# Onodera's prognostic nutritional index: Comparison of its role in the severity and outcomes of patients with COVID-19 during the periods of alpha, delta and omicron variant predominance

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**Abstract.** Coronavirus disease 2019 (COVID-19) has posed a severe public health threat worldwide, affecting the function of multiple organs in affected individuals, in addition to respiratory function. Several strains of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been circulating worldwide since it first arose, with some of these having the ability to escape from natural or vaccine-mediated immunity. The Onodera's prognostic nutritional index (OPNI), which is derived from the peripheral lymphocyte count and serum albumin, has been reported to be significantly associated with a poor survival rate and post-operative complications in patients with various diseases and in some studies on patients with COVID-19. The aim of the present retrospective study was to evaluate and compare the efficacy of OPNI as a prognostic indicator in patients with COVID-19 during the periods of alpha, delta and omicron variant predominance. Adult patients who visited or were hospitalized due to SARS-CoV-2 infection were included, covering the second, third (alpha variant), fourth (delta variant) and fifth (omicron variant) pandemic waves. According to the results obtained, OPNI exhibited a statistically significant difference among patients with mild/moderate, severe and critical disease, with the lowest values observed in patients with critical disease in all the pandemic waves examined. Moreover, OPNI was found to be an independent prognostic biomarker of intubation and mortality in patients with COVID-19, according to multivariate logistic regression analysis, including as confounders an age >65 years, the male sex and the presence of comorbidities in all periods examined.

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*Key words:* coronavirus disease 2019, coronavirus, prognosis, prognostic nutritional index, albumin, mortality

## Introduction

The coronavirus disease 2019 (COVID-19) was first discovered in Wuhan, China, and rapidly spread worldwide, posing a severe threat to public health. Almost half of the patients with COVID-19 suffer from dyspnea, with concomitant hypoxia at 1 week following disease onset, which is primarily characterized as fever, cough and exhaustion (1). The functions of other organs can also be affected, in addition to respiratory function (2-4). In critically ill patients, complications, such as cardiac injury, acute renal injury, acute gastrointestinal injury, coagulopathy and liver dysfunction are highly common, and have been associated with poor outcomes in patients with COVID-19 (5,6).

Several strains of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been circulating worldwide since it first arose. Variants of concern are those that have the potential to evade natural or vaccine-mediated immunity. The alpha variant (B.1.1.7), which is considered to be 40-80% more transmissible than wild-type SARS-CoV-2, was initially discovered in November, 2020 in a sample obtained in September in the United Kingdom, and by mid-December, 2020, it had spread rapidly, coinciding with an increase in the number of infections (7). The delta variant (B.1.617.2), which was initially discovered in India, and a more virulent mutant, also known as omicron, arose in South Africa in November, 2021 (B.1.1.529). As these variants were more transmissible than the progenitor variants and rapidly propagated, they attracted worldwide attention (8).

The cytokine release syndrome, which plays a key role in the course of COVID-19 infection, is considered to be the cause of organ damage. The stimulation of the innate and adaptive immune systems produced by SARS-CoV-2 is responsible for the release of excessive cytokines in patients with COVID-19. In COVID-19, the imbalance of the immune response and excessive inflammation is a major component of its pathogenesis (9). Several immune and inflammatory indicators, including the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, eosinophil-to-lymphocyte ratio, immature granulocytes, ferritin, fibrinogen, C-reactive protein, interleukin (IL)-6 and lactate dehydrogenase, have been shown to be associated with disease severity and mortality in patients with COVID-19 (10-14).

An additional index, Onodera's prognostic nutritional index (OPNI), has been reported as a severity and outcome indicator in patients with COVID-19 (15). The OPNI is made up of serum albumin and total lymphocyte count. The validity of OPNI to predict the prognosis of patients undergoing gastrointestinal surgery was initially reported by Onodera *et al* (16). Since then, OPNI validation has been performed in patients with end-stage liver illness, active tuberculosis, atypical mycobacterial infection and gastrointestinal malignancies (17,18). The aim of the present study was to assess and compare the clinical utility of OPNI as a prognostic indicator in patients with COVID-19 during the periods of alpha, delta and omicron variant predominance.

## Patients and methods

*Study design*. The design of the present study was retrospective. Data collection was performed at the Laiko General Hospital (Athens, Greece) between September 20, 2020 and March 31, 2022. The study was approved by the Institutional Board of Laiko General Hospital and was in line with the declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

*Participants and data collection*. In the present study, adult patients who visited or were hospitalized in the COVID-19 Unit of Laiko General Hospital due to SARS-CoV-2 infection were included, covering the second, third (alpha variant), fourth (delta variant) and fifth (omicron variant) pandemic waves. The patients were divided into three cohorts. The first (cohort A) was comprised of unvaccinated consecutive patients predominantly infected with the alpha SARS-CoV-2 variant who were admitted to Laiko University Hospital between September 20, 2020 and June 30, 2021 for COVID-19 (second and third pandemic waves). The second cohort (cohort B) included consecutive patients irrespective of vaccination status, who were admitted between July 1, 2021 and December 25, 2021 (fourth pandemic wave, predominance of the delta SARS-CoV-2 variant). The third cohort (cohort C) was comprised of consecutive patients irrespective of vaccination status, who were admitted between December 26, 2021 and March 31, 2022 (fifth pandemic wave, predominance of the omicron SARS-CoV-2 variant).

All patients were uniformly treated according to the National Institutes of Health (NIH) protocols (19). SARS-CoV-2 infection was confirmed by the positive detection of SARS-CoV-2 nucleic acid in examined nasopharyngeal samples with the use of reverse transcription-polymerase chain reaction (RT-PCR). Demographic and clinical data were extracted retrospectively from electronic medical records. Data on age, sex, comorbidities (cardiovascular disease, arterial hypertension, diabetes mellitus, neurological and hematological disorders, other malignancies, immunosuppression), vaccination status, disease severity and outcomes (recovery, intubation and mortality) were extracted. The patients were classified into the following severity of illness categories: Mild/moderate, severe and critical based on the clinical spectrum of SARS-CoV-2 infection (19). Laboratory investigations (complete blood count and albumin levels) were recorded from the first electronic medical record following hospital admission. The OPNI was calculated according to the following formula (16): OPNI=10 x serum albumin (g/dl) + 0.005 x peripheral lymphocyte count (/$mm^3$). The OPNI was associated with disease severity and outcomes in the three studied cohorts.

*Statistical analysis*. Statistical analysis was performed using IBM SPSS-Statistics version 26.0 (IBM Corp.). Categorical variables are presented as the number and percentage, and continuous variables as the mean ± standard deviation (SD). The normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Normally distributed variables were compared using an independent samples Student's t-test on factors with two groups and one-way analysis of variance (ANOVA) with Bonferroni post hoc pairwise comparisons on factors with three groups. Categorical variables were examined using the Fischer's exact test or the Chi-squared test and are shown as absolute numbers (frequency percent). Multivariate logistic regression analysis was conducted to identify independent variables. Associations are presented as odds ratios (OR) with their corresponding 95% confidence intervals (95% CI). The discriminative ability of variables was evaluated by using the area under the receiver operating characteristic curve (ROC). Values of $P<0.05$ were considered to indicate statistically significant differences.

## Results

*Cohort A*. Cohort A comprised of 588 patients (352 males), predominantly infected with the alpha SARS-CoV-2 variant, with a mean age of 64.09±16.29 years. The demographic characteristics of cohort A are presented in Table I. In total, 48 patients (8.2%) had mild/moderate disease, 365 patients

Table I. Demographic characteristics of the patients in cohorts A, B and C.

| Parameter | Cohort A (n=588) | Cohort B (n=494) | Cohort C (n=523) |
|---|---|---|---|
| Age (years), mean ± SD | 64.09±16.29 | 63.46±17.46 | 68.60±16.65 |
| Sex, n (%) | | | |
| Female | 236 (40.1) | 208 (42.1) | 232 (44.4) |
| Male | 352 (59.9) | 286 (57.9) | 291 (55.6) |
| Disease severity, n (%) | | | |
| Mild/moderate | 48 (8.2) | 94 (19) | 137 (26.2) |
| Severe | 365 (62.1) | 269 (54.5) | 223 (42.5) |
| Critical | 175 (29.8) | 131 (26.5) | 163 (31.2) |
| Comorbidities, n (%) | | | |
| No | 107 (18.2) | 93 (18.8) | 44 (8.4) |
| Yes | 481 (81.8) | 401 (81.2) | 479 (91.6) |
| Age >65 years, n (%) | | | |
| No | 293 (49.8) | 259 (52.3) | 199 (38.2) |
| Yes | 295 (50.2) | 235 (47.7) | 324 (61.8) |
| Intubation, n (%) | | | |
| No | 528 (89.8) | 451 (91.3) | 482 (92.1) |
| Yes | 60 (10.2) | 43 (8.7) | 41 (7.9) |
| Mortality, n (%) | | | |
| No | 487 (82.8) | 399 (80.8) | 403 (77) |
| Yes | 101 (17.2) | 95 (19.2) | 120 (23) |
| Vaccination status, n (%) | | | |
| Vaccinated | 0 (0) | 167 (33.8) | 234 (44.8) |
| Unvaccinated | 588 (100) | 327 (66.2) | 289 (55.2) |

The data for age are presented as the mean ± SD, while those for all other parameters as number and percentage. SD, standard deviation.

(62.1%) had severe disease and 175 patients (29.8%) had critical disease. The mean OPNI value was 47.80±6.35 in patients with mild/moderate disease, 46.76±23.34 in patients with severe disease and 41.35±6.32 in patients with critical disease. There was a statistically significant difference in the mean OPNI values between the three different disease severity groups, with the lowest value observed in the patients with critical disease (P=0.005) (Fig. 1 and Table II).

The mean OPNI value was 41.32±5.96 in patients who were intubated and 45.68±19.86 in patients that were not (P=0.092). The mean OPNI value was 40.09±6.08 in patients who did not survive and 46.3±20.49 in patients who recovered. There was a statistically significant difference in the mean OPNI values between patients who did not survive and patients who recovered (P=0.003; Table II).

According to the univariate analysis, there was a statistically significant association between an age >65 years and mortality (P=0.01) and between an age >65 years and intubation (P=0.003). Moreover, there was a statistically significant association between the presence of comorbidities and mortality (P=0.01), and between the presence of comorbidities and intubation (P=0.015) (Table III).

Following multivariate logistic regression analysis, including as confounders an age >65 years and the presence of comorbidities, an independent association was found between

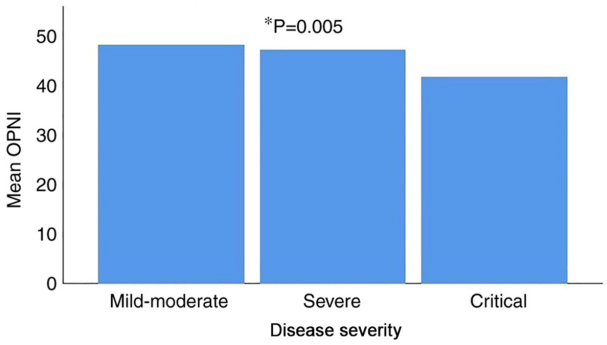


Figure 1. Mean OPNI values in the different groups as regards COVID-19 severity in cohort A. There was a statistically significant difference in the mean OPNI values between the three different disease severity groups, with the lowest value observed in patients with critical disease (*P=0.005). OPNI, Onodera's prognostic nutritional index.

OPNI and intubation (OR, 0.928; 95% CI, 0.885-0.972; P=0.002) (Table IV).

An independent association was also detected between OPNI and mortality (OR, 0.886; 95% CI, 0.848-0.925; P=0.001). Other factors independently associated with mortality in this cohort were an age >65 years and the presence of comorbidities (Table IV).

Table II. Mean values of OPNI in the patients in cohort A.

| Group | OPNI (mean ± SD) | P-value |
|---|---|---|
| Females | 43.95±6.05 | 0.179 |
| Males | 46.09±23.97 | |
| Disease severity | | 0.005 |
| Mild/moderate | 47.80±6.35 | 0.759[a] |
| Severe | 46.76±23.34 | 0.001[b] |
| Critical | 41.35±6.32 | 0.003[c] |
| Comorbidities | 44.88±20.77 | 0.341 |
| No comorbidities | 46.81±5.76 | |
| Age >65 years | 42.93±7.91 | 0.003 |
| Age ≤65 years | 47.56±25.47 | |
| Intubation | 41.32±5.96 | 0.092 |
| No intubation | 45.68±19.86 | |
| Mortality | 40.09±6.08 | 0.003 |
| Recovery | 46.3±20.49 | |

[a]Mild/moderate vs. severe; [b]mild/moderate vs. critical; [c]severe vs. critical. OPNI, Onodera's prognostic nutritional index; SD, standard deviation.

Table III. Univariate analysis for cohort A (intubation and mortality).

| Parameter | Survivors | Non-survivors | P-value |
|---|---|---|---|
| Age >65 years | 207 | 88 | 0.01[a] |
| Age ≤65 years | 280 | 13 | |
| Males | 289 | 63 | 0.571 |
| Females | 198 | 38 | |
| Comorbidities | 382 | 99 | 0.01[a] |
| No comorbidities | 105 | 2 | |
| **Parameter** | **Non-intubation** | **Intubation** | **P-value** |
| Age >65 years | 254 | 41 | 0.003[a] |
| Age ≤65 years | 274 | 19 | |
| Males | 311 | 41 | 0.158 |
| Females | 217 | 19 | |
| Comorbidities | 425 | 56 | 0.015[a] |
| No comorbidities | 103 | 4 | |

[a]P<0.05.

Table IV. Multivariate logistic regression analysis of factors independently associated with intubation and mortality in cohort A.

Multivariate analysis for mortality

| Variable | P-value | Odds ratio | 95% CI | |
|---|---|---|---|---|
| Age >65 years | 0.000 | 0.176 | 0.093 | 0.331 |
| Comorbidities | 0.019 | 0.174 | 0.041 | 0.746 |
| OPNI | 0.001 | 0.886 | 0.848 | 0.925 |

Multivariate analysis for intubation

| Variable | P-value | Odds ratio | 95% CI | |
|---|---|---|---|---|
| Age >65 years | 0.138 | 1.583 | 0.863 | 2.902 |
| Comorbidities | 0.139 | 2.252 | 0.769 | 6.599 |
| OPNI | 0.002 | 0.928 | 0.885 | 0.972 |

CI, confidence interval; OPNI, Onodera's prognostic nutritional index.

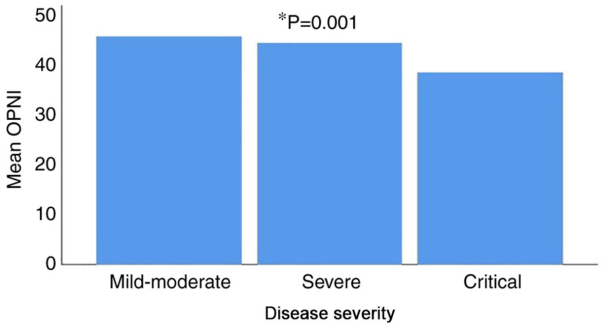


Figure 2. Mean OPNI values in the different groups as regards COVID-19 severity in cohort B. There was a statistically significant difference in the mean OPNI values between the three different disease severity groups, with the lowest value observed in patients with critical disease (*P=0.001). OPNI, Onodera's prognostic nutritional index.

*Cohort B*. Cohort B comprised of 494 patients (286 males), predominantly infected with the delta SARS-CoV-2 variant, with a mean age of 63.46±17.46 years. The demographic characteristics of the patients in cohort B are presented in Table I. A total of 94 (19%) patients had mild/moderate disease, 269 patients (54.5%) had severe disease and 131 patients (26.5%) had critical disease. The mean OPNI value was 45.80±5.92 in patients with mild/moderate disease, 44.42±6.04 in patients with severe disease and 38.58±6.37 in patients with critical disease. There was a statistically significant difference in the mean OPNI values between the three different disease severity groups, with the lowest value observed in patients with critical disease (P=0.001) (Fig. 2 and Table V).

The mean OPNI value was 38.55±5.88 in patients who were intubated and 43.59±6.61 in patients that were not. The mean OPNI value was 37.35±6.20 in patients who did not survive and 44.50±6.05 in patients who recovered. There was a statistically significant difference in the mean OPNI values between patients who were intubated and those who were not intubated and between patients who did not survive and patients who recovered (P=0.001; Table V).

According to the univariate analysis, there was a statistically significant association between an age >65 years and mortality (P=0.01) and between an age >65 years and intubation (P=0.01). Moreover, there was a statistically significant association between the presence of comorbidities and

Table V. Mean OPNI values in the patients in cohort B.

| Group | OPNI (mean ± SD) | P-value |
|---|---|---|
| Females | 42.67±7.01 | 0.193 |
| Males | 43.48±6.44 | |
| Disease severity | | 0.001 |
| Mild/moderate | 45.80±5.92 | 0.067[a] |
| Severe | 44.42±6.04 | 0.001[b] |
| Critical | 38.58±6.37 | 0.001[c] |
| Comorbidities | 44.88±20.77 | 0.341 |
| No comorbidities | 46.81±5.76 | |
| Age >65 years | 40.92±6.53 | 0.001 |
| Age ≤65 years | 45.21±6.17 | |
| Vaccinated | 42.52±6.75 | 0.153 |
| Unvaccinated | 43.45±6.66 | |
| Intubation | 38.55±5.88 | 0.001 |
| No intubation | 43.59±6.61 | |
| Death | 37.35±6.20 | 0.001 |
| Recovery | 44.50±6.05 | |

[a]Mild/moderate vs. severe; [b]mild/moderate vs. critical; [c]severe vs. critical. OPNI, Onodera's prognostic nutritional index; SD, standard deviation.

Table VI. Univariate analysis for cohort B (intubation and mortality).

| Parameter | Survivors | Non-survivors | P-value |
|---|---|---|---|
| Age >65 years | 153 | 82 | 0.01[a] |
| Age ≤65 years | 246 | 13 | |
| Males | 232 | 54 | 0.817 |
| Females | 167 | 41 | |
| Comorbidities | 308 | 93 | 0.01[a] |
| No comorbidities | 91 | 2 | |
| **Parameter** | **Non-intubation** | **Intubation** | **P-value** |
| Age >65 years | 204 | 31 | 0.01[a] |
| Age ≤65 years | 247 | 12 | |
| Males | 255 | 31 | 0.048[a] |
| Females | 196 | 12 | |
| Comorbidities | 359 | 42 | 0.014[a] |
| No comorbidities | 92 | 1 | |

[a]P<0.05.

Table VII. Multivariate logistic regression analysis of factors independently associated with intubation and mortality in cohort B.

Multivariate analysis for intubation

| Variable | P-value | Odds ratio | 95% CI | |
|---|---|---|---|---|
| Age >65 years | 0.020 | 2.489 | 1.155 | 5.366 |
| Male sex | 0.010 | 2.634 | 0.856 | 0.953 |
| Comorbidities | 0.622 | 1.108 | 0.738 | 1.662 |
| OPNI | 0.001 | 0.903 | 0.856 | 0.953 |

Multivariate analysis for mortality

| Variable | P-value | Odds ratio | 95% CI | |
|---|---|---|---|---|
| Age >65 years | 0.001 | 6.793 | 3.430 | 13.450 |
| Comorbidities | 0.736 | 1.068 | 0.727 | 1.571 |
| OPNI | 0.001 | 0.840 | 0.798 | 0.884 |

CI, confidence interval; OPNI, Onodera's prognostic nutritional index.

Table VIII. Mean OPNI values in the patients in cohort C.

| Group | OPNI (mean ± SD) | P-value |
|---|---|---|
| Females | 41.83±7.36 | 0.758 |
| Males | 42.04±7.48 | |
| Disease severity | | 0.001 |
| Mild/moderate | 44.61±7.56 | 0.036[a] |
| Severe | 42.94±6.95 | 0.001[b] |
| Critical | 38.36±6.57 | 0.001[c] |
| Comorbidities | 41.74±7.51 | 0.035 |
| No comorbidities | 44.25±5.91 | |
| Age >65 years | 40.55±6.92 | 0.001 |
| Age ≤65 years | 44.25±7.63 | |
| Vaccinated | 42.82±7.91 | 0.018 |
| Unvaccinated | 41.23±6.93 | |
| Intubation | 39.21±6.04 | 0.001 |
| No intubation | 42.17±7.49 | |
| Mortality | 37.42±6.52 | 0.014 |
| Recovery | 43.29±7.14 | |

[a]Mild/moderate vs. severe; [b]mild/moderate vs. critical; [c]severe vs. critical. OPNI, Onodera's prognostic nutritional index; SD, standard deviation.

mortality (P=0.01), and between the presence of comorbidities and intubation (P=0.014). In addition, there was a statistically significant association between the male sex and intubation (P=0.048) (Table VI).

Following multivariate logistic regression analysis, including as confounders an age >65 years, the male sex and the presence of comorbidities, an independent association was found between OPNI and intubation (OR, 0.903; 95% CI, 0.856-0.953; P=0.001). Other factors independently associated with intubation in this cohort were an age >65 years and the male sex (Table VII).

An independent association was also detected between OPNI and mortality (OR, 8.40; 95% CI, 0.798-0.884; P=0.001).

Table IX. Univariate analysis for cohort C (intubation and mortality).

| Parameter | Survivors | Non-survivors | P-value |
|---|---|---|---|
| Age >65 years | 218 | 106 | 0.01[a] |
| Age ≤65 years | 185 | 14 | |
| Males | 222 | 69 | 0.625 |
| Females | 181 | 51 | |
| Comorbidities | 363 | 116 | 0.022[a] |
| No comorbidities | 40 | 4 | |
| Vaccinated | 189 | 45 | 0.66 |
| Unvaccinated | 214 | 75 | |
| **Parameter** | **Non-intubation** | **Intubation** | **P-value** |
| Age >65 years | 294 | 30 | 0.292 |
| Age ≤65 years | 188 | 11 | |
| Males | 266 | 25 | 0.453 |
| Females | 216 | 16 | |
| Comorbidities | 440 | 37 | 0.765 |
| No comorbidities | 40 | 4 | |
| Vaccinated | 219 | 15 | 0.281 |
| Unvaccinated | 263 | 26 | |

[a]P<0.05.

Table X. Multivariate logistic regression analysis of factors independently associated with mortality in cohort C.

| Multivariate analysis for mortality | | | | |
|---|---|---|---|---|
| Variable | P-value | Odds ratio | 95% CI | |
| Age >65 years | 0.001 | 0.176 | 0.093 | 0.925 |
| Comorbidities | 0.019 | 0.174 | 0.041 | 0.746 |
| OPNI | 0.001 | 0.886 | 0.848 | 0.925 |

CI, confidence interval; OPNI, Onodera's prognostic nutritional index.

Another factor independently associated with mortality in this cohort was an age >65 years (Table VII).

*Cohort C*. Cohort C comprised of 523 patients (291 males), predominantly infected with the omicron SARS-CoV-2 variant, with a mean age of 68.60±16.65 years. The demographic characteristics of the cohort are presented in Table I. In total, 137 patients (26.2%) had mild/moderate disease, 223 patients (42.5%) had severe disease and 163 patients (31.2%) had critical disease. The mean OPNI value was 44.61±7.56 in patients with mild/moderate disease, 42.94±6.95 in patients with severe disease and 38.36±6.57 in patients with critical disease. There was a statistically significant difference in the mean OPNI values between the three different disease severity groups, with the lowest value observed in patients with critical disease (P=0.001) (Fig. 3 and Table VIII).

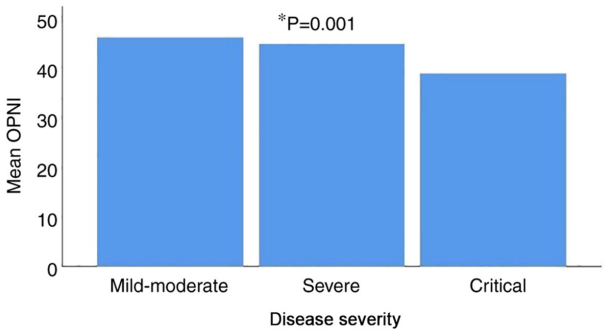


Figure 3. Mean OPNI values in the different groups as regards COVID-19 severity in cohort C. There was a statistically significant difference in the mean OPNI values between the three different disease severity groups, with the lowest value observed in patients with critical disease (*P=0.001). Onodera's prognostic nutritional index.

The mean OPNI value was 39.21±6.04 in patients who were intubated and 42.17±7.49 in patients that were not. The mean OPNI value was 37.42±6.52 in patients who did not survive and 43.29±7.14 in patients who recovered. There was a statistically significant difference in the mean OPNI values between patients who were intubated and those who were not intubated, and between patients who did not survive and patients who recovered (P=0.001 and P=0.014 respectively; Table VIII).

According to the univariate analysis, there was a statistically significant association between the presence of comorbidities and mortality (P=0.022) and between an age >65 years and mortality (P=0.01). No statistically significant association was found between the presence of comorbidities and intubation, between age an >65 years and intubation, between the vaccination status and intubation, and between sex and intubation (Table IX).

An independent association was detected between the OPNI and death according to the multivariate logistic regression analysis (OR, 0.886; 95% CI 0.848-0.925; P=0.001). Other factors independently associated with mortality in this cohort were an age >65 years and the presence of comorbidities (Table X).

ROC analysis revealed that OPNI had no discriminative ability for mortality and intubation in all cohorts [cohort A: area under the curve (AUC, 0.272 for mortality and 0.356 for intubation; cohort B: AUC, 0.193 for mortality and 0.268 for intubation; cohort C: AUC, 0.272 for mortality and 0.377 for intubation]. OPNI exhibited an acceptable discriminative ability for severe disease in all cohorts (cohort A: AUC, 0.615; cohort B; AUC, 0.620; and cohort C: AUC, 0.610). The ROC curves for OPNI in cohorts A, B and C are presented in Figs. 4, 5 and 6, respectively.

## Discussion

According to the results of the present study, OPNI was an independent indicator of disease severity and mortality in all the pandemic waves. OPNI, which is derived using albumin and lymphocyte levels, is an objective measure of

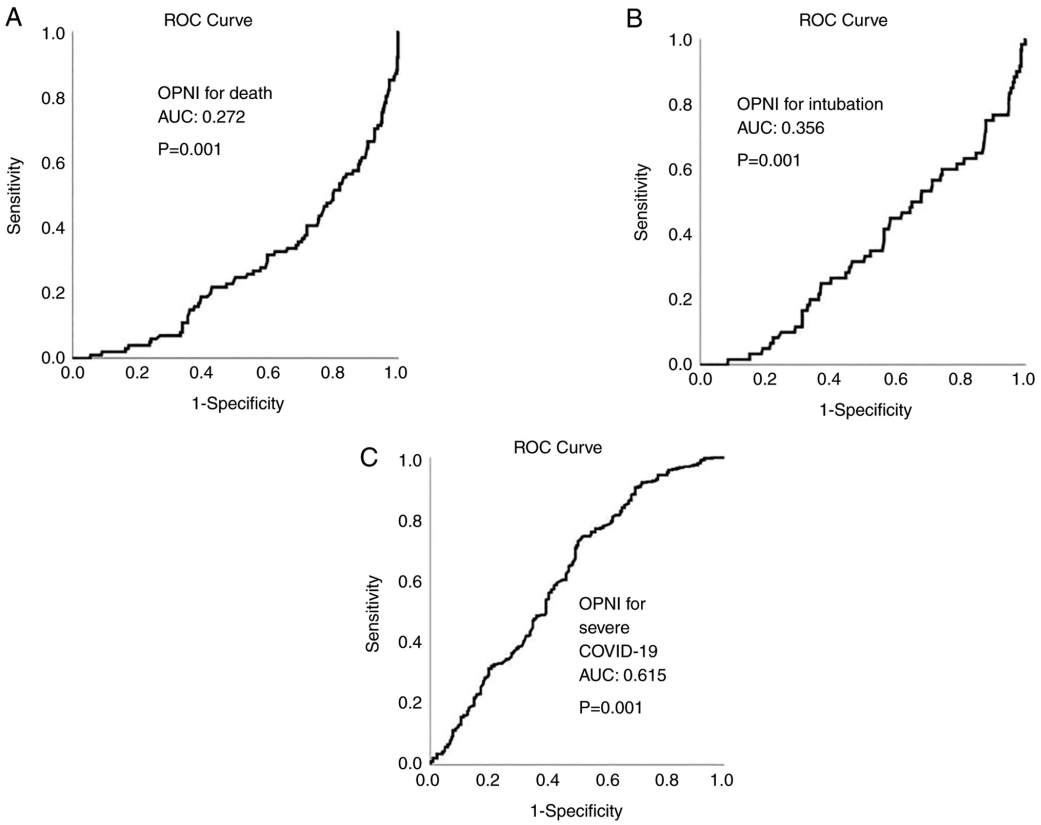


Figure 4. ROC curves illustrating the discriminative ability of OPNI in cohort A for (A) mortality (P=0.001); (B) intubation (P=0.001); and (C) severe COVID-19 infection (P=0.001). ROC, receiver operating characteristic; AUC, area under the curve; Onodera's prognostic nutritional index.

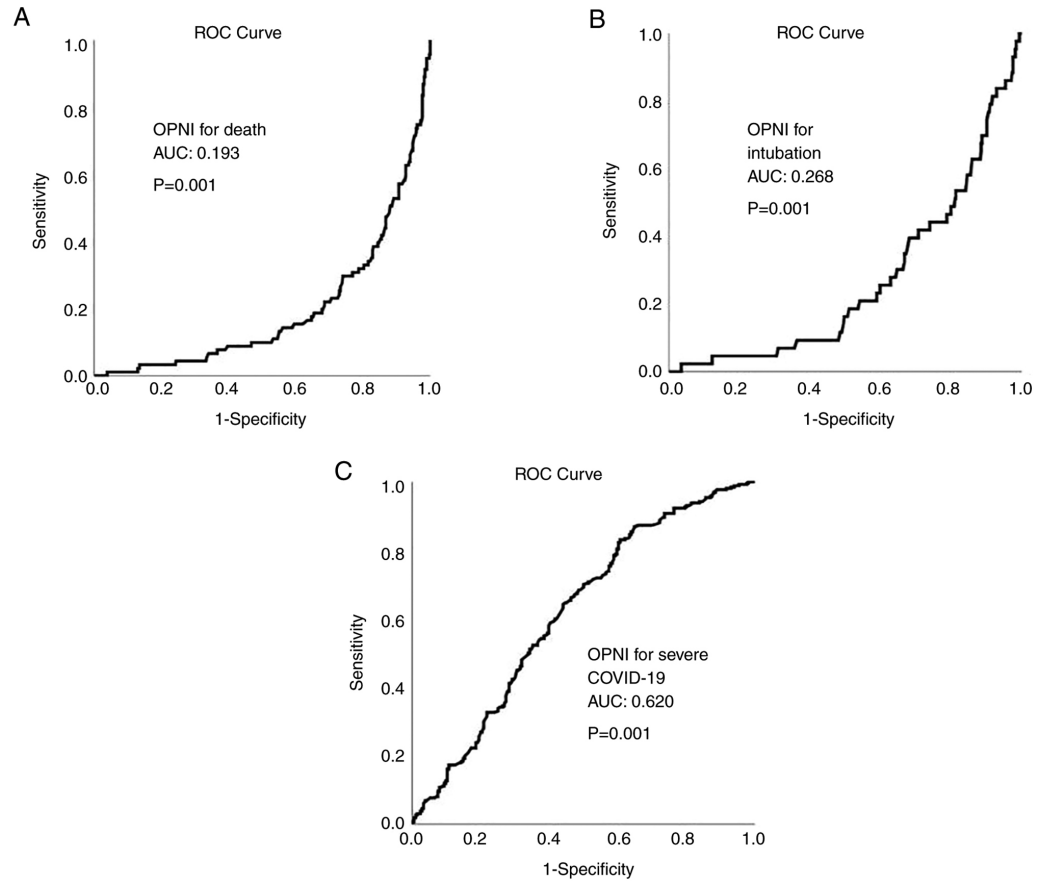


Figure 5. ROC curves illustrating the discriminative ability of OPNI in cohort B for (A) mortality (P=0.001); (B) intubation (P=0.001); and (C) severe COVID-19 infection (P=0.001). ROC, receiver operating characteristic; AUC, area under the curve; Onodera's prognostic nutritional index.

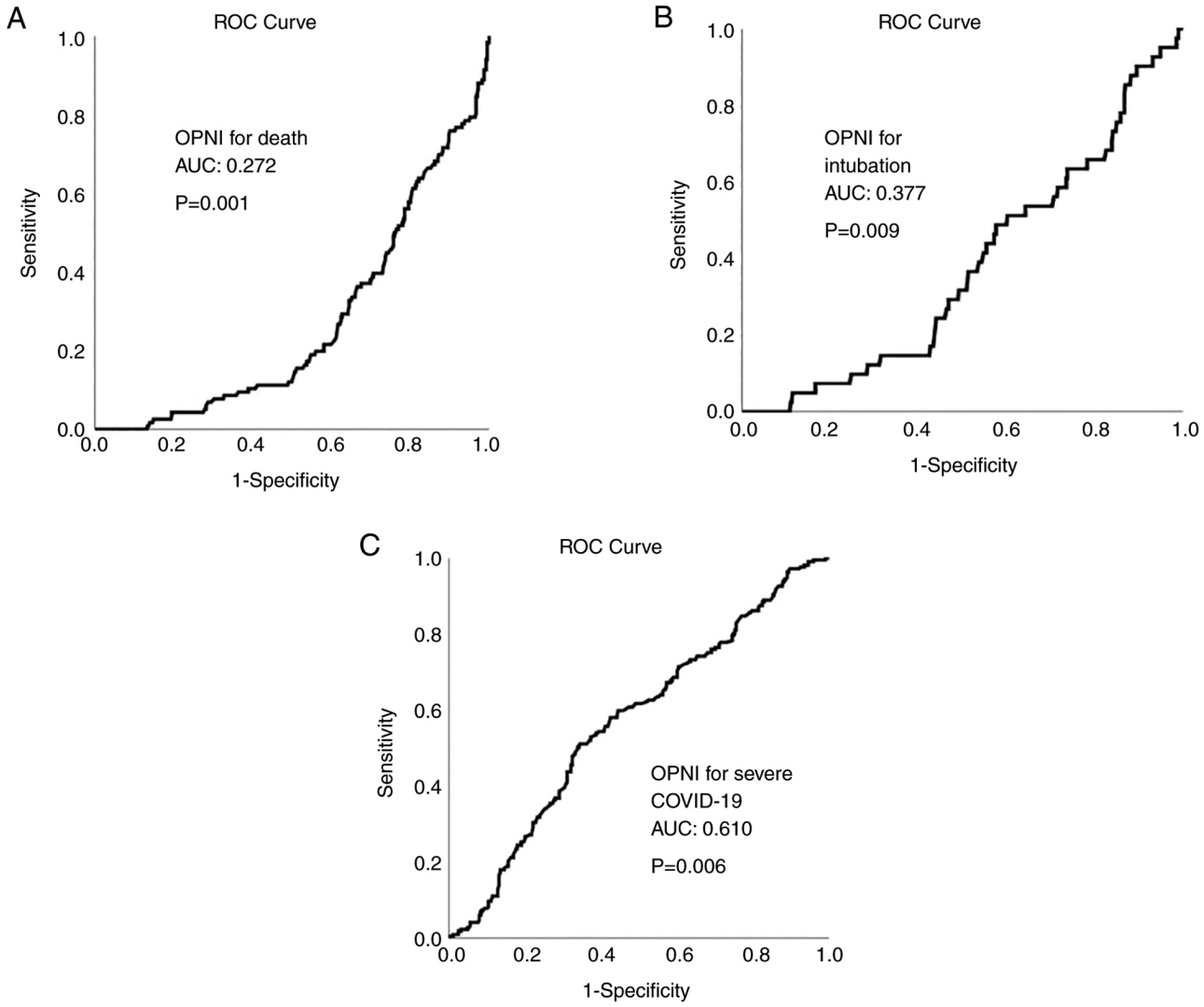


Figure 6. ROC curves illustrating the discriminative ability of OPNI in cohort C for (A) mortality (P=0.001); (B) intubation (P=0.009); and (C) severe COVID-19 infection (P=0.006). ROC, receiver operating characteristic; AUC, area under the curve; Onodera's prognostic nutritional index.

inflammation and nutritional status. Previous research has indicated that albumin levels were inversely associated with disease progression and a poor prognosis in patients with COVID-19 (20,21). Low albumin levels in non-survivors may be attributed to intubation-induced insufficient intake, impaired synthesis due to liver failure and increased consumption due to organ injury. Several mechanisms can mediate the link between poor outcomes and low albumin levels. The albumin level is an indication of liver function as it is produced by hepatocytes (22). Inflammatory cytokines, such as IL-6 and tumor necrosis factor α (TNF-α) can suppress hepatocyte synthesis, leading to a decline in albumin levels in the blood. As already aforementioned, severe organ damage in patients with COVID-19 is caused by a cytokine storm characterized by a large release of cytokines, such as IL-1, IL-6, TNF-α, monocyte chemotactic protein (MCP)-1, inducible protein-10 (IP-10), interferon-γ and granulocyte colony-stimulating factor (G-CSF) (23). Cytokines, such as IL-1ra, IL-2R, IL-6, IL-10, TNF-a, IP-10 and MCP-3 have been found to be associated with disease severity and progression in patients with COVID-19. As a result, low albumin levels in patients with COVID-19 may signal a severe cytokine storm and organ damage, including liver impairment (24-26).

Moreover, a low albumin level may result in the exudation of intravascular fluid, exacerbating the severity of pulmonary edema. In patients with COVID-19, serum albumin levels have been found to be inversely associated with the development of acute respiratory distress syndrome (ARDS). The onset of ARDS is unquestionably a risk factor for poor outcomes of patients with COVID-19. As a result, low albumin levels do not contribute to favorable outcomes of patients with COVID-19 by decreasing pulmonary function (27).

As a typical metric of nutritional status, low albumin levels in critically ill patients may reflect a high consumption status induced by tissue injury and hypermetabolism. A poor nutritional status, as reflected by albumin levels, is not conducive to tissue regeneration and recovery in patients with COVID-19.

The lymphocyte count is another essential component of OPNI. Decreased peripheral lymphocyte numbers in patients with COVID-19 are due to a reduction in the numbers of T-cells, namely $CD3^+$, $CD4^+$ and $CD8^+$ T-cells (28). The reduction in the numbers of $CD4^+$ and $CD8^+$ T-cells, as well

as their increased activation, are critical features of immunocompromise and are associated with an unfavorable disease progression in patients with COVID-19 (29). The numbers of T-cells may be reduced as a result of direct viral assault on lymphocytes, antigen presentation cell malfunction, and apoptosis induced by excessive cytokine production (26,30,31). In patients with COVID-19, lymphopenia has been identified as an independent risk factor for disease severity and poor outcomes. The lower lymphocyte count may be interpreted as a sign of poor immunological function and rapidly increasing cytokine levels (32). Thus, taken together, as a combination of both serum albumin levels and peripheral lymphocyte count, OPNI may more accurately indicate the nutritional and inflammatory state in patients with COVID-19.

OPNI has been reported as an independent indicator of COVID-19 severity (33-35). Moreover, OPNI has been found to be independently associated with the mortality of patients with SARS-CoV-2 infection (15,35-37). To the best of our knowledge, the present study is the first to demonstrate that OPNI is an independent marker of COVID-19 severity and outcomes in all three different pandemic waves examined. More specifically, OPNI exhibited an independent association with disease severity and mortality, even in the period of omicron variant predominance. It has been well established that the omicron variant contains a markedly higher number of novel mutations than other variants in its spike protein, the majority of which are in its receptor binding region, which increases transmissibility, while decreasing antibody and vaccination responses (38).

The key strengths of the present study are the large number of participants, and the availability of detailed information on the characteristics and outcomes of patients with COVID-19. The limitations of the study are that it was a single-center study, it was conducted retrospectively, and that there was no healthy control group. Moreover, no other inflammatory indices, potentially relevant in COVID-19 related outcomes, were evaluated.

In conclusion, the results of the present study, to the best of our knowledge, provide the first direct evidence that a lower OPNI value is associated with greater disease severity in patients with COVID-19. OPNI values upon admission were independent predictors of intubation and mortality in patients with COVID-19 in all pandemic waves examined.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

VEG and NM conceptualized the study. VEG, NM, MZ, CD, MT, AK, SS, GK, SP, PS, GF, NT, KT and PP advised on patient treatments, obtained data, wrote and prepared the draft of the manuscript. DAS, VEG and NVS were involved in the study design, and analyzed the data and provided critical revisions. VEG and NVS confirm the authenticity of all the data. All authors contributed to manuscript revision, and have read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

Ethical approval for the study was obtained from the Research Ethics Committee of Laiko General Hospital (Athens, Greece). The study was in line with the declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Due to the retrospective design of the study, a waiver for informed consent was granted by the Institutional Review Board.

**Patient consent for publication**

Not applicable.

**Competing interests**

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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