short if the duration of interruption was $\leq$2 days, and as long if the duration of interruption was >2 days to 30 days.[11]
2 Permanent – If drug/drugs were not restarted after interruption
3 Lost to follow up – If all drugs were discontinued for more than one month.[10]

The AEs of any drug involved in the treatment regimen were collected. According to the World Health Organization active drug safety monitoring project, serious adverse events (SAEs) include death or a life-threatening event, hospitalization or prolongation of hospitalization, persistent or significant disability, or congenital anomaly. SAEs included grade 3–5 AEs (grade 3: serious; grade 4: life threatening; grade 5: death). Minor AEs included those of grade 1 (mild) and grade 2 (moderate).[7,12–14]

Treatment regimen

Enrolled patients received a treatment regimen of bedaquiline with companion drugs which were individually constructed based on drug resistance pattern as per recommendations of PMDT for management of DR-TB.[10] Bedaquiline was given at 400 mg daily for two weeks and then 200 mg thrice weekly for 22 weeks.

Patient management

After obtaining informed written consent, eligible patients' case summaries including demographic details, body mass index (BMI), drug susceptibility test report of National Reference Laboratory {available for rifampicin, isoniazid, pyrazinamide, second-line injectable drugs (i.e., amikacin, kanamycin, or capreomycin), flouroquinolones both low and high dose, cycloserine, ethionamide, clofazimine, linezolid and *p*-amino salicylic acid}, radiological profile including presence of cavity and extent of involvement as per National Tuberculosis Association of USA[15] were recorded. Relevant blood investigations including serum electrolytes, thyroid function tests, audiometry, and baseline QTc in resting ECG using Fridericia's formula (QTcF) were done at baseline. ECG was repeated every week in first two months followed by monthly for next four months. Patients were monitored during the first six months of treatment period according to recommendations of PMDT for management of DR-TB.[10] A designated treatment supporter visited the patient within 24 h of interruption, documented the episode and cause of interruption, and addressed the reason of interruption.

Where he/she was unable to convince the patient, medical officer visited the patient's house. If still unsuccessful, help was requested of district tuberculosis officer (DTO) to convince the patient to continue with treatment. All these issues were documented in patient treatment card. The interruption episodes which occurred during the first six months of treatment were studied for the type of interruption, whether temporary or permanent, duration for which the drug/drugs were interrupted and reason for interruption. The individual drugs which were interrupted, and organ system predominantly affected were also studied.

Data management and analysis

Patient characteristics were summarized using frequencies and percentages for categorical variables, and median and interquartile ranges (IQRs) for continuous variables. Chi-square test was used to assess the relationship between categorical variables. Student *t*-test was used to test difference between proportions and means between study populations. Statistical analysis was done using Statistical Package for Social Sciences (IBM, Armonk, NY, USA) version 21.0. A p-value of <0.05 was considered statistically significant.

Results

A total of 275 patients were enrolled. The demographic, radiological, microbiological characteristics, drugs used and number of drugs in the treatment regimen are summarized in Table 1. Among the 275 study subjects, 56.4% were males, median age was 25 (IQR, 21—36) years and median BMI was 18.73 kg/m^2 [IQR, 15.5—20.16]. At treatment initiation, 63.6% had cavity in chest x-ray and 73.8% were Pre-XDR (MDR + Fluoroquinolone resistant – 70.2%; MDR + Injectable resistant – 3.6%). Patients having XDR TB {MDR-TB plus resistance to any fluoroquinolone and at least one of three second-line injectable drugs (i.e., amikacin, kanamycin, or capreomycin)} were 22.6%.

Type of interruptions

Among the 275 patients, interruption episodes occurred in 86 (31.3%) patients with 122 total episodes of interruption. Out of 86 patients, 21 (24.4%) patients had more than one interruption episode. Out of 275 patients, 17 (6.2%) patients were LTFU, 33 (12%) patients had permanent interruption and 50 (18.2%) had temporary interruption. Among the interruption episodes, 70 (57.4%) were temporary interruptions, out of which 56 (80%) episodes were long interruptions. Among 122 interruption episodes, 78.7% episodes occurred after two weeks of treatment period.

Reasons for interruptions

The various factors analyzed for reasons of interruptions were drug related AEs, personal, provider and environmental related factors and are summarized in Table 2. The AEs due to drugs was the commonest reason in temporary (81.4%) and permanent (97.1%) interruption groups whereas

Table 1 Baseline patient demographic, disease features, resistance pattern and drugs used in OBR of 275 study subjects.

Patient demographic, disease features, resistance pattern and drugs used in OBR	*n* (%)
Age, years - median (range)	25 (21—36) years
Male	155 (56.4%)
BMI, kg/m^2 - median (range)	18.73 [15.5—20.16]
BMI - <18.5 kg/m^2	122 (44.4%)
Addiction habits	39 (14.2%)
Diabetes mellitus	33 (12%)
Hypertension	5 (1.8%)
Alcoholic liver disease	3 (1.1%)
Chronic renal disease	2 (0.7%)
Hypothyroidism	2 (0.7%)
Seizure disorder	2 (0.7%)
HIV-positive	2 (0.7%)
Other Comorbidities[a]	4 (1.5%)
Contact with a DR-TB case	39 (14.2%)
Previously treated with second-line drugs	163 (59.2%)
Cavities on chest x-ray	175 (63.6%)
Bilateral disease on chest x-ray	218 (79.3%)
DST profile	10 (3.6%)
Pre-XDR-TB resistant to injectable	193 (70.2%)
Pre-XDR-TB resistant to FQs	62 (22.6%)
XDR-TB	10 (3.6%)
Poly drug resistant	
Drugs used in OBR	260 (94.5%)
Linezolid	242 (88%)
Clofazimine	204 (74.2%)
Second Line Injectable	186 (67.6%)
Ethionamide	182 (66.2%)
Cycloserine	132 (48%)
Pyrazinamide	119 (43.2%)
Moxifloxacin -High dose	70 (25.5%)
P-amino salicylic acid	58 (21.1%)
Amoxicillin-clavulanate	47 (17.1%)
Delamanid	45 (16.4%)
Imipenem	21 (7.6%)
Ethambutol	8 (2.9%)
Isoniazid -High dose	8 (2.9%)
Moxifloxacin -Normal dose	2 (0.7%)
Levofloxacin	
Number of drugs in the regimen	14 (5.1%)
5 drugs	80 (29.1%)
6 drugs	146 (53.1%)
7 drugs	31 (11.3%)
8 drugs	4 (1.4%)
9 drugs	

BMI – Body mass index; DR-TB- Drug resistant tuberculosis; DST – Drug sensitivity test; XDR – Extensive drug resistant; FQs-Fluoroquinolones; OBR -optimized background regimen.

[a] Other Comorbidities = glaucoma – 2, hearing loss – 1, bronchial asthma – 1.

Table 2 Reason for interruptions in various episodes.

Reasons	Any interruption *n* (%)	Temporary interruption of any drug *n* (%)	Permanent interruption of ≥1 drug *n* (%)	LTFU *n* (%)
Drug related AEs	92 (75.4%)	57 (81.4%)	34 (97.1%)	1 (5.9%)
Personal factors	30 (24.6%)	13 (18.6%)	1 (2.9%)	16 (94.1%)
[a]Busy schedule	1 (0.8%)	0	0	1 (5.9%)
[b]Lack of family support	18 (14.8%)	13 (18.6%)	0	5 (29.4%)
[c]Addictions	1 (0.8%)	0	1 (2.9%)	0
[d]No improvement	10 (8.2%)	0	0	10 (58.8%)
Total	122 (100%)	70 (100%)	35 (100%)	17 (100%)

LTFU – lost to follow up; AEs - adverse events.

Table 3 Classification of adverse drug reactions as per Common Terminology Criteria for Adverse Events.

Adverse events (%)	Grade	No. of episodes *n* (%)
Minor	I – Mild	30 (15.6%)
	II - Moderate	65 (33.9%)
Serious	III - Severe or medically significant	95 (49.5%)
	IV - Life-threatening consequences	2 (1.0%)
	V - Death related to AEs	0
Total		192

personal factors were the commonest reason in LTFU (94.1%) group. The service provider and environmental related factors were not associated with any interruption episode.

A total of 192 episodes of AEs occurred within first six months of treatment in 109 patients (Table 3). Out of these 192 episodes, 95 (49.5%) were classified as minor (grade 1–2) and 97 (50.5%) were classified as serious (grade 3–5). However, only 92 of these episodes of AE were associated with interruption. The type of AEs leading to temporary or permanent interruption episodes is shown in Table 4. The most common AEs in temporary and permanent interruption episodes were QTcF prolongation (45.7%) and nervous system (20.5%) related AEs, respectively.

Drugs associated with interruption

Among the drugs associated with temporary and permanent interruptions, bedaquiline was the most common temporarily interrupted drug (8.7%), the mean duration of stoppage being 5.4 days. Linezolid was the most common permanently stopped drug (5%).

Effect of interruption on interim treatment outcome and mortality

After excluding 17 LTFU patients for interim outcome analysis, the interim successful outcome among non-interrupters and interrupters at the end of six months of treatment were 86.8% and 81.2% respectively. However, the difference was not statistically significant (p = 0.260). 33 (12%) patients expired within six months of treatment initiation and more than half (57.6%) of these expired within first three months. As per the assessment by causality assessment committee of the institute none of the deaths was found to be causality related to AEs due to drugs. Also 22 (66.7%) patients among those who died were culture converted before death.

Discussion

This is the first observational study on treatment interruption patterns and various reasons for interruptions during the first six months of treatment among DR-TB patients from a TB endemic country who received a bedaquiline containing regimen under the national TB programme. This study also analyzed the frequency and severity of AEs due to anti-TB drugs in this cohort of patients.

The study observed that among the 275 patients, around one third of patients had treatment interruption episodes, in more than half of these patients the interruptions were temporary, and three-quarters of the interruptions were due to drug related AEs. The commonest drugs associated with temporary and permanent interruption episodes were bedaquiline (8.7%) and linezolid (5%), respectively. A retrospective study done by E. Sanchez-Padilla et al.[16] found drug related AEs (11.6%) and need for return to work (24.4%) as the main cause for interruptions.

Personal factors like busy schedule, lack of family support and no improvement with treatment were the major causes (94.1%) for interruption in LTFU group. More than half of the patients (59%) interrupted treatment due to no or slow response, as many of these patients had advanced disease at baseline. Every effort should be made to retrieve these

Table 4 Type of Adverse event associated with temporary and permanent interruption episodes.

AE type	No. of episodes	
	Temporary *n* (%)	Permanently stopped *n* (%)
QTcF prolongation	32 (45.7)	7 (17.9)
Electrolyte abnormalities	9 (12.9)	1 (2.6)
Gastrointestinal problems	4 (5.7)	3 (7.7)
Neurological problems	7(10)	8 (20.5)
Skin problems	0	1 (2.6)
Blood count abnormalities	8 (11.4)	7 (17.9)
Ophthalmological	3 (4.3)	5 (12.8)
Nephrotoxicity	1 (1.4)	3 (7.7)
Hearing abnormalities	6 (8.6)	1 (2.6)
Others[a]	0	3 (7.7)
Total	70 (100%)	39 (100%)

AE – Adverse Event; QTcF - QTc in resting ECG using Fridericia's formula.
[a] Drug allergy, bradycardia and hyperuricemia.

patients at the earliest and restart the treatment in timely manner. It is important that patients be actively counselled by treatment supporter on each visit to continue with the treatment.

In our study, no interruptions were observed due to service delivery and environmental related factors, thus highlighting the relatively good performance of PMDT services in study area. However, in a study by I. Zão et al.[17] healthcare system related factors were one of the reasons for delay in diagnosis and management of TB patients although less common than patient related factors.

In our study, QTc prolongation was more frequent than reported in bedaquiline-treated patients in previous studies,[14,18–21] possibly because most patients (96.4%) received one or more additional QTc-prolonging drugs such as moxifloxacin (high dose) (43.2%), clofazimine (88%) or delamanid (17.1%). However, majority of the events were associated with dyselectrolytemia and once corrected, bedaquiline could be reintroduced in the majority of patients. Although bedaquiline was associated with temporary treatment interruptions in around 8.7% of patients, it required permanent discontinuation in only 2.9% of patients, indicating bedaquiline may have good safety profile. However, a retrospective study by Lorenzo Guglielmetti et al.[22] found that bedaquiline was permanently discontinued in 6.7% patients due to QTc prolongation.

In our study, linezolid required permanent discontinuation in 5% patients out of total 260 patients who received linezolid in their regimen. These observations are similar to studies by N. Ahmad et al.,[23] Z. Lan et al.[24] and R. Singla et al.[25] which found that linezolid was associated with SAEs more often compared to other drugs used in the treatment regimen. Anemia was the significant SAE responsible for permanent interruption of linezolid in our study, similar to findings in systematic review and meta-analysis done by G. Sotgiu et al.[26] Therapeutic drug monitoring can be utilized to measure drug levels in patients receiving long term linezolid therapy.

There are concerns regarding the use of bedaquiline and delamanid together in patients having extensive level of drug resistance beyond XDR-TB because of increased propensity for cardiotoxicity. Delamanid was used as one of companion drugs in 17% of such patients in our study, but it required permanent discontinuation in only two patients. This indicates that the addition of delamanid to bedaquiline containing regimen may not lead to significant increase in SAEs. Efficacy of this combination could not be evaluated in this study.

In India as per PMDT guidelines, patients on bedaquiline containing regimen need to be more closely monitored during first two weeks of treatment.[10] However, it was observed that almost 80% of interruptions were reported after second week of treatment initiation and these interruptions were mainly due to drug related AEs. Hence, all patients on bedaquiline containing regimen need intense monitoring by the treatment supporters during follow up even after two weeks of treatment. Directly observed treatment (DOT) improves adherence to TB treatment by identifying AEs earlier and manages them appropriately. In a systematic review and meta-analysis by Toczek et al.[27] lower default rates for drug-resistant TB were seen with DOT.

Twelve percent of the patients expired within six months of treatment initiation which was very similar to the studies done by Sergey E. Borisov et al.[28] (13.4%) and Kathryn Schnippel et al.[29] (12.6%). The India TB report 2019, at national level, also shows a death rate of 14%.[30] Mortality is higher in patients with advanced or disseminated forms of TB and as found by L. Meira et al[31] in their study that 36% of patients who died in first six months of TB treatment had disseminated disease. Similarly, poor general condition and severe form of disease were the main cause for mortality rather than treatment failure in patients who died, thus indicating the good efficacy of these drugs.

The interim successful outcome was 80% at the end of six months of treatment. These results are far better than the previously reported successful outcomes among the severe forms of DR—TB patients treated with conventional regimens in India.[32] This may indicate that bedaquiline added to a background regimen can improve the rate of successful outcome among severe DR—TB patients. The successful outcome was higher in patients among non-interrupters group, although it was not statistically significant.

The strengths of this study are that this is the first study analyzing various reasons of treatment interruptions in the first six months of treatment of bedaquiline containing regimens especially in high TB burden countries, like India, under programmatic conditions. Secondly the safety profile and QTc prolongation effect of bedaquiline given along with other QTc prolonging drugs in a large number of patients was also analyzed. This study also had significant number of patients on bedaquiline with delamanid combination, with or without other QTc prolonging drugs, and showed a reassuring safety profile when used together as part of a multi-drug regimen.

There were some limitations of this study. The patients in this study cohort represented most patients with severe disease with extensive drug resistance pattern. Extrapolation of results to other MDR-TB patients without extensive disease, and extensive resistance patterns may not be appropriate.

To conclude, the study observed that drug related AEs and personal factors are the most important risk factors associated with treatment interruptions. Hence, it is important to identify AEs earlier and manage them appropriately. Although, the treatment outcome among non-interrupters was better, it was not statistically significant. Hence, larger studies may be required to evaluate this.

Conflict of interest

None.

Author contribution

Rupak Singla and Sekar Natarajan conceived this study and supervised all aspects of its implementation. Neeta Singla and Jose A. Caminero collaborated in the inception of the study. Amartya Chakraborty carried out the analysis of the data. Amitesh Gupta and Vikas Kumar collected the data and collaborated in the analysis. All the authors contributed to the interpretation of the results and the proof reading of the manuscript.

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ORIGINAL ARTICLE

Impact of the COVID-19 pandemic on tuberculosis services

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Diagnostic delay

Abstract
Background: In Portugal, Outpatient Tuberculosis Centres (OTBC) are responsible for the diagnosis, treatment, screening and prevention of tuberculosis (TB), and only severe or resistant cases are hospitalized.
Aim: To understand how infection control norms and standards were applied and how these centres responded during the pandemic.
Method: We sent an electronic questionnaire to all coordinators of OTBC. The questionnaire included questions on infection control during the COVID-19 pandemic and evaluation of the functioning of the OTBC in two periods: during the 1st National State of Emergency and after 1 year.
Results: Thirty-two responses were obtained (52.5%). The infection control norms were globally applied; diagnosis, treatment, and prevention were kept, and contact screening was only affected during the 1st State of Emergency. However, half of the respondents (53.1%) believed that there were diagnostic delays during the 1st State of Emergency, rising to 68.8% after 1 year. Only 31.3% performed Directly Observed Therapy (DOT) in all patients during the 1st State of Emergency, and 59.4% after 1 year. Half the inquiries expected an increase in TB incidence in the near future.
Conclusion: The pandemic affected OTBC functioning, although the services were kept open; diagnostic delay and DOT appliance were the most affected.

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Introduction

Since the beginning of 2020, the coronavirus disease 2019 (COVID-19) pandemic has caused a significant disruption in all areas of healthcare worldwide.[1—3] The functioning and response of many health services, including tuberculosis (TB) services, were profoundly affected by the policies adopted to respond to the pandemic, such as country lockdowns, reallocation of health professionals, materials, and diagnostic tools, and reduction of outpatient care.[4—8]

Hence, it is not surprising that several studies, carried in high-burden countries for TB, report a significant decrease in TB detection and notifications in the first months of the pandemic.[9—11] Following this, a modelling analysis from Glaziou[12] and the "Stop TB Partnership"[13] predicted, for a 3-month lockdown period, an annual increase in TB deaths between 200,000 — 400,000, raising the total deaths to ~1.6 — 1.8 million, numbers comparable to the ones seen between 2012 and 2015.[12,13]

Low-burden countries for TB also report significant changes in TB detection and patient care. A study carried out in Spain compared data from March-June in 2019 and 2020, and described an increase in latent and active TB in children of patient households (5.3% *vs* 7.7% in 2019 and 2020, respectively, $p < 0.001$); additionally, patients with the active disease diagnosed during the pandemic showed more severe manifestations.[14]

In a worldwide study by the Global Tuberculosis Network, a significant decline in detection of TB (and multidrug-resistant TB) cases and TB infection was observed, with an increase in telehealth consultations.[2]

Although much was written on the impact of COVID-19 on TB services and workplace safety resulting from infection control practices, not much is known on this,[15,16] and country-specific analyses are not available.

In Portugal, before the pandemic, there was a downward trend in the incidence and notification rate of TB over the last 10 years.[17] Between 2015 and 2019, there was a 24.6% decrease in the notification rate, placing it at 17.2 cases per 100 thousand inhabitants in 2019, with an estimated incidence rate of 19.0 cases per 100 thousand inhabitants.[18] The National Tuberculosis Program is responsible for the monitoring and surveillance of TB; implementing control and elimination strategies, action plans, and protocols for the management of the disease.[19]

The diagnosis, screening, treatment, and follow-up of individual patients are performed at Outpatient TB Centres (OTBC), overseen by the National Tuberculosis Program. Aguiar *et al.*[20] already described the adaptions made by one Portuguese OTBC during the pandemic, like the establishment of teleconsultations for individuals with presumptive TB, or the improvement of digital connectivity solutions between professionals. Still, different OTBC may have faced other problems and opted for different strategies - considering the panorama of the disease being different in the subregions of the country.[21,22]

Through the Directorate-General of Health, the Portuguese Government has published several norms and orientations regarding infection control in healthcare units during the pandemic.[23—25] Those included: the provision of a surgical mask (if the user does not have his/her mask) and provision of sanitizing solution at entrance to clinic, as well as FFP2 masks and individual protection equipment to healthcare professionals; the need to keep a safe distance from other people; frequent surface washing and disinfection; the creation and regular update of a COVID-19 Contingency Plan made known to all professionals.[23—26]

In this study, we aimed to: understand how the different national OTBC have adjusted to comply with the above infection control norms and standards; to perceive the OTBC's coordinators' perception regarding their centres' responsiveness to the restrictive measures and adjustments during the pandemic and its impact on tuberculosis diagnosis, treatment, and screening. Finally, we aimed to compare the Portuguese experience with that of other countries.[27]

Methods

Study design and study population

We conducted a cross-sectional study using an electronic online questionnaire created in Google Forms. A pilot survey was performed in two OTBC to assess the questionnaire's relevance and understandability, and the final version was sent via e-mail to all OTBC's coordinators. The National Tuberculosis Program provided the list with the coordinator's electronic addresses. Responses were collected during March and April 2021. Participation was entirely voluntary, and the anonymity of the participants was ensured.

Ethical approval

Ethical approval was obtained from the Ethics Committee of the Institute of Public Health of the University of Porto on September 19, 2020 (reference CE20170).

According to the Ethical Principles for Medical Research involving human subjects expressed in the Declaration of Helsinki and the current national legislation, all participants are asked to give their informed consent. Furthermore, because this was an online survey, participants had to choose "*I accept to participate*" to continue with the questionnaire.

Data collection

An online questionnaire was prepared. The questionnaire consisted of 32 questions, divided into three sections. The first part contained 4 demographic questions: age, sex, profession, and workplace. To guarantee the anonymity of the responders and further explore possible asymmetries between regions, workplaces were grouped into Regional

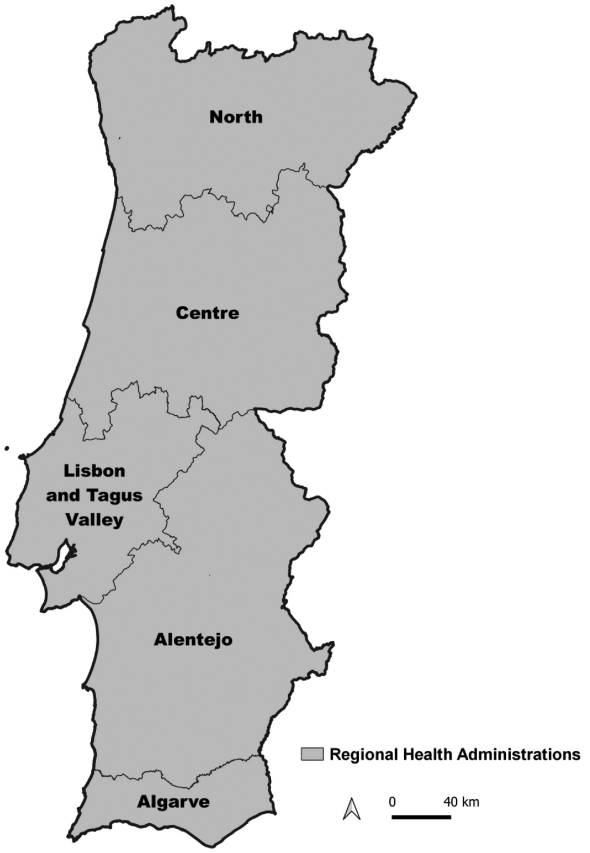

Fig. 1 Map of Portugal's Region Health Administrations.

Health Administrations: North, Centre, Lisbon and Tagus Valley, Alentejo, and Algarve (Fig. 1).

The second part (8 questions) addressed infection control measures during the pandemic, namely the provision of alcoholic solutions and masks to professionals and patients; the existence of personal protective equipment; the correct disinfection of places and surfaces; and the existence of a contingency plan, in accordance with the norms of the Directorate-General of Health.[11-12]

Finally, the third section (20 questions) aimed to evaluate the functioning of the OTBC in two distinct periods: during the 1st State of Emergency (an exceptional national state, declared by the President of the Republic, that took place from March 18, 2020, to May 2, 2020, in which a set of measures like partial suspension of rights, freedoms, and guarantees of citizens took place, in order to face a possible public calamity), and at the date in which participant answered to the questionnaire (1 year after the 1st State of Emergency). The questions addressed the following topics: consultation and teleconsultation; patient's resource to the OTBC; delays in the diagnosis of active disease; follow-up and treatment of patients with active or latent disease; screening of contacts of patients with active disease; screening of patients' candidate for biological therapy; and management of directly observed therapy (DOT).

Questions were mostly closed (e.g., yes/no), but contained an "*other*" option where inquires could justify their answers, when appropriate. The last question was completely open, and responders were free to share their final comments.

Comparison with other countries

The results of the survey were compared with the findings of a recent Global Tuberculosis Network study.[2]

Results

Thirty-two OTBC coordinators accepted to answer the questionnaire, from a total of 61 (52.5% response rate). The Regional Health Administrations most represented were Alentejo and Algarve, with a 66.7% response rate each. Two locations were kept undisclosed (one didn't answer, and the other was not revealed to protect the anonymity of the responder). OTBC coordinator's characteristics and response rate by region are summarised in Table 1.

Hygiene and safety measures

Answers concerning hygiene and safety measures during the pandemic are summarised in Table 2. Surgical masks and alcohol sanitizing solution were provided to healthcare professionals in all OTBC, but FFP2 masks were not supplied in 2 centres. Also, in 2 centres, patients were not routinely provided with surgical masks or sanitizing solution. Disinfection of common areas was carried out, at least once a day, in all OTBC except one.

In 83.9% of all OTBC, there was a contingency plan for managing cases with suspected or confirmed SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2). The majority (81.3%) considered that their OTBC complied with the safety standards established by the Directorate-General of Health.

Functioning of the outpatient TB centres

Comparing the functioning of the OTBC during the 1st State of Emergency and after 1 year (Table 3), responders stated that those consultations (face-to-face and/or by telephone)

Table 1 Outpatient Tuberculosis Centres coordinator's characteristics and response rate by region.

OTBC coordinator's characteristics	n (%)
Male	14 (43.8)
Mean age (years)	55.8
Profession	
Pulmonologist	11 (34.4)
General Practitioner	11 (34.4)
Other Medical Speciality	4 (12.5)
Nurse	6 (15.6)
OTBC response rate	n/total (%)
RHA North	12/21 (57.1)
RHA Centre	2/11 (18.2)
RHA LTV	6/12 (50.0)
RHA Alentejo	4/6 (66.7)
RHA Algarve	6/9 (66.7)
Other*	2
Total	32/61 (52.5)

* Undisclosed location
LTV: Lisbon and Tagus Valley; OTBC: Outpatient Tuberculosis Centres; RHA: Region Health Administration

Table 2 Compliance to hygiene and safety measures during the pandemic. Results are presented as relative frequencies (%).

Question	RHA North			RHA Centre			RHA LTV			RHA Alentejo			RHA Algarve			Others*			Total		
Are surgical masks and alcoholic solution (SABA) provided to healthcare professionals?	Yes	No		Yes	No		Yes	No		Yes	No		Yes	No		Yes	No		Yes	No	
	100	0		100	0		100	0		100	0		100	0		100	0		100	0	
Are FFP2 protective masks provided to healthcare professionals?	Yes	No		Yes	No		Yes	No		Yes	No		Yes	No		Yes	No		Yes	No	
	100	0		100	0		100	0		75	25		83.3	16.7		100	0		93.7	6.3	
Are surgical masks provided to patients who do not have them, as well as SABA?	Yes	No		Yes	No		Yes	No		Yes	No		Yes	No		Yes	No		Yes	No	
	100	0		50	50		100	0		75	25		100	0		100	0		93.7	6.3	
Is a safe distance between patients in the waiting room guaranteed?	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell
	100	0	0	100	0	0	100	0	0	50	0	50	100	0	0	100	0	0	93.7	0	6.3
Is there a contingency plan for the management of cases with suspected or confirmed diagnosis of SARS CoV-2?	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell
	91.7	0	8.3	50	50	0	83.3	16.7	0	66.7	33.3	0	83.3	0	16.7	100	0	0	83.9	9.7	6.4
Is there personal protective equipment available if needed?	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell
	100	0	0	100	0	0	66.7	16.7	16.7	100	0	0	66.7	0	33.3	100	0	0	87.5	3.1	9.4
Is disinfection carried out, at least once a day, in all areas?	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell
	100	0	0	100	0	0	100	0	0	100	0	0	83.3	0	16.7	100	0	0	96.9	0	3.1
Do you consider that your OTBC complies with the standards established by the DGH during the pandemic?	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell	Yes	No	Can't tell
	100	0	0	100	0	0	66.7	16.7	16.7	50	50	0	66.7	33.3	0	100	0	0	81.3	15.6	3.1

* Undisclosed location

DGH: Directorate-General of Health LTV: Lisbon and Tagus Valley; OTBC: Outpatient Tuberculosis Centres; RHA: Region Health Administration

Table 3 Functioning of the Outpatient Tuberculosis Centres during the 1st State of Emergency (SE) and at the current date. Results are presented as relative frequencies (%).

Question	RHA North				RHA Centre				RHA LTV				RHA Alentejo			
During the 1st State of Emergency, were there telephoneor face-to-face consultations?	Yes		No		Yes		No		Yes		No		Yes		No	
	100		0		100		0		83.3		16.7		100		0	
Currently, are there telephoneor face-to-face consultations?	Yes		No		Yes		No		Yes		No		Yes		No	
	100		0		100		0		100		0		100		0	
Are there limitations in the number of consultations carried out daily?	Yes		No		Yes		No		Yes		No		Yes		No	
	58.3		41.7		50		50		66.7		33.3		50		50	
Are there delays in the scheduling of new appointments?	Yes		No		Yes		No		Yes		No		Yes		No	
	16.7		83.3		0		100		0		100		0		100	
During the 1st State of Emergency, did patients resortedless to OTBC?	Yes		No		Yes		No		Yes		No		Yes		No	
	75		25		50		50		50		50		50		50	
Currently, do patients resort less to OTBC?	Yes		No		Yes		No		Yes		No		Yes		No	
	66.7		33.3		50		50		33.3		66.7		50		50	
During the 1st State of Emergency, were there delays in the diagnosis of active TB?	Yes	No	Maybe		Yes	No	Maybe		Yes	No	Maybe		Yes	No	Maybe	
	58.3	41.7	0		0	50	50		83.3	16.7	0		25	75	0	
Currently, are there delays in the diagnosis of active TB?	Yes	No	Maybe		Yes	No	Maybe		Yes	No	Maybe		Yes	No	Maybe	
	83.3	16.7	0		50	50	0		83.3	16.7	0		75	25	0	
During the 1st State of Emergency, did some patients not have the proper follow-up?	Yes		No		Yes		No		Yes		No		Yes		No	
	16.7		83.3		50		50		16.7		83.3		25		75	
Currently, do some patients not have the adequate follow-up?	Yes		No		Yes		No		Yes		No		Yes		No	
	16.7		83.3		0		100		16.7		83.3		25		75	
During the 1st State of Emergency, were the screenings of contacts of patients with active TB carried out in the appropriate time?	Yes		No		Yes		No		Yes		No		Yes		No	
	50		50		0		100		60		30		50		50	
Currently, are the screenings of contacts of patients with active TB carried out in the appropriate time?	Yes		No		Yes		No		Yes		No		Yes		No	
	91.7		8.3		100		0		80		20		75		25	
During the 1st State of Emergency, were screenings of patients who are candidates for biological therapy carried out?	Yes (all)	Yes (HR)[1]	No		Yes (all)	Yes (HR)[1]	No		Yes (all)	Yes (HR)[1]	No		Yes (all)	Yes (HR)[1]	No	
	75	16.7	8.3		50	50	0		66.7	16.7	16.7		75	25	0	
Currently, are screenings carried out on patients who are candidates for biological therapy?	Yes (all)	Yes (HR)[1]	No		Yes (all)	Yes (HR)[1]	No		Yes (all)	Yes (HR)[1]	No		Yes (all)	Yes (HR)[1]	No	
	100	0	0		50	50	0		100	0	0		75	25	0	
During the 1st ES, did you initiate treatments for latent TB?	Yes		No		Yes		No		Yes		No		Yes		No	
	100		0		100		0		83.3		16.7		100		0	
Currently, do you initiate treatments for latent TB?	Yes		No		Yes		No		Yes		No		Yes		No	
	100		0		100		0		100		0		100		0	
During the 1st ES, was DOT used in patients with active TB?	Yes (all)	Yes (HR)[1]	No	Other[2]	Yes (all)	Yes (HR)[1]	No	Other[2]	Yes (all)	Yes (HR)[1]	No	Other[2]	Yes (all)	Yes (HR)[1]	No	**Other[2]**
	41.7	16.7	0	41.7	50	0	50	0	0	33.3	33.3	33.3	50	25	25	0
Currently, is DOT used in patients with active TB?	Yes (all)	Yes (HR)[1]	No	Other[2]	Yes (all)	Yes (HR)[1]	No	Other[2]	Yes (all)	Yes (HR)[1]	No	Other[2]	Yes (all)	Yes (HR)[1]	No	Other[2]
	75	0	0	25	100	0	0	0	16.7	33.3	33.3	16.7	75	25	0	0
Do you believe the pandemic will have an impact on the incidence of TB (rise/drop)?	Yes (rise)	Yes (drop)	No	Other[2]	Yes (rise)	Yes (drop)	No	Other[2]	Yes (rise)	Yes (drop)	No	Other[2]	Yes (rise)	Yes (drop)	No	Other[2]
	58.3	16.7	8.3	16.7	0	50	0	50	50	16.7	0	33.3	50	25	0	25

Table 3 (*Continued*)

Question	RHA Algarve				Others*				Total			
During the 1st State of Emergency, were there telephoneor face-to-face consultations?	Yes	No			Yes	No			Yes	No		
	100	0			100	0			96.9	3.1		
Currently, are there telephoneor face-to-face consultations?	Yes	No			Yes	No			Yes	No		
	100	0			100	0			100	0		
Are there limitations in the number of consultations carried out daily?	Yes	No			Yes	No			Yes	No		
	50	50			100	0			59.4	40.6		
Are there delays in the scheduling of new appointments?	Yes	No			Yes	No			Yes	No		
	0	100			0	100			93.7	6.3		
During the 1st State of Emergency, did patients resortedless to OTBC?	Yes	No			Yes	No			Yes	No		
	66.7	33.3			100	0			64.5	35.5		
Currently, do patients resort less to OTBC?	Yes	No			Yes	No			Yes	No		
	83.3	16.7			50	50			64.5	35.5		
During the 1st State of Emergency, were there delays in the diagnosis of active TB?	Yes	No	Maybe		Yes	No	Maybe		Yes	No	Maybe	
	50	50	%		0	100	0		50	46.9	3.1	
Currently, are there delays in the diagnosis of active TB?	Yes	No	Maybe		Yes	No	Maybe		Yes	No	Maybe	
	33.3	66.7	0		50	50	0	68.8	31.2	0		
During the 1st State of Emergency, did some patients not have the proper follow-up?	Yes	No			Yes	No			Yes	No		
	33.3	66.7			0	100			21.9	78.1		
Currently, do some patients not have the adequate follow-up?	Yes	No			Yes	No			Yes	No		
	16.7	83.3			0	100			15.6	84.4		
During the 1st State of Emergency, were the screenings of contacts of patients with active TB carried out in the appropriate time?	Yes	No			Yes	No			Yes	No		
	66.7	33.3			100	0			58.1	41.9		
Currently, are the screenings of contacts of patients with active TB carried out in the appropriate time?	Yes	No			Yes	No			Yes	No		
	100	0			100	0			90.3	9.7		
During the 1st State of Emergency, were screenings of patients who are candidates for biological therapy carried out?	Yes (all)	Yes (HR)[1]	No		Yes (all)	Yes (HR)[1]	No		Yes (all)	Yes (HR)[1]	No	
	83.3	16.7	0		50	50	0		71.9	21.9	6.2	
Currently, are screenings carried out on patients who are candidates for biological therapy?	Yes (all)	Yes (HR)[1]	No		Yes (all)	Yes (HR)[1]	No		Yes (all)	Yes (HR)[1]	No	
	100	0	0		100	0	0		93.8	6.2	0	
During the 1st ES, did you initiate treatments for latent TB?	Yes	No			Yes	No			Yes	No		
	100	0			100	0			96.9	3.1		
Currently, do you initiate treatments for latent TB?	Yes	No			Yes	No			Yes	No		
	100	0			100	0			100	0		
During the 1st ES, was DOT used in patients with active TB?	Yes (all)	Yes (HR)[1]	No	Other[2]	Yes (all)	Yes (HR)[1]	No	Other[2]	Yes (all)	Yes (HR)[1]	No	Other[2]
	16.7	33.3	33.3	16.7	50	50	0	0	31.3	25	18.7	25
Currently, is DOT used in patients with active TB?	Yes (all)	Yes (HR)[1]	No	Other[2]	Yes (all)	Yes (HR)[1]	No	Other[2]	Yes (all)	Yes (HR)[1]	No	Other[2]
	33.3	16.7	33.3	16.7	100	0	0	0	59.4	12.5	12.5	15.6
Do you believe the pandemic will have an impact on the incidence of TB (rise/drop)?	Yes (rise)	Yes (drop)	No	Other[2]	Yes (rise)	Yes (drop)	No	Other[2]	Yes (rise)	Yes (drop)	No	Other[2]
	50	16.7	33.3	0	50	0	50	0	50	18.8	12.5	18.8

* Undisclosed location

[1] Was only carried in high-risk patients

[2] DOT only at certain days of the week, supervised by phone-calls, or supervised by a family member

DOT: Directly Observed Therapy; HR: High-risk; LTV: Lisbon and Tagus Valley; OTBC: Outpatient Tuberculosis Centres; RHA: Region Health Administration; TB: Tuberculosis; SE: State of Emergency

were maintained in both periods (except during the 1st State of Emergency). Almost 60% reported limitations in the number of consultations carried out daily, although only 6.3% referred to delaysinschedulingnewappointments.

More than two-thirds of the respondents considered that, in both periods, there were fewer outpatient visits to the OTBC; three coordinators suggested that this was due to a decrease in referral by other health units. In addition, half of the respondents believed that there were delays in diagnosing active disease in the 1st State of Emergency, increasing to 68.8% after 1 year. Once again, two coordinators referred to delays in referrals from other health units as a possible cause. Regarding patient follow-up, 21.9% considered that it was insufficient during the 1st State of Emergency, in contrast to 15.6% after 1 year. One inquiry mentioned a reduction in DOT, and another delay in referrals, as plausible explanations.

The use of DOT across the different centres varied. During the 1st State of Emergency, only 31.3% reported using DOT with all patients (either face-to-face or video call); 25% report using it only in high-risk patients; 25% used it 1-3 days of the week, via phone call, or with the help of family member; and 18.7% did not use DOT at all. Three responders point to the lack of human resources as the justification for these results. After 1 year, DOT use in all patients increased to 59.4%, but 15.9% continued to report not using DOT in any patient. It is important to highlight that the National Tuberculosis Program recommends DOT in all cases of TB.[28]

Contact screening for risk individuals was not performed routinely in 41.9% of OTBC during the 1st State of Emergency, decreasing to 9.7% after 1 year; two coordinators mentioned imagological and laboratory delays during the 1st State of Emergency. Screening of high-risk patients who were candidates for biological therapy was carried out in all centres except 2 during the 1st State of Emergency, and in all centres after 1 year. Treatment for latent tuberculosis was carried out in all but one centre during the 1st State of Emergency, and by all centres after 1 year.

Half of the responders believed the pandemic will lead to an increased incidence of TB in Portugal in the near future. On the final question, the following problems were raised: the occupation of the OTBC installations by other services; patients missing their appointments more often since the beginning of the pandemic; fear of the effect of immunosuppression used to treat COVID-19 patients in TB epidemic and severity of the disease; patients fears about to recourse to health units; lack of cameras to make video calls; and delays in patient's referral from primary care units.

Discussion

Overall, there were no apparent asymmetries between Portuguese Regional Health Administrations. However, there were some irregularities in particular areas: one region changed OTBC practice during the 1st State of Emergency, and two had difficulties related to the disposable masks. Regarding the latter, the inquires did not clarify if this happened at the beginning or throughout the pandemic, but several newspapers reported a lack of provision of masks at various health facilities at the onset of the pandemic, particularly in primary care units;[29,30] additionally, there were also reports of mask thefts in some units.[31] Nevertheless, most OTBC complied with the norms established by the Directorate-General of Health regarding hygiene and safety measures. It should be noted that mask use and hand hygiene was mandatory not only in Portugal, but in most countries worldwide.[27]

Nearly all were able to maintain treatments for latent TB and screenings of high-risk patients' candidates for biological therapy. Contact tracing and screening were negatively impacted during the 1st State of Emergency, but significantly improved after one year. Conversely, a worrisome percentage of coordinators mentioned delays in diagnosing active disease and not using DOT in both periods. There was an overall decrease in the number of patients seeking or referred to the OTBC.

The management of latent TB varied between different countries. The Global Tuberculosis Network study reports a decrease in newly diagnosed TB infections in 2020, comparing with 2019 (363 $\pm$ 51 per month in 2019 versus 248 $\pm$ 76 per month in 2020; p = 0.0007).[2] Similarly, Migliori *et al.*[1] conducted a study carried in 33 centres from 16 different countries that evaluated the volume of TB-related healthcare activities in the first 4 months of the pandemic (during national lockdowns), and compared it to the same period in 2019. Most centres reported reductions in newly diagnosed cases of active and latent TB and in total active and latent TB outpatient visits; they explained, furthermore, that some centres didn't consider latent TB a high priority during the pandemic.[1] In England, the latent TB program was paused in response to the pandemic,[32] and in China, many TB-directed services were closed and reorganized into COVID-19 centres, and presumptive TB patients could not seek medical assistance due to movement restrictions.[33] This contrasts with what happened in Portugal: OTBC were kept open, latent TB screening and treatments continued throughout the pandemic, and mobility for health reasons was permitted.

Contact tracing was compromised during the 1st State of Emergency in 41.9% of the OTBC. In comparison Aznar *et al.*[14] investigated 13 Spanish centres during the same period and reported slightly worse results, with 53.8% of centres reporting changes in contact screening programs. Additionally, follow-up of patients was either cancelled or delayed by 76.9%. In our study, only 21.9% considered that patient follow-up was inadequate during 1st State of Emergency. It should also be noted that both contact tracing and patient follow-up improved significantly after 1 year.

Overall, fewer patients accessed the OTBC, which matches what is described in published literature.[1,5,14,15,33] Lower referrals from primary care units and patient's fear of contracting the disease were referred to as possible causes. The Regulatory Authority for Health report confirmed that the number of face-to-face appointments in primary care units in Portugal decreased substantially during the 1st State of Emergency (33%, 73%, and 66% during March, April, and May 2020, respectively)[34]. On the other hand, patient fear was often interpreted as the general decrease in healthcare service's use.[1,33,35] Other plausible reasons for this reduction include movement restrictions, enforced isolation measures, and widespread discouragement to seek medical care in health facilities if only mild symptoms were present.[1,5]

TB diagnostic delays were described in both periods. The reduction of diagnostic and treatment delay is a priority to the National Tuberculosis Program,[17] so changes need to be made to reverse this outcome. It is important to note, however, that other countries faced the same problem[10,14,33,36] The Global Tuberculosis Network study reports a significant decline in newly diagnosed TB disease in outpatient clinics (613 $\pm$ 57 per month in 2019 versus 475 $\pm$ 90 per month in 2020; p = 0.0005) and in drug-resistant TB disease (393 $\pm$ 31 per month in 2019 versus 127 $\pm$ 32 per month in 2020; p $<$ 0.001), despite the significant increase of telehealth activities in 2020.[2] Narita *et al*.[37] described the stories of three patients in the United States of America with TB diagnosis delays: one had risk factors for TB and had to wait a month to get chest radiography; the second was tested 13 times for SARS-CoV-2 before her TB diagnosis; and the third had a chest radiograph that revealed right-upper-lobe opacities without cavities, so TB was not considered until 2 months later when her symptoms and chest radiography got worse.[37] Additionally, they interviewed 29 TB patients diagnosed in March 2020 or later: 4 reported delays in their TB diagnosis because of issues related to the pandemic, and 3 did not seek immediate care because of fear of contracting COVID-19. Overall, it seems that delays in active TB diagnosis are a result of multiple factors: patient's fear of seeking care, referral delays, the insufficient response of health and diagnostic units, and incorrect diagnoses due to the similarities between TB and COVID in terms of signs, symptoms, and chest radiography findings.[38] More awareness of TB should be sought during the pandemic, and emphasis placed on active case finding and fast referral.

The use of DOT was significantly affected in both periods, even though the National Tuberculosis Program recommends its use in all patients with active disease.[28] So far, not many studies have addressed the use of DOT during the pandemic. Zimmer *et al*.[39] surveyed 845 TB stakeholders (TB patients, healthcare workers, national TB program and policy officers, TB researchers, and TB civil societies, advocates, and survivors) from Europe, Africa, Asia, and America. About 70% of healthcare workers and program and policy officers reported a reduction in TB patients receiving DOT since the pandemic. Some factors that may have contributed to these findings have already been mentioned: lockdown measures and restriction in local public transportation services, restriction of liberties, fear of COVID-19 (which was reported by 55% of all surveyed participants with active TB), and stigmatization.[39] In our survey, the lack of material and human resources was the main reason for the lack of DOT use. Hiring more staff for centres struggling to use DOT is a possible solution but may not be feasible during the pandemic. Another option is the acquisition of cameras for more widespread use of Video Observed Therapy, which seems to be as effective as DOT.[40]

Our study has some limitations that needed to be highlighted. First, the response rate was not homogeneous across all Regional Health Administrations, which limits our comparisons between different regions. Still, we consider a 52.5% response rate to be fairly representative of the national panorama. Secondly, variables concerning the 1st State of Emergency were collected retrospectively.

Apart from this, some strengths should be highlighted. This is, as far as we know, the first national study being conducted on this theme; we achieved a significant participation rate in the regions with the highest incidence of TB and highest number of OTBC. The accuracy of findings allows us to discuss the example of Portugal in comparison with recent multi-country studies published by the Global Tuberculosis Network.

Conclusions

Overall, most OTBC's were able to follow the set of norms published by the Directorate-General of Health and maintain diagnostic, treatment, screening and prevention of TB during the pandemic, which contributed to protecting Portugal from the worse consequences of the subsequent waves of the COVD-19 pandemic. Nevertheless, attention should be given to enhance COVID-19 prevention (by encouraging anti-COVID-19 vaccination) and, specifically for TB, to reduce diagnostic delay and barriers to DOT implementation.

Authors' contributions

IR and RD formulated the initial research questions and study methodology. IR and RD contributed to refining the research and study methodology. IR was responsible for data analysis. All authors were involved in data interpretation. IR wrote the first draft of the paper. AA, RD and GBM reviewed the document. All authors provided inputs on and approved the final version of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest to declare.

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LETTER TO THE EDITOR

Can the post-COVID-19 functional status scale discriminate between patients with different levels of fatigue, quality of life and functional performance?

Remarkable mortality and increasing reports of prolonged morbidity have been observed worldwide since the beginning of the coronavirus disease 2019 (COVID-19) pandemic.[1] Hundreds of thousands of individuals have managed to recover from the disease,[2] and functional and psychological sequelae in these people have been described in the literature.[3] The Post-COVID-19 Functional Status (PCFS) is a simple and rapid self-report scale that allows monitoring of the functional impact of the disease, adding value beyond binary outcomes such as mortality.[3] The PCFS was recently validated by Machado et al.,[4] who demonstrated its construct validity in a large sample of adults with confirmed or presumed COVID-19. However, so far it is unknown whether this scale is able to discriminate between patients with different characteristics. The aim of the present study was, at the time of hospital discharge following acute recovery from a SARS-CoV-2 infection, to compare fatigue, health-related quality of life (HRQoL) and functional performance between people classified according to the different grades of the PCFS scale. Moreover, predictors of poor functional status were investigated.

This was a cross-sectional study carried out in two Brazilian hospitals; one in Fortaleza-CE and the other in Brasília-DF, after recruiting convenience samples. The study was conducted partially following the protocol for the Life AFTER covid-19 (LATER-19) study (from Australia).[5] Inclusion criteria were: individuals over 18 years of age admitted with a confirmed COVID-19 diagnosis and ability to provide informed consent. Individuals with pre-existing conditions that affected the assessment results were excluded (e.g. neuromuscular disorders, mental illness or if they had significant communication or cognitive impairment). All participants provided written informed consent. The study was approved by the Ethics Committees of the recruiting institutions (approval numbers: 4.105.468, 4.324.0069). Participants were recruited to the study between June 2020 and January 2021.

The following variables and outcomes were assessed in this study at the time of hospital discharge: sociodemographic, anthropometric, and clinical characteristics (including self-reported regular physical activity); fatigue symptoms via the Fatigue Severity Scale (FSS),[5] HRQoL via the EuroQol 5 dimensions — 5 response level (EQ-5D-5L),[5,6] and functional performance via the 1-minute sit-to-stand test (1STS).[7] Functional status after COVID-19 was assessed using the PCFS scale, which has four questions to classify each patient into one of five categories with different degrees of functional limitation.[3,4]

The Shapiro-Wilk test was used to assess the distribution of the data. The chi-square, one-way ANOVA or Kruskal-Wallis tests were used to compare outcomes across the PCFS groups. A logistic regression model with calculation of the odds ratio (OR) and 95% confidence intervals (95% CI) was undertaken to identify the predictors of poorer functional status at hospital discharge (i.e. PCFS grade 3-4). Variables related to the pre-hospitalization period and the hospital length of stay (LOS) were included in the univariate models, and those that reached $p<0.20$ were subsequently included in the multivariate model. The statistical program SPSS version 22.0 (IBM, Armonk, NY, USA) was used, and the significance level adopted was $p<0.05$.

One hundred and thirty-three individuals with a confirmed diagnosis of COVID-19 were included (75 from Fortaleza-CE and 58 from Brasília-DF). Table 1 shows the characteristics of the participants. The mean age was 60 ± 15 years, and they were on average overweight. The majority of the sample had at least one comorbidity, and the most prevalent comorbidities were hypertension (50%) and diabetes (23%). Due to the small number of individuals in each category of the PCFS, participants were divided in three PCFS scale grade groups: (i) grade 0 (no functional limitations), 27%; (ii) grade 1-2 (negligible or mild functional limitations), 50%; and (iii) grade 3-4 (moderate or severe functional limitations), 23%.

Table 2 shows the comparison of sex, age, body mass index (BMI), number of previous diseases, and hospital LOS across groups according to the PCFS scale. There was a greater proportion of males (66%) in the PCFS grade 1-2 group, and a greater LOS in the PCFS grade 3-4 group. Participants who had a PCFS grade 3-4 presented with more symptoms of fatigue, poorer HRQoL and worse functional performance than those with PCFS grade 0. In addition, participants with PCFS grade 1-2 reported poorer HRQoL than those with PCFS grade 0, and better functional performance than those with PCFS grade 3-4. The following variables

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Table 1 Sociodemographic, anthropometric and clinical characteristics, physical and psychological function of participants at hospital discharged following a COVID-19 hospitalization (n=133).

Characteristic	n	Value
Male sex, n (%)	133	75 (56)
Age, years	132	60 ± 15
BMI pre-hospitalization, kg/m^2	104	28.8 ± 4.4
Current smoker pre-hospitalization, n (%)	133	45 (34)
Regular physical activity pre-hospitalization, n (%)	128	41 (32)
Number of morbidities pre-hospitalization, n (%)	133	
0		39 (29)
1		54 (41)
2 or more		40 (30)
Morbidities pre-hospitalization, n (%)*	133	
Hypertension		67 (50)
Diabetes		31 (23)
ADL limitation pre-hospitalization, n (%)	133	14 (11)
COVID-19 symptoms pre-hospitalization, n (%)*	133	
Dyspnea/breathlessness		68 (51)
Fever		66 (50)
Cough		59 (44)
Adynamia/Asthenia/Myalgia		47 (35)
Headache		30 (23)
Ageusia		17 (13)
Hospital length of stay, days	133	8 ± 8
PCFS scale grade at discharge, n (%)	130	
0		35 (27)
1/2		65 (50)
3/4		30 (23)
Fatigue at discharge (FSS)	124	
Total mean score		4.2 ± 2.3
Relevant fatigue (≥4 points), n (%)		71 (57)
Quality of life at discharge (EQ-5D-5L)		
Index score	133	0.90 ± 0.15
VAS	118	77 ± 20
Functional performance at discharge (1STS test)		
Total number of repetitions	129	16 ± 6
Total number of repetitions, % predicted	101	59 ± 21
Subjects below the LLN, n (%)	101	54 (54)

Data presented as absolute (relative frequency) or mean ± standard deviation. BMI: body mass index; ADL: activities of daily living; COVID-19: coronavirus disease 2019; PCFS: post-COVID-19 functional status; FSS: fatigue severity scale; EQ-5D-5L: EuroQol 5 dimensions − five response level; VAS: visual analogue scale; 1STS: 1-minute sit-to-stand; LLN: lower limit of normal.

* Only conditions with a prevalence >10% were presented.

were identified as potential predictors of poorer functional status (i.e. PCFS 3-4) in univariate models: sex, physical activity status, diabetes before hospitalization, and hospital LOS. In the multivariate model, only the hospital LOS remained a statistically significant predictor (OR 1.17 [95% CI 1.07 − 1.27]).

This study showed that the PCFS scale is a simple and rapid self-report instrument which is valuable for discriminating between groups with various physical and psychological health outcomes. In addition, variables that could predict a poorer functional status and potentially, the need for rehabilitation at the time of hospital discharge, were identified.

Machado et al.[4] also compared the EQ-5D-5L scores and the intensity of fatigue symptoms between PCFS grades and observed similar results. However, functional performance was not investigated in their study.[4] Our study supports the validity of the PCFS scale by showing that individuals in higher PCFS grades showed a lower 1STS (expressed as % predicted) than those in lower grades. The fact that there was no significant difference in functional performance at discharge when assessed by the 1STS test total number of repetitions, but there was a significant difference when using the 1STS test % predicted, can be explained by the larger proportion of male subjects in the group of participants with PCFS grade 1/2. This larger proportion of males might have led to a greater number of 1STS repetitions in this group, which prevented the comparison of total number of repetitions to reach statistical significance. Another study suggests that the PCFS tracks responses to pulmonary rehabilitation, as six out of 10 patients with perceived restrictions due to COVID-19 at baseline showed no restrictions (i.e. PCFS 0) in the post-rehabilitation assessment.[8]

Table 2 Comparison of sociodemographic, anthropometric and clinical characteristics, physical and psychological function between Post-COVID-19 Functional Status scale grades in participants at hospital discharged following a COVID-19 hospitalization (n=133).

	PCFS grade 0 (n=35)	PCFS grade 1/2 (n=65)	PCFS grade 3/4 (n=30)	p value
Male sex, n (%)	16 (46)	43 (66)	13 (43)	0.046
Age, years	62 ± 14	58 ± 14	60 ± 16	0.431
BMI pre-hospitalization, kg/m^2	29.20 ± 5.97	29.38 ± 3.71	27.44 ± 3.96	0.194
Number of morbidities pre-hospitalization, n (%)				0.119
0	12 (34)	18 (28)	8 (27)	
1	8 (23)	32 (49)	13 (43)	
2 or more	15 (43)	15 (23)	9 (30)	
Hospital length of stay, days				
Fatigue at discharge (FSS)	6 ± 4	7 ± 4	15 ± 13†,‡	0.001
Total mean score	3.31 ± 2.21	4.34 ± 2.39	4.86 ± 1.86†	0.050
Quality of life at discharge (EQ-5D-5L)				
Index score	0.989 ± 0.025	0.906 ± 0.082†	0.795 ± 0.264†	<0.001
VAS	92 ± 13	75 ± 14†	67 ± 26†	<0.001
Functional performance at discharge (1STS test)				
Total number of repetitions	17 ± 6	17 ± 6	14 ± 7	0.091
Total number of repetitions, % predicted	65 ± 21	62 ± 22‡	48 ± 25†	0.018

Data presented as absolute (relative frequency) or mean ± standard deviation. COVID-19: coronavirus disease 2019; PCFS: post-COVID-19 functional status; BMI: Body mass index; FSS: fatigue severity scale; EQ-5D-5L: EuroQol 5 dimensions – five response level; VAS: visual analogue scale; 1STS: 1-minute sit-to-stand.

† $p \leq 0.05$ vs. PCFS grade 0.

‡ $p \leq 0.05$ vs. PCFS grade 3/4.

We also confirmed that LOS was the only predictor of a higher PCFS grade and reduced function at hospital discharge in a multivariate model. That is, our findings suggest that an increase of one day in hospital LOS is associated with a 17% increased risk of presenting with poor functional status at the time of hospital discharge. Our findings also reinforce the compounding influence of COVID-19 severity and detrimental impact of increasing duration of hospitalization on the patient's functional status, and further highlight the importance of applying preventive interventions such as early mobilization. The main limitations of this study are the cross-sectional design, which prevents a cause-and-effect analysis, the small sample size from only two centers, and the absence of a non-hospitalized group. Moreover, we were not able to characterize the sample regarding the type of treatment received during hospitalization (e.g. mechanical ventilation). Future studies including the repeated application of the PCFS after discharge are warranted to determine, define and compare the duration to functional recovery after COVID-19 and similar illnesses resulting in hospitalization.

In conclusion, the PCFS scale was demonstrated to be a discriminatory instrument for groups with measured varying degrees of fatigue, HRQoL, and functional performance. In addition, hospital LOS was the only predictor of a poorer functional status at hospital discharge.

Declaration of Competing Interest

None.

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LETTER TO THE EDITOR

Recovery of exercise capacity after COVID-19 pneumonia: Key role of right ventricular-pulmonary circulation unit

The role of pulmonary vasculature in exercise after COVID-19 pneumonia

Dear Editor

Cardiopulmonary exercise test (CPET), which is the gold standard for the evaluation of exercise capacity, combined with exercise Doppler echocardiography (EDE) allows to specifically explore the role of right ventricular-pulmonary circulation unit in the exercise limitation. We present here the data obtained through this technique during the follow-up evaluation of COVID-19 survivors.

We evaluated consecutive patients admitted to ASST Santi Paolo e Carlo (Milan, Italy) during the first wave of the pandemic that hit Italy in February-April 2020,[1] who attended the COVID-19 respiratory follow-up clinic between May and August 2020. Given the limited availability of CPET-EDE exams, due to the need of specific resources and time to perform it, we focused on patients recovering from pneumonia. Inclusion criteria considered were: 1) age >18 years, 2) previous molecular (Reverse Transcription — Polymerase Chain Reaction) diagnosis of SARS-CoV-2 infection, 3) a radiologically confirmed diagnosis of pneumonia. Exclusion criteria were the absence of a signed informed consent, acute respiratory exacerbation in the previous 4 weeks and the presence of medical conditions contraindicating CPET. The use of these data for research purposes was approved by Milan Area 1 Ethics Committee (2020/ST/407).

All patients underwent full lung function testing and chest computed tomography (CT) evaluation, as previously described.[2] Echocardiography at rest was performed according to current recommendations of the American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI).[3] Exercise doppler echocardiography measurements (Epic 5; Philips, Amsterdam, The Netherlands) were continuously obtained during the incremental exercise test on a semi recumbent cycle ergometer laterally tilted by 20—30° to the left. Left ventricular (LV) outflow tract diameter at rest was obtained. Exercise measured echocardiographic doppler parameters were: tricuspid annular plane systolic excursion (TAPSE), tricuspid regurgitant velocity (TRV), early mitral peak (E) and late wave (A) flow velocities, early (e′) diastolic velocities (by tissue Doppler imaging - TDI) at the septal and lateral corner of the mitral annulus. Through these parameters we obtained an estimation of cardiac output (CO) and systolic and mean pulmonary artery pressures (PASP and mPAP).[4] Mitral E velocity, corrected for relaxation estimate (E/mean e′ ratio), was used to estimate LV filling pressures. Symptom-limited, incremental (ramp protocol), exercise testing was performed using the Vmax Spectra Cardiopulmonary Exercise Testing System (SensorMedics, Yorba Linda, USA). Gas exchange variables were acquired breath-by-breath.[5] An arterial blood sample was collected at the peak of the exercise.

Sixteen patients (median (interquartile ranges - IQR) age 61 (56-70) years) underwent combined CPET-EDE (12 males) at a median time of 111 days (IQR 87-143) after discharge. The unbalanced gender uniformity reflects the higher incidence of pneumonia in males seen during the first wave of pandemic in Italy.[1] Four patients required orotracheal intubation and mechanical invasive ventilation, 9 continuous positive airway pressure (CPAP) or non-invasive mechanical ventilation (NIMV), 2 supplemental low-flow oxygen while 1 patient was treated at home after in-hospital monitoring. One patient had a history of well controlled asthma and 5 patients had a history of systemic hypertension.

Fifteen patients (94%) still presented some degree of parenchymal involvement at CT, with mild-to-moderate impairment of diffusing lung capacity for carbon monoxide test (DLCO) (Table 1). Median peak exercise capacity was mildly reduced, with a peak oxygen consumption (peak VO_2) of 74% (IQR 71-92) of predicted. No patient had a ventilatory limitation, with the slope of the relation between ventilation and carbon dioxide output during exercise (VE/VCO_2 slope) presenting median values in the limit of normal and an arterial-alveolar gradient for oxygen at the limit of normal.

Doppler echocardiography showed a normal biventricular function at rest with a preserved contractile reserve of the

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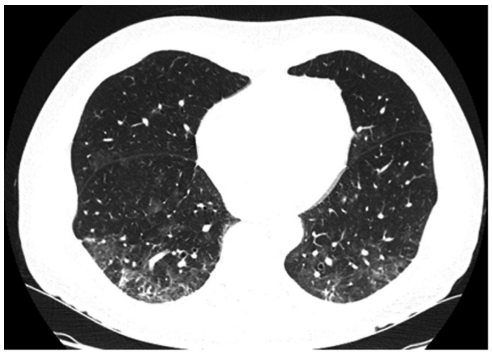
Table 1 Baseline, cardiopulmonary exercise test and echocardiographic data.

Baseline characteristics			
Male/Female n (%)	12/4 (75/25)	FEV1 %predicted	104 (89-118)
BMI kg/m^2	27.7 (25.9-31.1)	FVC %predicted	100 (90-115)
Age years	61 (56-70)	DLCO %predicted	65 (59-82)
Smoking status never/current/ex-smoker (%)	10/0/6 (62/0/38)	KCO %predicted	77 (66-95)
Pack x year	3.8 (10.0-2.0)	Alveolar Volume % predicted	87 (70-92)
Time from discharge days	111 (87-143)	CT abnormal/total n (%)	15/16 (94%)
mMRC at the time of CPET (0/1/2/3/4)	7/7/2/0/0	%V-RPI at CT	25 (15-35)
Cardiopulmonary exercise test variables			
VO_2 peak %predicted	74 (71-92)	Oxygen pulse peak %pred	91 (87-101)
VO_2 peak absolute, ml/min/kg	18.9 (13.6-23.0)	Breathing reserve %	44 (32-56)
Work peak %predicted	85 (72-94)	VE/VCO_2 slope L/L	27.9 (25.9-33
Anaerobic Threshold %VO_2 max predicted	51 (45-55)	PaO_2 at peak mmHg	86 (75-90)
VO_2/work slope ml/min/W	9.8 (9.3-10.7)	Alveolar-arterial gradient for O_2 mmHg	36 (30-45)
Respiratory Exchange Ratio at peak	1.25 (1.18-1.36)	$PaCO_2$ at peak mmHg	36 (32-39)
Heart rate reserve %	16 (5-21)	Lactate at peak mmol/L	6.7 (4.0-9.2
Heart rate at rest bpm	77 (65-89)	Borg scale of dyspnea at peak	4.0 (2.5-6.5
Heart rate at peak bpm	131 (120-148)	Borg scale of perceived exertion at peak	5.0 (3.5-6.5
Echocardiographic assessment			
Rest LVEF %	60 (58-61)	Peak PASP* mmHg	41 (36-46)
Rest RV/LV diameter	0.70 (0.64-0.81)	Rest TAPSE/PASP° mm/mmHg	0.92 (0.79-1.16)
Rest RV end-diastolic volume mm	31 (27-34)	Peak TAPSE/PASP* mm/mmHg	0.73 (0.60-0.84)
Rest RV fractional area change %	46 (40-55)	mPAP/CO slope#	1.6 (0.7-2.3)
Rest S wave velocity cm/s	13 (11-16)	Rest CO L/min	5.6 (4.6-6.7)
Rest TAPSE mm	24 (19-27)	Peak CO L/min	12.4 (10.5-14.5)
Peak TAPSE mm	31 (28-35)	Rest E/e' ratio	7 (6-8)
Rest PASP° mmHg	26 (22-28)	Peak E/e' ratio	8 (6-9)

All quantitative data median (interquartile range), qualitative data as frequencies and percentages.
° available for 6 patients.
* available for 8 patients.
# available for 7 patients; BMI: Body mass index; mMRC: modified medical research council scale for dyspnea; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; DLCO: Diffusing capacity of the lung for carbon monoxide; KCO: carbon monoxide transfer coefficient; CT: computed tomography; %V-RPI: visual percentage of residual parenchymal involvement at chest CT; VO_2: Oxygen consumption; VCO_2: Carbon dioxide output; VE: Ventilation; PaO_2: partial arterial pressure for oxygen; $PaCO_2$: partial arterial pressure for carbon dioxide; TAPSE: tricuspid annular plane systolic excursion; CO: cardiac output; PASP: pulmonary artery systolic pressure; mPAP: mean pulmonary artery pressure; E: early diastolic transmitral velocity; e': early diastolic mitral annular tissue velocity.

right ventricle through the exercise and progression of cardiac output in all patients, without signs of abnormally increased filling pressure of the LV elicited by the stress. Estimation of resting PASP was possible in 6 patients, while measurement of mPAP/CO slope in 7, which resulted normal, reflecting a proportionally adequate increase in pulmonary artery pressure to the increase in CO. TAPSE/PASP ratios suggested a preserved RV length-force relationship during exercise.

Our data add new evidence on long-term cardiopulmonary outcomes of COVID-19 survivors. Baratto et al. showed no major pathological changes in the pulmonary vascular response to exercise circulation of moderate-to-severe COVID-19 survivors at combined CPET-EDE, already at the time of hospital discharge.[6] In contrast to these findings, which showed an augmented exercise hyperventilation, our data seem to confirm a recovery in time. In particular, in patients with a mild impairment in resting DLCO, an efficient vascular recruitment by cardiac output and pulmonary blood flow increase might play a prominent compensatory role[7] (Fig. 1). In addition, the role of peripheral muscular function is suggested in literature to be a factor in explaining residual exercise intolerance in some patients.[2,8] Systematic studies on larger samples are warranted to clarify these aspects, including stratification for severity and a specific focus on the role of the muscle.



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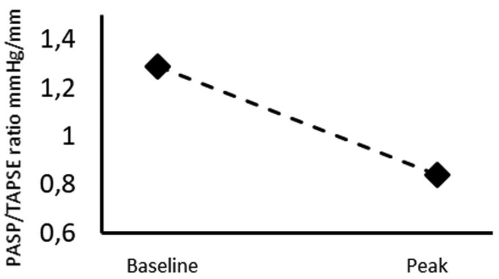

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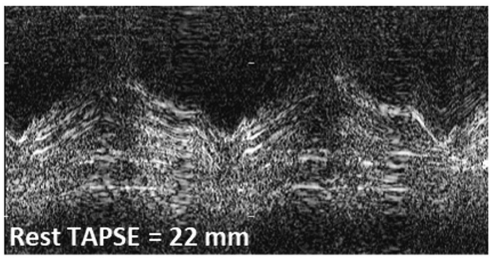

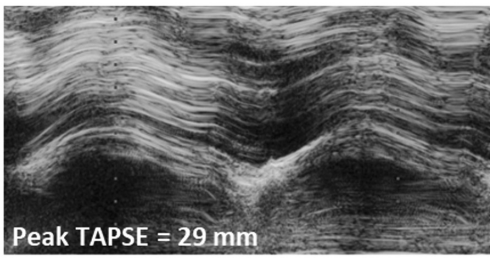

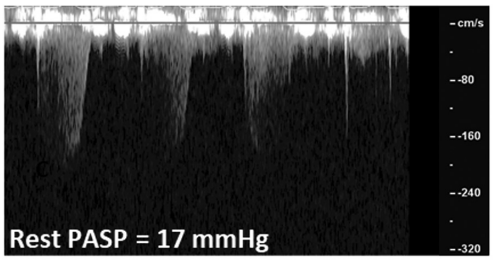

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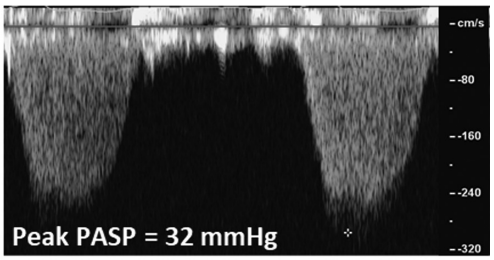

D

Cardiopulmonary Exercise Test		Pulmonary Lung Function	
Peak VO_2 % predicted	93	FVC % predicted	111
VE/VCO_2 slope	29	FEV1 % predicted	114
Alveolar-arterial gradient for O_2 mmHg	33	DLCO % predicted	61

E

Fig. 1 Typical case of residual involvement at CT and DLCO, with preserved exercise capacity. A) chest CT image showing bilateral residual ground glass opacities (visual percentage of residual parenchymal involvement of 35%), B) TAPSE/PASP ratio kinetic from baseline to peak, C) Basal tricuspid annular plane systolic excursion and tricuspid regurgitant velocity, D) Peak tricuspid annular plane systolic excursion and tricuspid regurgitant velocity, E) Key parameters from CPET and PFT. FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; DLCO: Diffusing capacity of the lung for carbon monoxide; VO_2: Oxygen consumption; VCO_2: Carbon dioxide output; VE: Ventilation; TAPSE: tricuspid annular plane systolic excursion; PASP: pulmonary artery systolic pressure.

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Conflict of Interest

Dr. Rinaldo: none declared. Prof. Guazzi: none declared. Dr. Rusconi: none declared. Dr. Parazzini: none declared. Dr. Pitari: none declared. Dr. Mondoni: none declared. Dr. Balbi:

none declared. Prof. Di Marco: none declared. Prof. Centanni: none declared.

CRediT authorship contribution statement

R.F. Rinaldo: Conceptualization, Data curation, Formal analysis, Project administration, Methodology, Investigation, Writing — original draft, Writing — review & editing. **M. Guazzi:** Conceptualization, Data curation, Methodology, Investigation, Writing — original draft, Writing — review & editing. **F. Rusconi:** Conceptualization, Data curation, Methodology, Investigation, Writing — original draft, Writing — review & editing. **E.M. Parazzini:** Conceptualization, Investigation, Writing — review & editing. **F. Pitari:** Data curation, Investigation, Writing — review & editing. **M. Mondoni:** Conceptualization, Data curation, Project administration, Investigation, Writing — review & editing. **M. Balbi:** Data curation, Investigation, Methodology, Writing — review & editing. **F. Di Marco:** Conceptualization, Methodology, Formal analysis, Supervision, Writing — original draft, Writing — review & editing. **S. Centanni:** Conceptualization, Methodology, Supervision, Writing — review & editing.

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LETTER TO THE EDITOR

The use of superlatives in news articles pertaining to asthma treatment

To the Editor

The use of superlatives — exaggerated language meant to influence perceptions — is a technique used by journalists to attract and persuade readers. However, superlatives used to describe medical therapies have the potential to misrepresent their efficacy. Previous studies have found the use of superlatives in news articles related to cancer therapies.[1] This type of sensational reporting is problematic, because consumers use online search engines to browse treatment recommendations rather than reference evidence-based medical literature, because of feasibility. While ways to evaluate the quality of news articles exist, such as the Health on the Net Foundation (HONcode),[2] treatment recommendations found through news outlets may spread medical misinformation, especially if not HONcode certified.[3] Here, we sought to quantify the use of superlatives in news stories related to asthma treatments.

Our methodology was adapted from Abola and Prasad.[1] On October 15, 2021, four investigators (R.M., C.H., C.S., H.M.) used the advanced search feature on Google News (https://news.google.com) to search "asthma treatment" with 10 separate superlative terms (Table 1) for articles published between October 15, 2020 and October 15, 2021. These terms were initially selected by Abola and Prasad.[1] The articles were screened by two authors (C.S. and H.M) in double-blinded, duplicate fashion, followed by reconciliation and third party (R.M.) adjudication as needed. The following information was extracted if the superlative in the article was in reference to an asthma treatment: URL, website name, superlative(s), drug(s) or treatment(s), Food and Drug Administration (FDA) approval status, clinical data and support presence, author background, mention of COVID-19 or coronavirus and whether its mention was tangential to the focus of the article, and presence of HONcode certification listed on the website in which the article was found.

The initial search returned 102 news articles. Following removal of duplicates and subscription articles, 85 articles were selected for full-text review. Thirty-one news articles met inclusion criteria (Fig. 1). The characteristics of superlatives in reference to asthma treatments are displayed in Table 1. There were 49 instances of a superlative referencing asthma treatments, with "breakthrough" as the most common superlative used (n=23). The superlatives "marvel", "home run", and "revolutionary" were not found in articles meeting inclusion criteria. The two most common asthma treatments with superlatives in reference were budesonide (13/31, 41.9%) and tezepelumab (12/31, 38.7%). Nearly half (15/31, 48.4%) of the articles mentioned COVID-19 or coronavirus. Only 9.7% (3/31) of the articles were written by a medical writer, with 87.1% (27/31) of articles written by a journalist/editor, and one with author information not listed. Nine of the treatments were FDA approved, and four were in clinical trials. None of the included websites were HONcode certified.

A large percentage of articles in our study used superlatives to describe tezepelumab, a monoclonal antibody still in clinical trials. Interestingly, the article using the most superlatives referencing an asthma treatment pertained to preliminary stages of pharmacological development. Exaggerated language in reference to asthma treatments lacking FDA approval may mislead reader perception of therapeutic efficacy. The mention of COVID-19 or coronavirus in nearly half of the articles intending to cover asthma treatments may indicate a focus misalignment. The addition of the pandemic in these articles is likely meant to attract readers ("clickbait"),[4] and may complicate their understanding of which disease the treatment targets. Further, none of the websites were HONcode certified, questioning the reliability of the articles' health information due to lack of regulation.[2]

The pronounced lack of regulation across websites the news articles were found in may explain the presence of superlatives used toward non-FDA approved treatments, as well as the mention of COVID-19 or coronavirus, as each of these can potentially complicate readers' understanding of asthma treatments instead of enhancing it. Overall, our findings indicate many news articles covering asthma treatments use exaggerated language and reference COVID-19, potentially complicating the publics' understanding and trust of important medical information.

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Table 1 Characteristics of superlatives in news articles pertaining to asthma treatments.

Drug/Treatment included in news Article	News articles with superlative (s) used (n=31), N (%)	Superlative (s) used (n=40), N (%)	Superlative(s) used	Drug class	FDA approved?	News articles that provided clinical data, N (%)	News articles that provided link for clinical data, N (%)
1,10 phenanthroline-5,6-dione (T5-8)	1 (3.2)	1 (2.5)	Breakthrough (1)	Bifunctional quinone oxidant	In clinical trial	1 (100)	1 (100)
Albuterol	1 (3.2)	1 (2.5)	Cure (1)	Bronchodilator	Yes	0 (0)	0 (0)
Anticalin	1 (3.2)	1 (2.5)	Miracle (1)	Ligand-binding protein	In clinical trial	1 (100)	0 (0)
Budesonide	13 (41.9)	17 (42.5)	Game Changer (7), Breakthrough (6), Groundbreaking (2), Miracle (1), Cure (1)	Corticosteroid	Yes	12 (92.3)	4 (30.8)
Ivermectin	1 (3.2)	1 (2.5)	Breakthrough (1)	Antihelminthic	Yes	1 (100)	0 (0)
Dexamethasone	3 (9.7)	5 (12.5)	Breakthrough (2), Groundbreaking (1), Game Changer (1), Miracle (1)	Corticosteroid	Yes	3 (100)	2 (66.7)
Favipiravir	1 (3.2)	1 (2.5)	Breakthrough (1)	Antiviral	Yes	1 (100)	0 (0)
Niclosamide	1 (3.2)	1 (2.5)	Breakthrough (1)	Antihelminthic	Yes	1 (100)	0 (0)
Benralizumab	1 (3.2)	1 (2.5)	Groundbreaking (1)	Monoclonal antibody	Yes	0 (0)	0 (0)
Mepolizumab	1 (3.2)	1 (2.5)	Groundbreaking (1)	Monoclonal antibody	Yes	0 (0)	0 (0)
Montelukast	1 (3.2)	1 (2.5)	Cure (1)	Leukotriene-receptor antagonist	Yes	1 (100)	0 (0)
Tezepelumab	12 (38.7)	15 (37.5)	Breakthrough (10), Transformative (3), Groundbreaking (2)	Monoclonal antibody	In clinical trial	11 (91.7)	5 (41.7)
Whole-genome sequencing	1 (3.2)	3 (7.5)	Breakthrough (1), Groundbreaking (1), Life Changing (1)	N/A	In clinical trial	0 (0)	0 (0)

*The superlatives marvel, home run, and revolutionary were not found in the news articles which met inclusion criteria

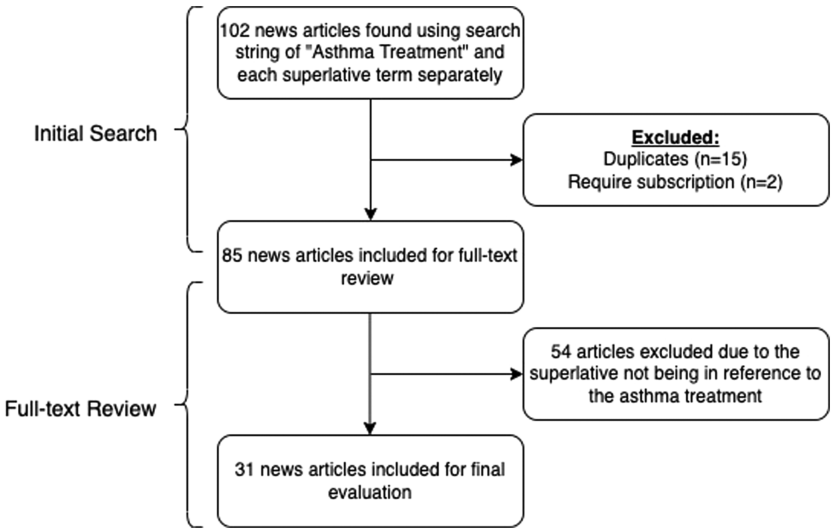

Fig. 1. Screening and Selection Flowchart for Online News Articles

Declaration of Competing Interest

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LETTER TO THE EDITOR

Concomitant allergic bronchopulmonary aspergillosis and eosinophilic granulomatosis with polyangiitis after *Aspergillus niger* infection

Aspergillus species can cause lung disease by direct infection, such as invasive pulmonary aspergillosis (IPA), aspergillosis, etc.; or by hypersensitivity reactions to fungal proteins, such as allergic bronchopulmonary aspergillosis (ABPA).[1] We here describe a patient that simultaneously developed ABPA and eosinophilic granulomatosis with polyangiitis (EGPA) in the context of an *Aspergillus niger* airway infection and discuss the overlapping criteria of these conditions.

A 27-year-old Indian male, resident in Portugal for the past two years, presented mild intermittent bronchial asthma. He developed progressive non-productive cough and dyspnoea over the course of six weeks, and was admitted to the emergency department for the sudden onset of intense right chest pain.

Physical examination was unremarkable. Blood tests revealed leucocytosis (13.1×10^9/L), with neutrophilia (10.7×10^9/L), eosinophilia (1.5×10^9/L) and elevated C-reactive protein (CRP) 9.4mg/dL (normal <0.5). Imaging showed a 6 cm-long right hilar mass, extending to the pleura and enlarged hilar lymph nodes. Bronchoscopy observed bulky secretions obstructing the anterior segment of the right upper lobe (RB3). Cultures of bronchial aspirate, lavage and biopsies were all positive for *Aspergillus niger*. Eosinophils were abundant on bronchial aspirate, with *Charcot-Leyden* crystals, and in bronchial biopsies.

The patient was hospitalized and voriconazole was initiated. Two weeks later, voriconazole was changed to liposomal amphotericin B due to drug-induced hepatotoxicity. After three weeks of antifungal treatment, no clinical improvement was observed (increasing fever, neutrophilia $13.84 \times 10\text{^}9$/L, CRP 27.59mg/dL). Imaging showed a growing lung mass with suspected superinfection (Fig. 1A-D). Empirical piperacillin-tazobactam and vancomycin were initiated. After 10 days of antibiotic therapy, neutrophilia and CRP had diminished ($8.9 \times 10\text{^}9$/L, 7.34mg/dL, respectively). However, anaemia developed (Hb 8.6g/dL, normal 13.0-17.5) and clinical manifestations continued to deteriorate, with asthenia, fever, dyspnoea and cough.

In view of the poor response to antifungals and antibiotics, alternative diagnoses were considered. Further investigations showed elevated total IgE (5175IU/mL, normal <100), eosinophilia (0.71×10^9/L), negative procalcitonin (while CRP again increased to 13.29mg/dL), positive p- antineutrophil cytoplasmic antibodies (ANCA) and anti-myeloperoxidase (MPO) (8.5IU/ml, negative <3.5), while c-ANCA and anti-proteinase 3 (PR3) were negative. Specific IgE (sIgE) and specific IgG (sIgG) to *Aspergillus fumigatus* were strongly positive (sIgE 9.16kU/L, normal <0.35; sIgG 281.00mgA/l, normal <83.00). Skin prick test to *Aspergillus fumigatus* was positive (3mm).

At this point, the patient fulfilled diagnostic criteria for both ABPA and EGPA (Table 1). Despite the initial evidence of fungal colonization/infection and subsequent bacterial superinfection, it was considered that T2 inflammation played the dominant role in the disease. Methylprednisolone was started at 1mg/kg/day, together with itraconazole. Nasal computed tomography (CT) scan during treatment with systemic glucocorticoids showed mild maxillary sinusitis.

Clinical recovery was rapid and occurred after two days of glucocorticoids, with resolution of fever and subsequently of asthenia and cough. On day 10, CRP (0.49mg/dL), blood eosinophils (0.09×10^9/L) and haemoglobin (13.8g/dL) were all normal.

The patient was discharged asymptomatic 20 days after initiating systemic corticosteroids. Itraconazole was maintained for 20 weeks and corticosteroids were tapered until suspension. At the end of antifungal treatment, the chest X-ray was normal (Fig. 1E) and there was no relapse of the symptoms. Four months after discharge, CT scan showed reduced lung mass but large varicoid bronchiectasis in both lungs, particularly in the right upper lobe (Fig. 1F-H).

This is a rare case of simultaneous development of ABPA and EGPA in the context of *Aspergillus niger* pulmonary infection. The identification of *Aspergillus* in airway samples complicated ABPA/EGPA diagnosis. On hospitalization, "proven IPA" could not be confirmed (no open lung biopsy was performed), but the patient fulfilled the criteria for "putative IPA"[2] (Table 1). Novel criteria for invasive fungal disease were published by the EORTC/MSGERC consensus,[1] after the described episode occurred.

Aspergillus is known to contribute to the development of ABPA[3] and concomitant IPA and ABPA have been described.[4]

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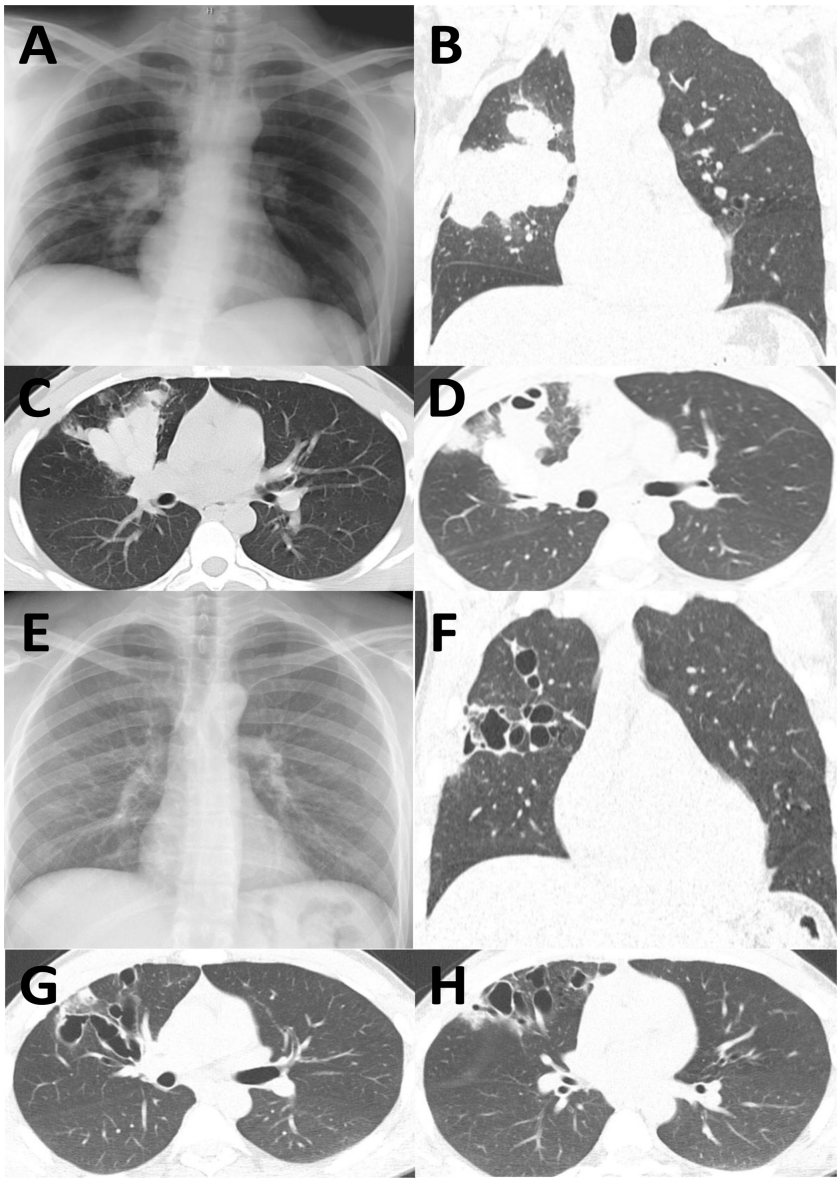

Fig. 1 Comparison of chest X-ray and CT at admission (A-D, a 6 cm-long right hilar mass is observed, extending to the pleura and enlarged hilar lymph nodes) and 4 months after disease resolution (E-H, large varicoid bronchiectasis in both lungs can be observed, particularly in the right upper lobe.).

In contrast, the role of *Aspergillus* in the pathophysiology of EGPA remains largely speculative.[5] The relationship between ABPA and EGPA is also incompletely understood. Several diagnostic criteria are common to both diseases and differential diagnosis is recommended.[6] Recently, reports described the sequential occurrence of allergic bronchopulmonary mycosis (ABPM) and EGPA, or vice versa.[7] How one established disease may be predisposed to the other is unknown but may include eosinophil recruitment by Th2-driven ABPM, or EGPA lung tissue damage and sequelae predisposing to fungal colonization and subsequent hypersensitivity.

Concomitant ABPA and EGPA at presentation seem to be rarer than sequential development. In the case described here, no past investigations were available. However, the patient was largely healthy before this episode, and we consider that ABPA and EGPA occurred simultaneously. To the best of our knowledge, only three other cases of simultaneous ABPA/EGPA have been reported.[7]

The possibility that EGPA and ABPA may co-exist in the same patient has important clinical implications. Besides differential diagnosis at presentation, long-term follow-up of one disease should explore for "de novo" development of the other disease. A fine understanding of the mechanisms involved in ABPA, EGPA, or their simultaneous presentation, will be required for the choice of targeted therapies.

Data availability

Informed consent was signed by the patient.

Table 1 Diagnostic criteria of IPA, ABPA, EGPA. Criteria fulfilled by the patient are indicated by "+", while unfulfilled criteria are marked "-". NA, not assessed; NT, not tested.

Disease and diagnostic criteria	Present in this case
Putative invasive pulmonary aspergillosis - all four criteria must be met (Blot SI, et al. Am J Respir Crit Care Med. 2012 Jul 1;186(1):56-64.	
1. Aspergillus-positive lower respiratory tract specimen culture (= entry criterion)	+
2. Compatible signs and symptoms (one of the following)	+
○ Fever refractory to at least 3 days of appropriate antibiotic therapy	-
○ Recrudescent fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause	+
○ Pleuritic chest pain	NA
○ Pleuritic rub	+
○ Dyspnoea	-
○ Haemoptysis	+
○ Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support	+
3. Abnormal medical imaging by portable chest X-ray or CT scan of the lungs	+
4. Either 4a or 4b	-
4a. Host risk factors (one of the following conditions)	
• Neutropenia (absolute neutrophil count, $<500/mm^3$) preceding or at the time of ICU admission	
• Underlying haematological or oncological malignancy treated with cytotoxic agents	
• Glucocorticoid treatment (prednisone equivalent, .20 mg/d)	
• Congenital or acquired immunodeficiency	
4b. Semiquantitative Aspergillus-positive culture of BAL fluid (+ or ++), without bacterial growth together with a positive cytological smear showing branching hyphae Aspergillus respiratory tract colonization	+
ABPA - ISHAM criteria (Agarwal R, et al. Clin Exp Allergy. 2013 Aug;43(8):850-73.)	
Predisposing conditions	
○ Bronchial asthma	+
○ Cystic fibrosis	-
Obligatory criteria (both should be present)	
○ Total IgE>1000IU/ml*	+
○ Positive Aspergillus specific IgE or skin prick test	+
Other criteria (2 out of 3)	
○ Raised Af IgG or precipitins	+
○ Eosinophils>500 cells/uL	+
○ Radiological features consistent with ABPA	+
ABPA - Rosenberg-Patterson criteria (Rosenberg M, et al. Ann Intern Med. 1977; 86:405-414)	
Major criteria	
1. Asthma	+
2. Presence of transient pulmonary infiltrates (fleeting shadows)	+
3. Immediate cutaneous reactivity to *A. fumigatus*	+
4. Elevated total serum IgE	+
5. Precipitating antibodies against *A. fumigatus*	+
6. Peripheral blood eosinophilia	+
7. Elevated serum IgE and IgG to *A. fumigatus*	+
8. Central/proximal bronchiectasis with normal tapering of distal bronchi	+
Minor criteria	
1. Expectoration of golden brownish sputum plugs	-
2. Positive sputum culture for Aspergillus species	+
3. Late (Arthus-type) skin reactivity to *A. fumigatus*	NT
EGPA (Masi AT, et al. Arthritis Rheum. 1990 Aug;33(8):1094-100. & Jennette JC, et al. Arthritis Rheum. 1994 Feb;37(2):187-92).The presence of four or more criteria yields a sensitivity of 85% and a specificity of 99.7%.Four or more criteria:	
○ Asthma (wheezing, expiratory rhonchi)	+
○ Eosinophilia of more than 10% in peripheral blood*	+
○ Paranasal sinusitis	+
○ Pulmonary infiltrates (may be transient)	+
○ Histological proof of vasculitis with extravascular eosinophils	+
○ Mononeuritis multiplex or polyneuropathy	-

Authors' contributions

IAC and FSR were attending physicians during hospitalization and follow-up, collected the data and prepared the manuscript. ML, FL, CV and ER were attending physicians for the patient during hospitalization and collected patient's data. JSC and TA contributed to the diagnosis and the manuscript.

Conflicts of interest

The authors report no conflicts of interests regarding this manuscript. FSR reports speaker and advisory fees from AstraZeneca, Novartis, Sanofi, GSK, Teva, Takeda, Kedrion and Lusomedicamenta, all outside the submitted work.

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LETTER TO THE EDITOR

Impact of *CFTR* large deletions and insertions on the clinical and laboratory severity of cystic fibrosis: a serial case report

Dear editor,

Cystic fibrosis (CF OMIM: #219700) is an autosomal recessive disorder caused by pathogenic variants in the *CFTR* (*Cystic Fibrosis Transmembrane Conductance Regulator*).[1] Among the 2,106 variants described in *CFTR*, large deletions or insertions are considered rare [59 (2.80%)].[2] The identification of large alterations in the *CFTR* is challenging and might result in wrong diagnosis, indicating false-negative in carriers of rare variants that are potentially severe.[3,4] Thus, the implementation of additional techniques in the CF diagnosis workflow becomes necessary, which includes the use of Multiplex Ligation Probe Amplification (MLPA) to identify chromosome rearrangements, deletions, and insertions.[3] So we aimed to describe the genetic profile of large deletions or insertions in *CFTR* identified using MLPA and to describe its influence on CF patients' phenotype in a referral center.

Five CF patients (chloride over 60 mEq/L in two sweat tests) presenting at least one pathogenic variant in the *CFTR* characterized as a large deletion or insertion were included after the study approval by the Ethics Committee (#78192216.2.0000.5404). The caregivers of the CF patients who participated in our study signed the consent to publish patients' data. The screening of the pathogenic variants in the *CFTR* was carried out as previously desbribed.[5] The following markers were described: patients' age at diagnosis; ethnic group; spirometry, classified according to the forced expiratory volume (FEV_1) at different levels of obstruction: mild ($\geq$70%), moderate (60-69%), moderately severe (50-59%), severe (35-49%), and very severe ($<$35%); Shwachman-Kulczycki score graded as excellent (86-100), good (71-85), mild (56-70), moderate (41-55), and severe ($\leq$40)[6]; immunoreactive trypsinogen; and sweat test results. The microbiological evaluation was carried out for the colonization by 11 microorganisms. In addition, the comorbidities and medication used by the patients were described.

All the patients had one identified variant, c.1521_1523delCTT (F508del; p.Phe508del). The MLPA technique also identified four variants considered large deletions or insertions, namely, *CFTR*dele7-18, *CFTR*dup6b-16, *CFTR*dele14b+*CFTR*dup9, and *CFTR*dele16-20. The variant *CFTR*dele16-20 was identified in two patients. The *CFTR* genotype, race, and diagnostic tests were described (Table 1), as well as the comorbidities, Shwachman-Kulczycki score, microorganism profile, and medication used by the patients (Table 2).

In our cohort, four patients were self-declared Caucasians, and one was of mixed race; four of them were female. Two patients were diagnosed when they were five months old; two were two months old; and one was one month old. The Shwachman-Kulczycki score varied distinctly for each participant. All participants were colonized by *Pseudomonas aeruginosa* and *Staphylococcus aureus*, while unequal colonization by other microorganisms was observed in the patients. All participants used inhaled antibiotics, mucolytic agents, nutritional supplements, and pancreatic enzymes; four patients used bronchodilator and one used inhaled corticosteroid. In addition, all patients in our study cohort had pancreatic insufficiency (Table 2).

Since the *CFTR* pathogenic variants present different effects on the phenotype, it seems relevant to optimize the detection method to avoid inaccurate and/or delayed diagnosis.[7,8] In such contexts, the MLPA technique implementation in the CF diagnosis should be optimized.[7] For instance, Atag et al. (2019) evaluated 250 CF patients that presented 80 genetic distinct variants in the *CFTR* and, out of those, five (*CFTR*dele2, *CFTR*dele4-11, *CFTR*dele5-10, *CFTR*dele12, and *CFTR*dele19-21) were characterized as large deletions and occurred in 16 CF patients. Large deletions were associated to the worst pulmonary phenotype, pancreatic insufficiency and liver involvement.[8] The same findings were reported by Martins et al. (2019) who reported the presence of a severe phenotype with pancreatic insufficiency and infection by *P. aeruginosa*[9] in five patients with large deletions or insertions in the *CFTR*.

The identification of all types of *CFTR* variants, including large deletions and insertions, should be one of the main points to be considered in the patients' differential diagnosis.[4] For example, in a study carried out in Serbia, twenty-two different *CFTR* variants were identified in the population studied, evidence of high heterogeneity. Most of these variants had not been reported in neighboring countries, possibly due to the use of commercial tests for CF diagnosis in those places, which did not include the MLPA technique. Due to the use of different molecular analysis techniques,

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Table 1 Description of genotype, race, and diagnostic tests results in cystic fibrosis patients in the presence of *CFTR* large deletions or insertions.

Marker		**BSD**	**JDQS**	**EVFM**	**JVQS**	**ECM**
CFTR Genotype	Allele 1	F508del	F508del	F508del	F508del	F508del
	Allele 2	*CFTR*dele7-18	*CFTR*dele16-20	*CFT*Rdup6b-16	*CFTR*dele16-20	*CFTR*dele14b and CFTRdup9
Race		Caucasian	Caucasian	Caucasian	Mixed race	Caucasian
IRT (ng/mL)*		204/131	86/138	262/354	159/147	260/410
Sweat chloride ion (mEq/L)*		89/92	95/92	95/90	110/106	116/128

F508del; p.Phe508del = c.1521_1523delCTT; IRT: immunoreactive trypsinogen; *CFTR*: Cystic Fibrosis Transmembrane Regulator.
* , first and second dosages were demonstrated.

Table 2 Comorbidities, Shwachman-Kulczycki score and medications in cystic fibrosis patients in the presence of *CFTR* large deletions or insertions.

Marker	**BSD**	**JDQS**	**EVFM**	**JVQS**	**ECM**
Comorbidities					
Nasal polyposis	Yes	No	No	No	No
Meconium ileus	No	No	No	No	Yes
Pancreatic insufficiency	Yes	Yes	Yes	Yes	Yes
Liver involvement	No	No	Yes	No	Yes
Growth deficit	No	Yes	No	Yes	Yes
Persistent respiratory symptom	No	No	No	No	Yes
Metabolic disorder	No	No	Yes	No	No
Shwachman-Kulczycki score (age, months)	54	18	71	104	138
General activity	20	25	25	20	25
Physical examination	20	25	25	20	25
Nutrition	25	25	20	15	25
Thorax X-ray	10	20	20	20	25
Total score	75	95	90	75	25
Score classification	Good	Excellent	Excellent	Good	Excellent
Bacteria					
Pseudomonas aeruginosa	Yes	Yes	Yes	Yes	Yes
mucoid *Pseudomonas aeruginosa*	No	Yes	No	No	No
Staphylococcus aureus	Yes	Yes	Yes	Yes	Yes
Streptococcus pneumoniae	No	Yes	No	No	No
Stenotrophomonas maltophilia	No	Yes	No	No	Yes
Haemophilus influenzae	No	No	Yes	Yes	No
Klebsiella pneumoniae	No	No	Yes	No	No
Escherichia coli	No	No	Yes	No	No
Moraxella catarrhalis	No	No	No	Yes	Yes
Acinetobacter baumannii	No	No	No	No	Yes
Burkholderia cepacia complex	No	No	No	No	No
Bronchodilator					
Short-acting β_2-agonist	No	No	No	Yes	Yes
Long-acting β_2-agonist	Yes	No	No	Yes	Yes
Anticholinergic	Yes	Yes	No	No	No
Inhaled corticosteroid	No	No	No	No	Yes
Inhaled antibiotic					
Colomycin	No	No	Yes	No	Yes
Tobramycin	Yes	Yes	Yes	Yes	Yes
Mucolytic					
Dornase alfa	Yes	Yes	Yes	Yes	Yes
N-Acetylcysteine	Yes	No	No	No	No
Saline solutions					
0.9%	Yes	No	No	Yes	Yes
3%	Yes	No	No	Yes	No
Oral medication					

Table 2 (*Continued*)

Marker	BSD	JDQS	EVFM	JVQS	ECM
Comorbidities					
Azithromycin	No	Yes	Yes	Yes	Yes
Ibuprofen	No	No	No	Yes	No
Corticosteroid	No	No	No	No	Yes
Proton pump inhibitors	No	No	Yes	No	No
H_2 Blockers	Yes	Yes	Yes	No	No
Ursodeoxycholic acid	Yes	No	No	No	Yes
Pancreatic enzymes	Yes	Yes	Yes	Yes	Yes
Nutritional supplement	Yes	Yes	Yes	Yes	Yes
P. aeruginosa eradication treatment	Yes	Yes	No	Yes	No

an increase from 54.45% to 72.8% was observed in the effectiveness rate to identify the *CFTR* genotype.[10]

The description of clinical manifestations along with the identification of large deletions or insertions in the *CFTR* pointed out a more severe phenotype of these patients in our serial case report. And, although younger patients do not present some symptoms, there is still great potential for developing them in the future. Currently, there is no corrective therapy for *CFTR* large deletions or insertions, due to the difficulties of modulating the impact of these large deletions and insertions in the gene expression mechanisms.[11]

In conclusion, our study identified four genetic variants of the type *CFTR* large deletions and insertions, which were characterized by their low genotypic and diagnostic frequency. Two participants presented the same variant, while the variants identified in the other three participants were unique. The identification of large deletions and insertions through a broader genetic analysis is very important for CF diagnosis, since those variants, despite being rare, might be associated with the disease higher severity phenotypes.

Author contribution

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

Data availability: The complete data collected to perform the study is presented in the manuscript.

Conflict of interest

None.

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PHOTO

Dental implant screwdriver aspiration

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A 71-year-old male, former smoker, with past medical history of Chronic Obstructive Pulmonary Disease presented to pulmonology outpatients with persistent cough for the last four months, since dental procedure. Chest radiography showed a retrocardiac opacity in the right hemithorax (Fig. 1A). Computed tomography scan revealed a foreign body image in the distal portion of the intermediate bronchus, prior to division into basal pyramid (Fig. 1B). Rigid bronchoscopy confirmed the presence of a foreign body in the intermediate bronchus, without total obstruction and surrounded by granulation tissue, compatible with dental implant screwdriver (Fig. 1C-D). The dental instrument was removed and the patient initiated a short course of glucocorticoid with successful improvement of cough.

Foreign body aspiration related to dental procedures is rare, the incidence of aspiration in root canal treatment being 0.001 per 100000.[1] The small instruments used for treatment, under saliva slippery environment, associated with local anesthesia and supine position, are favorable for instrument drop and aspiration.[1] Persistent cough is the most common symptom and can mimic chronic respiratory disease.[2] Aspiration episodes are often not recorded/valued.[2] Prompt diagnosis and intervention, guided by high index of clinical suspicion, are critical in minimizing the potentially severe complications of retained a foreign body.

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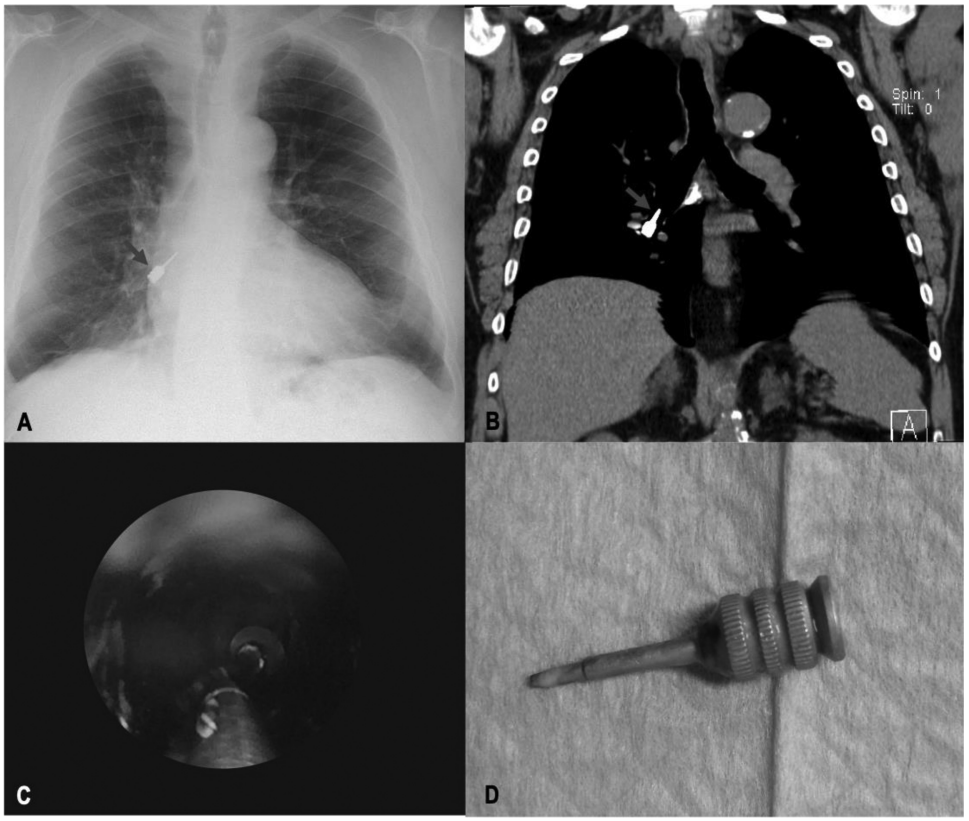

Fig. 1 A - Posteroanterior chest radiography showed a right lower retrocardiac radiopaque foreign body (blue arrow). B - Chest computed tomography scan revealed a dental instrument foreign body in the distal portion of the intermediate bronchus, immediately prior to division into the right basal pyramid (blue arrow). C - Extraction of endobronchial metallic foreign body using by rigid bronchoscopy (*Karl Storz® Universal Bronchoscope for Adults 10318BP, size 8,5 and Hopkins® Telescope 10320AA*) using grasping forceps (*Karl Storz® Forceps for Bronchoscopy 10370U),* under general anesthesia with manual jet ventilation. D - The extracted foreign body was compatible with dental implant screwdriver.

Patient's consent

Informed consent was obtained concerning the publication of this case report.

Conflicts of interest

The authors have no conflicts of interest to declare.

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PHOTO

The azygos lobe of the lung

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A 53-year-old woman presented to the emergency department with shortness of breath. A chest radiograph taken with a digital portable unit demonstrated an abnormality in the superior lobe of the right lung concerning for neoplasm, warranting workup with computed tomography (CT). CT of the chest demonstrated the rare anatomical variant of an azygos lobe. The azygos vein was identified as separating the superior lobe from an azygos lobe.

The azygos system is a paired venous pathway of the posterior thorax with numerous congenital anomalies such as the absence of the azygos vein, azygos and hemiazygos continuation of the inferior vena cava, and partial anomalous pulmonary venous return.[1-3] The azygous vein is surrounded by two visceral layers and two parietal layers of pleura due to its entrapment in the lung parenchyma.[3,4] The azygos lobe, a congenital azygos anomaly, presents as an accessory lobe of the right lung that can be confused with pathologic processes such as a bulla, abscess, or neoplasm.[2,4,5] It is a rare anatomical variant seen only in 0.4 percent of the population radiologically and 1 percent of specimen during anatomical dissection.[4,5]

The azygos lobe is formed due to incomplete medial migration of the right posterior cardinal vein, one of the precursors of the azygos vein, into the apex of the lung instead of normal migration over it during embryogenesis.[2,3,6] The abnormal azygos migration results in a classic para-tracheal shadow on x-ray along with several other key x-ray findings. 1) The laterally displaced azygos vein or mesoazygos is found between folds of parietal pleura, creating a teardrop shape; 2) The mesoazygos indents the right upper lobe and creates an accessory azygos fissure, creating a shape like an inverted comma; 3) The azygos lobe is bordered superiomedially by the accessory azygos fissure, laterally by the pleural folds of the mesoazygos, and medially by the tracheobronchial angle, which appears empty on x-ray.[3,4]

Most cases of azygos lobe are incidentally discovered but there are cases of tumors, pneumothorax, and consolidations found in the azygos lobe.[1,3,4] A displaced azygos vein can often be confused with a pulmonary nodule and a consolidated azygos lobe can be confused with a pulmonary mass.[1-4] An understanding of the azygos lobe anatomy is

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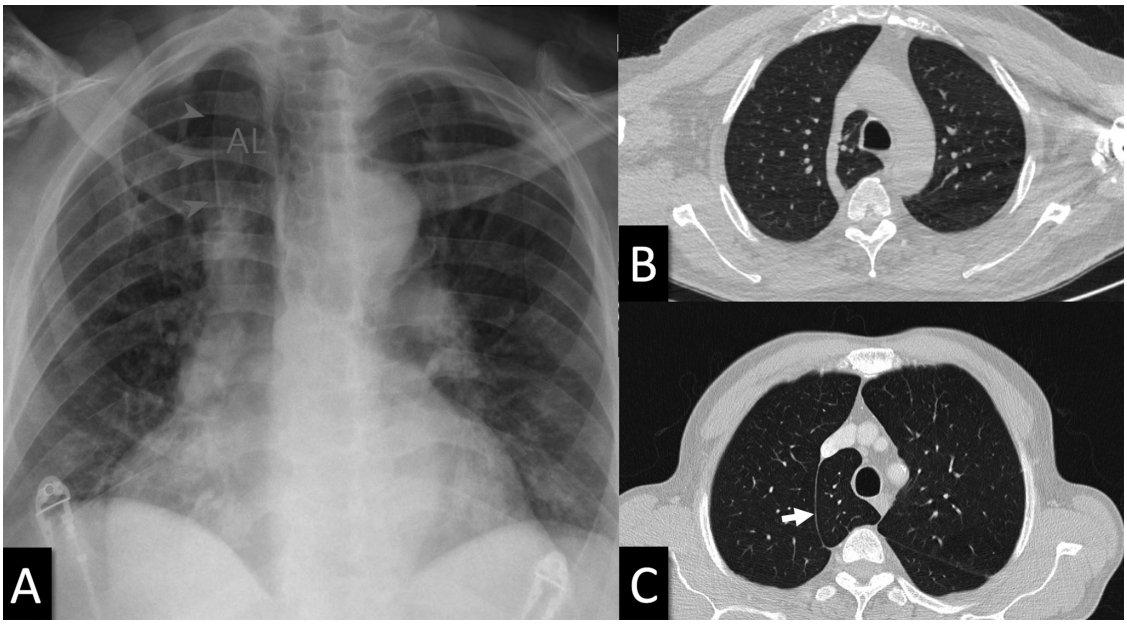

Fig. 1 Chest frontal view radiograph (A) demonstrating the hyperdense lateral borders (arrowheads) of the azygos lobe (AL). Radiographs were taken with a 32kW Mobile X-ray unit (70 kVp, 320 mA, 0.5 sec). Superior (B) and inferior (C) axial CT images identifying the azygos vein (B) which separate the azygos lobe from the superior lobe. CT imaging was high resolution CT (HRCT) (slice thickness: 1 mm, scan time: 1 sec, 120 kV, 100 mA). The white arrow (C) shows the boundary of the lobe which is separated by 2 layers of visceral and pleura.

important for all clinicians especially pulmonologists, radiologists, and thoracic surgeons (Fig. 1).

Disclosures

None.

Declaration of Competing Interest

None.

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None.

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