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# Clinical outcomes in vaccinated and unvaccinated patients with COVID-19: a population-based analysis

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**Abstract. – OBJECTIVE: Real-life data for vaccination against COVID-19 are sorely needed. This was a population-based analysis aiming at investigating the hospitalization risk for COVID-19 of 98,982 subjects and compare features of vaccinated and unvaccinated patients.**

**PATIENTS AND METHODS: Hospitalized patients with COVID-19 between 01/07/2021 and 11/02/2022 were included in the study.**

**RESULTS: 582 patients were included in the analysis [males: 58.6% (n=341), vaccinated patients: 28.5% (n=166), unvaccinated patients: 71.5% (n=416)]. Median age of vaccinated patients was significantly higher compared to median age of unvaccinated [74.0 (95% CI: 72.0-77.0) *vs*. 59.0 (95% CI: 57.0-62.0), *p*=0.0001]. Mean latency time (±SD) from the second dose to hospitalization was 5.7±2.6 months. Between 01/07/2021 and 01/12/2021, unvaccinated subjects had higher risk for hospitalization compared to vaccinated [HR: 2.82, 95% CI: 2.30-3.45, *p*<0.0001]. Between 02/12/2021 and 11/02/2022, unvaccinated subjects presented with higher risk for hospitalization than subjects that had received booster dose [HR: 2.07, 95% CI: 1.44-2.98, *p*=0.005], but not than subjects that got two doses. Median value of hospitalization days was higher in unvaccinated patients compared to vaccinated [7.0 (95% CI: 7.0-8.0) *vs*. 6.0 (95% CI: 5.0-7.0), *p*=0.02]. Finally, age-adjusted analysis showed that hospitalized unvaccinated patients presented with significantly higher mortality risk compared to hospitalized vaccinated patients [HR: 2.59, 95% CI: 1.69-3.98, *p*<0.0001].**

**CONCLUSIONS: Vaccination against COVID-19 remains the best way to contain the pandemic. There is an amenable need for booster dose during the omicron era.**

*Key Words:*
Vaccination, COVID-19, Cumulative incidence, Hospitalization risk, Mortality, Booster dose.

## Introduction

The emergence and spread of 2019 coronavirus disease (COVID-19) have been constantly causing a growing global public health crisis over the past two years[1-3]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in more than 3.6 million cases of COVID-19 and more than 30,000 deaths in Greece. Despite advances in treatment, vaccination remains the best way to contain the pandemic and reduce its devastating medical and socioeconomical burden[4-6]. Between December 2020 and June 2021, vaccines were gradually available for the great majority of population by means of conditional marketing approval, full approval and emergency use authorization pathways on the basis of short-term safety and efficacy against COVID-19[7-10]. Nevertheless, an increase in post-vaccination SARS-CoV-2 infections during the fall and early winter of 2021 arose concerns about the long-term vaccination effectiveness, as well as their effectiveness against new variants, such as the B.1.1.529 (omicron) variant[11,12]. Therefore, the ideal time point for the booster COVID-19 vaccine dose is a matter of ongoing debate[13]. Despite the exponential increase in our understanding of vaccine effectiveness and safety, the time point

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of booster dose administration is still puzzling and seems to be among the most crucial decisions towards pandemic management[14-17]. To this end, it is more than evident that real-life data for vaccination against COVID-19 are sorely needed. Towards this direction, we conducted a population-based analysis aiming at investigating the risk for hospitalization for COVID-19 of 98,982 subjects and compare features of vaccinated and unvaccinated patients.

## Patients and Methods

### Study Design and Patient Selection

In this prospective study, we included consecutive patients with positive real-time reverse transcriptase polymerase chain reaction of an upper respiratory nasopharyngeal swab for SARS-CoV-2 admitted to our COVID-19 department in the University Hospital of Patras, Greece, between 01/07/2021 and 11/02/2022. Data collection and analysis were approved by the Institutional Review Board and the Local Ethics Committee (protocol number: 558/25-10-2021). Informed consent was obtained from all individual participants included in the study.

For hospitalized patients with COVID-19, we recorded age, vaccination history for SARS-CoV-2, smoking history, comorbidities, duration of hospitalization, worst PaO2/FiO2, as well as outcome of hospitalization.

### Outcome Measures

The primary outcome was the risk for hospitalization due to COVID-19 between vaccinated and unvaccinated subjects for SARS-CoV-2. Secondary outcomes included duration of hospitalization, worst PaO2/FiO2, mortality risk and mean latency time from the second dose of vaccination to hospitalization.

### Statistical Analysis

With regards to baseline data, summary descriptive statistics were generated with categorical data displayed as absolute numbers and relative frequencies. Continuous data were denoted as mean ± standard deviation (SD) or medians with 95% Confidence Interval (95% CI), following Kolmogorov-Smirnov's test for normality. Mann-Whitney or *t*-test were used for the investigation of differences between groups based on the absence or presence of normality. The primary outcome was presented with the Kaplan-Meier method and cumulative incidence curves were compared between the two groups. Given the advent of B.1.1.529 (Omicron) variant in Greece on 02/12/2021, we performed two distinct analyses in an effort to better assess waning effectiveness of COVID-19 vaccines in correlation with the emergence of new and more transmissible variants. In particular, we estimated the risk for hospitalization between vaccinated and unvaccinated subjects in two periods: Delta variant era (between 01/07/2021 and 01/12/2021) and Omicron variant era (between 02/12/2021 and 11/02/2022). Moreover, given the heterogeneity of median age between vaccinated and unvaccinated, we used as cut-off threshold the lowest value of 95% CI in the vaccinated group (72 years of age) and estimated mortality risk in a homogenized population (vaccinated and unvaccinated subjects with ≥ 72 years of age). Mortality risk was presented with the Kaplan-Meier method. In the adjusted analysis, the stratified Cox proportional-hazards model was used to estimate the hazard ratio and 95% CI. $p$-values < 0.05 were considered statistically significant.

## Results

### Patient Demographics and Disease Characteristics

We identified 582 hospitalized patients with COVID-19 [vaccinated patients: 28.5% (n=166), unvaccinated patients: 71.5% (n=416)]. Baseline characteristics of patients are summarized in Table I. Median age of vaccinated patients was significantly higher compared to median age of unvaccinated [74.0 (95% CI: 72.0-77.0) *vs.* 59.0 (95% CI: 57.0-62.0), $p$=0.0001]. Hospitalized patients with COVID-19 were predominantly male (58.6%, n=341). Strikingly, the majority of patients were never-smokers (63.3%, n=105 in the vaccinated group, 67.1%, n=279 in the unvaccinated group). Most common comorbidities were arterial hypertension (57.8% in vaccinated group, 35.8% in unvaccinated group), chronic heart disease (34.9% in vaccinated group, 15.1% in unvaccinated group), dyslipidemia (30.7% in vaccinated group, 19.0% in unvaccinated group), diabetes mellitus (30.1% in vaccinated group, 16.3% in unvaccinated group) and long use of immunosuppressive agent (19.3% in vaccinated group, 6.0% in unvaccinated group) (Table II).

**Table I.** Baseline characteristics of patients included in the study.

| Characteristics | Vaccinated (N, %) | Unvaccinated (N, %) | *p*-value |
|---|---|---|---|
| Number of patients | 166, 28.5% | 416, 71.5% | NA |
| Median age (95% CI) | 74 (72 to 77) | 59 (57 to 62) | <0.0001 |
| Males/Females | 110 (66.3%)/56 (33.7%) | 231 (55.5%)/185 (44.5%) | NA |
| Current | 6 (3.6%) | 35 (8.4%) | NA |
| Ex-smokers | 55 (33.1%) | 102 (24.5%) | NA |
| Never smokers | 105 (63.3%) | 279 (67.1%) | NA |

CI: Confidence Interval.

### Risk for Hospitalization

Cumulative incidence of hospitalization in our cohort was 5.4%, 37.3% and 100% one, five and twelve months following second dose, respectively. Mean latency time (±SD) from the second dose to hospitalization was 5.7 ± 2.6 months (Figure 1). Between 01/07/2021 and 01/12/2021, unvaccinated subjects had higher risk for hospitalization compared to vaccinated [HR: 2.82, 95% CI: 2.30-3.45, $p<0.0001$] (Figure 2, A). Between 02/12/2021 and 11/02/2022, unvaccinated subjects presented with higher risk for hospitalization than subjects that had received booster dose [HR: 2.07, 95% CI: 1.44-2.98, $p=0.005$], but not than subjects that got two doses (Figure 2, B). Median value of hospitalization days was higher in unvaccinated patients compared to vaccinated [7.0 (95% CI: 7.0-8.0) *vs.* 6.0 (95% CI: 5.0-7.0), $p=0.02$] (Figure 3, A). Worst PaO2/FiO2 during hospitalization was lower in unvaccinated patients compared to vaccinated [151.0 (95% CI: 133.0-166.3) *vs.* 237.5 (95% CI: 190.6-276.0), $p=0.002$] (Figure 3, B).

### Mortality Risk

Hospitalized unvaccinated patients ≥ 72 years of age presented with significantly higher mortality risk compared to hospitalized vaccinated patients ≥ 72 years of age [HR: 2.59, 95% CI: 1.69 to 3.98, $p<0.0001$]. Multivariate Cox regression for this group showed that lack of vaccination, history of immunosuppression, chronic heart failure, increased CRP, increased D-dimer and increased neutrophil to lymphocyte ratio were independent risk factors for mortality (Figure 4, A-B).

## Discussion

To the best of our knowledge, this is the first population-based study in Greece demonstrating that booster dose significantly reduced the hospitalization risk for COVID-19 during the Omicron era. Vaccinated patients were hospitalized for fewer days and experienced less severe disease than unvaccinated subjects. These results highlight the cardinal role of vaccination as a measure to contain the pandemic.

This study showed that vaccination reduced the risk of hospitalization for COVID-19 and led to less severe disease. Importantly, booster dose seemed to be crucial for the decrease of hospi-

**Table II.** Comorbidities of patients included in the study.

| Comorbidity | Vaccinated (N, %) | Unvaccinated (N, %) |
|---|---|---|
| Hypertension | 96/166 (57.8%) | 149/416 (35.8%) |
| Dyslipidemia | 51/166 (30.7%) | 79/416 (19.0%) |
| Depression | 24/166 (14.5%) | 46/416 (11.6%) |
| Diabetes Mellitus | 50/166 (30.1%) | 68/416 (16.3%) |
| Chronic Heart Disease | 58/166 (34.9%) | 63/416 (15.1%) |
| Hypothyroidism | 18/166 (10.8%) | 54/416 (13.0%) |
| Asthma | 7/166 (4.2%) | 15/416 (3.6%) |
| COPD | 17/166 (10.2%) | 21/416 (5.0%) |
| GERD | 3/166 (1.8%) | 16/416 (3.8%) |
| Obesity | 20/166 (12.0%) | 49/416 (11.8%) |
| Immunosuppressive agent (Long use) | 32/166 (19.3%) | 25/416 (6.0%) |

*Abbreviations:* GERD: Gastroesophageal reflux disease, COPD: Chronic obstructive pulmonary disease.

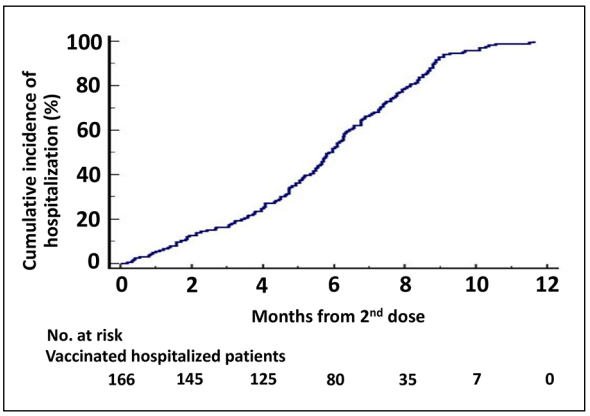


**Figure 1.** Cumulative incidence of hospitalization in our cohort following second dose of vaccination. Mean latency time (±SD) from the second dose to hospitalization was 5.7 ± 2.6 months.

talization risk during the Omicron era. In line with our notion, previous reports[18-20] showed effectiveness of booster dose for preventing severe outcomes related to COVID-19. In Israel, an observational study[18] among 1,158,269 individuals eligible to be included in the third dose group demonstrated that a third dose of BNT162b2 mRNA vaccine was effective in protecting individuals against COVID-19-related admission to hospital, severe disease, and COVID-19-related death. Our results were further corroborated with evidence[19] showing that subjects who received a booster dose at least 5 months after a second dose of BNT162b2 had 90% lower mortality due to COVID-19 than subjects who did not receive a booster one. With regards to age groups, the booster dose reduced the rate of confirmed infection and severe illness by a similar factor in the age groups studied, although in the youngest age group, a larger reduction factor against confirmed infections was observed[20]. Moreover, despite the putative reduced vaccine effectiveness against the Omicron variant as compared with

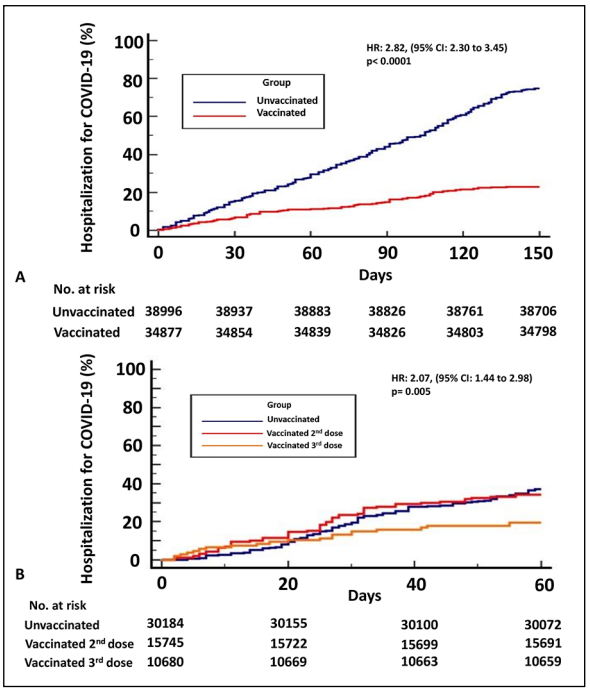


**Figure 2.** Kaplan-Meier curves for risk for hospitalization. Between 01/07/2021 and 01/12/2021 unvaccinated subjects had higher risk for hospitalization compared to vaccinated [HR: 2.82, 95% CI: 2.30-3.45, $p$<0.0001] (**A**). Between 02/12/2021 and 11/02/2022 unvaccinated subjects presented with higher risk for hospitalization than subjects that had received booster dose [HR: 2.07, 95% CI: 1.44-2.98, $p$=0.005], but not than subjects that got two doses (**B**).

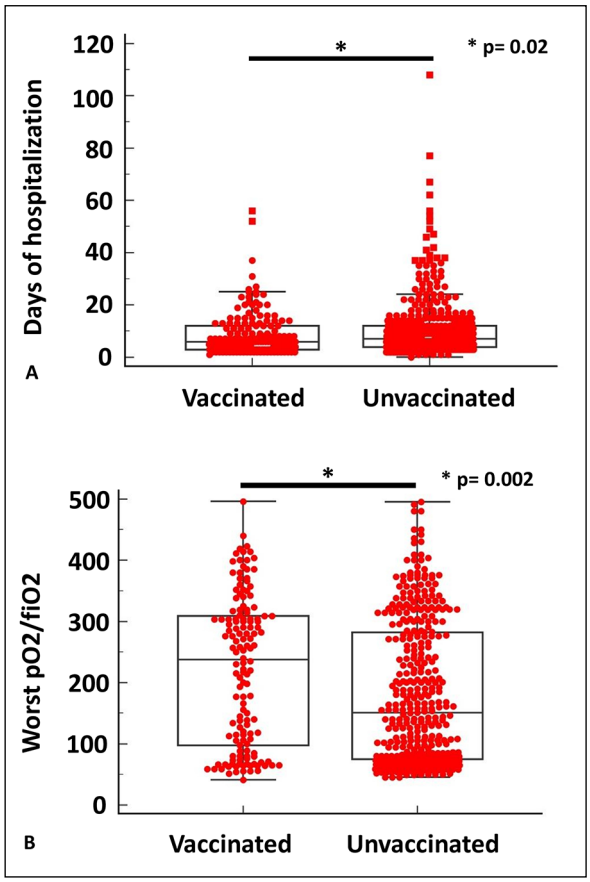


**Figure 3.** Median value of hospitalization days was higher in unvaccinated patients compared to vaccinated [7.0 (95% CI: 7.0-8.0) *vs.* 6.0 (95% CI: 5.0-7.0), $p$=0.02] (**A**). Worst PaO2/FiO2 was lower in unvaccinated patients compared to vaccinated [151.0 (95% CI: 133.0-166.3) *vs.* 237.5 (95% CI: 190.6-276.0), $p$=0.002] (**B**).

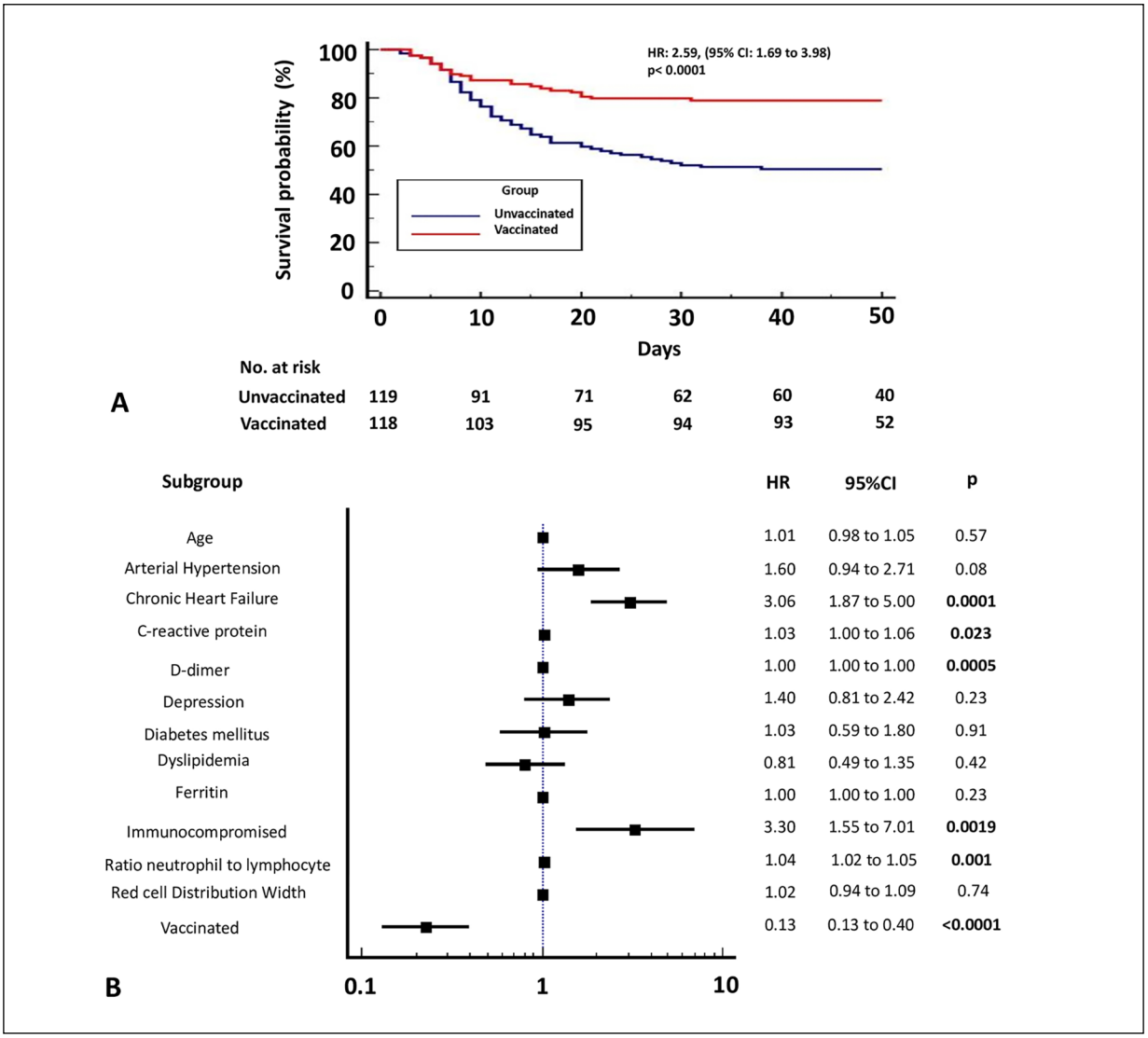


**Figure 4.** Kaplan-Meier curves for mortality risk. Age-adjusted analysis showed that hospitalized unvaccinated patients presented with significantly higher mortality risk compared to hospitalized vaccinated patients [HR: 2.59, 95% CI: 1.69-3.98, $p<0.0001$] (**A**). Multivariate Cox regression survival analysis for hospitalized patients with COVID-19 (**B**).

the original strain of SARS-CoV-2 or the Delta (B.1.617.2) variant, booster doses substantially increased protection, although waning occurred over time[11]. With regards to the duration of protection, our real-life clinical data supports the concept that vaccine performance and clinical protection fall considerably over time, as mean latency time from the second dose to hospitalization was 5.7 months and cumulative incidence of hospitalization increased substantially 5 months after the second dose.

Our findings are also in line with recent *in vitro* studies[21-24] identifying a decline in neutralization titer with time for up to 8 months after SARS-CoV-2 infection or vaccination. More specifically, modeling of the duration of immune protection after vaccination showed that neutralization level is highly predictive of immune protection and provide an evidence-based model of SARS-CoV-2 immune protection that will assist in developing vaccine strategies to control the future trajectory of the pandemic[24]. COV-BOOST trial[25] enrolling 2,878 adults in UK demonstrated increased reactogenicity of a third booster dose within at least 70 days after the second dose with minimal adverse events, indicating an optimal efficacy and safety profile. Importantly, the study showed that enhanced

vaccine effectiveness following the third dose that was observed in large-scale populations, was not only attributed to amplified humoral, but also to T cellular immunity that provenly confers longitudinal protection, an observation consistent with the results of an earlier study suggesting that SARS-CoV-2 variants of concern partially escape humoral but not T cell responses in COVID-19 convalescent donors and vaccine recipient[26]. This above evidence seems quite encouraging in light of the worrisome news arising from the waning humoral immunity, as indicated by reduced neutralizing antibodies within 8-16 weeks after the second dose of BNT162b2 and the recently emerged Omicron variants of concern[27]. Similarly with the fruitful effects of the third dose, the need for a fourth dose seems amenable for the elderly and for patients at increased risk for severe disease due to their comorbidome[28]. In the context of the global expansion of the Omicron variant, a strategy of repeated booster vaccination with existing vaccines seems inevitable to confront virus evolution until the development and administration of the greatly anticipated new generation of broadly effective vaccines[29].

### Limitations and Strengths

Our study presents with some limitations. First of all, identification of specific subtypes and variants of SARS-CoV-2 is not available in our hospital; yet, we were able to present data during Delta variant and Omicron variant era. Secondly, our sample size with regards to hospitalized patients is moderate, thus we were not able to perform other subgroup analyses; yet, our study clearly indicated the beneficial role of the booster dose.

## Conclusions

Collectively, this study highlighted real-life effectiveness of vaccination against COVID-19. Vaccination reduced the risk of hospitalization, days of hospitalization and led to less severe disease during Delta and Omicron era. To the best of our knowledge, this is the first study showing that vaccination led to less severe disease as assessed by PaO2/FiO2. Booster dose seemed to be crucial during the Omicron era. Our findings should prompt national authorities to prioritize vaccination approaches and highlight the role of booster doses. Based on the fact that long COVID-19 syndrome is associated with disease severity, vaccination could potentially decrease the likelihood for long COVID-19 sequelae[30,31]. Future larger studies aiming at identifying the ideal time point for administration of booster doses of vaccination for COVID-19 are greatly anticipated.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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### Informed Consent

Informed consent was obtained from all individual participants included in the study.

### Availability of Data and Material

Data are available upon request.

### Authors' Contribution

Ourania Papaioannou and Theodoros Karampitsakos: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft. Panagiota Tsiri, Vasilina Sotiropoulou, Electra Koulousousa, Panagiotis Tasiopoulos, Georgios Schinas, Matthaios Katsaras, Eirini Zarkadi, Elli Malakounidou, Vasiliki Georgiopoulou, Fotios Sampsonas, Alexandros Spyridonidis, Karolina Akinosoglou and Markos Marangos: Data curation, Investigation, Writing - review & editing. Argyrios Tzouvelekis: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Supervision, Validation, Writing - original draft. All authors: (1) conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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### Ethics Approval

The University Hospital of Patras, Institutional Review Board and the Local Ethics Committee (protocol number: 558/25-10-2021) approved the study.

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