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ORIGINAL ARTICLE

Prognostic Role of Prognostic Nutritional Index in Intensive Care Unit Patients with a Diagnosis of COVID-19

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Abstract

Introduction: In this study, we aimed to evaluate the prognostic value of the prognostic nutritional index (PNI) in intensive care unit (ICU) patients with coronavirus 19 (COVID-19).

Methods: Our retrospective study included the data of 149 patients who were admitted to the COVID-19 ICU of a tertiary care center. Data of patients under 18, pregnant patients, or patients who were in the ICU for <48 h were excluded. Complete blood count, biochemistry panel, and blood gas analysis results were gathered and compiled.

Results: 149 ICU patients with COVID-19 (PCR-positive) were included in the study. The patients were divided into two groups according to PNI values (PNI<37.9 vs. PNI≥37.9). The patients with lower PNI needed longer hospitalization (11.7 vs. 8.3, p=0.04) and demonstrated higher in-hospital mortality (73.6% vs. 48.3%, p=0.003). A multivariate regression analysis was performed to predict in-hospital mortality. The PNI score (OR: 0.93 [0.87–0.99]) and the APACHE II (OR:1.09 [1.03–1.14]) score predicted in-hospital mortality.

Discussion and Conclusion: In this study, we showed that a PNI score at admission can predict in-hospital mortality in ICU patients diagnosed with COVID-19.

Keywords: COVID-19; intensive care unit; prognostic nutritional index.

Coronavirus 19 (COVID-19) has caused global pandemics since December 2019 and caused millions of human deaths worldwide. Severe acute respiratory syndrome coronavirus 2 caused this pandemic[1]. The very high number of cases creates a necessity to determine patients who require closer follow-up and more intensive treatments. The parameters that define the risk situation and prognosis of patients are very essential for clinicians. Practical and easily obtainable parameters are beneficial for routine clinical use.

There are well-known risk factors for COVID-19, like immunosuppression, malignancy, diabetes, hypertension, etc. These risk factors cause a more severe prognosis and higher mortality[2]. The nutritional status of patients is also important to predict a poorer prognosis,[3-5] and malnutrition has been found to be a prevalent risk factor in hospitalized COVID-19 patients[6,7]. The prognostic nutritional index (PNI) has been investigated as a marker of nutritional status in the literature, and its' ability to predict prognosis in various diseases like malignancy, cardio-

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vascular diseases, etc. has been demonstrated[8-10]. PNI has been investigated as a marker of disease severity in COVID-19 in previous studies[11-13]. There are some data about the predictive value of PNI for the prognosis of COVID-19 in the overall or hospitalized population, and PNI has been associated with a poorer prognosis and higher in-hospital mortality[14-19]. However, there are insufficient data in the literature to evaluate the predictive value of PNI in the high-risk COVID-19 population, like ICU patients with COVID-19. In this study, we aimed to evaluate the prognostic value of PNI in intensive care unit (ICU) patients with COVID-19.

Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki.

Patient Selection

COVID-19 adult patients hospitalized at the University of Health Sciences Sultan Abdulhamit Han Education and Research Hospital ICU between June 01, 2020, and January 01, 2022, were the focus of this single-center, retrospective study. COVID-19 diagnoses were made by a positive result from a real-time reverse-transcriptase (RT) polymerase chain reaction (PCR) assay of nasal and pharyngeal swab specimens. Patients who had negative RT-PCR results or who were not admitted to the ICU and patients under 18 years old were excluded from the study.

149 patients were included in the study. The patients were divided into two groups according to PNI level: low and high PNI groups (group-2). A flowchart of patient selection is given in Figure 1.

The demographics, clinical characteristics, and laboratory parameters of the participants during their hospitalization were obtained from the hospital's electronic medical records. Ethical approval for the study protocol was given by the institutional review board of Health Sciences University Sultan 2. Abdülhamid Han Training and Research Hospital, with protocol code E-46418926-050.99—132788.

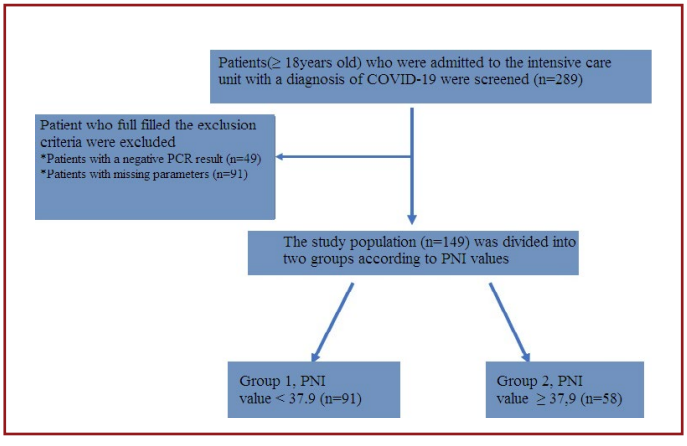


Figure 1. Flowchart of patient selection.

Laboratory Analysis

Blood samples were obtained on the 1st day of ICU admission. Immediately after sampling, complete blood count parameters were determined by a hematology analyzer (ABX Pentra DX 120). Biochemical parameters were measured by the Roche Cobas Integra 800 (Roche Diagnostic Limited, Switzerland) device. The serum albumin level was determined using the bromocresol green method. For each case, the PNI was calculated by the following formula: PNI=(10xalbumin [mg/dL]) + (0.005xlymphocyte count [per mm^3])[16].

ICU Evaluation Criteria

The patients were admitted to the ICU according to the following criteria: (1) Meeting criteria for acute respiratory distress syndrome or needs O_2 > 6 LPM to maintain SpO_2 > 92% (or rapid escalation of oxygen requirement); (2) Respiratory rate>30/min; (3) Systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg, tachycardia, and other signs of shock; (4) Arterial blood gas with a pH <7.3 or partial CO2 pressure >50 mmHg or above the patient's baseline, lactate >2 mmol/L; 5) Concerning clinical appearance. The decision of ICU admission was based on the criteria set by Brigham and Women's Hospital's COVID-19 guidelines, which were updated on December 20, 2020[20].

Outcomes

The primary outcome was defined as all-cause in-hospital mortality in this study.

Statistical Analysis

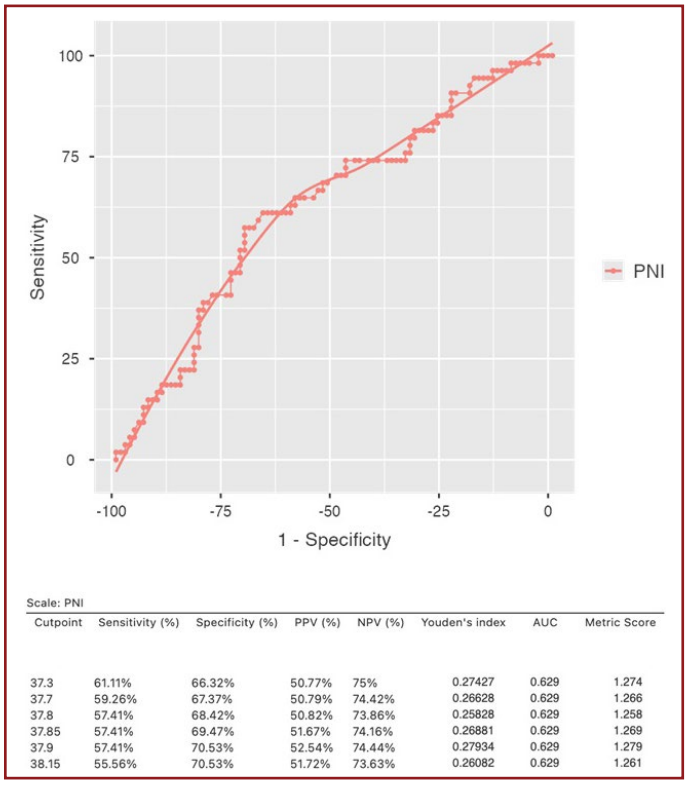
Continuous variables were presented as mean (SD) or median (IQR), according to the data distribution, and as absolute numbers (and percentages) for categorical variables; the distribution was tested by the Shapiro-Wilk test. Differences between patient outcomes were studied by t-test for independent groups or by Wilcoxon rank test if non-parametric analysis was required. A study of differences between groups of categorical data was carried

out using chi-square statistics. The mortality probability for patients who were admitted to the ICU was analyzed with logistic regression analysis. We used a stepwise logistic regression analysis, where variables with a p-value <0.05 were included in the multivariable model. Due to a need for comparison, we used the APACHE II score in model 1, and then we included PNI in model 2 to compare model performances. Besides, we calculated the predicted probability of PNI according to model 2. For model performance comparison between models 1 and 2; AIC, Nagelkerke's R2, likelihood ratio, and C-index were calculated. All intervals of confidence interval (CI) were established at 95%; the two-tailed significance level was established to be <0.05. Statistical data analysis was performed using R v4.01(Vienna, Austria) with the "rms" and "hmisc" packages.

Table 1. Demographic, clinical and laboratory parameters of all groups and PNI subgroups

Age	69.6±14.7	72±13	65.8±16	0.01
Sex (Male)	90(60.4%)	53(58.2%)	37(63.8%)	0.50
Hypertension	89(59.7%)	35(38.5%)	25(43.1%)	0.57
Diabetes mellitus	53(35.6%)	28(30.8%)	25(43.4%)	0.12
COPD	21(14.1%)	13(14.3%)	8(13.8%)	0.93
CVD	67(45%)	44(48.4%)	23(39.7%)	0.30
Hematologic malignancy	6(4%)	3(3.3%)	3(5.2%)	0.57
Oncologic malignancy	24(16.1%)	17(18.7%)	7(12.1%)	0.28
Stroke history	24(16.1%)	19(20.9%)	5(8.6%)	0.05
Renal disease	21(14.1%)	17(18.7%)	4(6.9%)	0.06
Procalcitonin	0.34(0.10-2.29)	0.73(0.14-3.35)	0.19(0.09-0.67)	0.63
Interleukin-6	56.3(21-117)	73.1(40-141)	37.6(14.8-68.1)	0.009
ESR	60.5(40-81)	68(47-84)	51(30-72)	0.02
Ferritin	381(158-894)	431(178-1092)	332(119-667)	0.05
CRP	94(44-147)	120(75-170)	56.2(15.7-103)	<0.001
PDW	16.3±0.44	16.3±0.43	16.3±0.46	0.46
White blood cell	10.6±6.7	10.6±6.7	10.4±6.8	0.84
Hemoglobin	11.6±2.5	11.2±2.5	12.2±2.3	0.01
MPV	10.2±1.3	10.1±1.3	10.3±1.3	0.53
RDW	14.6±1.8	14.9±1.9	14.2±1.3	0.02
Neutrophil	9.2±8.8	9.9±10.2	8.06±5.9	0.21
Monocyte	5.4±3.9	5.0±3.5	6.10±4.4	0.08
Lymphocyte	1.32±1.82	0.93±7.57	1.93±2.66	<0.001
aPTT	29.6±7.2	30.5V8.3	27.9±4.05	0.06
Fibrinogen	565±171	575±187	548±143	0.38
Albumin	3.0±0.6	2.78±0.49	3.48±0.40	<0.001
PNI score	36.5±10.5	31.3±5.1	44.5±11.6	<0.001
ALT	24(15-44)	22(14-40)	25(16-56)	0.07
AST	30(19-51)	30(20-50)	29(17-55)	0.085
Total bilirubin	0.7(0.43-1)	0.63(0.44-1.09)	0.73(0.41-0.96)	0.80
Potassium	4.33±0.72	4.3±0.7	4.3±0.7	0.75
Sodium	137±6.4	137±6.7	136.3±5.9	0.52
Creatinine	2.01±2.04	2.15±2.0	1.78±2.0	0.28
Troponin	36(10-192)	40(14-144)	23(7-276)	0.72
APACHE II score	22.9±10	24.8±9.9	19.8±9.4	0.003

COPD: Chronic obstructive pulmonary disease; CVD: Cardiovascular disease; ESR:Erythrocyte sedimentation, rate; CRP: C-reactive protein; PDW: Platelet distrubition width; aPTT: Activated partial thromboplastin time; PNI: Prognostic nutritional index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MPV: Mean platelet volume; RDW: Red-cell distrubition width; Continous variables were given as mean sd or median IQR (25-75th). Categorical variables were given as an absolute number and percentage.



Scale: PNI

Cutpoint	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden's index	AUC	Metric Score
37.3	61.11%	66.32%	50.77%	75%	0.27427	0.629	1.274
37.7	59.26%	67.37%	50.79%	74.42%	0.26628	0.629	1.266
37.8	57.41%	68.42%	50.82%	73.86%	0.25828	0.629	1.258
37.85	57.41%	69.47%	51.67%	74.16%	0.26881	0.629	1.269
37.9	57.41%	70.53%	52.54%	74.44%	0.27934	0.629	1.279
38.15	55.56%	70.53%	51.72%	73.63%	0.26082	0.629	1.261

Figure 2. Roc Curve.

Results

The 149 ICU patients with COVID-19 (PCR-positive) were included in the study. The mean age for the overall population was 69.6 years and 90 (60.4%) of the patients were male. The PNI cut-off value was found to be 37.9 to predict in-hospital mortality (Fig. 2). The patients were divided into two groups according to PNI values (PNI<37.9 vs. PNI≥37.9). Demographic, clinical, and laboratory parameters of all groups and PNI subgroup comparisons are given in Table 1. The first group (PNI<37.9) included 91 patients, while the higher PNI group (≥37.9) comprised 58 patients. The patients in the lower PNI group were older (72 vs. 65.8, p=0.01), while the gender distribution was similar (p=0.50). Inflammatory laboratory markers including interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) demonstrated significantly higher values in the lower PNI group (p=0,009, 0.02, and <0.001, respectively). Hemoglobin values were lower in the lower PNI group (11.2 vs. 12.2, p:0.01). The APACHE II score was higher in the lower PNI group (24.8 vs. 19.8, p=0.003).

PNI subgroup comparison related to medication and therapy was given in Table 2. The intubation requirement percentage was higher in the lower PNI group (45.1% vs. 27.6%, p=0.03). The patients with lower PNI needed longer hospitalization (11.7 vs. 8.3, p=0.04) and demonstrated higher in-hospital mortality (73.6% vs. 48.3%, p=0.003).

A univariable logistic regression analysis to predict in-hospital mortality is given in Table 3. Age, IL-6, ESR, ferritin,

Table 2. All groups and PNI subgroups comparison according to medication and therapy

Variables	PNI<37.9, n:91	PNI≥37.9, n:58	p
Pneumonic infiltration on CT	86 (94.5%)	53 (91.4%)	0.45
Mask O_2	28 (30.8%)	26 (44.8%)	0.08
High flow	19 (20.9%)	16 (27.6%)	0.35
CPAP	31 (34.1%)	20 (34.5%)	0.96
Intubation	41 (45.1%)	16 (27.6%)	0.03
Favipravir	81 (89%)	51 (88%)	0.84
Entecavir	1 (1.1%)	1 (1.7%)	0.99
Ritonavir-lopinavir	1 (1.1%)	3(5.2%)	0.30
Apheresis	-	2 (2.2%)	0.52
Tocilizumab	13 (13.1%)	7 (12.1%)	0.99
Corticosteroid	43 (47.4%)	26 (44.8%)	0.87
IVIG	4 (4.4%)	4 (6.9%)	0.71
Colchicine	23 (25.3%)	20 (34.5%)	0.27
LMWH	85 (93%)	55 (95%)	0.99
Antiaggregant	41 (45.1%)	29(50%)	0.61
Hospital duration	11.7±10.8	8.3±6.5	0.04
Mortality	67 (73.6%)	28 (48.3%)	0.003

CT: Computed tomography; CPAP: Continious positive airway pressure; IVIG: İntravenous immunglobulin; LMWH: Low-molecular weight heparin; PNI: Prgonostic nutritional index. Continous variables were given as mean sd or median IQR (25–75th). Categorical variables were given as an absolute number and percentage.

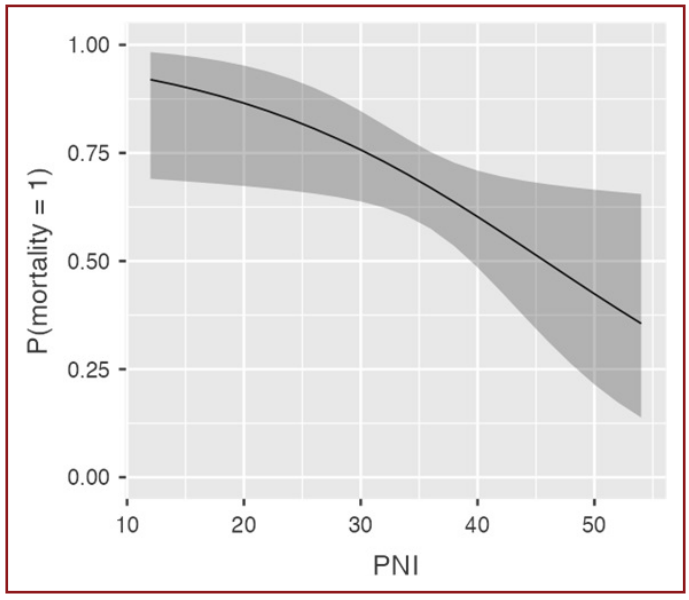


Figure 3. Mortality-PNI chart.

CRP, hemoglobin, red cell distribution width, lymphocyte count, albumin, PNI, and APACHE II score were included in the univariate logistic regression analysis. Older age, higher CRP, lower albumin, lower PNI, and higher APACHE II scores predicted in-hospital mortality in univariate analysis (odds ratio (OR): 1.03 (1.01–1.06), 1.00 (1.00–1.01), 0.40 (0.21–0.75), 0.90 (0.85–0.95), and 1.10 (1.06–1.16), respectively; and p=0.004, 0.04, 0.005, <0.001, and <0.001, respectively).

Multivariable logistic regression analysis to predict in-hospital mortality is present in Table 3. Two separate models were presented. In Model-1 age, CRP, albümin, and APACHE II score were included in the model. Only the APACHE II score predicted in-hospital mortality in model 1 (OR: 1.09 (1.04–1.15), p<0.001). Age, CRP, PNI score, and APACHE II score were included in model 2. PNI score and APACHE II score predicted in-hospital mortality (OR: 0.93 (0.87–0.99) and 1.09 (1.03–1.14), respectively; p:0.03 and <0.001, respectively).

The probability of mortality regarding the PNI score and including model 2 parameters is given in Table 4. PNI values were 28.3, 35.4, and 42.4 for mean 1 standard deviation (SD), mean, and mean+1SD, respectively. The probability of mortality was 0.78 (CI: 0.65–0.87) for mean-1 SD, 0.68 (CI: 0.58–0.76) for mean, and 0.56 (CI: 0.42–0.68) for mean+1 SD (Fig. 3). A performance comparison of model 1 and model 2 is presented in Table 5.

Table 3. Univariable and multivariable (Model-1, Model-2) logistic regression to predict in hospital mortality

Variables	Univariable OR(CI:95%)	p	Model-1	p	Model-2	p
Age	1.03 (1.01–1.06)	0.004	1.02 (0.9–1.05)	0.15	1.02 (0.99–1.05)	0.12
Interleukin-6	1.00 (0.99–1.01)	0.24				
ESR	1.00 (0.99–1.01)	0.90				
Ferritin	1.00 (1.00–1.00)	0.39				
CRP	1.00 (1.00–1.01)	0.04	1.00 (0.99–1.01)	0.06	1.00 (0.99–1.01)	0.21
Hemoglobin	0.95 (0.83–1.09)	0.50				
RDW	1.13 (0.92–1.38)	0.23				
Lymphocyte	1.00 (1.00–1.00)	0.71				
Albumin	0.40 (0.21–0.75)	0.005	0.70 (0.34–1.43)	0.32		
PNI	0.90 (0.85–0.95)	<0.001			0.93 (0.87–0.99)	0.03
APACHE II score	1.10 (1.06–1.16)	<0.001	1.09 (1.04–1.15)	<0.001	1.09 (1.03–1.14)	<0.001

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; PNI: Prognostic nutritional index; RDW: Red-cell distrubition width; OR: Odds ratio.

Table 4. Probability of mortality according to PNI (When Model-2 parameters are included)

PNI	Probability of mortality	Standard error	Confidence interval
28.3 (Mean-1SD)	0.78	0.06	0.65–0.87
35.4 (Mean)	0.68	0.04	0.58–0.76
42.4 (Mean+1SD)	0.56	0.07	0.42–0.68

PNI: Prognostic nutritional index.

Table 5. Model-performance comparison

	AIC	Nagelkerke's R2	Likelihood X2	C-Index
Model-1	170	0.284	34.6	0.764
Model-2	166	0.313	38.7	0.784

Discussion

Inflammation is a key factor to decide the progression and severity of COVID-19. Exaggregated immune responses and excessive inflammation lead to cytokine storms, which trigger severe disease and mortality[21]. A reduced lymphocyte count is also a marker of disease severity in COVID-19[22,23]. Reduced lymphocyte count in COVID-19 may be caused by the mobilization of lymphocytes through the infection sites and consequently the reduction of these immune cells in the peripheral blood. This pathophysiological process may explain the association of reduced lymphocyte counts with cytokine storms and disease severity in COVID-19[24]. Lymphocyte count is a component of PNI; therefore, PNI may reflect the inflammatory process during COVID-19.

Malnutrition relates to an impaired immune response due to reduced complement activation, decreased T-cell development (thymic atrophy), and less response to vaccines[25]. Serum albumin level is another component of PNI, and it has been shown in the literature that hypoalbuminemia is associated with a higher nutritional risk and inflammation[26,27].

PNI seems to predict a more severe course of the disease and higher in-hospital mortality in previous studies by these mechanisms regarding inflammation and malnourishment[11-19]. Most previous studies have proceeded in the overall or hospitalized COVID-19 population; therefore, there is a question of whether PNI predicts in-hospital mortality in high-risk populations like ICU patients. There is a scarcity of data about this issue. A recent study by Kosovali et al.[28] suggested that PNI is an independent predictor of in-hospital mortality in ICU patients with COVID-19. In our study, we also found PNI as a predictor of in-hospital mortality in univariate and multivariate logistic regression analyses. Different cut-off values of PNI for COVID-19 patients were suggested in different studies[13,14,28]. This may be caused by differences in the patient population in these studies. Our PNI cut-off value calculated by ROC curve analysis was found to be 37.9, which defines a lower value than previous studies. This may be caused by a higher-risk population in our study with lower PNI values.

PNI may be used as an inexpensive, practical, and easily obtainable parameter that can be used for risk stratification in ICU patients with COVID-19, according to our study and previous data in the literature. Risk determination in ICU patients is essential for clinicians in evaluating patients more precisely; therefore, better risk evaluation can help clinicians to take appropriate management actions.

Limitations

Firstly, we could not obtain the body weight and height of the patients because they were in isolation units in the ICU. The analysis to evaluate the association of PNI with BMI was not feasible. Secondly, the retrospective nature of this single-center study is another limitation. Lastly, the relatively small sample size is another limitation.

Conclusion

PNI is a practical parameter that can be easily obtained from routine laboratory parameters. In this study, we showed that a PNI score at admission can predict in-hospital mortality in ICU patients with a diagnosis of COVID-19.

Ethics Committee Approval: Ethical approval for the study protocol was given by the institutional review board of Health Sciences University Sultan 2. Abdülhamid Han Training and Research Hospital, with protocol code E-46418926-050.99—132788.

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Authorship Contributions: Concept: B.Ç.G.; Design: B.Ç.G., M.K.; Supervision: B.Ç.G., M. K.; Fundings: B.Ç.G., Z.S., B.D., N.T., E.Ö.; Materials: B.Ç.G., S.Z., B.D., N.T., E.Ö.; Data Collection or Processing: B.Ç.G., Z.S., B.D., N.T., E.Ö.; Analysis or Interpretation: B.K., A.K.; Literature Search: B.Ç.G., B.K.; Writing: B.Ç.G., B.K.; Critical Review: M.K.

Conflict of Interest: None declared.

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