Can prognostic nutritional index predict mortality in intensive care patients with COVID-19?

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Abstract

Objectives: PNI is a calculated parameter using the albumin and the lymphocyte count from the CBC, which demonstrates the immunological and nutritional status of the patient. The aim of this study is to show the relationship between PNI and mortality in COVID-19 patients and to reveal a PNI cut-off value for mortality.

Materials and Methods: Data of 690 PCR positive COVID-19 ICU patients were recorded. COVID-19 ICU patients were divided into two groups; the first group consisted of survivors, while the second group consisted of patients who died in the ICU. Patients were also evaluated in two groups according to the PNI cut-off value that predicted mortality (PNI ≤ 42.00, PNI ≥ 43) and were compared in terms of demographics, laboratory parameters, clinical findings and mortality rates.

Results: When 690 COVID-19 patients were divided into two groups as survivors (50.6%) and deceased (49.4%) in intensive care, PNI value was significantly lower in the deceased group compared to the surviving group (P < .001). The PNI cut-off value predicting mortality was determined as ≤42. Patients were classified into two groups according to the PNI cut-off value. PNI ≤42 was determined as an independent risk factor for mortality (OR:2.9 P < .001). AUC values for PNI, albumin, and lymphocyte were 0.628, 0.612, and 0.590, respectively; P < .001 for all.

Conclusion: PNI is an inexpensive method that can be easily calculated on the basis of routine laboratory parameters. We believe that the PNI value of COVID-19 patients on admission to the ICU may be an independent factor to predict mortality.

1 | INTRODUCTION

The first case of Coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was seen in Wuhan, China at the end of December 2019. The disease has spread rapidly all over the world from that date on. The World Health Organization (WHO) declared a pandemic on March 11th 2020.¹ On the same day, the first COVID-19 case was announced in Turkey by the Ministry of Health.² Various measures have been taken to prevent the spread of the disease in our country as well as all over the world. Nevertheless, millions of people got infected and lost their lives. COVID-19 can be asymptomatic or can present with a wide range of symptoms changing from respiratory failure requiring hospitalization or even intensive care, acute respiratory distress syndrome (ARDS), multi-organ failure and severe clinical situations requiring extracorporeal life support.

COVID-19 pneumonia can be seen in patients with COVID-19, and these patients may require intensive care due to hypoxemia and respiratory failure. Radiological findings, complete blood count and markers of systemic inflammation are used to predict the clinical course of the disease. In the complete blood count (CBC) results frequently show lymphopenia as in other viral infections. Lymphopenia
has been shown to be a poor diagnostic factor for COVID-19. Another parameter indicating poor prognosis especially in the intensive care unit is low albumin levels. Hypoalbuminemia in the critically ill can be caused by various reasons including poor nutritional status, altered liver function or increased loss especially via the kidneys. It is very common in systemic inflammation as well.

Prognostic Nutritional Index (PNI) is a calculated parameter using the albumin and the lymphocyte count from the CBC, which demonstrates the immunological and nutritional status of the patient. PNI has been shown to be a prognostic factor for malignancies, infections and cardiovascular diseases.

The aim of this study is to show the relationship between PNI and mortality in COVID-19 patients and to reveal a PNI cut-off value for mortality.

2 | MATERIAL AND METHODS

2.1 | Patient data

In this study, the data of COVID-19 patients hospitalized in the pandemic intensive care unit (ICU) between March 20th and July 31st 2020 were collected and reviewed retrospectively through the hospital information management service, after the ethics committee approval (E1-20-1368). 690 intensive care patients older than 18 years diagnosed with COVID-19 (PCR-RT positive) by SARS-CoV-2 detection in the nasopharyngeal swab by real time polymerase chain reaction (PCR-RT) technique were included in the study. Patients younger than 18 or negative for PCR-RT were excluded.

The patients’ age, gender, Acute Physiology and Chronic Health Evaluation II score (APACHE II) in the first 24 hours in the ICU, laboratory parameters on admission to ICU; complete blood count (leucocyte, lymphocyte, haemoglobin, platelet), D-dimer, fibrinogen, ferritin, interleukin-6 (IL-6), urea, creatinine, albumin, C-reactive protein (CRP), procalcitonin, aspartate transaminase (AST), alanine transaminase (ALT), arterial blood gas analysis (pH, PaO2, PaCO2, HCO3, lactate), as well as PNI, need for mechanical ventilation (MV), duration of MV and ICU, and mortality rates were recorded. PNI was calculated based on the albumin and lymphocyte counts of the patients on admission to the ICU, using the formula 10 × serum albumin (g/dL) + 0.005 × peripheral lymphocyte count (/mm³).

COVID-19 intensive care patients were divided into two groups; the first group consisted of survivors, while the second group consisted of patients who died in the ICU. Patients were also evaluated in two groups according to the PNI cut-off value that predicted mortality (PNI ≤ 42.00 and PNI ≥ 43) and were compared in terms of demographics, laboratory parameters, clinical findings and mortality rates.

2.2 | Statistical analysis

In order to decide on the appropriate statistical method, the Shapiro Wilk normality test was used first and if any of the groups did not provide the normality assumption, non-parametric test methods were selected. In this context, Student’s t test and Mann-Whitney U test were used to compare the variables obtained by measurement in two independent groups, and Chi-square and/or Fisher’s exact test were used to examine the relationship between categorical variables or differences between groups. In order to determine the risk factors for mortality, univariate logistic regression analysis was performed and variables with a significance level of 0.25 and below were included in the multivariate logistic regression model. The remaining variables in the model and their Odds at the end of the analysis are summarized in the tables with 95% confidence intervals and “P” values. Other demographic and group comparison results of the study are presented as ratio in qualitative variables, mean ± SD and median (minimum-maximum) in quantitative variables. Spearman correlation coefficients were calculated in order to evaluate the relationships between the variables, and were given with P values, which express the statistical significance. Diagnostic performance of parameters that can be used in daily practice such as PNI, albumin and lymphocyte count were evaluated by receiver operating characteristic (ROC) curve analysis, and critical cut-off points were calculated according to the Youden Index for the variables found to be statistically significant. SPSS 15.0 program was used in the statistical analysis of the study and P < .05 was accepted as the limit for statistical significance.

3 | RESULTS

The mean age of 690 intensive care patients diagnosed with COVID-19 with positive PCR-RT was 69.25 and 379 (54.9%) of the patients were male. Laboratory values, APACHE II scores, MV requirement, length of stay in the ICU and MV time of all patients are shown in Table 1.

When 690 COVID-19 patients were divided into two groups as survivors (50.6%) and deceased (49.4%) in intensive care, the mean
age was 72.62 in the deceased group while it was 65.96 in the surviving group, and the difference was significant (P < .001). Gender distribution was similar in both groups (P = .472). The APACHE II scores in the deceased group were significantly higher (P < .001).

All patients in the deceased group required MV, also the length of stay in the ICU and the MV times were shorter in this patient group than in the surviving group (P < .002, .001, respectively). When the laboratory data of the two groups were compared, the leukocyte count, urea, creatinine, AST, CRP, procalcitonin, d-dimer, ferritin, IL-6 and lactate values were significantly higher in the deceased group while lymphocyte and thrombocyte counts, albumin, pH, and HCO3 values were significantly lower (Table 1). The PNI value was significantly lower in the deceased group (37.55) compared to the surviving group (40.25) (P < .001) (Table 1).

The PNI cut-off value predicting mortality was determined as ≤42.00 (sensitivity 80.65%, specificity 40.69%). Patients were classified into two groups according to the PNI cut-off value (PNI ≤ 42.00 and PNI ≥ 43). There were 482 (69.85%) patients with PNI ≤ 42.00 and 208 (30.15%) patients with PNI ≥ 43. The ages were similar in both groups (P = .266); however, there was a significant difference in terms of genders (P = .027) (Table 2). The APACHE II scores and the number of patients requiring MV were significantly higher in the group with PNI ≤ 42.00 (P < .001 for both) (Table 2).

In addition to the determined cut-off value, multivariate logistic regression analysis was used to reveal the relationship of PNI with mortality. PNI ≤ 42 was determined as an independent risk factor for mortality (OR: 2.9 P = .001) (Table 3). Age, APACHE II score, patients older than 65 years, and leukocyte count were also identified as independent risk factors for mortality (OR: 1.020, 1.175, 1.096, and 3.104, respectively; P = .004, <.001, <.001 and <.001, respectively). (Table 3).

The ROC curve was plotted, and the AUC was calculated to show the relationship of PNI, as well as albumin and lymphocyte values constituting PNI with mortality. AUC values for PNI, albumin, and lymphocyte were 0.628, 0.612, and 0.590, respectively; P < .001 for all (Figure 1).

4 | DISCUSSION

In this study, an answer was sought to the question of whether PNI could predict mortality in COVID-19 intensive care patients or not. Studies using PNI have been reported in the literature to determine hospital mortality and disease severity in hospitalized COVID-19 patients.\(^{13,14}\) In the results of this study, the mean age of 690 PCR positive COVID-19 intensive care patients was higher than the mean age of patients in previous studies.\(^{12,13}\) This may be due to the fact that all patients are ICU patients, and the severity of COVID-19 disease increases with age, as reported by the Centers for Disease Control and Prevention (CDC), therefore these patients are more likely to require intensive care.\(^{14,15}\) It has also been reported that mortality in the ICUs is higher in COVID-19 patients with advanced age.\(^{16}\) Consistently, the mean age of the patients in the deceased group was higher than the surviving group in this study as well. In previous studies, the prevalence of COVID-19 and mortality were reported more frequently in males.\(^{17}\) In this study, there was no difference between the deceased and surviving groups in terms of gender, while the number of male patients in the PNI ≤ 42 group was higher in the classification made according to the PNI cut-off value, which may be associated with mortality.

Albumin is an important plasma protein that maintains intravascular fluid balance, binds drugs as well as various molecules and controls their passage in and out of the cell. It is also a practical laboratory parameter that reflects malnutrition and is used to evaluate malnutrition. The relationship between malnutrition and poor prognosis in ICU patients has been well known for a long time. Hypoalbuminemia in the ICU patients may occur due to renal or gastrointestinal loss, impaired albumin synthesis due to liver failure, dilutional hypoalbuminemia as a result of intravenous fluid therapy, or leak of albumin to the interstitial space due to increased capillary permeability.\(^6\) In addition, the synthesis of albumin, which is a negative acute phase reactant, is suppressed by inflammatory cytokines in the presence of inflammation. Thus, albumin level decreases in inflammation.\(^8\) It has been reported that low albumin levels are inversely related to the severity of the disease in COVID-19, which is associated with widespread inflammation.\(^{19}\) Lymphopenia is one of the laboratory findings of viral infections and one of the characteristic laboratory parameters of COVID-19. Just like albumin, lymphocyte count is inversely related to the severity of COVID-19 as can be seen in many studies.\(^4,20\) It has also been reported that lymphopenia worsens as the severity of the disease and the mortality increases.\(^{20,21}\) In clinical studies examining the pathogenesis of COVID-19, lower T lymphocyte levels and lymphopenia were found in critically ill patients, and hypoalbuminemia and lymphopenia were mentioned in the ‘cytokine storm’ period, which is caused by the release of chemokines in COVID-19. After infection with SARS-CoV-2, monocytes, macrophages and dendritic cells are activated. It causes the development of cytokine storm by initiating reactions in cis signaling and trans signaling pathways, especially through IL-6 released from these cells. In lymphocytes, Janus kinases (JAKs) and signal transducer and activator of transcription 3 (STAT3) mediated CDB+ cytotoxic T cell, activated B cell, T helper 17 cell as well as T follicular helper cell differentiation increases, T regulatory cell development decreases and it is reflected in peripheral blood as lymphopenia. At the same time, an increase in CRP, fibrinogen, ferritin, serum amyloid, hepaticidin, thrombopoietin and a decrease in albumin levels are observed.\(^22\) In this study, albumin and lymphocyte levels were significantly lower in the patient group who died and in the patient group with PNI ≤ 42, with results similar to the literature. In addition to low albumin and lymphocyte levels in cytokine storm, high leukocyte, ferritin, IL-6, D-dimer, CRP, and procalcitonin are associated with mortality.\(^{20,21}\) In the results of this study, the parameters mentioned were higher in the deceased group than in the surviving group.

PNI is a simple, objective numerical value calculated by lymphocyte and albumin value, which can be related to the severity of
| Variables                        | Total n = 690 | Survived n = 349 | Deceased n = 341 | P      |
|---------------------------------|--------------|-----------------|-----------------|-------|
| **Age (mean ± SD)**             | 69.25 ± 13.95 (22-100) | 65.96 ± 14.6 (23-100) | 72.62 ± 12.39 (22-99) | <.001 |
| **Gender**                      |              |                 |                 |       |
| Female n(%)                     | 311(45.1)    | 162 (46.4)      | 149 (43.7)      | .472  |
| Male n(%)                       | 379 (54.9)   | 187 (53.6)      | 192 (56.3)      |       |
| **Leucocyte x 10^9/L (median)** | 7.83 (0.12-67.71) | 7.23 (1.8-29.51) | 8.81 (0.12-67.71) | <.001 |
| **Lymphocyte x 10^9/L (median)**| 0.72 (0.01-27.73) | 0.77 (0.16-10.22) | 0.67 (0.01-27.73) | <.001 |
| **Hb, g/dL**                    | 12.5 (5.9-20.3) | 12.6 (5.9-20.3) | 12.3 (6.1-17.5) | .398  |
| **PLT, x 10^9/L**               | 237 (17-823) | 246 (17-823)    | 225 (23-649)    | .003  |
| **Urea, mg/L**                  | 54 (9-419)   | 43 (9-241)      | 66 (10-419)     | <.001 |
| **Creatinine, mg/L**            | 0.94 (0.04-18.08) | 0.85 (0.23-18.08) | 1.07 (0.04-9.5) | <.001 |
| **Albumin, g/L**                | 35 (17-47)   | 36 (17-46)      | 34 (18-47)      | <.001 |
| **AST, U/L (median)**           | 45 (3-11824) | 40 (3-468)      | 53 (5-11824)    | <.001 |
| **ALT, U/L (median)**           | 29 (1-3349)  | 29 (3-562)      | 30 (1-3349)     | .925  |
| **CRP, g/L**                    | 0.124 (0-0.001-0.764) | 0.1 (0-0.76) | 0.15 (0-0.62) | <.001 |
| **Procalcitonin, µg/L**         | 0.22 (0.005-511.41) | 0.12 (0.01-78.83) | 0.37 (0.03-511.41) | <.001 |
| **D-dimer, mg/L**               | 1.6 (0.2-80) | 1.4 (0.2-80)   | 2 (0.3-35.2) | <.001 |
| **Ferritin, µg/L**              | 530 (8-126386) | 474 (8-10520) | 666 (20-126386) | <.001 |
| **IL-6, pg/mL**                 | 61.7 (2-1688) | 45.6 (2-1000) | 91 (9.47-1688) | <.001 |
| **Fibrinogen, g/L**             | 5.08 (0.5-12.3) | 5.08 (0.5-12.3) | 5.12 (0.88-9) | .675  |
| **PNI (median)**                | 39.3 (20.35-171.65) | 40.25 (21.8-86.1) | 37.55 (20.35-171.65) | <.001 |
| **pH(median)**                  | 7.42 (6.73-7.6) | 7.44 (6.98-7.6) | 7.4 (6.73-7.57) | <.001 |
| **PaCO₂, mmHg**                 | 36.5 (7.39-180.7) | 36.5 (7.39-77.8) | 36.6 (12-180.7) | .350  |
| **PaO₂, mmHg**                  | 44.5 (17.1-256.9) | 44.7 (17.1-256.9) | 44.2 (18.5-207) | .967  |
| **HCO₃, mmol/L**                | 23 (3.7-38) | 24.1 (3.7-36.5) | 21.9 (4.6-38) | <.001 |
| **Lactate, mmol/L**             | 1.86 (0.09-14.17) | 1.69 (0.09-6.95) | 2.11 (0.1-14.17) | <.001 |
| **Length of stay in the ICU, days** | 9 (1-53) | 10 (1-53) | 8 (1-45) | <.001 |
| **Intubation n(%)**             | 385 (55.8) | 44 (12.6) | 341 (100) | <.001 |
| **Mechanical ventilation time, days** | 5 (1-135) | 16 (1-135) | 4 (1-45) | <.001 |
| **APACHE II score (median)**    | 13 (2-54) | 9 (2-54) | 18 (4-50) | <.001 |
| **BMI, kg/m² (mean ± SD)**      | 25.86 ± 1.6 (19.37-34.13) | 25.84 ± 1.59 (20.81-34.13) | 25.89 ± 1.63 (19.37-33.65) | .353  |

Abbreviations: ALT, alanin transaminase; APACHE II, Acute Physiology and Chronic Health Evaluation II score, min-max; AST, aspartate transaminase; BMI, Body mass index; CRP, C-reactive protein; Hb, haemoglobin; HCO₃, bicarbonate; ICU, intensive care unit; IL-6, interleukin-6; minimum and maximum value; PaCO₂, partial pressure of carbondioxide; PaO₂, partial pressure of oxygen; PLT, platelet; PNI, prognostic nutritional index. p value <.05 is statistically significant.
| Variables                                      | PNI≤42 (n = 482) | PNI≥43 (n = 208) | P   |
|------------------------------------------------|-----------------|-----------------|-----|
| Age (mean ± SD) (min-max)                      | 69.82 ± 13.42 (22-100) | 67.92 ± 15.06 (23-98) | .266 |
| Gender                                         |                 |                 | .027 |
| Female n(%)                                     | 204 (42.3)     | 107 (51.4)      |     |
| Male n(%)                                       | 278 (57.7)     | 101 (48.6)      |     |
| Leucocyte,×10^9/L (median)(min-max)            | 7.83 (0.12-67.71) | 7.805 (2.81-39.54) | .688 |
| Lymphocyte,×10^9/L (median) (min-max)          | 0.61 (0.01-3.04) | 1.13 (0.33-27.73) | <.001|
| Hb, mg/dL (median) (min-max)                   | 12.2 (6.1-20.3) | 13.2 (5.9-17.2)  | <.001|
| PLT,×10^9/L (median) (min-max)                 | 237 (17-695)   | 236.5 (90-823)  | .685 |
| Urea, mg/dL (median) (min-max)                 | 56 (9-419)     | 45 (13-353)     | <.001|
| Creatinine, mg/dL (median) (min-max)           | 0.96 (0.04-18.08) | 0.9 (0.23-5.72) | .079 |
| Albumin, g/L (median) (min-max)                | 33 (17-40)     | 39 (27-47)      | <.001|
| AST, U/L (median) (min-max)                    | 50 (4-11824)   | 39.5 (3-321)    | <.001|
| ALT, U/L (median) (min-max)                    | 31 (1-3349)    | 28 (3-452)      | .032 |
| CRP, g/L (median) (min-max)                    | 0.139 (0.001-0.621) | 0.091 (0.00077-0.764) | <.001|
| Procalcitonin, µg/L (median) (min-max)         | 0.27 (0.03-511.41) | 0.11 (0.005-57.19) | <.001|
| D-dimer, mg/L (median) (min-max)               | 2 (0.3-80)     | 1.18 (0.2-47)   | <.001|
| Ferritin, µg/L (median) (min-max)              | 683.5 (22-126386) | 295.5 (8-4837) | <.001|
| IL-6, pg/mL (median) (min-max)                 | 65.9 (2-1000)  | 49.2 (3.93-1688) | <.001|
| Fibrinogen, g/L (median) (min-max)             | 5.16 (0.5-9)   | 4.92 (0.83-12.3) | .028 |
| pH (median)(min-max)                            | 7.41 (6.73-7.59) | 7.42 (7.09-7.53) | .538 |
| PaCO₂, mmHg (median) (min-max)                 | 36 (7.386-180.7) | 37.4 (14.6-74.3) | .128 |
| PaO₂, mmHg (median) (min-max)                  | 44.6 (18.5-256.9) | 43.9 (17.1-207) | .419 |
| HCO₃, mmol/L (median) (min-max)                | 22.5 (3.7-38)  | 24 (8.7-36.5)   | .017 |
| Lactate, mmol/L (median) (min-max)             | 1.92 (0.09-14.17) | 1.77 (0.1-8.36) | .065 |
| Length of stay in the ICU, days (median) (min-max) | 9 (1-45)     | 8 (1-53)        | .065 |
| Intubation n (%)                                | 305 (63.3%)    | 80 (38.5%)      | <.001|
| Mechanical ventilation time, days (median) (min-max) | 5 (1-135)   | 4.5 (1-80)      | .903 |
| APACHE II (median) (min-max)                   | 14 (3-45)      | 11 (2-54)       | <.001|
| Mortality, n(%)                                 | 275 (57.1)     | 66 (31.7)       | <.001|
| BMI, kg/m² (mean±SD) (min-max)                 | 25.91 ± 1.5 (19.37-31.59) | 25.76 ± 1.82 (21.48-34.13) | .68 |

Abbreviations: ALT, alanine transaminase; APACHE II, Acute Physiology and Chronic Health Evaluation II score, min-max; AST, aspartate transaminase; BMI, Body mass index; CRP, C-reactive protein; Hb, haemoglobin; HCO₃, bicarbonate; ICU, intensive care unit; IL-6, interleukin-6; minimum and maximum value; PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of oxygen; PLT, platelet; PNI, prognostic nutritional index. p value <.05 is statistically significant.
COVID-19. Before COVID-19, the theory that PNI could be related to diseases, malnutrition and immune response was emphasized. In addition to the similar theory in COVID-19, the development of cytokine storms caused by immune response may also be important in the relationship between PNI and COVID-19.

A specific PNI cut-off value that can be used in all diseases has not yet been specified. However, in various studies on malignancies in the literature, low PNI has been reported to be associated with poor prognosis in different cancer types and different cut-off values for PNI in different diseases have been reported. Wang et al found the PNI cut-off value associated with the clinical severity of COVID-19 to be <43, while Hu et al found it to be <49. In this study, the PNI cut-off value for mortality was determined as ≤42 which was lower than both of the reported studies. This may be due to the difference in patient populations. In both reports by Wang et al and Hu et al the cut-off value indicating the severity of the disease was determined according to the hospital admission PNI value of patients diagnosed with COVID-19. These patients consist of both ward and ICU patients. In the present study, the PNI cut-off value was calculated for only COVID-19 ICU patients (patients who survived or died in the ICU) on admission. Another reason for the lower PNI cut-off value is that while the reported studies determined the PNI cut-off value that determines the severity of COVID-19, our study was designed to predict the PNI cut-off value for mortality in COVID-19 ICU patients.

When the patients were divided into two groups according to the PNI cut-off values, the need for intubation, the APACHE II scores (which is an important indicator of mortality in the ICU), and the mortality rates were significantly higher in the group with PNI ≤42. Similar to previous studies, we also found PNI to be an independent risk factor for mortality. Although lymphopenia and hypoalbuminemia indicate poor prognosis for COVID-19 and are risk factors for mortality in COVID-19 patients; it has also been shown that PNI formula, which consists of albumin and lymphocyte count, is superior to albumin and lymphocyte alone in determining mortality in COVID-19.

The difference of the study from other studies is that it has a population consisting of COVID-19 ICU patients and that the PNI cut-off value predicts mortality instead of disease severity. In addition, the cytokine storm period and other parameters such as IL-6, ferritin, D-dimer, which may be risk factors for mortality for COVID-19 patients were also reviewed which were not taken into account in previous studies. On the other hand, the limitation of the study is that it is single-centered and retrospective.

### TABLE 3
Multivariate logistic regression analysis for factors affecting mortality

| Variable   | Odds Ratio | 95% Confidence Interval | P   |
|------------|------------|-------------------------|-----|
| PNI≤42     | 2.9        | 2.022-4.122             | <.001|
| Age        | 1.02       | 1.006-1.034             | .004|
| APACHE II score | 1.17   | 1.140-1.212             | <.001|
| Leucocyte  | 1.09       | 1.048-1.145             | <.001|
| >65 age    | 3.10       | 2.208-4.363             | <.001|

FIGURE 1 ROC curve for PNI, albumin and lymphocyte
CONCLUSION

PNI is an inexpensive method that can be easily calculated on the basis of routine laboratory parameters. We believe that the PNI value of COVID-19 patients on admission to the ICU may be an independent factor to predict mortality.

CONFLICT OF INTEREST

No potential conflict of interest was reported by the author(s).

AUTHOR CONTRIBUTIONS

BDK: Study initiation and design, data analysis, patient recruitment, data collection and drafting of manuscript. BK: Data collection and OBS: Statistical analysis, Critical revision of the manuscript. NMM: Study design, critical revision of the manuscript.

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