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RESEARCH ARTICLE

PATIENT CHARACTERISTICS AND PREDICTION OF COVID-19 IN-HOSPITAL MORTALITY: A RETROSPECTIVE COHORT STUDY IN CRETE, GREECE BEFORE AND AFTER THE ONSET OF A TARGETED VACCINATION STRATEGY IN 2021

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Abstract

Background: CoviD-19 in-hospital mortality rates show variations across time, setting, patient populations and health-systems.

Aim: The aim of the present study was to explore the association of patient characteristics with in-hospital mortality taking into consideration temporal changes of CoViD-19 prevention and treatment, focusing on the negative predictive value of specific biomarker thresholds for death and oxygen requirements.

Methods: This retrospective study included a sample of 425 vaccine-naive patients hospitalized for CoViD-19 in Crete, Greece. Time-specific mortality rates and negative predictive values of biomarkers on admission were calculated. The association of patient characteristics with mortality was assessed using multivariate logistic regression models.

Results: The overall in hospital case fatality rate (CFR) was 19.53%. The in-hospital CFR [95% CI] dropped from 22.74% [17.96-27.52] to 11.9% [6.17-17.63] before and after 31/03/2021, as did the mean age of hospitalized patients. LDH & D-dimers ≥240 or ≥0.5), CRP & D-dimers (≥3 or ≥0.5), CRP & Ferritin (≥3 or ≥205) had negative predictive values [95% CI] for mortality of 100% [86.7-100], 96.1% [80.3-99.9] and 95.4% [84.5-99.4] %, but the respective negative predictive values for oxygen requirements were 19.2% [6.5-39.3], 19.2% [6.5-39.3] and 27.2% [14.9-42.7] .

Conclusion: A decreasing trend of in-hospital case fatality rates over the course of our study was associated with a decreasing age of hospitalized patients, which could be associated with community vaccination uptake in people over 60 in Greece through reduction of persons "susceptible" to severe disease. Mortality prediction formulas incorporating biomarkers should be used cautiously for the risk stratification of patients with CoViD-19 in the setting of the emergency department assessment.

Keywords: CoViD-19, mortality, Greece, biomarkers, risk stratification.

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INTRODUCTION

CoViD-19 is a disease with a wide spectrum of severity in the general population, with the earlier studies reporting 81% of cases being of mild or moderate severity, 19% cases being defined as severe or critical and an estimated general population case fatality rate of 2,3%[1]. In times of high epidemiological burden, high in-hospital mortality rates of around 24% were recorded.[2,3] However, measured case fatality rates, both for hospitalized patients and the general population, have shown significant fluctuations, but mainly a decreasing tendency[4–6] Possible reasons that have been proposed and investigated to explain this, include methodological issues around case detection, reporting and differences in demographic characteristics of study populations[7], adjustment and change in capacity, preparedness and "learning"[4] of health systems (including health workforce), advances in testing capacity and therapeutics, different virulence of variants of SARS-CoV-2[8] and, in the last years, the effect of vaccination[9] .

In Greece, most of the published observational studies report data from the spring of 2020 (the "first wave" of the pandemic), when the epidemiological burden of Greece was especially low and report also low in-hospital mortality rates.[10–12] A study on a sample of 50 intensive care unit (ICU) patients in Athens in the spring of 2020 suggested hospital resources as an important factor to explain differences in internationally reported in-hospital case fatality rates.[13] Additionally, case load (even when capacity is not exceeded) and regional disparities seemed to also influence mortality rates of the critically ill.[14]

However, it has proven challenging to assess the relative contribution of the former factors in the measured case fatality rates, which are characterized from extreme heterogeneity. For example, Horwitz et al. present an improvement in case fatality rates in a single health system in the United States over six months, that persists after adjusting for decreasing median age and frequency of comorbidities, but organizational and administrative changes could not be quantified.[6] Changing admission thresholds and management protocols complicate further the evaluation of in-hospital fatality rates and constitute a form of chronologic bias.

What is beyond doubt is that, age and comorbidities have been convincingly associated with death and other adverse outcomes from CoViD-19 through a variety of studies, such as observational cohort studies, systematic reviews and meta-analyses.[15–18] An observational study from the US with a sample of 540667 hospitalized adults showed the link of CoViD-19 mortality and morbidity with both the type and the number of underlying medical conditions, including diabetes mellitus with complications, coronary artery disease and other heart disease, obesity, chronic obstructive pulmonary disease, chronic kidney disease and anxiety related disorders as some of the most impactful risk factors.[19] Certain ethnicities, such as African American and Hispanic American have also emerged as risk factors for death and severe disease in the US, presumably in connection with social determinants of health.[2,20,21] Migrants in high income countries are also at higher risk of exposure and infection, but outcome data are lacking.[22]

Despite the extensive literature on risk factors, it stands to reason that clinical symptoms (such as dyspnoea and altered mentation) and oxygen saturation measurements have remained as the main indicators of deterioration and criteria for hospital admission in national guidelines. Clinical symptoms are evaluated within a continuum of care approach, that is commonly practiced for the management of CoViD-19 based on clinical need including self-assessment tools, clinician telehealth evaluation, dedicated outpatient clinic and emergency room evaluations and if necessary in-patient management.

Nevertheless, in specific clinical situations, clinicians often find themselves in doubt regarding patient management decisions, as in patients with evidence of lower respiratory tract involvement with normal oxygen saturation. Considering the often unexpected and rapid course of the disease and the subjective nature of symptom reporting, more complex disease severity prediction models soon appeared in the international literature, most often incorporating symptoms plus a constellation of risk factors such as age, vital signs, comorbidities and imaging findings. Unfortunately, most of these models have been evaluated as having a high risk of bias, while the validation of the most robust among them is still necessary in different populations.[23]

Another aspect that merits reflection, is that most models draw their data from hospitalised patient populations and focus on an

assessment of in hospital mortality,[23] instead of also aiming to identify patients that can be safely discharged and thus being more "pragmatic" or practical in times of scarce health care resources. Douillet et al. have developed a "rule" to identify a subgroup of CoViD patients with a very low risk of adverse outcomes and were able to safely discharge 41% patients with probable or confirmed CoViD-19 presenting to the emergency department with only 4 out of 1239 developing a severe adverse outcome (0.32% false negative rate) in a prospective multicentre study.[24]

The capitalization of evidence on CoViD-19 accumulated at the regional and national level together with an evaluation of whether and how international knowledge applies in Greece is of importance in order to review current standards of care for patients with CoViD-19. To our knowledge, there have been limited observational studies on the characteristics and outcomes of hospitalized patients in Greece. This study aimed to evaluate the relation between patient characteristics with in-hospital mortality taking into consideration temporal changes of CoViD-19 prevention and treatment.

METHODOLOGY

Study Design, Procedures and Definitions

This is a retrospective cohort study, using routine data collected for the purposes of treatment of CoViD-19 patients in Venizelion General Hospital, Heraklion, Crete, Greece from March 2020 to end of April 2021.

The diagnosis was confirmed with reverse transcriptase polymerase chain reaction (rt-PCR) for SARS-CoV-2 for all patients, conducted in the Laboratory of Clinical Virology, University of Crete, Heraklion, Crete, Greece. Specimens for testing were collected using a nasopharyngeal swab technique.

Only blood laboratory tests collected at admission were recorded for the purposes of this study. These are defined, as tests for which the blood sample was drawn within 24 hours since the time of presentation to the emergency room for patients, which were diagnosed with CoViD-19.

Individuals were designated as having moderate illness when they show evidence of lower respiratory disease during clinical assessment or imaging and they have an oxygen saturation (SpO2) ≥94% on room air at sea level[25].

Individuals are designated as having severe illness when they have SpO2<94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%[25].

The study endpoint for most analyses is CoVID-19-related death. This was defined as, death of a patient with confirmed SARS-COV-2 infection, regardless of comorbidities, during a hospitalisation that was necessitated following an acute illness with symptoms compatible with CoViD-19. Oxygen therapy support at any point during hospitalisation was also examined as an outcome in the analysis for the predictive value of biomarkers.

Inclusion and Exclusion Criteria

This study evaluated the admission, hospitalisation, and outcome data for all patients with CoViD-19 disease that were admitted in our hospital between 01/03/2020 and 01/05/2021.

Pregnant patients without severe CoViD-19 that were hospitalised only in expectancy for labour, as well as their newborns are excluded from this study.

Data Collection, Protection and Validation Procedures

The data for this study were collected from the electronic databases of the 7th Health Prefecture of Greece, patient files and the patient registers, in July 2021. All patients found in the database, who were eligible according to the inclusion and exclusion criteria, were included in the study. The data collected referred to demographic information, duration and outcome of hospitalisation, comorbidities, diagnostic tests, and therapeutic interventions.

The data were directly extracted in a study-specific anonymized database. Unique patient characteristics that could lead to identification were not included in the study database. To ensure data validity, data from the electronic databases were cross-checked with patient files.

We assessed the levels of vaccination in the population in Greece as an independent variable. We used the monthly percentage of vaccination coverage for persons over 60 years of age reported at the ECDC for the Epiweek that included the 15th day of the respective month.

Data regarding cases in the region of Crete and vaccination uptake in Greece were found in the freely accessible databases of the ECDC.[26,27]

Data Analysis

All analyses were conducted in Stata 13.1 Statistics/Data Analysis Software. Patient characteristics and outcomes were described using the appropriate descriptive statistics. Continuous and categorical variables are described using median (25^{th}, 75th) and frequencies and proportions, respectively. Normality testing was performed for all continuous variables using the Shapiro-Wilk test. Age group breakdown with 65, 75 and 85 years as cut-off points is also presented, as this is a commonly used classification in national management algorithms and surveillance reports. Differences in the characteristics of survivors and non survivors were investigated using the Wilcoxon-Mann-Whitney test, chi squared test or Fisher' exact test, where appropriate. Cases and deaths were plotted against time to create the epidemiological curve and monthly hospitalized case fatality rates were calculated (monthly hospital CoViD-19 deaths/monthly hospital CoViD-19 admissions). Monthly in-hospital case fatality rates were plotted only for months for which more than 50 cases were recorded.

We selected some laboratory tests for further investigation regarding their predictive value, based on the statistical significance of the difference between survivors and non survivors in our cohort, previous evidence in the literature and specificity to CoViD -19. The predictive value of these laboratory tests was assessed through univariate logistic regression, followed by plotting the receiver operator characteristic (ROC) curve and reporting the area under the curve. Sensitivity, specificity, negative predictive values and their 95% confidence intervals are reported for empirical cut-off values, based on clinical practice conventions and with the goal of maximizing sensitivity and negative predictive value. The association of age, gender, comorbidities and selected biomarkers with mortality was assessed through univariate logistic regression, followed by age-adjusted logistic regression and multivariate logistic regression models. Taking into account the number of deaths (n=83) and to avoid over fitting in the model, eight variables were chosen for multivariable analysis on the basis of the univariate analysis and clinical considerations.

Ethics

The research protocol for this study was drafted in accordance with the Helsinki declaration and approved on 10/06/2021 by the Scientific Council of Venizelion General Hospital. Informed consent was waived for this retrospective observational study. No risks were foreseen for the participants of this study. All the patients in this study had received the recommended institutional treatment and all laboratory tests had been performed in the context of routine monitoring during hospitalisation. The database of this study is anonymized and protected.

RESULTS

Medical and demographic information, as well as outcomes were recorded for 425 CoViD-19 patients hospitalized for a median [25^{th}, 75^{th}] duration of 6 days [3-12 days]. The median age of the participants was 65.1 years and the majority of them (71.7%) suffered from comorbidities. The main characteristics and outcomes of the patients are presented in Table 1. The overall case fatality rate was 19.5% [95% CI: 15.7-23.3]. The recorded case fatality rates for age groups <65, 65-75, 75-85 and over 85 years were 5.2% [2.1-8.2], 24.0% [15.7-32.3], 40% [29.4-50.5] and 52% [32.9-72.0], respectively**.** Regarding chronological differences there were significant case fatality rate differences up to and after 31/03/2021, 22.74% [17.96-27.52] and 11.9% [6.17-17.63] respectively. The time point was selected according to the vaccination strategy that was initiated for elderly people in January 2021.

In Figure 1, we present the recorded hospitalised cases, deaths, and case fatality rate. The case fatality ratio, the mean age of hospitalised cases and vaccination uptake for persons over 60 years in Greece during November 2020 - April 2021 are shown in Figure 2. The epidemiological curve of the 14-day case notification rate for the region of Crete, which represents the source population of our study is shown in Figure 3.

We recorded the routine battery of tests, hematology, clinical chemistry and clotting studies, done for CoViD-19 patients on admission, as well as their diagnosed comorbidities We present

overall, as well as outcome specific frequencies and p values on Table 2. Median values of CoViD-19 patients for Lymphocyte Absolute Count, Ferritin, CRP, D-dimers and LDH are higher than the normal reference values of the laboratory for the general population. Hemoglobin and lymphocyte absolute count were found decreased in non-survivors in comparison to survivors, while white blood count, neutrophil absolute count, ferritin, CRP, D-dimers, SGOT, troponin, LDH, creatinine, urea, INR, PT, aPTT were found to be significantly elevated in non-survivors. Laboratory Reference values and information on data completeness can be found in the supplementary material.

As presented on table 2, Arterial Hypertension (39.1%), Cardiac Disease (25.2%) and Diabetes Mellitus (19.8%) were the most common comorbidities. Unspecified Cardiac Disease, Coronary Artery Disease, Atrial Fibrillation, unspecified Pulmonary Disease, Chronic Obstructive Pulmonary Disease, Arterial Hypertension, Diabetes Mellitus (unspecified type), Chronic Kidney Disease and Malignancy were found to be more common in non-survivors.

Regarding treatment modalities, most of the patients received supplemental oxygen therapy (89.3%), dexamethasone (89.8%), low molecular weight heparin (92.2%) and empiric antibiotic therapy (97.1%). Patients with characteristics of more severe disease also received high fractional oxygen concentrations (36.7%), high flow nasal cannulae oxygen therapy (10.8%), remdesivir (29.7%) and tocilizumab (1.6%). More information on treatment modalities is available in the supplementary material.

We examined the potential association of admission laboratory parameters with mortality. Ferritin, C reactive protein (CRP), D-dimers and Lactate Dehydrogenase (LDH) levels and the De Ritis ratio were found to have statistically significant positive associations. However, the areas under the ROC curve (AUC) for all biomarkers ranged from 0.613 to 0.649, indicating overall suboptimal discriminatory ability of these tests for survival. The odds ratios, 95% confidence intervals and Area under the (ROC) curve as well as the individual ROC curves are available as supplementary material.

Additionally, we investigated the association of age, gender and chronic non-communicable diseases with CoViD-19 mortality. Age was significantly associated with COVID-19-related death; a 10-year age increment resulted in a 2.49-fold increase in the risk of death [95%Cis: 1.95-3.18]. Gender was not found to be significantly associated with the risk of mortality. Arterial Hypertension, Diabetes Mellitus, Cardiac Disease, Pulmonary Disease, Malignancy, Chronic Kidney Disease were all associated with increased mortality in univariate analysis. However, after age adjustment, the effect persisted only for Chronic Obstructive Pulmonary Disease (OR 2.57[95% CI: 1.27-5.22]), Malignancy (OR 3.92[95% CI: 1.62-9.52]) and Cardiac Disease (OR 2.05[95% CI 1.17-3.60]). Admission after 31/03/2021 was associated with reduced mortality (OR 0.45[95% CI: 0.25-0.83)], however the effect did not persist after age adjustment. In multivariate analysis we found that age (OR 2.73 [1.85-4.02]), cardiac disease (OR 2.47[1.17-5.22]), chronic obstructive pulmonary disease (OR 3.36[1.29-8.71]), CRP (OR 1.05[1.00-1.10]) and LDH (OR 1.38[1.08-1.77]) are independently associated with death. Further results are shown in Table 3.

Empirical cut-off points, derived from clinical practice and the literature, to maximize the sensitivity and negative predictive value of the tests for mortality were investigated, as well as the respective NPV for oxygen support, and are shown on Table 4. The combination of more than one parallel test can maximize the negative predictive value for death, which reached 100[86.7-100] % for the combination of LDH and D-dimers, 96.1 [80.3-99.9] % for the combination of D-dimers and CRP and 95.4[84.5-99.4] % for the combination of CRP and Ferritin. However, the same thresholds demonstrated low negative predictive values of 19.2 [6.5-39.3] %, 19.2 [6.5-39.3] % and 27.2[14.9-42.7] % for the same combinations of tests regarding the need for oxygen support.

DISCUSSION

Main Findings

This study addresses the association of patient characteristics with in-hospital mortality in a tertiary hospital in the region of Crete in a vaccine-naive patient sample, before and after the onset of a targeted vaccination campaign. Most of the cases and deaths were recorded towards the end of the study period, February to April of 2021, in accordance with the regional epidemi-

ological burden. The overall in-hospital case fatality rate was ascertained at 19.53% [15.74-23.31], in the same order of magnitude as reported from other international settings, with a similar sample mean age prior to the advent of SARS-COV-2 vaccination[2,28]. The association of increased age, specific chronic non-communicable diseases, and increased biomarkers with mortality, which has been incontrovertibly asserted in the international literature, is confirmed in our study. Interestingly, a decreasing case fatality rate was observed towards the end of the study period, which was associated with a lower mean age of hospitalized individuals, most likely due to the reduction of "susceptible" elderly individuals in the community due to increasing vaccination coverage. We have additionally identified combinations of routine biomarker cut-off values that can be utilized to select the patients with minimal risk of dying from CoViD-19 at the time of admission but cannot reliably distinguish patients needing supplemental oxygen.

Time period, case load and in-hospital mortality

Early in-hospital CFR estimates reported from March to July 2020 in Greece are ranging from 4.2 to 12.8%. However, these estimates could be affected by methodological limitations, including small sample sizes.[10–12,29] Our study cannot estimate mortality rates for that period, as there were hardly any hospitalized cases in Crete, in accordance with a very low epidemiological burden. However, we report overall comparably higher mortality rates than the studies mentioned above with most of our cases and deaths occurring in the last quarter of 2020 and for the first third of 2021. It has been proposed that, in Greece and internationally, high hospital occupancy is associated with higher in hospital mortality rates, independently of patient population changes in different times of the SARS-COV2 pandemic, as are other aspects of care like quality, which are difficult to standardize.[14] Other factors that might influence this are differences in case-mix, emerging variants of concern[30] changes in community behavior, vaccination programmes,[31] as well as advances in patient management and therapeutics.[32]

We reported a decreasing case fatality rate from February 2021 to April 2021, months with consecutively increasing caseloads for the hospital, and while most aspects of care and management protocols remained stable. This was associated with a decreasing mean age of hospitalized individuals in these months. Even if no patients in our sample were vaccinated for SARS-COV-2, increasing vaccination coverage rates among the elderly in the community that reached a considerable coverage during the same period was the driving force behind this reduction in mortality. For example 10,4 % of persons over 60 years of age had received at least one dose SARS-COV-2 vaccine and 4,4% had received two doses in the middle of February 2021, while 47,1 % had received at least one dose and 19,4% had received two doses in the middle of April 2021.[26] Despite the plausible coincidence of the two trends, a causal relation cannot be ascertained with our study design. Also, genomic sequencing data from Greece show a relative stability in SARS-COV-2 variants during those months[33] (February 2021-April 2021)

Individual patient factors and in-hospital mortality

The role of age and chronic diseases as risk factors for adverse CoViD-19 outcomes is well recognized internationally and these factors are incorporated in most risk prediction equations.[23,24,34]

A relevant challenge for low resource or remote settings, is that many non-communicable diseases are under-diagnosed due to lack of relevant diagnostics and effective primary health care systems, which could complicate the risk assessment.[35,36]

On the other hand, in the context of the global nature of the SARS-COV-2 response, the applicability of all these diagnostic and prognostic models to all resource-limited settings is crucial, where resource allocation is even more challenging. Even if all the reported diagnostics in our study are included in the WHO Essential Diagnostic List they are not available in all settings.[37]

In the context of this lack of information and pressure of health systems during outbreaks, the idea that combinations of biomarkers can be used in addition of clinical information to rule out death in hospitalized patients can seem very appealing. Many scores have been developed, with different degrees of bias, and can achieve a high negative predictive value for mortality.[38] Unfortunately, this does not equal a rule for safe discharge, as many of these patients are recorded as survivors after supplemental oxygen therapy. Consequently, more pragmatic studies looking at endpoints other than death and ICU admission are needed to develop safe discharge criteria, for which

these biomarkers could play an important role.

Strengths and Limitations

Our study is constrained by the limitations of routine hospital data collection, like risks of data omission and error, which can only be exacerbated in the context of disease outbreaks and stress of health systems. For example, socioeconomic factors, mental health conditions, smoking habits and body mass index (BMI) information were not recorded systematically for all hospitalized patients.

The strengths of this study probably include a representative sample of our source population, i.e. persons suffering from moderate and severe CoViD-19 in Crete, as our hospital received a large share of all the patients of the region. Regarding in-hospital case fatality rates in association with different time periods, we were able to calculate monthly rates for months with a sufficient number of patients, such data are lacking in earlier studies in Greece. On the subject of the use of biomarkers for outcome risk stratification, the approach of using admission laboratory tests for predictive analyses has the advantage of eliminating the bias related to different phases of disease evolution and health seeking behaviour and are most pertinent for predictive models. Lastly, the targeted analytic approach to find indicators with high negative predictive value is tailored for the context of an epidemic where accurate triage and pragmatic decision-making procedures that maximize efficiency of scarce resources allocation are critical.

CONCLUSION

The investigation of fluctuations of in-hospital fatality rates in different phases of an epidemic is important; to understand and mitigate healthcare and surge associated factors that can increase mortality and develop targeted public health interventions. Lower age of hospitalized individuals can have severe impact on mortality and targeted vaccination strategies for the elderly could be instrumental for this and should be adopted when vaccines are scarce.

Evidence based and accurate risk estimation scores to safely discharge patients with moderate CoViD-19 after assessment are still needed, but oxygen requirements and other adverse effects should be taken into account as most available tools were developed using only mortality as an endpoint.

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Disclosure Statement

The authors report no conflict of interest.

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ANNEX

TABLE 1. Overview of the characteristics and outcomes of patients admitted for CoViD-19 in Venizelion General Hospital, Heraklion, Greece March 2020- end of April 2021.

Total Number of patients	**425**
Age in years, median [25th – 75th]	65.13 [50.60-75.20]
Number of patients, Age <65 years	211 (49.6%)
Number of patients, Age 65-74 years	104 (24.4%)
Number of patients, Age 75-84 years	85(20%)
Number of patients, Age ≥85 years	25 (5.8%)
Male to Female (percentage ratio)	244/181 (57.41%/42.59%)
Patients with Comorbidities, n (%)	305 (71.7)
Vaccinated patients, n (%)	0 (0)
Duration of hospitalization in days, median [25th – 75th]	6 [3-12]
Number of ICU admissions	54
Number of deaths	83
In hospital case fatality rate, overall [95%CI]	19.53% [15.74-23.31]
In hospital case fatality rate, by age group [95%CI]	
(patients <65 years old)	5.21% [2.19-8.22]
(patients 65-74 years old)	24.03% [15.76-32.31]
(patients 75-84 years old)	40% [29.49-50.50]
(patients≥85 years old)	52% [32.95-72.04]
Age of fatalities in years, mean (SD)	76 (10.37)
In hospital case fatality rate, by time of admission [95%CI]	
01/03/2020-31/03/2021	22.74% [17.96-27.52]
01/04/2021-01/05/2021	11.9% [6.17-17.63]

TABLE 2. Median (Q1, Q3) values of admission laboratory tests and frequency (%) of comorbidities in patients admitted for CoViD-19 in Venizelion General Hospital, Heraklion, Greece March 2020- end of April 2021 (N=425).

Parameter[1]	Overall (N=425)	Non-survivors (n=83)	Survivors (n=342)	p value[2]
Cardiac Disease	107 (25.2%)	41 (38,3%)	66 (61,6%)	<0.001
Coronary Artery Disease	56 (13%)	20 (35.7%)	36 (64.2%)	0.002
Atrial Fibrillation	31 (7.3%)	13 (41.9%)	18 (58%)	0.003
Pulmonary Disease	68 (16%)	20 (29.4%)	48 (70.5%)	0.029
Chronic Obstructive Pulmonary Disease	45 (10.6%)	19 (42,2%)	26 (57.7%)	<0.001
Asthma	17(4%)	1 (5.8%)	16 (94.1%)	0.215
Pulmonary Embolism	1 (0.2%)	0	1 (100%)	-
Pulmonary Fibrosis	1 (0.2%)	0	1 (100%)	-
Arterial Hypertension	166 (39.1%)	45(27,1%)	121(72,8%)	0.001
Diabetes Mellitus	84 (19.8%)	29 (34.5%)	55(65.4%)	<0.001
Chronic Kidney Disease (>stage 3)	16 (3.7%)	7 (43.7%)	9 (65.2%)	0.02
Liver Disease	2 (0.4%)	0	2 (100%)	-
Malignancy	28 (6.6%)	12 (42.8%)	16 (57.1%)	0.005
Autoimmune Disease	23 (5.4%)	5 (21.7%)	18 (78.2%)	0.785
Immunosuppressed	8 (1.8%)	3 (37.5%)	5 (62.5%)	-
Hgb (g/dL)	13.1 (11.7 – 14.1)	12.4 (10.9-13.6)	13.2 (12-14.2)	0.0003
WBC (x 1000/μL)	5.95 (4.49-8.08)	8.09 (5.09-11.81)	5.71 (4.29-7.55)	<0.0001
Neu (x 1000/μL)	4.27 (2.89-6.28)	6.23 (3.6-8.87)	4.05 (2.7-5.7)	<0.0001
Lym (x 1000/μL)	1.01 (0.68-1.37)	0.75 (0.52-1.3)	1.04 (0.72-1.39)	0.0022
Plt (K/μL)	190 (154-240)	182 (148-245)	190 (155-240)	0.7859
Ferritin (ng/mL)	495 (242-948)	717 (366-1524)	464 (232-909)	0.002
CRP (mg/dL)	6.31 (3.11-12.15)	9.48 (4.88-17.05)	5.9 (2.71-10.55)	<0.0001
D-dimers (mg/L)	0.7 (0.5-1.3)	1.2 (0.5-2.2)	0.6 (0.4-1.0)	0.0003

SGOT (U/L)	30.5 (24-46)	39 (25-57)	29.5 (23-43)	0.0202
SGPT (U/L)	27 (18-43)	27 (18-45)	27 (18-43)	0.6299
γ-gt (U/L)	32 (20-52)	34 (21-59)	31 (20-50)	0.3011
Troponin (pg/mL)	6 (2.65-16.3)	22 (7.7-50)	4.7 (2.1-11.3)	<0.0001
LDH (U/L)	316 (241-421)	386 (291-504)	309 (236-404)	0.0003
Creatinine (mg/dL)	0.83 (0.73-1.03)	0.98 (0.81-1.39)	0.81 (0.72-0.98)	<0.0001
Urea (mg/dL)	33 (24-45)	47 (34-73)	31 (23-42)	<0.0001
INR	1 (1-1.1)	1 (1-1.2)	1 (1-1.1)	0.0137
PT (sec)	11.7 (11.2-12.3)	11.9 (11.4-13.4)	11.7 (11.2-12.2)	0.0103
aPTT (sec)	31.6 (29-35)	34.4 (30.4-39.1)	31 (28.7-34)	<0.0001

[1] Hgb: Hemoglobin,WBC: White Blood Count, Neu : Neutrophil Count, Lym: Lymphocyte Count, Plt : Platelet Count, CRP: C-Reactive Protein, SGOT: aspartate aminotransferase, SGPT : alanine aminotransferase, γ-GT : gamma-glutamyltransferase, LDH: Lactate Dehydrogenase, INR: International Normalized Ratio, PT : Prothrombin Time, aPTT :activated Partial Thromboplastin Time

[2] Wilcoxon-Mann-Whitney test

TABLE 3. Univariate, age-adjusted and multivariate logistic regression of patient characteristics on mortality for patients admitted for CoViD-19 in Venizelion General Hospital, Heraklion, Greece March 2020- end of April 2021.

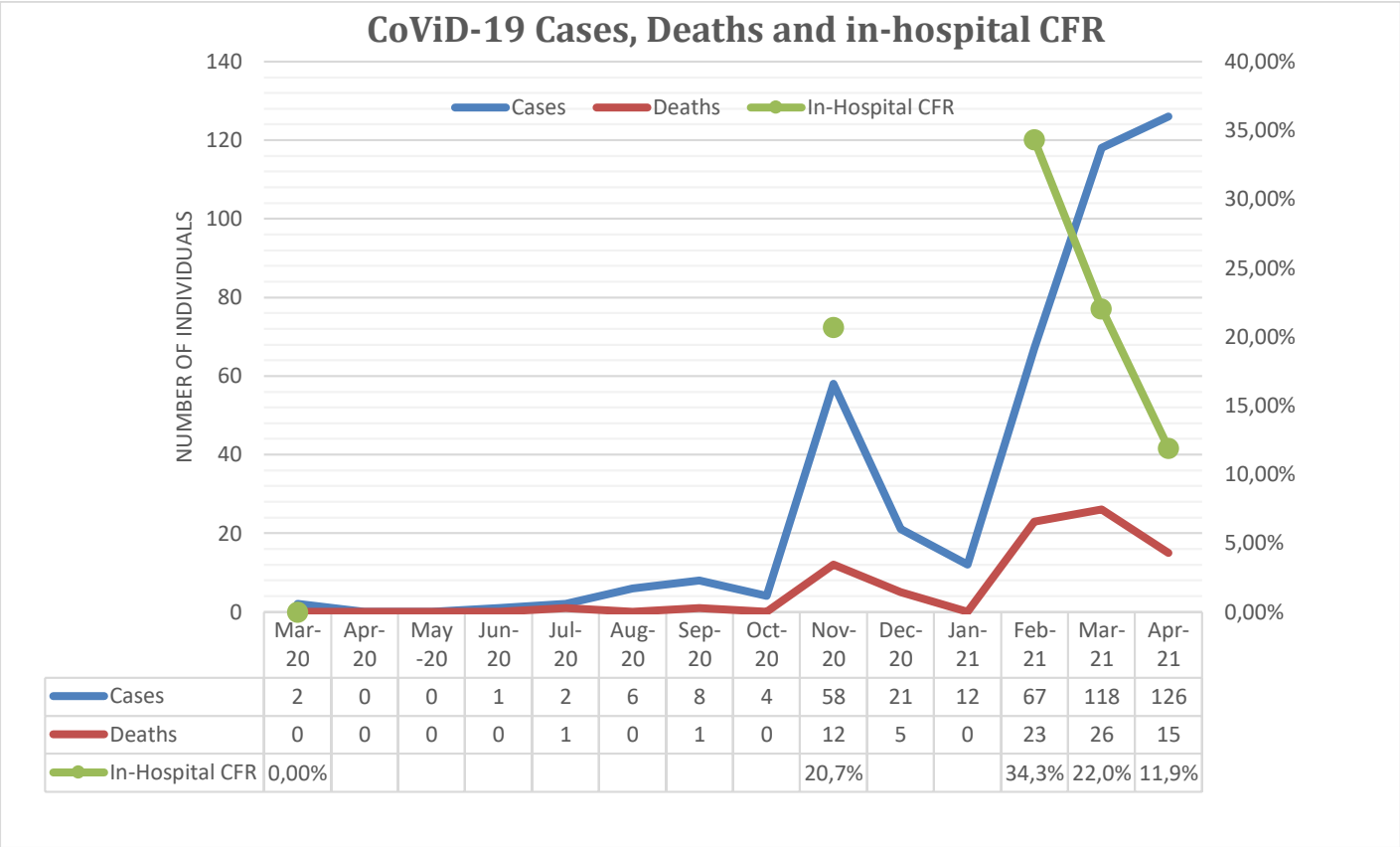
Variable	OR [95% CI] univariate	OR [95% CI] age-adjusted	OR [95 % CI] multivariate
Age (per 10 years)	2.49[1.95-3.18]	2.49[1.95-3.18]	2.73[1.85-4.02]
Sex			
Male	1.23[0.75-2.01]	1.32[0.74-2.35]	1.38[0.65-2.92]
Female	Reference	Reference	Reference
Cardiac Disease			
Yes	4.18[2.51-6.95]	2.05[1.17-3.60]	2.47[1.17-5.22]
No	Reference	Reference	Reference
Coronary Artery Disease			
Yes	2.74[1.48-5.05]	1.48[0.75-2.85]	
No	Reference	Reference	
Atrial Fibrillation			
Yes	3.39[1.58-7.24]	1.57[0.68-3.61]	
No	Reference	Reference	
Pulmonary Disease			
Yes	1.97[1.09-3.56]	2.06[1.06-4.00]	
No	Reference	Reference	
Chronic Obstructive Pulmonary Disease			
Yes	3.36[1.91-7.02]	2.57[1.27-5.22]	3.36[1.29-8.71]
No	Reference	Reference	Reference
Asthma			
Yes	0.25[0.32-1.91]	1.03[0.12-8.75]	
No	Reference	Reference	
Arterial Hypertension			
Yes	2.22[1.36-3.61]	1.04[0.60-1.80]	
No	Reference	Reference	
Diabetes Mellitus			
Yes	2.85[1.66-4.88]	1.68[0.93-3.04]	
No	Reference	Reference	
Chronic Kidney Disease			
Yes	3.45[1.24-9.56]	2.09[0.68-6.38]	
No	Reference	Reference	
Malignancy			
Yes	3.48[1.57-7.68]	3.92[1.62-9.52]	
No	Reference	Reference	
Autoimmune Disease			

Yes	1.18[0.42-3.29]	1.13[0.38-3.33]	
No	Reference	Reference	
Immunosuppressed			
Yes	2.55[0.59-10.93]	2.36[0.49-11.37]	
No	Reference	Reference	
Ferritin (per 100 ng/dl increase)	1.03 [1.00-1.05]	1.02[1.00-1.05]	1.00[0.97-1.03]
CRP (per unit of mg/dl increase)	1.07 [1.03-1.10]	1.05[1.01-1.08]	1.05[1.00-1.10]
D-dimers (per unit of mg/l increase)	1.11 [1.02-1.21]	1.06[0.98-1.15]	1.03[0.94-1.14]
LDH (per 100 international units/l increase)	1.27 [1.11-1.46]	1.23[1.06-1.42]	1.38[1.08-1.77]
Admission after 31/03/2021			
No	Reference	Reference	
Yes	0.45[0.25-0.83]	0.66[0.34.1.29]	

TABLE 4. Sensitivity, specificity, negative predictive value of admission laboratory tests for mortality and need for oxygen support using empirical cut-off points for patients admitted for CoViD-19 in Venizelion General Hospital, Heraklion, Greece March.

Test	Cut-off value	Sensitivity Mortality [95% CI]	Specificity Mortality [95% CI]	NPV Mortality [95% CI]	NPV Oxygen Support [95% CI]
Ferritin (ng/dl)	≥205	85.5% [76.1-92.3]	20.7% [16.5-25.4]	85.5% [76.1-92.3]	16.6% [9.5-26.6]
CRP (mg/dl)	≥3 mg/dl	89.1% [80.4-94.2]	27.4% [22.8-32.5]	91.2% [84.0-95.9]	20.3% [13.0-29.4]
D-dimers (mg/l)	≥0.5 mg/l	87.9% [78.9-94.0]	20.1% [16.0-24.8]	87.3% [77.9-93.7]	11.3% [5.3-20.5]
LDH (IU/l)	≥240 IU/l	84.3% [74.7-91.3]	25.7% [21.1-30.7]	87.1% [78.9-92.9]	15.8% [9.3-24.4]
De Ritis ratio	≥1	80.7% [70.5-88.5]	37.7% [32.5-43.0%]	88.9% [82.6-93.5]	11.7% [6.9-18.1]
LDH and D-dimers (IU/l and mg/l)	≥240 or ≥0.5	100% [95.6-100]	7.6% [5.0-10.9]	100% [86.7-100]	19.2% [6.5-39.3]
CRP and D-dimers (mg/dl and mg/l)	≥3 or ≥0.5	98.8% [93.4-99.9]	7.3% [4.7-10.6]	96.1% [80.3-99.9]	19.2% [6.5-39.3]
CRP and Ferritin (mg/dl and ng/dl)	≥3 or ≥205	97.5% [91.5-99.7]	12.2% [8.9-16.2]	95.4% [84.5-99.4]	27.2% [14.9-42.7]

FİGURE 1. CoViD-19 Cases, Deaths and in-hospital Case Fatality Rate (CFR) in Venizelion General Hospital, Heraklion, Greece March 2020-end of April 2021. Monthly CFR reported only for months with more than 50 cases.



	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21
Cases	2	0	0	1	2	6	8	4	58	21	12	67	118	126
Deaths	0	0	0	0	1	0	1	0	12	5	0	23	26	15
In-Hospital CFR	0,00%								20,7%			34,3%	22,0%	11,9%

FIGURE 1. Monthly CoViD-19 in hospital Case Fatality Rate, mean age of hospitalised cases in Venizelion General Hospital, Heraklion and community over 60 years vaccine uptake for at least one dose and two doses of SARS-COV-2 vaccines, Greece November 2020-April 2021.

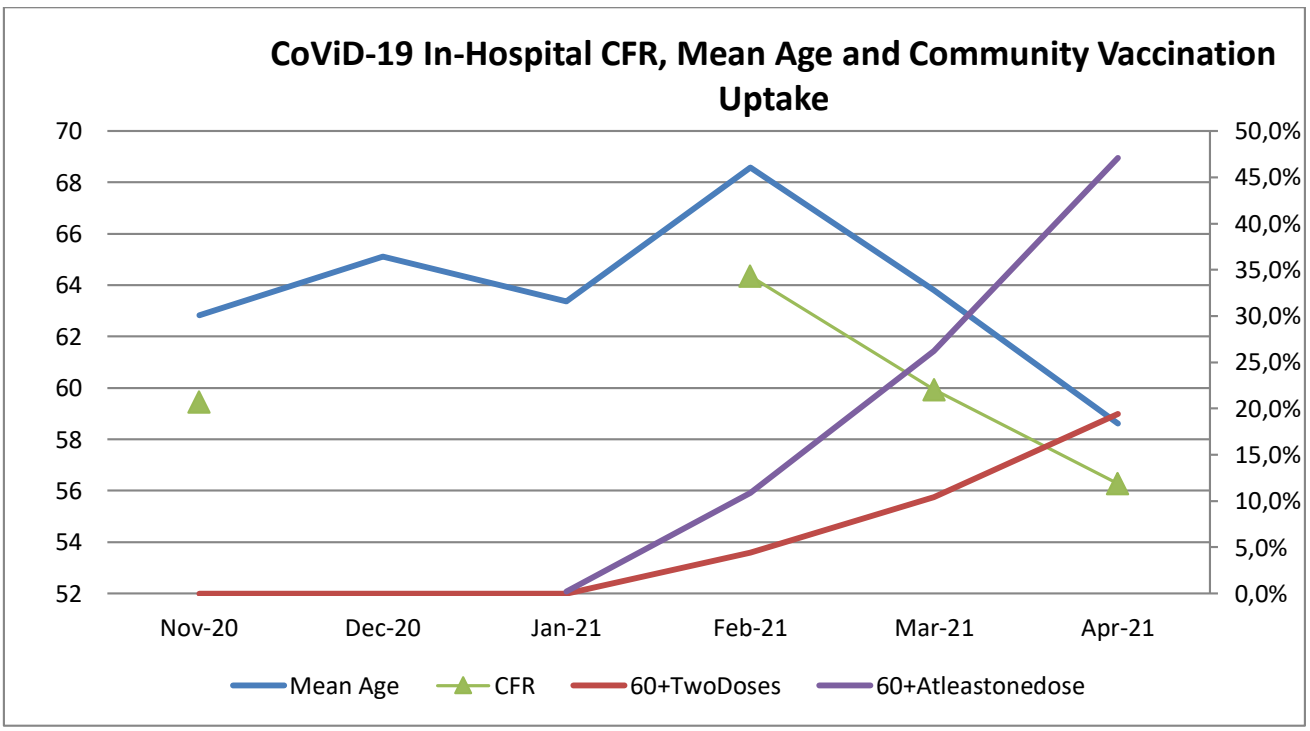


FIGURE 3. Regional weekly 14-day case notification rate/100.000 for the region of Crete, Greece EpiWeek 19 2020-EpiWeek 17 2021, ECDC da