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Letter to the Editor

Challenges posed by COVID-19 to refugee camps on the Greek islands: We are all humans after all
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Lung innate immunity, a non-specific first line of host defense, plays a key role in maintaining a healthy lung as hundreds of thousands of irritants, bacteria, viruses, pollen, and other insults get inhaled on a daily basis. It is when an imbalance in this system occurs that undesirable downstream consequences may happen, leading to disease with a varying degree of severity. In this Editorial we first provide a brief review of the literature of the genetics of the human innate immune molecules, SP-A1 and SP-A2, and their impact on the alveolar macrophage and the bronchoalveolar lavage at baseline and in response to ozone-induced oxidative stress, as well as on lung function, and survival after infection. Next, we discuss the potential differential role of SP-A variants on different COVID-19 patient subgroups.

The innate host defense molecules, human pulmonary surfactant proteins (SP)-A1 and SP-A2, have been identified with extensive genetic and epigenetic variability. Preclinical studies including animal, ex vivo, and cell culture experiments have resulted in a considerable body of information to indicate that SP-A1 and SP-A2 differentially affect the function and regulation of the alveolar macrophage, the sentinel cell of innate immunity, as well as the regulation of the type II epithelial cells, either at baseline conditions or in response to various insults, such as infection and ozone-induced oxidative stress. If survival were to be taken as the ultimate readout, it has been shown that mice that carry and express a different SP-A1 or SP-A2 variant, exhibit significantly different survival rates after Klebsiella pneumoniae infection, and the impact of these variants on lung mechanics also differs. Beyond preclinical animal studies, in humans, one variant that resulted in better survival in animals, also correlated with significantly better survival in lung transplant patients during the first year post-transplantation, which is the most critical time for these patients. Moreover, SP-A variants have been associated with disease susceptibility in a large number of pulmonary diseases, indicating their potential importance in determining lung disease susceptibility and/or severity.

SP-A1 and SP-A2 variants differentially affect the bronchoalveolar lavage
(BAL) proteome in response to infection and/or in the presence or absence of ozone-induced oxidative stress (OxS)\(^1\), as well as they differentially affect the function and regulation of the alveolar macrophages under various conditions, in terms of inflammatory cytokine expression\(^2,3\), phagocytic index\(^4,5\), proteome\(^6,7\), miRNome\(^8,9\), gene expression\(^10\), toponome\(^11\), and other. Because of the differential SP-A1- and SP-A2-mediated impact on BAL and alveolar macrophages, it is reasonable to postulate that the microenvironment in the hypophase (i.e. the fluid lining the alveolus and surrounding the AM) differs, especially in response to infection and/or OxS. Although differences in the alveolar macrophage proteome and toponome have been observed under baseline conditions, these may not be critical for the health or survival of these mice, as health and life span of these animals is similar regardless to which SP-A variant they carry. However, animals with these baseline or “resting” SP-A1- and SP-A2-mediated differences in the alveolar space and/or the alveolar cells in response to infection and/or OxS exhibit significantly different outcomes in a multitude of readouts, as noted above, including survival after infection\(^1\). This indicates that the SP-A variant-dependent baseline differences, in the face of an insult (i.e. bacteria, OxS, co-infecting pathogens in COVID-19 or SARS-CoV-2, or other), may be critical in determining disease susceptibility or severity as these baseline differences in response to a challenge may be magnified, synergistically or additively, or be nullified.

COVID-19 patients exhibit a wide spectrum of disease severity from extremely mild to extremely severe presentation of the disease. It remains to be determined whether and/or how the genetic variants of innate immune molecules, such as SP-A1 and SP-A2, shown previously to differentially affect function and regulation of the alveolar macrophage, could play a differential role against this viral infection and perhaps explain, in part, the variable outcome in terms of disease severity. Although the role of genetics of innate immune molecules on COVID-19 has not been addressed, as a prelude to future experimentation we consider three scenarios. 1) **Is it possible** that individuals with no other underlying disease and a certain SP-A1/SP-A2 genotype experience mild (or severe) symptoms in response to SARS-CoV-2 infection? Based on the significant amount of information available from preclinical studies this is highly likely. SP-A variants may differentially provide the first line of defense against the virus via perhaps its interaction with the alveolar macrophage and/or the regulation of the inflammatory response and/or via its regulation of the type II epithelial cell, the cell infected by SARS-CoV-2. 2) **Is it possible** that the genetics of innate immune molecules, SP-A1 and SP-A2, play a role in host defense against SARS-CoV-2 and/or in the host defense of co-infection with non-SARS-CoV-2 pathogens? About 26% of COVID-19 patients are also infected with other pathogens such as respiratory syncytial virus (RSV)\(^2\). SP-A has been shown to enhance RSV clearance in mice\(^2\) and recently a functional trimeric SP-A fragment has been shown to reduce RSV infection\(^2\). Moreover, an association has been observed between SP-A variants and RSV susceptibility\(^3\). Thus, the available data indicate that SP-A variants are likely to provide differential host defense against potential co-infecting pathogens and/or differentially modulate the inflammatory response in response to virus as shown in preclinical studies for other insults. 3) **Is it possible** that individuals with additional major disease burden, where inflammation and the OxS level in the alveolar microenvironment are high, could fare better in response to SARS-CoV-2 infection, if they carry a given SP-A1/SP-A2 genotype? This remains to be determined. Preclinical studies indicate that OxS differentially affects the oxidation level and function of SP-A variants and that the higher the level of SP-A oxidation the lower its activity\(^4\). SP-A oxidation also impairs its ability to interact with the macrophage\(^5\). Preclinical studies also indicate that SP-A is more susceptible to oxidation in response to ozone-induced OxS compared to the total protein present in the BAL\(^6\), raising the question of whether SP-A may serve as a “sacrificial antioxidant” (i.e. it eliminates ROS via its own oxidation to protect the function of proteins with perhaps more critical function). However, controlling and/or maintaining a redox balance, via antioxidant therapy regimens, may not only benefit/protect the functional activity of molecules and cells, such as SP-A and the alveolar macrophage, respectively, but may mitigate the negative effects of reactive oxidant species (ROS) and improve overall health. In fact, certain plant polyphenols considered to be strong antioxidants, protect SP-A from oxidation\(^7\) and antioxidant supplementation seem to protect from the negative effects of ozone\(^2\). A recent clinical study implicated the alveolar macrophage and innate immunity in COVID-19 with promising therapeutic results\(^3\). In this study patients were treated with a Bruton tyrosine kinase (BTK) inhibitor to inhibit the BTK-mediated signaling in the alveolar macrophage, and this treatment mitigated the “hyperinflammatory response” present in
these patients. Based on preclinical studies it is of interest to speculate whether the magnitude of this “hyperinflammatory response” varies as a function of SP-A genotype in the given microenvironment.

Children appear to be considerably less affected by COVID-19 than adults. SARS-CoV-2 uses the angiotensin converting enzyme 2 (ACE2) receptor to enter epithelial cells. A recent study showed that the nasal epithelial cells in children exhibit low, age-dependent activity of ACE2, the younger the children the lower of ACE2 activity. It was postulated that this may be a reason that children are spared for the most part from COVID-19. Of interest, SP-A is also expressed in nasal epithelial cells, however, currently nothing is known about the role of SP-A genetics in nasal disease. It is possible that the low ACE2 expression combined with a specific SP-A genotype provide a strong protection in most children from SARS-CoV-2 infection.

In summary, preclinical studies have given us a wealth of information on the differential impact of genetic SP-A1/SP-A2 variants on lung host defense and human studies have shown associations with disease susceptibility of a wide spectrum of pulmonary diseases. The latter is not surprising since these molecules provide the first line of defense and also contribute to surfactant-related functions. However, there is still a lot to learn, especially in humans. This pandemic may provide an opportunity for focused research on the role of the genetics of SP-A1/SP-A2 innate immune molecules on COVID-19 disease severity. For example, SP-A1 and SP-A2 animal models could be used to study progression and severity of disease in response to different SP-A variants/genotypes. SP-A markers (i.e. SNPs or other) associated with low and high risk in different groups of patients, could be identified to help with clinical management and/or treatment. SP-A1 and SP-A2 variants are differentially regulated, but virtually nothing is known how this regulation may be affected by infection or other insults. Such information is important if one were to think of therapeutic regimens for maintaining strong innate immunity in the face of infection and other underlying diseases.

CONFLICT OF INTEREST
None.

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Idiopathic Pulmonary Fibrosis patients’ COVID-19 quarantine; not just a routine

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Key words:
- Idiopathic pulmonary fibrosis
- Interstitial lung disease
- COVID-19, quarantine

Abbreviations:
IPF: Idiopathic pulmonary fibrosis
COVID-19: Corona Virus Disease 19
QoL: quality of life

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Amidst the Corona Virus Disease 19 [COVID-19] pandemic we have been receiving an increasing amount of open-hearted concerns from Idiopathic Pulmonary Fibrosis (IPF) patients regarding the unraveling global tragedy through phone call appointments, which have replaced outpatient visits during the national lockdown. Upon reflecting on their sincere thoughts one can sympathize with the predicament IPF patients are currently encountering, which is highly unrecognized because of global turmoil and the fact that this population is in many aspects (research, public awareness, media coverage…) underrepresented. Therefore, we decided to provide insights into the COVID-19 calamity from an IPF patient point of view, drawing inspiration from our patient’s confessions.

IPF remains a rapidly progressive disease with poor prognosis. It wasn’t until recently that disease modifying drugs, pirfenidone and nintedanib, were approved heralding a new era in the treatment of IPF. Prior to this benchmark event, patients had no choice but to come to terms with the fact that there is no treatment proven effective in slowing pulmonary function deterioration. Currently, they find themselves placed within a population susceptible to a novel disease that yet again lacks evidence-based therapeutic interventions.

Nowadays more than ever, IPF patients experience diminished quality of life, not only because of physical symptoms but also due to the associated anxiety and depression that are precipitated by the aftermath of the COVID-19 pandemic. In our small patient cohort, self-reported levels of quality of life (QoL) have been markedly reduced as strict measures are issued to combat viral transmission. It is well established that dyspnea, reduced mobility and cough underlie the diminished patient-reported QoL and are important inducers of anxiety and depression. Symptom-related discomfort can perturb involvement in daily activities (household maintenance, socializing, exercise…) and many aspects of the treatment plan (such as pulmonary rehabilitation and group therapy sessions), a sequence which culminates in additional negative emotion. Given that most patients are older adults and are therefore likely to have their own family, it is expected that the impact of IPF extends to their family members as well. IPF applies additional emotional pressure through concerns regarding: i) the disclosure of the diagnosis to close relatives (spouse, children, siblings…); ii) treatment-
related expenses that may strain the household budget; iii) the inability to take part in family activities; and iv) sexual dysfunction, that is increasingly recognized as an important issue⁴.

As if the life of an IPF patient wasn’t challenging enough, COVID-19 introduces another level of complexity. Implementation of home confinement, high predisposition to severe COVID-19 and increased hospital workload are likely to hamper access to healthcare facilities for routine physical examination, emotional support and prescription of medication. In cases of emergency, such as an IPF exacerbation, it is expected that IPF patients may be driven to delay their visit to the hospital on fear of contracting the virus in the process. Alternatively, some may misinterpret the signs of an acute flare as development of COVID-19 symptomatology precipitating domestic discomfort. Therefore, IPF patients may opt to spend most of the time away from the family amid transmission concerns, considering that their partners have to occasionally break the quarantine for household necessities. Most importantly however, it remains unknown when the global pandemic will be resolved. With the expectancy of IPF averaging 3 years, even a few months under such conditions amounts to a significant portion of the predicted lifetime. It is highly unfortunate that even prior progress in terms of symptom-relief could be wiped due to psychological unrest and abstinence from pulmonary rehabilitation, whose benefits fade following cessation⁴. One can only imagine how devastating that is for the morale of an IPF patient.

There is an ongoing effort to modernize IPF treatment as per the principles of personalized medicine. Comprehensive treatment plans are advocated that incorporate extension of survival in tandem with interventions aimed at enhancing QoL. The shifting paradigm of IPF management suggests that anxiety and depression are starting to be duly recognized by the scientific community as important variables in maintaining QoL. The pillars of the approach consist of individual assessment of patient needs and values, patient education, symptom and comorbidities relief, disease modification and timely discussion of end-of-life decisions⁴. To a sufficient degree, it is possible to allow patients under domestic confinement to follow aspects of the treatment plan. During the pandemic home based web-solutions have been increasingly employed for a variety of tasks (work, shopping, communication etc) and it would be prudent to continue this trend into the post COVID-19 era. Telemedicine services have successfully entered the market and promise to revolutionize the patient-doctor dynamic in the forthcoming years. Telemedicine providers are urged to utilize novel digital means to: i) become a vehicle of reliable information; ii) enable teleconference appointments with IPF specialists; iii) promote online group therapy sessions; iv) provide at-home pulmonary rehabilitation tutorials, or even v) host cognitive behavioral therapy sessions⁵. Apart from internet-based means, the combined effort of family members and specialized caregiver services are indispensable in ensuring comfort care. Delivery and administration of essential medicines, measurement of vital signs, meal preparation and psychological support are only some of the basic needs that can be effectively satisfied particularly from immobile patients.

Sooner or later COVID-19 will become a lesson from the past. In anticipation of the next epidemic/pandemic, authorities and healthcare systems are going to draw from this experience⁶ and be better prepared in terms of detection, containment and if required, development of a treatment. Special emphasis should be placed in establishing emergency protocols to assist people suffering from chronic, debilitating and rare conditions to maintain their physical and emotional well-being. By no means can such solutions replace personal contact between the patient and his partners, namely, family, physicians, nurses, caregivers and social circle. However, they do allow the patient to retain his progress and remain confident in his ability to overcome the hardships of his condition. Besides, for IPF patients, adopting Jo Nesbo’s words, losing their life is not the worst thing that can happen; the worst thing is to lose their reason for living.

CONFLICT OF INTEREST
None.

AUTHORS’ CONTRIBUTIONS
All authors contributed equally in the production of the manuscript.

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Smoking in Greece
Where we stand in 2020

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The American College of Greece
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ABSTRACT
BACKGROUND. Since 2008 Greece has the highest smoking prevalence in Europe. With a limited number of outdated publications and a recent enforcement of the tobacco control policy, our study aimed to estimate the smoking prevalence in Greece, describe smokers’ characteristics and the stance of the public towards the newly implemented law. METHODS. Sample was representative of the adult Greek population according to sex and age based on national census data. Data collection took place on February 2020 using computer assisted telephone interviewing. Differences between groups were assessed with chi-squared tests. Analysis was performed in STATA 13. RESULTS. 1976 adults participated in the survey, 48% male and 52% female. Smoking prevalence was 28%. Men presented a slightly higher smoking prevalence (29%) vs women (28%) and a higher ex-smoking prevalence (36% vs 29%), women presented a higher never-smoking prevalence (40% vs 34%), differences highly statistically significant (p=0.003). Statistically significant differences (p<0.001) were observed between ages, with highest smoking prevalence in 35-44-year-olds (36%) and lowest in 65+ year-olds (15%). History of smoking cessation was higher in men (67%) than women (59%), differences highly statistically significant (p=0.03). 32% of smokers reported a decreased use following the tobacco control law enforcement, 4% an increased use while for 64% remained the same. Finally, 85% believed adherence to the law was observed in public places. CONCLUSIONS. Smoking prevalence has declined in Greece and an impressive adherence to the tobacco law was observed. Sex and age differences were observed, indicating that tobacco control policies should be tailored to different subgroups’ needs.


INTRODUCTION
Since 2008, according to Eurobarometer, Greece has been placed 1st among the EU countries with the highest smoking prevalence1-4, ranging
National smoking prevalence has declined from 42% in 2008\(^1\) to 37% in 2017\(^2\). Nationally representative studies conducted by the Hellenic Statistical Authority in 2009 and 2014, showed that smoking prevalence in Greece, although still high, was however declining in 2014 (37.9% in 2009 vs 32.6% in 2014)\(^5\).

Limited studies have examined the smoking prevalence as well as smokers’ characteristics in Greece; the existing studies\(^6\)–\(^11\) have several limitations such as small sample sizes, examining certain age or social groups and small geographical areas. Even studies conducted as part of wider European or international surveys, although enrolling larger population samples, were criticized as having low response rates (<50%), many presenting conflicting results compared to those of national, more inclusive surveys\(^8\).

Furthermore, majority of the aforementioned studies are also considered outdated, not reflecting on the current affairs and the modified tobacco products market; the most recent and inclusive studies available to date, were conducted in 2014 by the Hellenic Statistical Authority\(^5\) and in 2017 by the Eurobarometer\(^2\), none of which has examined the use of novel tobacco products including electronic nicotine delivery systems (ENDS).

Additionally, the 2013 Global Adult Tobacco Survey (GATS)\(^12\) showed that, in contrast to the generally observed pattern, smoking prevalence in Greece was associated with higher education, a finding the authors attributed to the lack of anti-smoking campaigns; remarkably though, since 2009, several school-based smoking prevention programs started to be carried out in Greece\(^13\).

To the authors knowledge there is a lack in recent studies, that are examining smoking prevalence, smokers’ characteristics and use of tobacco and novel tobacco products, in a nationally representative population in modern Greece, especially following the tobacco control law implementation\(^14\) enforced in 2019.

Therefore the aim of the current study was to estimate, for the first time, the smoking prevalence in a nationally representative adult population in Greece in 2020, to describe the characteristics of smokers including products used, history and plans for cessation, as well as the stance and beliefs of the public towards the recently enforced tobacco control law. Moreover, the results of the current study are expected to reflect both on the effect of a decade of smoking prevention programs implementation, as well as on the effect of the successful law enforcement.

**METHODS**

A cross sectional survey based on a nationally representative sample of the adult Greek population was conducted in 2020, following the enforcement of the new tobacco control law.

**Sample**

Adult Greek residents 18 years old and above at the time of the survey were enrolled. Data collection was performed during the first week of February 2020.

**Methodology and data collection**

Survey was performed with quota sampling methodology by sex and age, in order to achieve a representative sample of the adult Greek population according to national census data of 2011, published by the Hellenic Statistical Authority\(^15\). Data collection was conducted using computer-assisted telephone interviewing (CATI). Maximum sampling error allowed was 2% at the 95% confidence limit. Data collection was performed by Kapa Research, a Greek survey organization\(^16\), member of The Market Research and Public Opinion Companies Association (SEDEA)\(^17\). Kapa Research conducts surveys according to the European Society for Opinion and Marketing Research (ESOMAR)\(^18\) code for conducting and publishing market research.

**Questionnaire and definitions**

Participants answered questions on their smoking status, tobacco products used, their willingness and history of cessation attempts, as well as on their stance towards the new tobacco control law enforcement. Based on their smoking behavior and smoking status, participants were classified in four categories: daily smokers (smoking at least one or two cigarettes per day), occasional smokers (smoking less than seven cigarettes per week), ex-smokers (ceased smoking for more than 6 months) and never-smokers (have never smoked)\(^19\).

**Statistical analysis**

The Chi-square test was used to assess differences between groups. Results are presented as frequencies or percentages. Analysis was performed in Stata 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, Texas: StataCorp LP).
RESULTS

Synopsis

A total of 1976 adults participated in the survey, 48% male (n=954) and 52% female (n=1022). Daily smokers were 17% and occasional smokers were 11%, adding up to a smoking prevalence of 28% (Table 1). Ex-smoking prevalence was 33%, never-smoking was 37%, while a 2% refused to answer regarding their smoking status.

With regards to smokers, majority (86%) reported single use of one tobacco product with it mainly being combustible cigarettes (57%), followed by roll-your-own (RYO) (29%), while a small proportion (14%) reported single use of other tobacco products (electronic cigarettes, Heat Not Burn Tobacco (HNBT), cigar, pipe or water-pipe).

Regarding smoking cessation, 63% of smokers reported having attempted cessation at some point, while 37% reported no cessation attempt. Additionally, 52% of smokers reported their willingness to quit in the future, 41% had no intention, while 7% were undecided.

Regarding their view on the tobacco control law implementation, majority (77%) had a positive opinion on the governmental measures for its enforcement, opinion which differentiated depending on the smoking status of the participants (p<0.001) (Figure 1).

Additionally, majority (85%) believed that adherence to the law was observed in public places, 13% believed that it was not applied, while 2% did not answer. Finally, 32% of smokers reported they have reduced their smoking amount following the law enforcement, 4% reported increased amount, while 64% reported it remained the same.

Analysis by smoking status

Highly statistically significant differences were observed between sexes and smoking status (p=0.003), with men presenting a slightly higher smoking prevalence compared to women (29% vs 28%), as well as a higher ex-smoking prevalence (36% vs 29%), while they presented a lower never-smoking prevalence (34% vs 40%) (Table 2).

Additionally, highly statistically significant differences were depicted between age groups (p<0.001), with the highest prevalence observed in 35-44-year-olds (36%) and the lowest in 65+ year-olds (15%), while in the rest age groups smoking prevalence was between 27% and 34%.

Regarding smoking cessation, daily smokers reported cessation attempts in a higher frequency compared to occasional smokers; 58% of daily smokers have tried to quit in the past (>6 months ago) vs 38% of occasional smokers, 12% of daily smokers reported a recent cessation attempt (<6 months ago) vs 15% of occasional smokers, while 30% of daily smokers have never tried to quit vs 48% of occasional smokers. These differences were highly statistically significant (p<0.001).

Regarding plans on smoking cessation, highly statistically significant differences were observed between daily and occasional smokers (p=0.006); 54% of daily smokers reported planning to quit smoking vs 48% of occasional

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TABLE 1. Sample characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=1976</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48%</td>
</tr>
<tr>
<td>Female</td>
<td>52%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>7%</td>
</tr>
<tr>
<td>25-34</td>
<td>14%</td>
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<tr>
<td>35-44</td>
<td>16%</td>
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<td>17%</td>
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<td>4%</td>
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<tr>
<td><strong>Smoking status</strong></td>
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<td>Smoker</td>
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</tr>
<tr>
<td>Non-smoker</td>
<td>70%</td>
</tr>
<tr>
<td>DK/NA</td>
<td>2%</td>
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</tbody>
</table>

Abbreviations: DK/NA: Do not know/No answer
smokers, 37% of daily smokers reported no plan to quit vs 48% of occasional smokers, while 9% of daily and 4% of occasional smokers were indecisive (Table 2).

Table 2. Characteristics by smoking status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Daily smoker N=338</th>
<th>Occasional smoker N=222</th>
<th>Ex-smoker N=644</th>
<th>Never smoker N=736</th>
<th>DK/NA N=36</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>173 (18%)</td>
<td>102 (11%)</td>
<td>343 (36%)</td>
<td>323 (34%)</td>
<td>13 (1%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>165 (16%)</td>
<td>120 (12%)</td>
<td>301 (29%)</td>
<td>413 (40%)</td>
<td>23 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>18-24</td>
<td>22 (16%)</td>
<td>16 (12%)</td>
<td>20 (14%)</td>
<td>76 (55%)</td>
<td>5 (4%)</td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td>57 (21%)</td>
<td>35 (13%)</td>
<td>50 (19%)</td>
<td>120 (44%)</td>
<td>8 (3%)</td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>59 (19%)</td>
<td>54 (17%)</td>
<td>74 (24%)</td>
<td>107 (35%)</td>
<td>15 (5%)</td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>80 (22%)</td>
<td>39 (11%)</td>
<td>113 (31%)</td>
<td>129 (35%)</td>
<td>5 (1%)</td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>81 (17%)</td>
<td>55 (12%)</td>
<td>167 (35%)</td>
<td>168 (36%)</td>
<td>1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>39 (12%)</td>
<td>20 (6%)</td>
<td>162 (48%)</td>
<td>113 (34%)</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>75+</td>
<td>0</td>
<td>3 (4%)</td>
<td>58 (68%)</td>
<td>23 (27%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.267</td>
</tr>
<tr>
<td>Single</td>
<td>284 (84%)</td>
<td>199 (90%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double</td>
<td>51 (15%)</td>
<td>22 (10%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple</td>
<td>2 (1%)</td>
<td>1 (0.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>1 (0.3%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type of products</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single use CC</td>
<td>172 (51%)</td>
<td>102 (46%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single use RYO</td>
<td>82 (24%)</td>
<td>60 (27%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single use HNBT</td>
<td>20 (6%)</td>
<td>14 (6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single use e-cig</td>
<td>1 (0.3%)</td>
<td>15 (7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other single use</td>
<td>9 (3%)</td>
<td>8 (4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENDS + other</td>
<td>39 (12%)</td>
<td>12 (5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other combinations</td>
<td>15 (4%)</td>
<td>11 (5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cessation attempt</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recent &lt;=6 months</td>
<td>39 (12%)</td>
<td>33 (15%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>197 (58%)</td>
<td>83 (38%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>102 (30%)</td>
<td>106 (48%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cessation plans</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Yes</td>
<td>182 (54%)</td>
<td>107 (48%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>124 (37%)</td>
<td>106 (48%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DK/NA</td>
<td>32 (9%)</td>
<td>9 (4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Post-law smoking amount</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.671</td>
</tr>
<tr>
<td>Increased</td>
<td>15 (4%)</td>
<td>7 (3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>105 (31%)</td>
<td>74 (33%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>218 (65%)</td>
<td>141 (64%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CC: combustible cigarette, RYO: roll-your own, HNBT: Heat not Burn Tobacco, e-cig: electronic cigarette, ENDS: electronic nicotine delivery system, DK/NA: Do not know/No answer
of females reported single use of combustible cigarettes vs 43% of males, while more males (28%) reported using roll-your own (RYO) vs females (23%). Additionally, more females reported single use of electronic cigarettes (e-cigarettes) than males (4% vs 1% respectively), while more males than females reported use of ENDSs in combination with other products (11% vs 7%). Highly statistically significant differences between sexes were also depicted regarding history of smoking cessation (p=0.03), with it being more frequent to men (67%) compared to women (59%). Additionally, regarding plans on smoking cessation, men showed more willingness to quit compared to women (56% vs 48%, p=0.08) (Table 3).

Analysis of tobacco products use by age groups

Highly statistically significant differences were observed in use of tobacco products and different age groups (p<0.001), with more 35-54-year-olds and 55-74-year-olds reporting single use of combustible cigarettes (56% and 50% respectively) compared to 18-34-year-olds (35%), while more 18-34-year-olds reporting single use of RYO products (46%) compared to the other age groups (Table 4).

DISCUSSION

The present study is the first to be conducted in Greece in the aftermath of the tobacco control law successful enforcement. The study is the first to show smoking prevalence in a nationally representative population in Greece in 2020, also describing the characteristics of smokers, including their smoking status and behavior, tobacco products used, motivation for, and cessation attempts, as well as the attitudes towards the law. In addition to the smoking prevalence, this study also highlights the widespread public trust expressed towards Health authorities and the almost unanimous adherence to the tobacco control law.

Smoking Prevalence

The present study showed smoking prevalence in Greece in 2020 is 28%, placing the country near the European countries average for smoking prevalence (26%)2. According to a 2012 nationally representative study20, smoking prevalence in Greece was 37% at the time, thus the country has achieved an impressive 24% decline in smoking prevalence, in the course of the past 8 years.

Age differences

The ever-evolving tobacco market is mainly targeting the youth, however, it is the younger ages that currently depict a lower smoking prevalence in Greece. A previous study21 has shown that smoking prevalence among teachers in Attica was significantly lower compared to that of the general public. Interestingly, in Greece, school-based smoking prevention programs are in effect since 200913 which may explain the lower prevalence among adolescents, young adults and teachers as well.

It is suggested that school based programs most likely had a significant contribution in the declining trend of smoking prevalence observed in recent years similarly to the reduction observed in 1978, when the first anti-smoking campaign was adopted in Greece22.

The highest smoking prevalence in our study was observed in the 25-34 and 35-44-year-olds, essential age groups for both the work production force and country demographics. Furthermore, the >65 years old group depicted a lower smoking prevalence and a high ex-smoking

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of products</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Single use CC</td>
<td>117 (43%)</td>
<td>157 (55%)</td>
<td></td>
</tr>
<tr>
<td>Single use RYO</td>
<td>77 (28%)</td>
<td>65 (23%)</td>
<td></td>
</tr>
<tr>
<td>Single use HNBT</td>
<td>16 (6%)</td>
<td>18 (6%)</td>
<td></td>
</tr>
<tr>
<td>Single use e-cig</td>
<td>4 (1%)</td>
<td>12 (4%)</td>
<td></td>
</tr>
<tr>
<td>Other single use</td>
<td>14 (5%)</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td>ENDS + other</td>
<td>30 (11%)</td>
<td>21 (7%)</td>
<td></td>
</tr>
<tr>
<td>Other combinations</td>
<td>17 (6%)</td>
<td>9 (3%)</td>
<td></td>
</tr>
<tr>
<td>Cessation attempt</td>
<td></td>
<td></td>
<td>0.034</td>
</tr>
<tr>
<td>At some point</td>
<td>185 (67%)</td>
<td>167 (59%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>90 (33%)</td>
<td>118 (41%)</td>
<td></td>
</tr>
<tr>
<td>Cessation plans</td>
<td></td>
<td></td>
<td>0.084</td>
</tr>
<tr>
<td>Yes</td>
<td>153 (56%)</td>
<td>136 (48%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>100 (36%)</td>
<td>130 (46%)</td>
<td></td>
</tr>
<tr>
<td>DK/NA</td>
<td>22 (8%)</td>
<td>19 (7%)</td>
<td></td>
</tr>
<tr>
<td>Post-law smoking amount</td>
<td></td>
<td></td>
<td>0.422</td>
</tr>
<tr>
<td>Increased</td>
<td>11 (4%)</td>
<td>11 (4%)</td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>95 (35%)</td>
<td>84 (29%)</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>169 (61%)</td>
<td>190 (67%)</td>
<td></td>
</tr>
</tbody>
</table>

prevalence, thus indicating their past smoking history. A previous study for the Health Related Quality of Life by smoking status and age, showed significant differences between smokers and never smokers especially for adult current smokers aged >45 years old23. Prevention policies and interventions should address the specific needs of each age group, aiming to reduce the overall smoking prevalence in order to achieve a healthier population across all age groups; considering that physical health declines with age and risk factors such as smoking accelerate this decline, it is suggested that age specific interventions will ultimately lead to a healthier senior population as well.

**Gender differences**

Smoking prevalence in Greece is similar among sexes, however, among smokers and in comparison with previous studies6, men depict a trend for reduction, while women depict a trend for increase. It is suggested that women in Greece most likely follow the pattern of increasing smoking prevalence associated with the delayed initiation of smoking by women due to socio-economic reasons24. More women are never smokers in Greece, more than half female smokers reported having tried to quit and yet, less women are ex-smokers compared to men and less women report to having reduced smoking since the smoking ban. Previous studies have shown that women are less likely to successfully complete a cessation attempt and more likely to relapse even after a successful cessation; while the cause for this difference remains yet to be determined, it is suggested that it depends on a complex interplay among geographical, environmental, psycho-social and biological factors24.

The higher use of novel tobacco products depicted by women in the current study, might indicate their desire to reduce smoking and associated adverse health effects, by choosing what is perceived as an alternative approach; as per previous studies, smokers are using e-cigarettes in order to withdraw from combustible cigarettes or to reduce the amount of smoking in a less stressful and financially more tolerable way as opposed to addressing to cessation clinics25. While men in Greece will benefit from smoking prevention programs, women would rather benefit from programs that augment motivation to quit and provide expert assistance through the cessation attempts. Financially affordable cessation programs with easy access and follow up for all smokers are considered crucial in terms of tobacco control policy.

**Tobacco and Novel tobacco Products used**

Majority of smokers in Greece use combustible cigarettes and the use of novel products is very low compared to the USA26,27 and the UK7. In Greece, e-cigarette users are a minority; occasional smokers with a slight female predominance are more likely to use e-cigarettes, as well as those >35 years old, a finding possibly explained by the increased income and smoking prevalence in this age group.

In Greece almost 1/3 of smokers use RYO and the young (18-34 years old) are more likely to report RYO use. Considering Greece has only recently started to emerge out of a decade-long severe financial crisis, the low income could have played a role in the observed RYO use prevalence.

Use of tobacco products may vary by country, mainly due to different tobacco control policies tailored to fit the specific market; however, Young et al showed that RYO cigarettes are more likely to be the choice of male,
low income individuals, younger than the users of combustible cigarette, who additionally are more likely to have a high degree of addiction and unwillingness to quit, while also, they are less likely to consider smoking socially denormalised\textsuperscript{28}.

**Smoking status following the tobacco control law enforcement**

The current study showed an impressive adherence to the tobacco control legislation, “a first” in Greece, as majority of participants reported adherence to the respective law. The public who expressed their general distrust to the government and health authorities in 2017\textsuperscript{29}, in 2020 totally reversed their stance across all ages, sharing a positive opinion towards the government and health authorities with regards to the smoke free law enforcement and the consequent protection from exposure to passive smoking.

Furthermore, 1/3 of smokers reported having reduced the amount of smoking since the law took effect. The long-requested enforcement of the legislation finally in place, provides therefore a favorable circumstance to enhance, recommend and apply smoking cessation programs. It is likely that the tobacco control law boosts cessation attempts for those who were already considering to quit, similarly to the boosting effect brought by the plain packaging and other tobacco control measures\textsuperscript{30}.

**CONCLUSION**

The current study is the first to show smoking prevalence is greatly declining in Greece, approaching the European average and presents the key age and sex differences among smokers, that will aid health care practitioners to achieve better results in smoking prevention and cessation interventions. Furthermore, this study also highlights the widespread public trust expressed towards Health authorities and the almost unanimous adherence to the tobacco control law.

Smoking prevention campaigns coupled with tobacco control policies and the successful implementation of the respective legislation in Greece have been widely accepted and greatly appreciated by the public.

**CONFLICT OF INTEREST**

None.

**FUNDING STATEMENT**

All authors declare that no funding was received for the work described in this manuscript.

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**ΠΕΡΙΛΗΨΗ**

Κάπνισμα στην Ελλάδα: Πού βρισκόμαστε το 2020

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**Εισαγωγή:** Από το 2008 η Ελλάδα εμφανίζει τον υψηλότερο επιπολασμό καπνιστών στην Ευρώπη. Στόχος της παρούσας μελέτης ήταν η εκτίμηση του επιπολασμού του καπνιστών στη σύγχρονη Ελλάδα, η περιγραφή των χαρακτηριστικών των Ελλήνων καπνιστών καθώς και η άποψη του κοινού αναφορικά με την πρόσφατη εφαρμογή του αντικαπνιστικού νόμου. **Μεθοδολογία:** Δέχθηκαν αντιπροσωπευτικά του ενηλίκου Ελληνικού πληθυσμού ανά φύλο και ηλικία. Η συλλογή των δεδομένων πραγματοποιήθηκε τον Φεβρουάριο 2020 με μεθοδολογία CATI (Computer Assisted Telephone Interviewing), οι διαφορές μεταξύ ομάδων εκτιμήθηκαν με Χ\textsuperscript{2}, η δε ανάλυση πραγματοποιήθηκε στο STATA 13. **Αποτελέσματα:** Στη μελέτη συμμετείχαν 1976 ενήλικες, 48% άνδρες και 52% γυναίκες. Ο επιπολασμός του καπνιστών ήταν 28%, λίγο υψηλότερος στους άντρες (29%) σε σχέση με τις γυναίκες (28%), όπως επίσης και ο επιπολασμός πρώην καπνιστών (36% άνδρες vs 29% γυναίκες). Οι γυναίκες υπερέχουν στον επιπολασμό ουδέποτε καπνιστών (40% vs 34%), διαφορές πολύ στατιστικά σημαντικές (p=0.003). Στατιστικά σημαντικές διαφορές (p<0.001) παρατηρήθηκαν μεταξύ ηλικιών, με τον υψηλότερο επιπολασμό...
καπνίσματος στις ηλικίες 35-44 (36%) και τον χαμηλότερο στις ηλικίες 65+ (15%). Ιστορικά διακοπή του καπνίσματος ήταν συχνότερο στους άντρες συγκριτικά με τις γυναίκες (67% vs 59%, p=0.03). 32% των καπνιστών ανέφεραν μειωμένη χρήση μετά την επιβολή του αντικαπνιστικού νόμου, 4% αυξημένη χρήση και 64% αμετάβλητη χρήση. Τέλος, 85% ανέφερε ότι ο νόμος εφαρμόζεται στους δημόσιους χώρους.

**Συμπεράσματα:** Ο επιπλοσμός του καπνίσματος έχει μειωθεί στην Ελλάδα, η δε αναφερόμενη συμμόρφωση με τον νόμο είναι εντυπωσιακή. Οι μεταξύ φύλων και ηλικιών διαφορές υποδεικνύουν την ανάγκη εξατομικευμένων μέτρων για επιτυχή πρόληψη και διακοπή σε κάθε υποομάδα.

**Πνεύμων 2020, 33(2):59-67.**

**Λέξεις - Κλειδιά:** Επιπλοσμός καπνίσματος, Ελλάδα, Νόμος κατά του καπνίσματος, Διακοπή καπνίσματος

**REFERENCES**

COVID-19 epidemic: Comparison of three European countries with different outcome using Gompertz function method

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Key words:
- Covid-19
- Coronavirus
- Gompertz function
- Disease progression dynamics

ABSTRACT
BACKGROUND: COVID-19 has shocked the world and fully alerted scientific community against means to tackle the pandemic. The current work tries to assess the impact of COVID-19 in three European countries and evaluate the outcome using Gompertz function methods. METHODS: Daily mortality data were collected and analyzed from European Centre for Disease Prevention and Control for Greece, France, and Italy. RESULTS: The results show a good fit between the observed data and those obtained by the Gompertz function methods for the three countries. Using standardization methods for population incidence parameters for comparison, Greece, France, and Italy show substantial differences among disease dynamics regarding incidence and mortality rates as well as disease doubling times. CONCLUSIONS: The availability of daily epidemiological data about confirmed cases gives opportunities for research contributions through mathematical models, such as Gompertz, regarding comparison and analysis of COVID-19 dynamics and future trends among regions and countries. Pneumon 2020, 33(2):68-73.

INTRODUCTION
The pandemic due to SARS-CoV-2 (severe acute respiratory syndrome coronavirus -2) and the corona virus disease 2019 (COVID-19) is associated as this manuscript is prepared- with more than 580,000 deaths globally since its appearance and has shocked the world due to the extreme measures taken worldwide to contain it. Initiated from China and the province of Wuhan in late 2019 it spread worldwide with high morbidity and mortality impact, especially in European countries and USA and currently in South America. The WHO, on 31 January, declared the COVID-19 outbreak a public health emergency of international concern (PHEIC). The outcome of the still ongoing pandemic is not clear with more than 10 million people diagnosed...
number of infections due to differences in testing policy among countries\textsuperscript{2}. Regarding Greece, the first confirmed case recorded at 28 February 2020 and subsequent cases reported in late February and early March. The first death recorded in 12 March and till today 3376 confirmed cases have been recorded with 191 deaths. This resulted in precautionary recommendations that escalated in restrictive lockdown measures on 23 March till 5 of May leading in a remarkable restriction in epidemic morbidity and mortality. However, that was not the case for other European countries, with the characteristic cost in human lives for Italy with more than 240.000 cases resulted I nearly 35.000 deaths, or France with 163.000 confirmed cases and approximately 30.000 deaths. The high incidence rates for Italy lead in total lockdown on 8 March whereas for France it was announced on March 16.

Apart of the quarantine and hygiene measures taken worldwide to contain the spreading of the disease, SARS-CoV2 awakened the scientific community in all medical associated scientific fields, in academia, industry, regulatory and hospital clinics. Efforts for development of successful tests, effective therapies, vaccine and supporting technologies are under progress and several clinical trials registered in WHO are ongoing till today\textsuperscript{1}. The continuing research is aiming to provide means for treatment in the current cases but also to prevent recurrence of future disease waves worldwide. In this respect, a key point is the exploitation of epidemiological data regarding frequency measures that analyze the current dynamics of the pandemic, but most importantly, predict future scenarios. The availability of daily data regarding COVID-19 provide means for epidemiological scientists to create analyze and evaluate several scenarios.

Modelling epidemic is a widely accepted method to study its features and to evaluate reasonable epidemiological factors during the infectious disease outbreaks\textsuperscript{4}. Important epidemiological parameters, during an outbreak like COVID-19 pandemic, include the final epidemic size, the duration and, some crucial time dimensions such as the turning time point and doubling time\textsuperscript{5}. Several methods have been used to describe crucial dynamic dimensions of a pandemic. The Gompertz model was described by Gompertz in 1825 and was used to study the populations' growth. The development of an epidemic infectious diseases has similar characteristics to those of the growth of certain biological systems and populations. In this short report, population morbidity/mortality incidence parameters are presented for the three countries, (Greece, France, and Italy) and furthermore the Gompertz sigmoidal function is employed to analyze and compare the dynamic properties of the COVID-19 pandemic.

MATERIALS AND METHODS

Epidemiological data regarding the latest available public data on COVID-19 were retrieved from the European Centre for Disease Prevention and Control (ECDPC) regarding Greece, Italy and France\textsuperscript{6}. The epidemiological data covered a period from February till June 10,2020. Data analysis was implemented through statistical software package Stata 14 (StataCorp. 2019. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). The study used time series analysis and direct standardization methods for comparison of mortality incidence parameters. The estimation of the doubling time of the disease (doubling time refers to the length of time (days) required for the cumulative confirmed COVID-19 cases to double in size) was explored at three distinct time points: i) the beginning of the outbreak after the day in which cases reached 2 per 10\textsuperscript{5} population for each country; ii) the week immediately prior the turning point of the epidemic curve and iii) the week 10 days after this. The Gompertz curve function was used to model the dynamics of the epidemic of the three countries. Generated fitted values were used to predict final epidemic size regarding the total mortality and confirmed cases. Moreover, using the first derivative of cumulative model we estimate the fitted values of the deaths and conformed cases per day to assess the time-dynamics of the outbreak such as the duration and the time turning-point.

RESULTS

Cumulative mortality incidence (per 10\textsuperscript{5} population) among several European countries are shown in Figure 1. It is evident that European countries showed different trends that can be stratified in three groups of “low”, “medium” and “high” cumulative incidence of mortality per 10\textsuperscript{5} of population, with Belgium demonstrating thus far the poorest outcome and the highest incidence of mortality (84 deaths per 10\textsuperscript{5} population). Greece demonstrate a “low” value (1.67 per 10\textsuperscript{5} population) while Italy had a “high” mortality rate (58 per 10\textsuperscript{5} population) and France grouped in “medium” mortality group (43 per 10\textsuperscript{5} population) respectively.

Figures 2 (top panel) displays the cumulative number
of observed infected persons against elapsed time (in day) as well as the daily cases (lower panel) to their fitted values, by country. An exceptionally good fit between observed and modelled data is noticed with $r^2$: 0.995 for Greece, $r^2$: 0.9914 for France and $r^2$: 0.9984 for Italy. The residuals of the fit were low and random (data not shown). Overall, the cumulative number of diagnosed positive cases is particularly large among the population of France and Italy and exceptionally low for Greece. From Figure 2, it is also revealed that the cumulative is flattening after 84, 96 and 124 days for Greece, Italy, and France, respectively, which is suggesting for these countries that currently epidemic is in the process of slowing down.

**FIGURE 1.** Cumulative incidence of mortality among several European countries till June 2020.

**FIGURE 2.** Cumulative and daily incidence of cases (per 10^5 population) between Greece, Italy and France (observed and modeled).
retreat. The modeled daily variation of the confirmed cases calculated as the first derivative of the Gompertz curve (which also showed good fit with the actual cases for all 3 countries, Figure 2, lower panel). The daily distribution of the confirmed cases demonstrates a positively skewed bell-shaped curve common for COVID-19 epidemic. However, it is clear that daily distribution of confirmed cases in Greece is flattened and scaled between 0-160 while this not the case for both Italy and France in which the daily number of diagnosed cases scaled between 0-7000.

The doubling time of mortality during the months of lockdown is represented for all three countries in Figure 3. Disease doubling time for Greece at the initiation of the epidemic is predicted approximately in 3.6 days while for Italy and France is 2.2 and 2.3 days respectively (Figure 3). As the epidemic progressed, the week just before the turning time-point, doubling time took longer for the cumulative incidence in all 3 countries, 8.9 days for Greece, 6.6 for Italy, and 5.6 days for France. Finally, a significant increase in the doubling time of mortality was observed during the de-escalated period of the epidemic curve, 59.8, 22.1 and 25.7 for Greece, Italy, and France, respectively. It is evident that for all three cases till March the doubling time remained low whereas in April had tripled and increased tenfold in the last month, indicating a sharp slowdown in the epidemic and a sharp drop in its dynamic which is now in its final slowdown as it is also estimated from the modeled curves (Figure 3).

![Figure 3. Disease doubling time in three different time points.](image)

The corresponding Gompertz curve and the data of total deaths (cumulative mortality) are shown in Figure 4 (top panel) for all 3 countries. Significant differences in the trend of the case fatality rates (CFR) till June 6 are calculated, and were approximately 5.9% for Greece, for Italy around 14.4%, and for France at 18.8%. A decline in the death rate is observed for Greece after the first week of April while for the Italy and France the decline delayed one week more beginning after April 8th and 15th respectively. Figure 4 also shows the daily deaths observed and modeled. A steady increased rate is observed with a characteristic peak at April 3 for France and April 5 for Greece whereas for Italy it is observed around April 10.

![Figure 4. Cumulative and daily incidence of deaths between Greece, Italy, and France (observed and modeled).](image)
DISCUSSION

Epidemiological and mathematical models are utilized today to describe and forecast progress of COVID-19 epidemic that could assist in decision making policies to contain the spreading of the disease\textsuperscript{7,8}. The implementation of Gombertz, or other logistic models have well-describe the epidemic progress, forecasting that COVID-19 will be in decay, in the countries that was first initiated\textsuperscript{9} as a result of the impact of containment and quarantine measures in the epidemic spread of COVID-19\textsuperscript{10,11}. Moreover based on the confirmed cases and considering that healthcare policies for containment will stay put, Gombertz and logistic models can be utilized to predict the overall impact of the epidemic during its progression\textsuperscript{12}. Utilizing available scientific data from ECDPC, this work tried using Gombertz function to describe the differences observed in Greece, Italy, and France. While, for Italy and France, prior studies tried to assess epidemic data such as infection, recovery, and mortality rates\textsuperscript{13}, for Greece thus far the implementation of epidemiological models such as Gompertz function methods, to our best knowledge, has not been reported. The precise measurement of the above outbreak parameters helps to understand not only the temporal pattern but also to estimate crucial dynamic features of an outbreak. Moreover, the instantaneous prediction of the epidemic size and growth is important factors especially if it achieved early. This information during an ongoing epidemic–such as COVID-19–could be extremely valuable for prevention and epidemic control\textsuperscript{14}. Overall, in this work the utilization of Gombertz curve function allowed to model the dynamics of COVID-19 in the three countries and describe the differences that were observed regarding the incidence and mortality rates that places them in three different categories of “low”, “medium”, and “high” impact regarding COVID-19 epidemic crisis.

Countries in Europe are lifting restrictive measures in an effort, to return to normalcy thus it is important to assess the dynamics of the COVID-19 pandemic. Under current conditions, analysis of data thus far propose that pandemic wave is near its end. This does not presuppose that its evolution cannot be different from the changes that take place in relation to the end of quarantine measures. Since Europe became the focus of the pandemic wave, generally it followed the time sequence and duration that was initially experienced in China. Regarding its intensity, Greece showed a lower incidence rate compared to other European countries such as Italy or France which suffered from high the attack rates resulted in high mortality and morbidity. This can be attributed to several factors such as lockdown and quarantine actions timely taken and complied from citizens, environmental factors geographical conditions that favor isolation or regional distancing (e.g. islands in Greece vs continental regions in other countries) and other factors all of which will be under investigation in the upcoming years from the scientific community.

CONFLICT OF INTEREST
None.

FUNDING OR GRANT SUPPORT
This work did not receive any funding or grant support.
ντα τα μοντέλα της συνάρτησης Gompertz. Μέθοδοι: Συλλέχθηκαν και αναλύθηκαν καθημερινά επιδημιολογικά δεδομένα θνησιμότητας από το Ευρωπαϊκό Κέντρο Πρόληψης και Ελέγχου Νόσων για την Ελλάδα, τη Γαλλία και την Ιταλία. Αποτελέσματα: Τα αποτελέσματα δείχνουν ότι ταιριάζουν μεταξύ των παρατηρούμενων δεδομένων και εκείνων που μοντελοποιούνται μέσω της συνάρτησης Gompertz για τις τρεις χώρες. Χρησιμοποιώντας μεθόδους για τα μέτρα συχνότητας της επιδημιολογικής πορείας της COVID-19 στον πληθυσμό, η Ελλάδα, η Γαλλία και η Ιταλία δείχνουν σημαντικές διαφορές μεταξύ της δυναμικής της νόσου όσον αφορά τα ποσοστά επιπτώσεων και θνησιμότητας καθώς και τους χρόνους διπλασιασμού των ασθενειών. Συμπεράσματα: Η διαθεσιμότητα καθημερινών επιδημιολογικών δεδομένων σχετικά με επιβεβαιωμένα κρούσματα της νόσου δίνει ευκαιρίες για ερευνητικές συνεισφορές μέσω μαθηματικών μοντέλων, όπως μέσω της συνάρτησης Gompertz, σχετικά με τη σύγκριση και ανάλυση της δυναμικής του COVID-19 και των μελλοντικών τάσεων εξέλιξης της επιδημίας μεταξύ περιοχών και χωρών.


Λέξεις - Κλειδιά: Covid-19, Κορονοϊός, Συνάρτηση Gompertz, Δυναμικότητα εξέλιξης νοσημάτων

REFERENCES

COVID-19 associated Aspergillosis

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Key words:
- Covid-19 associated pulmonary aspergillosis
- Invasive pulmonary aspergillosis
- Galactomannan

Abbreviations:
IPA: Invasive pulmonary aspergillosis
CAPA: COVID-19 associated pulmonary aspergillosis
BAL: bronchoalveolar lavage

ABSTRACT
Invasive pulmonary aspergillosis (IPA) may complicate severe COVID-19 patients. The incidence, although is not well confirmed, varies (20-35%) and the already recognized host factors for IPA in immunosuppressed patients are not identified in non-immunocompromised patients with COVID-19 associated pulmonary aspergillosis (CAPA). Additionally, clinical characteristics and radiological findings are not specific. Given the probable high burden of the co-infection, a screening diagnostic work-up, including serum and BAL galactomannan measurement, fungal cultures of upper and lower respiratory tract samples are considered mandatory in all mechanically ventilated patients with COVID-19.


Patients with severe coronavirus disease 2019 (COVID-19) are at increased risk of secondary infections, including invasive fungal infections. Such cases of invasive pulmonary aspergillosis (IPA) complicating COVID-19 disease are reported in the literature. IPA is well described in immunocompromised patients where certain risk factors, mainly neutropenia and steroid treatment, have been identified. Also patients with severe influenza are susceptible to IPA, possibly due to respiratory epithelium damage and local anosoparalysis. Similar pathophysiologic mechanisms, with lung damage due to viral replication and cytokine storm in combination with immune dysregulation, characterize COVID-19 associated pulmonary aspergillosis (CAPA).

The incidence of CAPA is unknown and may be underestimated while the used diagnostic criteria differ among the different studies. Van Arkel et al identified 6/31 (incidence 19.4%) COVID-19 patients with presumed IPA, based on the diagnostic criteria included in influenza-associated pulmonary aspergillosis case definition proposed by an expert panel. In this study tracheal aspirate and bronchoalveolar lavage (BAL) culture and serum and BAL galactomannan assays have been used to confirm the diagnosis while all patients were treated with antifungals. In another prospective study with 27 mechanically ventilated patients with COVID-19, probable IPA was diagnosed in one (4%) and putative IPA in 8 patients (incidence 30%). The cultures from respiratory specimens (BAL or bronchial aspirate), have been
collected three days after intubation while serum and BAL galactomannan levels in combination with serum β-D-glucan and quantitative real-time PCR (qPCR) in the serum or pulmonary specimens were used for the diagnosis. However, only two (2/9) patients received antifungal treatment. Rutsaert et al reported that among 20 intubated patients with COVID 19 pneumonia, 7 (incidence 35%) were suspected of IPA. In this study the AspICU algorithm was used for the evaluation of the patients. Four patients demonstrated proven IPA based on histopathological examination, one patient had negative histopathological examination but positive assays for galactomannan in BAL and serum, 2 patients had positive culture and/or BAL galactomannan post mortem while 6/7 patients received antifungal treatment with voriconazole or isavuconazole. In a retrospective study, putative IPA was diagnosed in 5/19 (incidence 26%) patients with COVID 19 - associated ARDS. For the diagnosis of IPA the modified AspICU algorithm was used also. A positive galactomannan test (≥1) in BAL or tracheal aspiration fluid or in two consecutive serum samples were also regarded as entry criteria. All patients received antifungal treatment. All the published until today studies contain a small number of patients but the key message is that the incidence of CAPA varies between 20-35% and depends on the used diagnostic criteria and the thresholds adopted in order to start antifungal treatment.

In the majority of patients with a definite diagnosis of CAPA the “conventional” host factors are not recognized. Most of the patients are immunocompetent, fact that limits the role of European Organization for Research and Treatment of Cancer Mycoses Study Group (EORTC-MSG) consensus criteria for the diagnosis of IPA. Also, the clinical characteristics do not differ among patients with and without CAPA. Additionally, radiological findings are not specific while a CT scan cannot always be performed due to the high risk of transportation. In a case series of 7 patients with suspected IPA and COVID 19 pneumonia, only one CT scan was performed without however being able to differentiate between the lesions, while ground glass opacities are common findings both in COVID 19 pneumonia and IPA. In a case report, one patient was diagnosed with IPA, 22 days after his admission to ICU for COVID-19. The patient deteriorated clinically and the chest CT showed bilateral ground-glass opacities and excavated lesions, one of which with crescent sign which did not pre-exist in previous CT. The BAL culture was positive for Aspergillus fumigatus and the patient was treated with voriconazole. However, CAPA is an early onset complication. The mean time from the intubation to the positive microbiological results for IPA is 8 days, the median time between ICU admission and IPA diagnosis 5 days and between COVID-19 symptom onset and IPA diagnosis 11.5 days.

COVID-19-associated aspergillosis seems to be related

### TABLE 1. The AspICU algorithm

<table>
<thead>
<tr>
<th>I. Proven invasive pulmonary aspergillosis</th>
<th>Microscopic analysis on sterile material</th>
</tr>
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<tbody>
<tr>
<td>- Histopathologic, cytopathologic or direct microscopic examination of a specimen obtained by needle aspiration or sterile biopsy in which hyphae are seen accompanied by evidence of associated tissue damage.</td>
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<tr>
<th>II. Putative invasive pulmonary aspergillosis (all four criteria must be met)</th>
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<tbody>
<tr>
<td>1. Aspergillus-positive lower respiratory tract specimen culture (= entry criterion)</td>
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<tr>
<td>2. Compatible signs and symptoms (one of the following)</td>
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<tr>
<td>- Fever refractory to at least 3 d of appropriate antibiotic therapy</td>
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<tr>
<td>- Recrudescent fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause</td>
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<td>- Pleuritic chest pain</td>
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<td>- Pleuritic rub</td>
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<td>- Dyspnea</td>
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<tr>
<td>- Hemoptysis</td>
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<tr>
<td>- Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support</td>
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<th>III. Aspergillus respiratory tract colonization</th>
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<tbody>
<tr>
<td>When ≥1 criterion necessary for a diagnosis of putative IPA is not met, the case is classified as Aspergillus colonization.</td>
</tr>
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</table>

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The AspICU algorithm

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 hours while still on antibiotics and without other apparent cause
   - Pleuritic chest pain
   - Pleuritic rub
   - Dyspnea
   - Hemoptysis
   - 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/mm³) preceding or at the time of ICU admission
      - Underlying hematological 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
with a high incidence and increase significantly the mortality of the patients. For this reason the systematic screening for specific IPA markers is mandatory in all mechanically ventilated patients with COVID-19. Consecutive measurements of serum and BAL galactomannan through bronchoscopy procedure, fungal cultures of tracheal / bronchial aspirate and BAL cultures are included in the diagnostic work-up. Also, the AspICU algorithm (Table 1) for distinguishing IPA in critically ill patients needs to be applied and tested. Molecular methods can also be used although the role of positive PCR in tracheal aspirate, BAL and serum needs to be further examined in non-neutropenic patients. However, serum galactomannan levels exhibit low sensitivity in patients with CAPA. In a recently published study, serum galactomannan levels were positive (≥0.5) in 2/5 patients with definite IPA (diagnosis confirmed with histopathological examination), b) in 3/5 patients with putative IPA (in the rest of the patients was not available) and c) in 2/9 patients with probable and putative IPA three days after intubation. In an autopsy study, in 6 patients the diagnosis of IPA was not confirmed post mortem although the BAL galactomannan levels were positive ante-mortem.

In conclusion, IPA may complicate COVID-19 and increase mortality. The incidence of CAPA is not well known, the diagnosis is difficult because a) the "traditional" risk factors for IPA development are not related to CAPA and b) of the lack of a diagnostic tool able to differentiate colonization from infection. For this reason, the high clinical suspicion, the evaluation of risk factors in conjunction with clinical and laboratory findings and the appropriate screening of critically ill patients may facilitate the timely diagnosis and contribute to the early treatment.

CONFLICT OF INTEREST None.
REFERENCES

The Breast and the Lung in systemic granulomatoses
A challenging cohabitation

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Key words:
- Breast and lungs
- Sarcoidosis
- Polyangiitis and granulomatosis
- Eosinophilic pneumonia

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ABSTRACT
Breast involvement in granulomatous disease is rare and may mimic cancer, while breast cancer may develop in the course of any systemic granulomatosis. We reviewed records of patients with breast disease and granulomatosis. Six females were included, all of whom diagnosed at some point with granulomatosis and a breast lesion either mimicking, breast involvement of the systemic disease, or proved to be breast cancer. This study reports the challenging cohabitation of breast cancer and any systemic granulomatosis. The rarity of said combination excludes possible pathogenetic relationship. What still remains a challenge is the unveiling of breast cancer in granulomatous diseases.


1. INTRODUCTION

Both sarcoidosis and granulomatosis with polyangiitis (GP), otherwise known as Wegener’s granulomatosis, are systemic granulomatous disorders of unknown etiology that may involve any organ or tissue1,3. Chronic eosinophilic pneumonia (CEP), although not a systemic granulomatous disease, may present with granulomas in histopathology in a consistent minority4-5.

Breast involvement seldom occurs in the above two systemic granulomatoses and even more rarely, do breast nodules constitute the presenting manifestation in both sarcoidosis and GP4-6. In any case, given the fact that in female patients it is the most common malignancy, breast cancer should always be excluded, especially as it may occur in an already established sarcoidosis5,10. We aim to describe our experience with patients presenting with the challenging combination of the above diseases in both organs.

* These authors contributed equally to this work
2. METHODS AND PATIENTS

We retrospectively reviewed the medical records of all patients diagnosed with breast disease and lung or systemic granulomatosis in a tertiary university hospital from 2014 to 2018. Epidemiological, clinical, radiological, functional and histopathological data were extracted and analyzed after patient's informed consent. Diagnosis of breast cancer, sarcoidosis, Wegener’s granulomatosis and eosinophilic pneumonia were according to international consensus criteria. The study was approved by the Medical Ethics Committee of "Attikon" University Hospital, Greece (ΕΒΔ 258/29-5-14).

3. RESULTS

Six female patients were included in the study. Their age ranged from 40 to 56 years and half of them were non-smokers. Sarcoidosis was documented in 4 patients. In the first patient sarcoidosis and breast cancer were diagnosed concomitantly during the work-up for sarcoidosis. The second one developed breast cancer 5 years post sarcoidosis onset, and the third patient presented with sarcoidosis 5 years post breast cancer diagnosis. The fourth patient presented with a breast nodule containing epithelioid non-necrotizing granulomas, compatible with sarcoidosis were documented through supraclavicular lymph-node surgical biopsy. The diagnosis of invasive ductal adenocarcinoma of the breast (Grade III) ER(-), PR(-) and HER2(+) was concomitantly evoked through surgical excision of the lesion.

The second report regards a 56-year-old non-smoker female patient who developed invasive lobular carcinoma of the breast (Grade II) ER(+), PR(+) and HER2(-) 5 years post sarcoidosis onset. Self-evaluation revealed a left breast mass that was further investigated by expert surgical clinical examination, mammography and surgical excision.

The third patient was a 55-year-old non-smoker asymptomatic female patient with a history of invasive ductal carcinoma (Grade II) ER(+), PR(+) and HER2(-) of a right accessory breast treated 5 years before. Two years after hormonal therapy, the disease relapsed necessitating surgical excision.

FIGURE 1. a, b. Posteroanterior chest radiograph of a 46-year-old non-smoker female patient disclosing asymmetrical bilateral hilar enlargement in a configuration characteristic of enlarged lymph nodes. ¹⁸F-fluoro-2-deoxyglucose positron-emission-tomography computed-tomography (¹⁸F-FDG-PET/CT) documented extensive mediastinal and hilar lymphadenopathy, especially on the right (SUV max=7.8). The diagnosis of sarcoidosis was established by biopsy of supraclavicular lymph nodes. c. Increased radiotracer uptake was also detected at the inferior outer quadrant of the left breast (SUV max=3.2) evoking further work-up for breast cancer that was documented through surgical excision of the lesion.
surgery, chemotherapy and radiotherapy followed once again by hormonal therapy. A routine yearly follow-up chest-CT 5 years post initial breast cancer revealed multiple micronodular (miliary type) lesions predominantly in the upper lung fields not existing in previous examinations (Figure 2). Increased serum Angiotensin Converting Enzyme (SACE) of 45.10 U/L (normal <42 U/L) and a lymphocytic bronchoalveolar lavage (35% lymphocytes) with a CD4/CD8 ratio of 7.6 led to the diagnosis of sarcoidosis. Apart from increased radiotracer uptake in the hilar and mediastinal lymph nodes (SUVmax=5.4) at 18F-FDG PET/CT, no other sites of activity were revealed neither at the micronodular lesions nor at the breasts and axilla regions.

Our fourth patient, a 40-year-old smoker female, underwent surgical excision of a palpable lesion in her left breast thus permitting the diagnosis of newly appearing sarcoidosis by revealing the presence of incompletely formed non-necrotizing granulomas compatible with sarcoidosis in an intramammary lymph node.

The fifth patient presented with a palpable mass in the right breast (Figure 3a) and with systemic manifestations including dry cough, fatigue, anorexia, low grade fever and body weight loss. Surgical excision of the subareolar breast nodule disclosed poorly formed granulomas, surrounded by palisading histiocytes and giant cells with central necrosis extending to the walls of arteries and veins compatible with granulomatosis with polyangiitis. She was cANCA [proteinase 3 antineutrophil cytoplasmic antibodies (PR3-ANCA)] positive and the lungs (multiple nodular lesions) (Figure 3b, 3c) and the left eye (scleritis) were also involved.

Finally, our last patient, a 54-year-old ex-smoker female presented with fever, newly appearing dyspnea on exertion and a chest CT revealing multiple bilateral infiltrates (Figure 4). She had a history of surgically treated ductal invasive breast carcinoma (Grade III) ER(-), PR(-) and HER2(+) and had also received adjuvant chemotherapy and radiotherapy 5 years before. She received glucocorticosteroids for a presumptive diagnosis of eosinophilic pneumonia based on peripheral blood and bronchoalveolar lavage eosinophilia. During prednisolone tapering symptoms relapsed and the chest CT showed newly formed infiltrates.

![FIGURE 2](image2.png)

**FIGURE 2.** High resolution computerized tomography (HRCT) scan at the level of the carina demonstrating multiple micronodular lesions (miliary pattern). It regards a 55-year-old non-smoker female patient with a history of adenocarcinoma of the breast 5 years before. No findings of relapse of the disease were documented and the diagnosis of sarcoidosis was established based on a combination of clinical, laboratory, bronchoscopic and 18F-FDG-PET/CT findings.

![FIGURE 3](image3.png)

**FIGURE 3.** a. Mammogram revealing a highly suspicious abnormality of the right breast performed after a palpable mass of the right breast was detected in a female patient with systemic manifestations, including dry cough, fatigue, anorexia, low-grade fever and body-weight loss. Surgical excision documented granulomatosis with polyangiitis. b, c. Indeed, computerized tomography (CT) of the chest revealed multiple bilateral nodular lesions which in combination with the scleritis of the left eye and the cANCA [proteinase 3 antineutrophil cytoplasmic antibodies (PR3-ANCA)] positive findings further completed the phenotype of the disease.
4. DISCUSSION

This study presents the challenging involvement of the breast in systemic granulomatoses which although rare may present a multitude of clinical scenarios: a) the breast as the first manifestation of systemic granulomatosis both in sarcoidosis and GP (2 patients), b) development of breast cancer in the course of an already established and diagnosed sarcoidosis (1 patient), c) breast cancer as an accidental finding during sarcoidosis work-up (1 patient) d) sarcoidosis onset in a patient with a history of breast cancer (1 patient) and finally, e) metastatic breast cancer triggering the development of chronic eosinophilic pneumonia as a paraneoplastic syndrome.

The development of sarcoidosis and breast cancer in the same patient is considered a rather unusual co-habitation. According to previous studies, sarcoidosis usually precedes breast cancer in approximately half of the patients; sarcoidosis follows breast cancer in one third of the patients and in the remaining both diseases develop almost concomitantly. In our case series, all three chronological connections were represented. The above-mentioned great variation of chronological association does not support any clear pathogenetic association between sarcoidosis and breast cancer although larger studies are needed to shed light on such a serious aspect of this cohabitation. Irrespective of the above considerations, any newly discovered breast lesion necessitates extensive imaging work-up by mammography, breast ultrasound, breast MRI and/or PET/CT as well as pathologic examination for documentation of its behavior. This is in accordance with the already published data recommending histological study of mammary lesions presenting either as a new finding or as a secondary finding in the background of another granulomatous or systemic disease.

In our case series, this approach permitted us to document through breast pathology the first manifestation of either sarcoidosis or GP. Breast involvement in sarcoidosis and GP is scarce and constitutes a diagnostic challenge for both the surgeon and the pathologist, especially when they consist the presenting site of disease development. In that case the differential diagnosis includes more frequent causes of granulomatous mastitis such as breast cancer with sarcoïd-like reactions, foreign body reactions, infec-
tions and rheumatoid nodules. A detailed evaluation of other signs and symptoms characteristic of each disease as well as specific serologic data may contribute to the final diagnosis. In case of uncertainty a second biopsy of another involved organ (e.g. the lung) may be determinant.

Surgical excision may also unveil the association between the breast and the lung in various atypical presentations of this challenging cohabitation. In our last patient eosinophilic pneumonia characterized by migrating infiltrates with BAL and peripheral eosinophilia was presumably triggered as a paraneoplastic syndrome of a lung metastatic breast cancer. To our knowledge this is the first report of such a paraneoplastic syndrome concerning breast cancer. Surgical biopsy of a remaining lung infiltrate after corticosteroid treatment contributed to the documentation of its metastatic nature. The inclusion of CEP in lung granulomatoses although arbitrary has its source on the fact that occasionally granulomas share the field with eosinophils in CEP histopathology.

5. CONCLUSION
In conclusion, this study reports the unusual and challenging cohabitation of breast cancer and any systemic granulomatous disease. Especially in sarcoidosis this may occur at any point of its clinical course. The rarity of said combination excludes any possible pathogenetic relationship. What still remains a challenge is the unveiling of breast cancer in granulomatous diseases.

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

Ethical approval: The study was approved by the Medical Ethics Committee of “Attikon” University Hospital, Greece (ΕΒΔ 258/29-5-14).

Declaration of conflict of interest: All authors declare that they have no conflict of interest related to this work.
REFERENCES
**TB epididymo-orchitis:**

A rare entity reveals the cause of a falsely diagnosed "COPD disease progression"

**ABSTRACT**

A 57-year-old male, diagnosed with chronic obstructive pulmonary disease (COPD) at the age of 49, with rapid disease progression over the last six months, presented with a palpable nodule in his right testicle which progressed to abscess not responding to common antibiotics and was finally submitted to right orchiectomy. The histology of the resected tissue revealed caseating granulomas that set the diagnosis of Tuberculosis (TB) and the patient was re-evaluated for the deterioration of his COPD. Mycobacterium tuberculosis was isolated in his sputum and he was treated successfully with six months of anti-tuberculous treatment. TB is included in the differential diagnosis of both testicular nodules and deteriorating COPD. Had TB been suspected in the patient's initial evaluation, he would have avoided a severe deterioration of his respiratory function, a high-risk surgery and an unnecessary orchiectomy.

**INTRODUCTION**

Tuberculosis (TB) is considered by World Health Organization (WHO) a global epidemic estimated as one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)). Apart from pulmonary disease, TB can most commonly involve pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones, and meninges, with or without concomitant pulmonary disease. However,

**Case Report**

**Abbreviations:**

epididymo-orchitis is an uncommon localization of TB and its diagnosis prior to that of pulmonary disease is rare and can be particularly challenging. Although it is rather infrequent in the developed world, TB can also be a cause of deterioration of chronic obstructive pulmonary disease (COPD)⁴. We present the case of a middle-aged man with right granulomatous epididymo-orchitis that evolved to abscess, the cause of which was diagnosed only after its resection. The patient was subsequently re-evaluated for his deteriorating COPD and was found to have concurrent pulmonary TB and received a six-month regimen of anti-TB treatment which resulted in significant improvement of his respiratory function.

CASE PRESENTATION

A 57-year-old male presented to the out-patient urology clinic with a testicular nodule, painful at palpitation, and low fever for a week. Clinical examination also revealed redness and swelling in the region. The patient's urination was not affected, while he did not have any sexual activity during this period. From his history, he was an ex-smoker (80 packyears) who was diagnosed with COPD eight years ago with slow decline of his lung function, treated with inhaled aclidinium bromide/formoterol fumarate twice a day, without need for supplemental long-term oxygen therapy (LTOT).

Six months prior to his visit he was evaluated for his COPD, which had deteriorated rapidly, with worsening dyspnea (modified medical research council (mMRC)=4 from 2), increased sputum production and hypoxia. He also had a weight loss of 8Kg. At that time, the patient had performed spirometry which had revealed significant forced expiratory volume in 1 second (FEV1) decrease (780ml (25% of predicted) from 1564ml (50% of predicted)) since his previous visit. Static lung volumes and diffusion capacity for Carbon Monoxide (DLCO) had revealed severe gas trapping with a residual volume (RV) at 3587ml (158% of predicted) plus an impaired DLCO at 31% of predicted. His arterial blood gas (ABG) analysis had showed type I respiratory failure with a pO2 at 53mmHg and LTOT was initiated. His chest computed tomography (CT) had revealed central bronchiectasis, panlobular emphysema and incipient fibrosis bilaterally and mass-like infiltrations in the upper left lobe and in the middle and lower right lobe (figure 1a – d). The patient had been subjected in bronchoscopy and the results of his biopsy and cytology came back negative for malignancy. Since no cause was identified, his deterioration was characterised as “disease progression”. His history was otherwise unremarkable.

At presentation, the patient’s white blood cells (WBC) were slightly elevated (10.670/μL (68.0% neutrophils, 22.2% lymphocytes)) and his c-reactive protein (CRP) was also elevated (7.48mg/dl). His scrotum ultrasound revealed a multispaced cystic lesion of the right testicle. A scrotum magnetic resonance imaging (MRI) was ordered and showed an enlarged right testis with heterogeneity seen on coronal T1 fat sat images and low signal intensity intratesticular lesions along with severe enlargement of the right epididymis seen on axial T2 fat sat images. After contrast material administration, an enhancement of the testicular lesions and peripheral enhancement of the epididymis were observed on axial and coronal T1 fat sat images. Right hydrocele was also visible (figures 2a – d).

Based on his scrotum imaging along with the compatible clinical findings, the patient was diagnosed with epididymo-orchitis and was treated with Ciprofloxacin which later changed to Piperacillin/Tazobactam plus Daptomycin although without success. His infection worsened and progressed to abscess formation, thus he was subjected to right orchiectomy, the histology of which revealed caseating granulomatous inflammation by lymphocytes, histiocytes and multinucleated giant cells (Langhans type).

With the histological diagnosis of testicular TB, he presented at the TB out-patient clinic where standard quadruple anti-TB treatment with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol was initiated. Interestingly his sputum culture grew positive for Mycobacterium tuberculosis sensitive to all first-line drugs. Thus the patient received 6 months of treatment (2RHEZ/4RE).

His sputum culture reversed to negative after 40 days of treatment and his sputum production decreased. At the end of treatment his dyspnea improved significantly (mMRC = 2) and he had regained 6Kg. A significant improvement in his pulmonary function was observed (FEV1=1387ml, 44% predicted from 780ml, 25% predicted, RV=2882ml, 127% predicted from 3587ml, 158% predicted) and his chest CT infiltrations dissolved, while his pO2 increased from 53mmHg to 73mmHg at room air. LTOT was discontinued.

DISCUSSION

The differential diagnosis of scrotal masses includes a wide variety of possible causes, the most common of which at our patient’s age are infection and malignancy⁵. The initial diagnosis of epididymo-orchitis was based on
FIGURE 1. a-d. Chest CT revealing central bronchiectasis, panlobular emphysema and incipient fibrosis bilaterally (a) and mass-like infiltrations in the upper left lobe (b) and in the middle (c) and lower right lobe (d).

FIGURE 2. a-d. Enlarged right testis with heterogeneity seen on coronal T1 fat sat images (a) and low signal intensity intratesticular lesions along with severe enlargement of the right epididymis seen on axial T2 fat sat images (b). After contrast material administration enhancement of the testicular lesions and peripheral enhancement of the epididymis are observed on axial (c) and coronal (d) T1 fat sat images. Right hydrocele.

clinical findings and duration of symptoms. However, the patient's scrotal nodule could have been of malignant origin without causing any symptoms until its contamination. This clinical scenario could have been investigated if a biopsy was taken from the lesion for microbiological, cytological and/or histological examination, but unfor-
Unfortunately was not. This was particularly relevant after the antibiotic treatment failure in order to identify the responsible pathogen and to guide treatment.

The emergence of the patient's scrotal mass along with the worsening of his COPD could have also raised concerns about a common causative factor and TB should have been included in the differential diagnosis. However, the patient's increased sputum production was initially attributed to the presence of bronchiectasis and his weight loss was attributed to a possible malignancy. Moreover, other specific symptoms or signs of TB, such as low fever, night sweats or hemoptysis, were lacking from the patient's history at his initial respiratory evaluation. Unfortunately culture for common bacteria, TB and non-tuberculous mycobacteria (NTM) was not performed. Patients with severe emphysema are often colonized with common bacteria and suffer from exacerbations, especially when they also have bronchiectasis\textsuperscript{6,7}. Emphysema and bronchiectasis are also predispositional factors for TB and NTM infections\textsuperscript{8,9}. Furthermore it is very likely that worsening of COPD was initially considered independently from the epididymo-orchitis and the two different physicians (respiratory physician and urologist) followed separate diagnostics paths. Indeed, testis is a rather uncommon localization of TB\textsuperscript{10,11}. Nonetheless, half of the patients with genitourinary TB, also present pulmonary TB\textsuperscript{12}. In a review of genitourinary TB, out of 3109 patients treated for TB in a medical center during an 11-year period, only 28 (0.9\%) had testicular or epididymal TB, while more recently, testicular TB was calculated at about 11.5\% of all genitourinary TB cases, with exact prevalence varying, depending on the area and the time period\textsuperscript{13,14}.

Testicular abscesses most commonly share the same pathogens with epididymo-orchitis\textsuperscript{12}. Thus, it is not unusual for patients with testicular TB to initiate treatment with common antibiotics before the diagnosis of TB\textsuperscript{13}. The imaging tools for the diagnosis of testicular TB include ultrasonography and MRI\textsuperscript{13,15}. However, MRI is more preferable, since ultrasonography may potentially miss testicular pathology\textsuperscript{15}. The diagnosis of testicular TB is confirmed with the isolation of the \textit{Mycobacterium tuberculosis} or the finding of caseating granulomas in the materials obtained from the affected area\textsuperscript{13,14}.

The first line of treatment in testicular TB is pharmacotherapy according to current guidelines for TB treatment\textsuperscript{16}. Surgery is the second line of treatment when pharmacotherapy fails or the first choice in cases of abscesses and cutaneous fistulas or extensive involvement of the epididymis and testis\textsuperscript{14}. The preferred time of surgery is 4-6 weeks after the initiation of pharmacotherapy\textsuperscript{17}. It has been reported in some cases that surgery was performed due to difficulty in differential diagnosis between abscess and malignancy\textsuperscript{14}. In the case described here, surgery was performed after the treatment failure with common antibiotics and the incipient necrosis so that sepsis would be avoided.

The diagnosis of TB was confirmed after the surgery based on the compatible clinical and histological findings, since the isolation of the \textit{Mycobacterium tuberculosis} was not attempted. Nevertheless, the diagnosis of the testicular disease led to the suspicion of pulmonary TB, which was later confirmed with the isolation of the \textit{Mycobacterium tuberculosis} from a sputum culture according to current guidelines\textsuperscript{18}. Although uncommon, there are cases in the literature, in which pulmonary TB was confirmed after the diagnosis of testicular disease\textsuperscript{19}. Regarding the treatment, in this case the patient received quadruple anti-TB treatment for two months (intensive phase) and Isoniazid plus Rifampicin alone for another four months (continuation phase) according to current guidelines for the treatment of microbiologically confirmed pulmonary TB and of genitourinary TB, by drug-susceptible Mycobacteria\textsuperscript{16}.

In conclusion, poor differential diagnostic effort, along with the confusion caused by the two independent diagnostic approaches led to an undesirable outcome. Had TB been suspected in his initial evaluations, the patient could have avoided a high-risk surgery and an unnecessary orchiectomy.

\textbf{CONFLICT OF INTEREST}

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Φυματιώδης ορχεοεπιδιδυμίτιδα: μία σπάνια οντότητα οδηγεί στην αποκάλυψη λανθασμένης διάγνωσης «επιδείνωσης ΧΑΠ»

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Ασθενής 57 ετών με χρόνια αποφρακτική πνευμοπάθεια (ΧΑΠ) διαγνωσθείσα από 8ετίας και ταχέως επιδεινωθείσα από εξαμήνου, προσήλθε με ψηλαφητό μόρφωμα δεξιού όρχεως, που εξελίχθηκε σε απόστημα. Λόγω μη ανταπόκρισης σε κοινά αντιβιοτικά διενεργήθηκε ορχεκτομή, η οποία αποκάλυψε νεκρωτικά κοκκιώματα. Στο πλαίσιο αυτό τέθηκε η διάγνωση της φυματιώδους ορχεοεπιδιδυμίτιδας και επανεκτιμήθηκε η επιδείνωση της ΧΑΠ. Στα πτύελα απομονώθηκε M. tuberculosis, και ο ασθενής έλαβε τετραπλή εξάμηνη αντιφυματική αγωγή, στην οποία ανταποκρίθηκε επιτυχώς. Η φυματίωση συμπεριλαμβάνεται στη διαφορική διάγνωση τόσο των μορφωμάτων του όρχεως όσο και της επιδείνωσης της ΧΑΠ. Αν η υπόνοια της φυματίωσης είχε τεθεί εξαρχής, ο ασθενής πιθανώς να είχε αποφύγει την επιδείνωση της ΧΑΠ αλλά και μία άχρηστη ορχεκτομή.


Λέξεις - Κλειδιά: Φυματίωση, Ορχοεπιδιδυμίτιδα, ΧΑΠ, Πρόοδος νόσου

REFERENCES


The therapeutic potential of inhaled-GM-CSF in severe a-PAP

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Autoantibodies against Granulocyte-Macrophage-Colony-Stimulating-factor (GM-CSF) disrupt signaling in alveolar macrophages to effectively remove surfactant from the alveoli and lead to autoimmune pulmonary alveolar proteinosis (aPAP). A 39-year-old woman diagnosed with a-PAP was referred to us for further evaluation and treatment initiation with inhaled (i)-GM-CSF. SaO₂ on room air was 70%, DLCO 20% predicted and anti-GM-CSF titer 71.5 μg/ml (normal <3). High-resolution computerized tomography (HRCT) of the chest demonstrated extensive lung parenchyma involvement with ground-glass opacity associated with thickened interlobular lines (cobble stone or crazy paving pattern) differentiating distinctly a-PAP affected lung from non-involved tissue (Figure 1A). Pending the approval of the National-Sanitary-System for the off-label i-GM-CSF administration, the patient was treated every other 4 days with drug (250μg) dispensed by other Greek patients, not yet expired. Despite immediate treatment initiation, the patient further deteriorated with high oxygen needs. We re-scheduled treatment to daily i-GM-CSF and plasmapheresis, and considered transfer to abroad for whole lung lavage. The patient gradually recovered with HRCT of the chest showing a clear improvement of ground glass opacities leaving no traction bronchiectasis or other signs of fibrosis (Figure 1B). A few months later she was in complete remission and we currently de-escalate i-GM-CSF.

In conclusion, as we are moving ahead from whole lung lavage treatment into the era of i-GM-CSF for aPAP, clinical paradigm may insight fully complement the studies, eagerly needed but hardly feasible, evaluating i-GM-CSF time and dose responses to refine the management of severe disease⁵．

Key words:
- Severe a-PAP
- Treatment
- Inhaled-GM-CSF

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Statement

This is to certify that the images have not been previously published and that the patient has provided written permission to publish the case.

REFERENCES

The unexpected clinical behavior of a-PAP

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Key words:
- a-PAP
- Bromhexine
- Remission

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A 42-year-old woman, smoker (20 pack/years) painter and sculptor exposed to dusts, diagnosed with pulmonary alveolar proteinosis (PAP) was referred to us on April-2019 for further evaluation and treatment with inhaled-granulocyte-macrophage-colony-stimulating-factor (i-GM-CSF) (Figure 1A, Figure 1B). Oxygen saturation on room air was 88% and DLCO 35% predicted. Meanwhile of the results of anti-GM-CSF titer and in relation of her moderately good clinical condition the patient was advised to quit smoking.

In this posteroanterior (PA) chest radiography (CXR) confluent ground glass and consolidation specifically distributed in the pericardial and lower lung fields are detected. Note that the lateral costophrenic angles should be filled with pleuritic fluid if this was a common cardiac failure.

In the synchronous high-resolution computerized tomography (HRCT) diffuse ground glass opacities not reaching the pleura are identified. There is also a diffuse interstitial involvement around the interlobular lines involved.

In this PA CXR four months later the lung parenchyma looks normal.

The synchronous HRCT depicts a normal lung without significant scars from the previous insult except a minimal ground glass opacity in the superior segment of the right lower lobe.
smoking, avoid any harmful professional exposure and to initiate oral bromhexine syrup daily. Three months later anti-GM-CSF titer documented autoimmune-PAP (101.16 μg/ml). Upon reevaluation on July-2019 we made the serendipitous observation that all clinical, physiological and radiological parameters (Figure 1C, Figure 1D) of the disease were totally normalized and the disease was unexpectedly in complete “spontaneous” remission. Anecdotal reports as well as our personal experience underline the possible beneficial effect of bromhexine in PAP that may act as facilitator of washing-out stagnant surfactant1-6.

Statement
This is to certify that the images have not been previously published and that the authors have no conflict of interest.

REFERENCES
Interesting CT imaging in patient with cavitary lung lesion

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A 41-year-old never-smoker male was admitted to our hospital with fever and hemoptysis during the last 10 days. The patient had undergone gastric tube interposition, reconstruction of the hypopharynx and gastric-hypopharyngial anastomosis, following sulfuric acid aspiration twenty-two years ago. He had been also diagnosed with pulmonary nocardiosis ten years ago and due to recurrent episodes of hemoptysis left upper lobectomy was performed.

Clinical evaluation on admission revealed: SaO2 97% on room air and body temperature 38°C. Physical examination of chest was normal. Chest Computed Tomography revealed cavitary lesion in lower left lobe, of 5.5 cm maximum diameter with air fluid, as well as adjacent bronchiectatic changes.

The patient received IV antimicrobial therapy with piperacillin/tazobactam 4.5g x 4, vancomycin 2gr x1, moxifloxacin 400mg x1, as well as trimethoprime/sulphamethoxazole x1, due to the past history of pulmonary nocardiosis. The purified protein derivative skin test (tuberculosis test) was negative. Microbiological analysis of patient’s sputum yielded no acid-fast, positive gram staining (Streptococcus Viridans). Gastroscopy and esophagography were performed during the patient’s hospitalization to exclude any anastomotic leaks or bronchoesophageal fistulas. Our patient was discharged after seven days of hospitalization, with significant clinical and radiological improvement.

FIGURE 1. Gastric tube interposition (Arrow), reconstruction of the hypopharynx and gastric-hypopharyngial anastomosis.

FIGURE 2. Cavitary lesion with air fluid of left lower lobe (black arrow). Gastric tube (white arrow).
Incidental finding of multiple pulmonary embolisms on chest X-Ray

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A 52-year-old female patient had multiple symptomatic osteoporotic compression fractures of the thoracic and lumbar spine. She underwent a vertebroplasty for vertebrae T11, T12, L1, uncomplicated, with a good therapeutic result. Two years later, the routine chest radiograph showed multiple tubular radiographically dense opacities corresponding to pulmonary vessels blocked with polymethyl methacrylate (PMMA) in several areas of the lungs (Figure 1). Obviously, this silent PMMA embolism had occurred following the multilevel vertebroplasty 2 years earlier. The patient did not have respiratory symptoms at any time after vertebroplasty. CT-scanning showed pulmonary embolism of right anterior branch of pulmonary artery from a high-density material and multiple unilateral micro-emboli of the lungs (Figure 2). Vertebroplasty is the injection of bone cement, generally (PMMA), into a vertebral body (VB). Injection of PMMA into the VB is undertaken after careful imaging confirming insertion of the trocar in the anteromedial portion of the VB. The injection must be done with the aid of live fluoroscopic guidance. If the PMMA begins to go into a blood vessel or toward the posterior cortical margin, the injection must be halted immediately. Complications have been reported; a review revealed 58 reported complications from 1999 through 2003 of approximately 200,000 procedures performed1. There is only one case with asymptomatic pulmonary embolism in a patient found 1 year after the procedure.

REFERENCE

Dear Editor

Only recently, Greece exited a 10-year financial rescue program which, among other consequences, had a negative impact on its national health system. In addition, since 2011 and the “Arab Spring”, the country faces a migrant and refugee crisis, which has led to overcrowded camps and hotspots on the Greek islands of Lesvos, Chios, Kos, Leros and Samos. As of the end of April, 2020, there were approximately 40,000 migrants and refugees in these facilities, whose capacity marginally exceeds 6,000.

Greece now, in a short period of time, must address a new crisis: the coronavirus disease 2019 (COVID-19) pandemic, for which there is still no effective vaccine. Admittedly, the Greek government effectively launched strict suppression measures early on, controlling successfully the first wave of COVID-19 in the country. However, the problem is even more complex. Greek authorities are called to prevent a second wave and to control the spread of the virus among thousands of migrants and refugees who live in close proximity into camps and hotspots, many of which lack basic infrastructure. For public health reasons, their movement has been restricted by law, with an enforced lockdown between 7 p.m. and 7 a.m., and only one person is allowed out per family. Additionally, the Greek government has implemented intensive cleaning of communal areas, compulsory temperature measurement of new arrivals, and setting up quarantine areas, while supporting with additional medical staff.

These measures can undoubtedly contribute in preventing the occurrence of a single COVID-19 case into these facilities. However, there is an important risk for an overwhelming spread of the infection after a single case, since social distancing or prompt isolation is practically impossible into these densely packed settings. Local outbreaks have already occurred in refugee camps on the Greek mainland. In a similar scenario in refugee facilities on the above-mentioned Greek islands, the healthcare capacity of the 5 local hospitals, 1 on each island, with a total of up to 20 intensive care beds, may be severely exceeded. Even more so given the fact that naval or air transportation are laborious due to infection control requirements.
It is easily understood that, despite the Greek government’s efforts and interventions, Greece will need all the help it can get from the European Union and the United Nations for an effective and prompt management of the COVID-19 pandemic problem in the islands that host refugee camps and hotspots. It is a global humanitarian duty to prevent a catastrophic COVID-19 spread in this vulnerable population.

CONFLICT OF INTEREST
None.

FUNDING
None.

REFERENCES
INSTRUCTIONS FOR AUTHORS

PNEUMON is an open access, single blind peer reviewed, published quarterly in English as the official scientific journal of the Hellenic Thoracic Society, both in print and online. The Journal publishes original papers of international interest on laboratory and clinical research that are pertinent to lung biology and disease. Clinical and experimental work dealing with the whole field of respiratory medicine, including allied health, cell and molecular biology, epidemiology, immunology, pathology, pharmacology, physiology, intensive and critical care, pediatric respiratory medicine and thoracic surgery will be considered for publication.

Articles published in PNEUMON address topics related to pneumonology and critical care medicine in the following categories: (1) Editorials, (2) Reviews, (3) Basic and Clinical Research Studies, (4) Case Reports, (5) Special Articles, and (6) Letters to the Editor. Details on the length and number of references for each type of publication can be found at the end of this text.

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PNEUMON requires that investigators register their clinical trials (other than phase 1 trials) in a public trials registry (e.g. http://www.clinicaltrials.gov). According to the WHO definition, a clinical trial is “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.” The name of the registry and the registration number should be clearly stated in the last paragraph of the Abstract and in the Materials and Methods section of the manuscript. Purely observational studies (those in which the assignment of the medical intervention is not the discretion of the investigator) do not require registration.

Further information on this subject can be found on the International Committee of Medical Journal Editors website (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html).

In manuscripts that report data from randomized clinical trials, authors should follow the flow diagram and/or checklist of the Consolidated Standards of Reporting Trials (CONSORT) format and provide all the information required (available at: http://www.consort-statement.org; accessed November 9, 2008).

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PNEUMON suggests that authors follow the international standards for other types of publications. For example, (1) meta-analyses and systematic reviews should conform to the QUOROM requirements (Moher D, et al. Lancet 1999; 356:1996-2000); (2) meta-analyses of observational studies in epidemiology should conform to the MOOSE requirements (Stroup DF, et al. JAMA 2000; 208-2012); (3) studies of diagnostic accuracy should conform to the STARD statement (available at http://www.stard-statement.org; accessed November 9, 2008); and (4) observational studies in epidemiology should conform to the STROBE statement (von Elm E, et al. BMJ 2007;335:806-808).

Conflicts of Interest

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The total number of words of the manuscript and the abstract.

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A structured abstract should be provided of up to 250 words. It should

Table 1. Suggested Maximum Length Requirements for Submitted Manuscripts (November 2008)

<table>
<thead>
<tr>
<th>Type of publication</th>
<th>Abstract (words)</th>
<th>Body of Manuscript (words)*</th>
<th>References (number)</th>
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<td>Editorial</td>
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<td>4500</td>
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<tr>
<td>Special Articles</td>
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<td>Images</td>
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<tr>
<td>Correspondence</td>
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<td>500</td>
<td>5</td>
</tr>
</tbody>
</table>

*excluding References, Tables, Acknowledgements and Figure Legends
n/a: not applicable
consist of our paragraphs, labeled Background, Methods, Results, and Conclusions. They should briefly describe, respectively, the problem being addressed in the study, how the study was performed, the most important results, and what the authors conclude from the results. Abbreviations should be avoided and, if used, they should be explained the first time mentioned.

Greek abstract is obligatory for Greek authors up to 250 words.

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Acknowledgements
Acknowledge the persons who provided a true contribution and who endorse the data and conclusions. Acknowledge any funding sources.

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