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# Epidemiological characteristics and outcomes from 187 patients with COVID-19 admitted to 6 reference centers in Greece: an observational study during the first wave of the COVID-19 pandemic

## Abstract

**Introduction:** Epidemiological data from patients with COVID-19 has been recently published in several countries. Nationwide data of hospitalized patients with COVID-19 in Greece remain scarce.

**Material and methods:** This was an observational, retrospective study from 6 reference centers between February 26 and May 15, 2020.

**Results:** The patients were mostly males (65.7%) and never smokers (57.2%) of median age 60 (95% CI: 57.6–64) years. The majority of the subjects (98%) were treated with the standard-of-care therapeutic regimen at that time, including hydroxychloroquine and azithromycin. Median time of hospitalization was 10 days (95% CI: 10–12). Twenty-five (13.3%) individuals were intubated and 8 died (4.2%). The patients with high neutrophil-to-lymphocyte ratio (NLR) (> 3.58) exhibited more severe disease as indicated by significantly increased World Health Organization (WHO) R&D ordinal scale (4; 95% CI: 4–4 vs 3; 95% CI: 3–4,  $p = 0.0001$ ) and MaxFiO<sub>2</sub>% (50; 95% CI: 38.2–50 vs 29.5; 95% CI: 21–31,  $p < 0.0001$ ). The patients with increased lactate dehydrogenase (LDH) levels (> 270 IU/ml) also exhibited more advanced disease compared to the low LDH group (< 270 IU/ml) as indicated by both WHO R&D ordinal scale (4; 95% CI: 4–4 vs 4; 95% CI: 3–4,  $p = 0.0001$ ) and MaxFiO<sub>2</sub>% (50; 95% CI: 35–60 vs 28; 95% CI: 21–31,  $p < 0.0001$ ).

**Conclusion:** We present the first epidemiological report from a low-incidence and mortality COVID-19 country. NLR and LDH may represent reliable disease prognosticators leading to timely treatment decisions.

**Key words:** COVID-19, severity, neutrophil-to-lymphocyte ratio, LDH, prognosticators

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## Introduction

The emergence and spread of 2019 novel coronavirus disease (COVID-19) and the associated

acute respiratory distress syndrome (ARDS) are causing a growing global public health crisis. The virus is presumed to have originated in Wuhan, Hubei province, China, in bats. On January 7<sup>th</sup>,

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2020, the virus was identified as a coronavirus with a > 70% similarity to the SARS-CoV and was named SARS-CoV-2 [1]. SARS-CoV-2 mainly affects the upper and lower respiratory tracts, entering into the respiratory mucosa through its receptor, the angiotensin-converting enzyme 2 (ACE2), and leading to a cascade of events, including pulmonary epithelial cell apoptosis, fibroblast proliferation, T-cell activation and a massive production of inflammatory cytokines [2]. The disease is mild in most people (80%) causing general symptoms such as cough, fever, general fatigue, and in some cases, dyspnea, anosmia and anorexia. In some patients, especially among the elderly and those with comorbidities, COVID-19 may progress to ARDS and multi-organ failure. There are no specific antiviral agents for COVID-19. All applied therapeutic regimens represent off-label use of non-COVID-19 drugs [3–6].

In Greece, the first case was reported on February 26<sup>th</sup>, and the peak incidence with 1.6 cases per 100,000 population per day (156 total cases) was reached on April 21<sup>st</sup> with regards to the first wave. Currently, we are facing the second wave of pandemic with far more cases (peak: 3,316 daily cases, November 12<sup>th</sup>, 2020). As of December 27<sup>th</sup>, 2020, which is the day that vaccination started in our country, 135,114 cases have been reported in Greece resulting in 4,553 deaths. Several epidemiological reports from all over the world have been recently published [7]. This article represents a summary of the ‘success story’ during the first wave in Greece. The aim of the study was to identify detailed baseline characteristics, outcomes and treatment approaches of a large (based on our national standards) cohort of hospitalized patients with COVID-19 during the first wave of the pandemic. Our paper represents the first epidemiological report from a low-incidence and mortality country during the first wave where the health-care system has not been overwhelmed by the pandemic. We provide scientific evidence that could potentially reflect the beneficial impact of early implementation of lockdown as well as other containment measures.

## Material and methods

This was an observational, retrospective study. From February 26<sup>th</sup>, when the first case was documented, till May 15<sup>th</sup>, 2020, epidemiological data from patients hospitalized for COVID-19 in 6 reference centers in north, central and south Greece, including the Department of Internal and Respiratory Medicine, University Hospital of Patras, 1<sup>st</sup> and 2<sup>nd</sup> Academic Department of Respi-

ratory Medicine, SOTIRIA and ATTIKON General Hospital, National and Kapodistrian University of Athens, 4<sup>th</sup> and 5<sup>th</sup> Department of Respiratory Medicine, SOTIRIA General Hospital, Athens and Department of COVID-19, Papanikolaou General Hospital, Thessaloniki, was retrospectively collected and analyzed. The study was approved by the Institutional Review Board and the Local Ethics Committee (Protocol Number: 8681/1-4-20). Diagnosis of COVID-19 was based on a positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) of an upper respiratory nasopharyngeal (or oropharyngeal) swab. Subsequently, we collected demographics and laboratory tests, including parameters of complete blood count (CBC), lactate dehydrogenase (LDH), pro-calcitonin and D-dimers. Comorbid conditions were also recorded. Disease severity was evaluated through maximum fraction of inspired oxygen % (FiO<sub>2</sub>%) during hospitalization, as well as through World Health Organization (WHO) R&D Blueprint ordinal scale on admission (minimum value: 1, maximum value: 7). Increased values of WHO R&D score were indicative of more severe disease.

## Statistical analysis

Median values of all laboratory tests were recorded. Median values were preferred, as the Kolmogorov–Smirnov test for normal distribution rejected normality. The Mann–Whitney test was applied to assess differences in maximum FiO<sub>2</sub>% during hospitalization and WHO R&D Blueprint ordinal scale on admission between the subgroups of patients split by the median value of the studied parameters (high and low subgroup). Follow-up assessment was performed from the date of admission till discharge or intubation or death (event). P-values < 0.05 were considered statistically significant. Results were illustrated in tables and figures.

## Results

### Clinical and radiological data

Baseline characteristics of the study population are presented in Table 1. A total number of 187 cases was enrolled and analyzed. The patients were mostly males (65.7%) of median age 60 (95% CI: 57.6–64) years and 16% had a recent travel history to a highly endemic country, including Italy, China and Israel. Strikingly, the majority of patients (57.2%) were non-smokers. Regarding clinical image, fever (85%), cough (51.3%) and general fatigue (50.3%) were the predominant features, while 1/10 experienced anosmia and only

34% of patients (64/187) suffered from dyspnea despite respiratory failure, as indicated by  $\text{SaO}_2 < 93\%$  in 66% of cases. Radiological findings were strikingly homogeneous across the vast majority of patients and involved features of bilateral interstitial infiltrates in plain chest x-ray (95%) and features resembling organizing pneumonia and non-specific interstitial pneumonia with areas of consolidation and ground-glass opacities with no upper or lower zone predominance in chest computed tomography (71%) (Table 2). Arterial hypertension was the most commonly encountered comorbidity (32.6%), while 10% and 4.8% of our patients suffered from diabetes mellitus and hypothyroidism, respectively. Interestingly, the incidence of chronic obstructive lung diseases, including asthma and chronic obstructive pulmonary disease (COPD), was very low with an overall frequency of 1.1% (Table 3). The vast majority of patients were treated with the standard-of-care therapeutic regimen at that time, including hydroxychloroquine and azithromycin for 7 days. Lopinavir and ritonavir was administered in 17.6% of our patients, while only 1.7% and 5.1% received remdesivir and colchicine, respectively, within the context of a clinical trial. Low-molecular weight heparin on a prophylactic basis was administered in 85.6% of patients. Biological agents including anti-IL6 (tocilizumab) and anti-IL1r (anakinra) were administered in 7 patients (3.9%) (Table 4). Median time of hospitalization was 10 days (95% CI: 10–12). Twenty-five (13.3%) patients were intubated and 8 died (4.2%). Missing data on outcome analysis was reported in 11/187 (5.8%).

### Laboratory data

Laboratory data of the study population are presented in Table 5. Lymphopenia ( $< 1200/\mu\text{L}$ ) was the most commonly encountered laboratory finding (53.5%) of our study population with median values of  $1112/\mu\text{l}$  (95% CI: 1000–1220). Subsequently, increased neutrophil-to-lymphocyte ratio (NLR) was also reported with a median value of 3.58 (95% CI: 2.98–3.91). Elevated ferritin levels ( $> 90\text{ng/ml}$ ) were present in most of our patients (67%) with a median value of 430.8 (95% CI: 363.1–483.9). Increased LDH levels ( $> 245 \text{ IU/ml}$ ) were present in the majority of the study population (58.8%) with a median value of 270 (95% CI: 250.7–291.2). Increased D-dimer levels ( $> 0.5 \text{ ng/ml}$ ) were present in 28/187 (15%) of the study population. Interestingly, the patients with high neutrophil-to-lymphocyte ratio ( $> 3.58$ ) exhibited more severe disease as indicated

**Table 1. Baseline characteristics of the patients enrolled in the study**

Characteristics	
Total number of patients	187
Age median (95% CI)	60 (57.6–64)
Males/females, n (%)	123 (65.8)/64 (34.2)
Current/ex-smokers, n (%)	80 (42.8)
Never smokers, n (%)	107 (57.2)
History of recent travel abroad, n (%)	30 (16)

CI — confidence interval

**Table 2. Clinical and radiological features on admission of the patients enrolled in the study**

Disease	
Fever, n (%)	159/187 (85.0)
Anosmia, n (%)	19/187 (10.2)
Anorexia, n (%)	46/187 (24.6)
Cough, n (%)	96/187 (51.3)
Dyspnea, n (%)	64/187 (34.2)
Fatigue, n (%)	94/187 (50.3)
$\text{SaO}_2 < 93\%$ , n (%)	124/187 (66.3)
Bilateral infiltrates (chest X-ray), n (%)	177/187 (94.7)
Bilateral infiltrates (chest computed tomography scan), n (%)	131/187 (70.1)

**Table 3. Comorbidities of the patients enrolled in the study**

Comorbidity	
Hypertension, n (%)	61/187 (32.6)
Diabetes mellitus, n (%)	17/187 (9.09)
Cancer, n (%)	13/187 (7.0)
Atrial fibrillation, n (%)	8/187 (4.3)
Heart failure, n (%)	5/187 (2.7)
Hypothyroidism, n (%)	9/187 (4.8)
Asthma, n (%)	2/187 (1.1)
Chronic obstructive pulmonary disease, n (%)	4/187 (2.2)

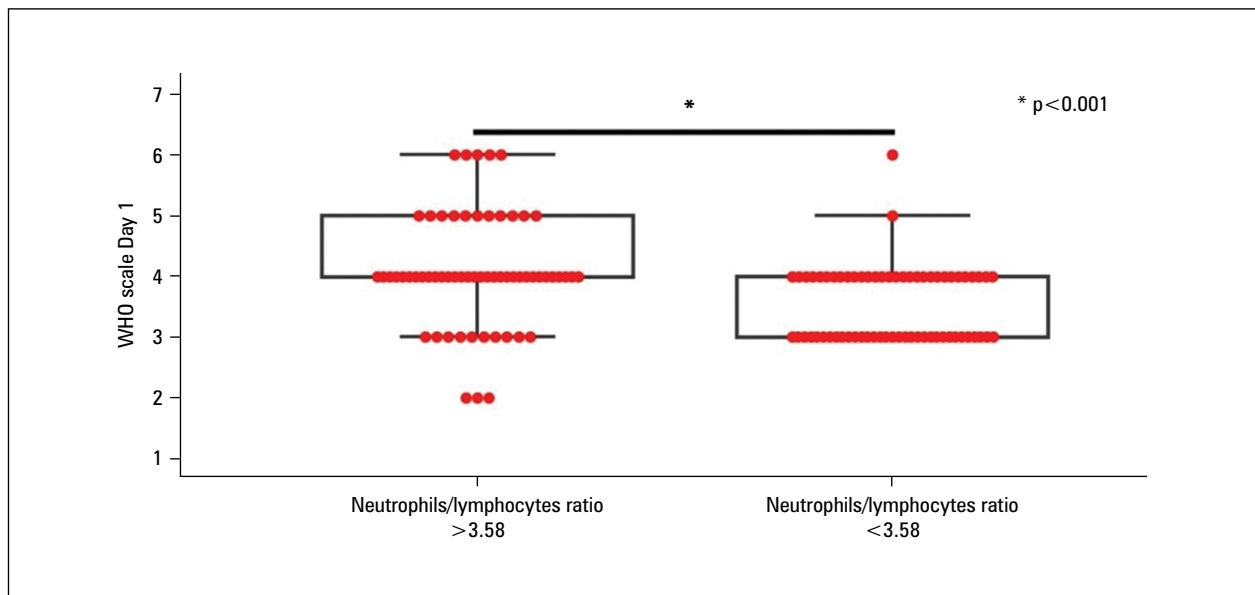
**Table 4. Therapeutic compounds administered to the study population**

Compound	
Hydroxychloroquine, n (%)	170/187 (90.9)
Azithromycin, n (%)	169/187 (90.4)
Lopinavir/Ritonavir, n (%)	33/187 (17.6)
Remdesivir, n (%)	3/187 (1.6)
Tocilizumab, n (%)	5/187 (2.7)
Anakinra, n (%)	2/187 (1.1)
Colchicine, n (%)	9/187 (4.8)
Other antibiotics, n (%)	157/187 (84.0)
Low molecular weight heparin (prophylactic dose), n (%)	160/187 (85.5)

**Table 5. Laboratory tests on admission of the patients enrolled in the study**

Laboratory tests	
Neutrophils (/μL, median, 95% CI)	3864 (95% CI: 3492–4153)
Lymphocytes (/μL, median, 95% CI)	1112 (95% CI: 1000–1220)
Neutrophils to lymphocytes ratio (median, 95% CI)	3.58 (95% CI: 2.98–3.91)
Monocytes (/μL, median, 95% CI)	461 (95% CI: 410–500)
Platelets (/μL, median, 95% CI)	201500 (95% CI: 185200–211500)
RDW (%), median, 95% CI)	12.8 (95% CI: 12.6–13.2)
MPV (fl, median, 95% CI)	9.3 (95% CI: 8.5–9.7)
LDH (IU/L, median, 95% CI)	270 (95% CI: 250.7–291.2)
Ferritin (ng/mL, median, 95% CI)	430.8 (95% CI: 363.1–483.9)
Procalcitonin (ng/mL, median, 95% CI)	0.07 (95% CI: 0.05–0.09)
D-dimers (μg/ml, median, 95% CI)	0.77 (95% CI: 0.68–0.95)

LDH — lactate dehydrogenase; MPV — mean platelet volume; RDW — red cell distribution width



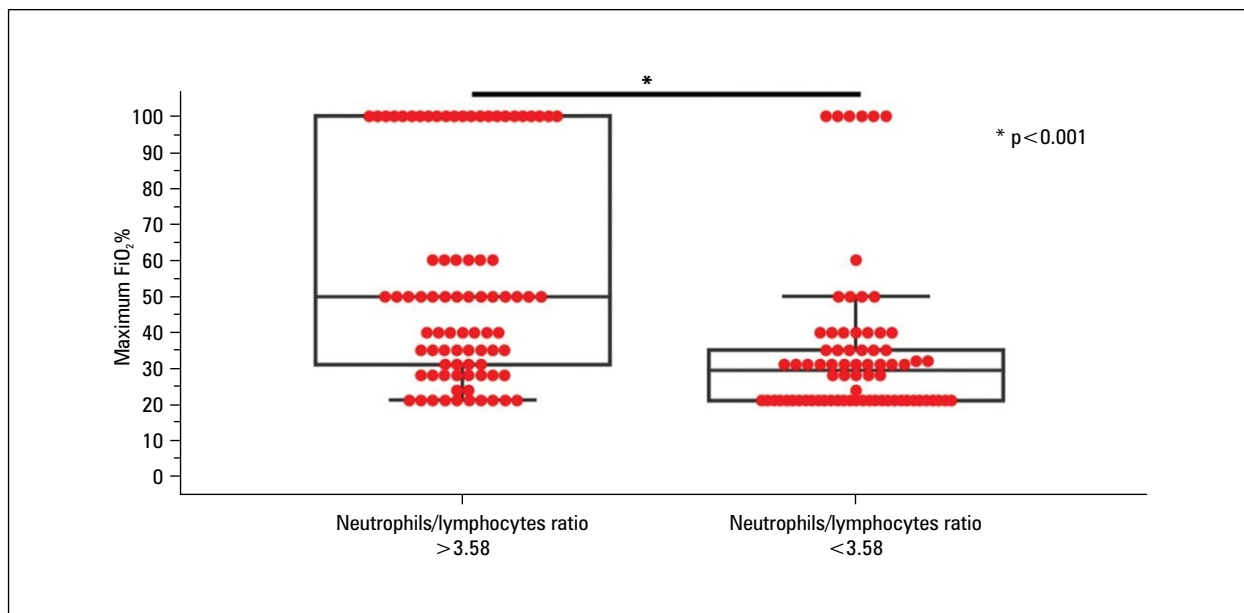
**Figure 1.** Median World Health Organization (WHO) R&D Blueprint score on admission was significantly higher for patients with baseline neutrophils-to-lymphocytes ratio  $> 3.58$  (median value: 4; 95% CI: 4–4) compared to patients with baseline neutrophils-to-lymphocytes ratio  $< 3.58$  (median value: 3; 95% CI: 3–4) ( $p < 0.001$ )

by significantly increased WHO R&D ordinal scale (4; 95% CI: 4–4 vs 3; 95% CI: 3–4,  $p = 0.0001$ , respectively) (Figure 1) and MaxFiO<sub>2</sub>% (50; 95% CI: 38.2–50 vs 29.5; 95% CI: 21–31,  $p < 0.0001$ , respectively) (Figure 2). The patients with increased LDH levels ( $> 270$  IU/ml) also exhibited more advanced disease compared to the low LDH group ( $< 270$  IU/ml) as indicated by both WHO R&D ordinal scale (4; 95% CI: 4–4 vs 4; 95% CI: 3–4,  $p = 0.0001$ , respectively) (Figure 3) and MaxFiO<sub>2</sub>% (50; 95% CI: 35–60 vs 28; 95% CI: 21–31,  $p < 0.0001$ , respectively) (Figure 4). Finally, the patients with elevated D-dimers ( $> 0.77$  μg/ml) displayed advanced disease compared to the low D-dimers ( $< 0.77$  μg/ml), as assessed

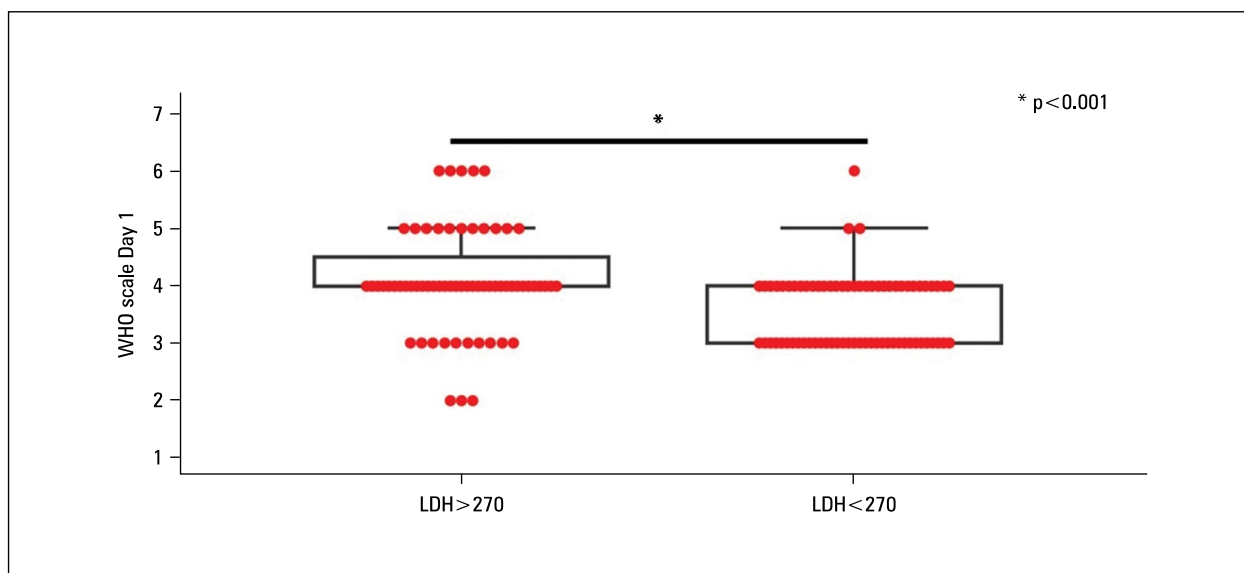
by increased WHO ordinal scale (4; 95% CI: 4–4 vs 3; 95% CI: 3–4,  $p = 0.006$ , respectively, Supplementary Table 1). No other differences in terms of disease severity, were observed between high and low subgroups of patients split by parameters of general blood tests (Supplementary Tables 1, 2)

## Discussion

This is the first epidemiological study reporting characteristics of patients with COVID-19 from 6 large reference centers in Greece during the first wave of the pandemic. This multicenter study further corroborated evidence from previous studies showing increased prevalence in middle-aged



**Figure 2.** Maximum fraction of inspired oxygen (FiO<sub>2</sub>) during hospitalization was significantly higher for patients with baseline neutrophils-to-lymphocytes ratio > 3.58 (median value: 50; 95% CI: 38.2–50) compared to patients with baseline neutrophils-to-lymphocytes ratio < 3.58 (median value: 29.5; 95% CI: 21–31) (p < 0.001)

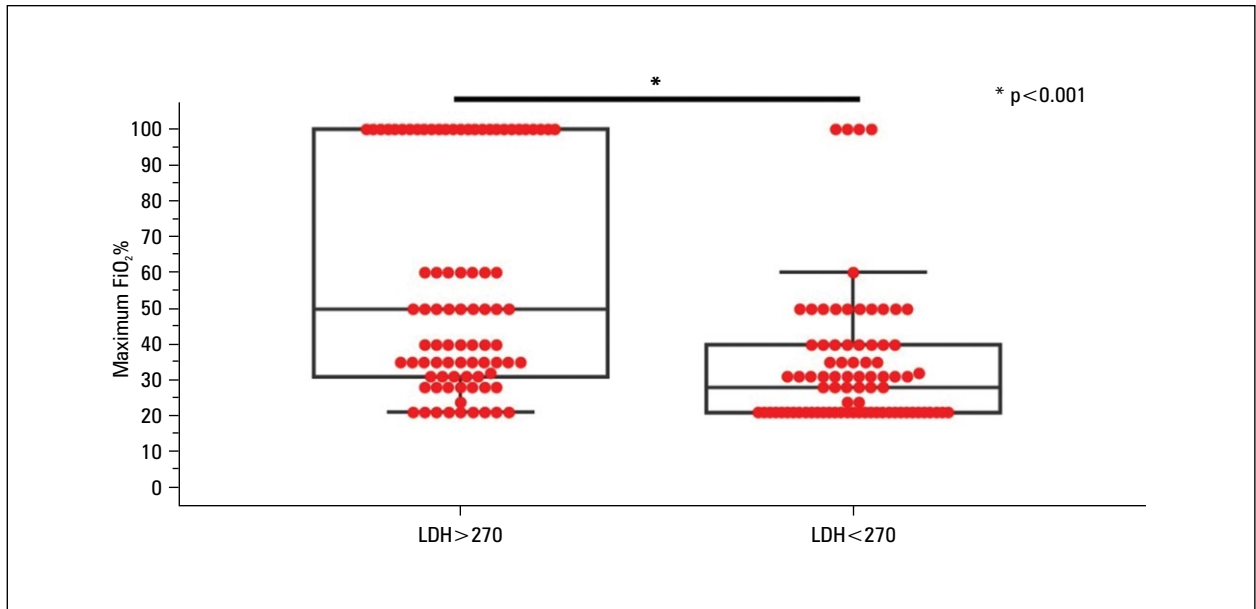


**Figure 3.** Median World Health Organization (WHO) R&D Blueprint score on admission was significantly higher for patients with baseline lactate dehydrogenase (LDH) > 270 IU/L (median value: 4; 95% CI: 4–4) compared to patients with baseline LDH < 270 IU/L (median value: 4; 95% CI: 3–4) (p < 0.001)

males, with cardiovascular risk profile (33% had arterial hypertension and 9% diabetes mellitus) and a case-fatality rate of 4%. Fever and cough were the most commonly encountered clinical features with only half of the patients experiencing dyspnea despite respiratory failure. Bilateral interstitial infiltrates with no lung zone predominance represented a strikingly homogeneous radiological picture in almost all patients. Combination of hydroxychloroquine and azithromycin

were applied in the vast majority of the study subjects (90%) according to the WHO guidelines at the time of data collection and analysis.

Besides the above highly reproducible epidemiological data, our study revealed some interesting observations. First, our cohort predominantly consisted of non-smokers. This is in line with previous reports demonstrating increased prevalence of COVID-19 among non-smokers compared to smokers [8]. On the other hand,



**Figure 4.** Maximum fraction of inspired oxygen (FiO<sub>2</sub>) during hospitalization was significantly higher for patients with baseline lactate dehydrogenase (LDH) > 270 IU/L (median value: 50; 95% CI: 35–60) compared to patients with baseline LDH < 270 IU/L (median value: 28; 95% CI: 21–31) ( $p < 0.001$ )

the studies have shown worse clinical outcomes among smokers [9, 10], with mechanistic data supporting the premise of ACE2 upregulation in the airway epithelial cells mediated by nicotine exposure specifically through the  $\alpha 7$  subtype of nicotine acetylcholine receptors ( $\alpha 7$ -nAChR) [11, 12]. At the time of this manuscript the available data suggests that smoking is associated with increased severity of disease and death in hospitalized COVID-19 patients. Nonetheless, there are currently no peer-reviewed studies that have evaluated the risk of SARS-CoV-2 infection and hospitalization among smokers. Population-based studies are needed to address these issues. Our study is severely underpowered and by no means provide any rigid epidemiological or mechanistic association between smoking and COVID-19 prevalence and severity.

Interestingly, our study population was characterized by low incidence of patients with asthma and COPD (3.3% combined). A decreased incidence of asthma and COPD has been previously reported in several countries affected by COVID-19 [13], indicating a relative protection. Experimental evidence to support this premise have suggested a role for inhaled corticosteroids (ICS) in the inhibition of coronavirus replication in infected epithelial cells. Investigation of gene expression of ACE2 and TMPRSS2 in the sputum of patients with asthma and COPD has shown reduced expression of these receptors in the presence of ICS [14] and attenuation of

ACE2 receptors in human and murine *in vitro* and *in vivo* models [15]. More recently systemic use of dexamethasone significantly reduced mortality among patients with COVID-19 who were receiving mechanical ventilation and oxygen support but had no clear effect in less severe cases [16]. On the other hand, preliminary data from a recent epidemiological (OpenSAFELY) group has suggested that the use of ICS in patients with asthma and COPD is associated with worse clinical COVID-19 outcomes [17, 18]. The impact of corticosteroids on the COVID-19 disease course needs to be further explored.

Another interesting epidemiological observation is the null incidence of interstitial lung diseases (ILDs) and particularly idiopathic pulmonary fibrosis among our cohort of patients with COVID-19 [19]. Although mechanistic link is missing, this finding may be supported by previous experimental data demonstrating reduced expression of ACE2 in the lungs of patients with IPF indicating a relative protection against SARS-CoV-2 infection [20]. On the other hand, patients with ILDs appear to be at increased risk of death from COVID-19 as shown by a large multicenter epidemiological study reporting a 49% mortality rate in patients with COVID-19 and various forms of lung fibrosis [21].

The aforementioned epidemiological observations could also reflect the beneficial impact of timely implementation of lockdown and other self-protection measures such as masks,

social distancing and hand hygiene leading to containment of the pandemic in an era with no established treatment [22]. They may also result from a well-educated, disciplined and compliant group of patients who meticulously applied all prophylactic measures and thus limited further viral transmission. Regarding the relatively low number of hospitalizations, following extended discussions with primary cases' physicians and fully considering our experience in hospitals emergencies, these findings suggest that in Greece primary care likely played a key role in the management of suspected cases of SARS-CoV-2, plausibly relieving the referral hospitals from suspect and mild cases and contributing thus critically to our success story during the pandemic. On the other hand, our study was an observational study and was not designed to address the origin of these phenomena.

Finally, we performed analysis of laboratory parameters and revealed that increased NLR ( $> 3.58$ ) could serve as a reproducible and clinician's friendly biomarker of disease severity as it reliably discriminated severe from non-severe cases based on WHO ordinal scale and MaxFiO<sub>2</sub>% on admission. Our findings further corroborate previous evidence for the negative prognostic role of increased NLR in patients with COVID-19 [23–26]. In particular, a very similar cut-off threshold (NLR  $> 4$ ) reliably predicted ICU admissions in a small cohort of patients with COVID-19 in Italy [27], while a threshold of 11.75 was significantly correlated with in-hospital mortality in a large cohort of 1004 COVID-19 patients [28]. Besides its prognostic significance, NLR provides interesting mechanistic links as SARS-CoV-2 initially infects and kills T-lymphocytes leading to profound lymphopenia while at the same time viral inflammatory response impairs lymphopoiesis and increases lymphocyte apoptosis. Similarly to NLR, increased LDH levels were associated with worse clinical outcomes, as assessed by WHO ordinal scale and MaxFiO<sub>2</sub>% on admission. Although LDH has been traditionally used as a marker of cardiac damage, elevated levels can result from multiple organ injury and may reflect decreased oxygenation with upregulation of the glycolytic pathway [29]. Nonetheless, it represents a marker with low specificity and sensitivity, as it can be increased in a variety of conditions resulting in tissue hypoxia, including infections, renal, lung and cardiac diseases. An association between elevated LDH blood levels with poor prognosis in patients with COVID-19 has been recently reported [30].

Our study exhibits a number of limitations that need to be treated cautiously. First, this was an epidemiological report and was not designed to provide mechanistic data. Second, as it happens with all hospital-based epidemiological studies that report patient characteristics, data quality tends to be scarce, underpowered and limited by sampling bias. Finally, follow-up assessment was short and thus valid conclusions cannot be drawn.

In conclusion, we present the first epidemiological report from a low-incidence and mortality COVID-19 country during the first wave of the pandemic. Our data validates previous findings supporting a relatively homogeneous clinical, laboratory and radiological appearance of COVID-19 on a global scale. NLR may represent a reliable disease prognosticator with important mechanistic links leading to timely and optimal treatment decisions. Low prevalence rates of chronic lung diseases, including COPD, asthma and ILDs could reflect the beneficial impact of early implementation of containment measures. Larger epidemiological studies and longitudinal population-based analyses are sorely needed to prove these concepts.

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### Conflicts of interest

AT received consultant honorarium and travel grants from Boehringer Ingelheim Hoffmann La Roche, Elpen Pharma and Chiesi Hellas outside the submitted work. DB received consultant honorarium and travel grants from Boehringer Ingelheim Hoffmann La Roche and Elpen Pharma outside the submitted work. EM received consultant honorarium and travel grants from Boehringer Ingelheim and Hoffmann La Roche

outside the submitted work. SP received consultant honorarium and travel grants from Boehringer Ingelheim and Hoffmann La Roche outside the submitted work. SL received consultant honorarium and travel grants from Boehringer Ingelheim, Chiesi Hellas, Astra Zeneca, Menarini and GlaxoSmithKline outside the submitted work. AB received honorarium and travel grants from Chiesi Hellas, Elpen Pharma and Menarini outside the submitted work. The rest authors have nothing to disclose.

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