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The role of the BUN/albumin ratio in predicting mortality in COVID-19 patients in the emergency department

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ABSTRACT

Introduction: Due to the high mortality and spread rates of coronavirus disease 2019 (COVID-19), there are currently serious challenges in emergency department management. As such, we investigated whether the blood urea nitrogen (BUN)/albumin ratio (BAR) predicts mortality in the COVID-19 patients in the emergency department.

Methods: A total of 602 COVID-19 patients who were brought to the emergency department within the period from March to September 2020 were included in the study. The BUN level, albumin level, BAR, age, gender, and in-hospital mortality status of the patients were recorded. The patients were grouped by in-hospital mortality. Statistical comparison was conducted between the groups.

Results: Of the patients who were included in the study, 312(51.8%) were male, and their median age was 63 years (49–73). There was in-hospital mortality in 96(15.9%) patients. The median BUN and BAR values of the patients in the non-survivor group were significantly higher than those in the survivor group (BUN: 24.76 [17.38–38.31] and 14.43 [10.84–20.42], respectively [$p < 0.001$]; BAR: 6.7 [4.7–10.1] and 3.4 [2.5–5.2], respectively [$p < 0.001$]). The mean albumin value in the non-survivor group was significantly lower than that in the survivor group (3.60 ± 0.58 and 4.13 ± 0.51, respectively; $p < 0.001$). The area-under-the-curve (AUC) and odds ratio values obtained by BAR to predict in-hospital COVID-19 mortality were higher than the values obtained by BUN and albumin (AUC of BAR, BUN, and albumin: 0.809, 0.771, and 0.765, respectively; odds ratio of BAR>3.9, BUN>16.05, and albumin<4.01: 10.448, 7.048, and 6.482, respectively).

Conclusion: The BUN, albumin, and BAR levels were found to be reliable predictors of in-hospital mortality in COVID-19 patients, but BAR was found to be a more reliable predictor than the BUN and albumin levels.

1. Introduction

The first case of coronavirus disease 2019 (COVID-19) was reported in Wuhan, China in December 2019 [1]. COVID-19 is a viral infectious disease that affects the respiratory system [2]. The World Health Organization (WHO) declared the existence of a COVID-19 pandemic in January 2020 [3]. According to the WHO data, approximately 101 million people have been infected worldwide as of this writing, and approximately 2% of them have died. Although the mortality rate is only approximately 2% worldwide, some publications state that in COVID-19 patients brought to the emergency departments of hospitals, the mortality rate is approximately 30% [4]. This has posed challenges in emergency department management and has caused insufficient bed capacity [5]. There is thus a need for accessible biomarkers that can easily and quickly predict the mortality of COVID-19 patients admitted to the emergency department.

The level of blood urea nitrogen (BUN) is a biomarker used to evaluate kidney function [6] and hypovolemia [7]. It is a parameter of the scoring system called CURB-65, which is used especially in pneumonia patients [8]. It has been shown that its level is higher in pneumonia [9], chronic obstructive pulmonary disease [10], pancreatitis [11], acute myocardial infarction [12], heart failure [13], sepsis [14], and geriatric patients [15] with mortality. There have also been studies that showed a higher BUN level in COVID-19 patients with mortality [16].

Albumin is a blood protein that is a negative acute phase reactant [17] and that is used to assess malnutrition [18]. It has been shown that its level is lower in pneumonia [19], acute coronary sendrom [20], and pancreatitis [21], and geriatric patients [22] with mortality. In addition, there have been studies that showed decreased albumin levels in COVID-19 patients with mortality [23].

There have been studies that aimed to predict mortality using the BUN/albumin ratio (BAR) in geriatric and pneumonia patients [7,15]. In the same studies, the mortality-predictive power of BAR was found to be higher than those of BUN and albumin. However, we did not come across any COVID-19 study in the existing literature that used BAR to predict COVID-19 mortality.

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Thus, in this study, we investigated the power of BUN, albumin, and BAR to predict in-hospital COVID-19 mortality. In addition, we investigated if the mortality predictive power of BAR is higher than those of the BUN and albumin levels.

2. Methods

Ethics committee approval for this single-center, retrospective, and observational study was obtained from the local committee.

This study was carried out in a tertiary university hospital from March to September 2020. Patients over the age of 18 who had been admitted to the emergency department and hospitalized for suspected COVID-19 and whose polymerase chain reaction (PCR) test result was positive were included in the study. Regardless of the number of tests that had been undergone by a patient, if at least one PCR test result was positive, the patient was considered to have had a positive PCR test result. Patients, who had a history of chronic renal failure (CRF) (only those on dialysis), who had sought hospital discharge against medical advice, and who had been referred to other hospitals were excluded from the study. Renal transplant patients and pre-dialysis CRF patients were included in the study.

The following data of the patients who were included in the study were recorded from the patients'e-files using the hospital information management system program: BUN level, albumin level, creatinine level, patient complaint (fever, cough, shortness of breath), comorbidity, ward/ICU admission information, and hospital outcome (discharge, in-hospital exitus). The BAR value (mg/g) was obtained by dividing the BUN level (mg/l) by the albumin level (g/l). The patients were assigned either to the survivor or non-survivor group according to whether in-hospital mortality occurred in their case or did not. The primary outcomes of the study are the prediction of in-hospital COVID-19 mortality using the BUN, albumin, and BAR values and investigating whether the mortality predictive power of BAR is higher than those of the BUN and albumin levels.

Statistical analysis of the recorded data was done using the SPSS 20.0 package program (SPSS Inc., Chicago, IL). Normality analyses of the data were conducted using histograms and the Kolmogorov–Smirnov test. The non-normally distributed quantitative data were expressed as median values (25–75% quartiles) while the normally distributed quantitative data were expressed as mean ± standard deviation values. The categorical variables were expressed as frequency (percentage) values. The differences between the groups were investigated using the Mann–Whitney *U* test for the non-normally distributed quantitative variables and using the Student's *t*-test for the normally distributed quantitative variables. Intragroup comparisons of the categorical variables were made using the chi square test and the Fisher's exact test. Receiver operating characteristic (ROC) analysis was performed to determine the in-hospital mortality predictive power of the BUN, albumin, and BAR levels. The optimum cut-off levels of the biochemical parameters were determined using Youden's index (sensitivity +1 − specificity). The sensitivity, specificity, and positive and negative predictive values of the parameters were calculated for the optimum cut-off levels. The odds ratios of the groups categorized by the optimum cut-off values of BUN, albumin, and BAR in predicting in-hospital COVID-19 mortality were calculated using univariate logistic regression analysis. The area under the curve (AUC) and odds ratio values were used to compare the mortality predictive power of BAR to those of the BUN and albumin levels. Statistical significance was set at $p < 0.05$.

3. Results

A total of 643 patients who were brought to the emergency department with suspected COVID-19 within the period from March to September 2020 and who had a positive PCR test result were identified. Of these 643 patients, 28 were excluded from the study because they had a history of CRF and were undergoing dialysis, 5 because they sought hospital discharge against medical advice, and 8 because they were referred to another hospital. The remaining 602 patients were included in the study.

Of the 602 patients who were included in the study, 312(51.8%) were male, their median age was 63 years (49–73), and their median length of hospital stay was 8 days (5–13 days).The median BUN, mean albumin, median BAR, and median creatinine values were found to be 15.51 mg/dl (11.49–22.39), 4.05 ± 0.55 g/dl, 3.7 (2.7–5.8) mg/g, and 1.02(0.87–1.26) mg/dl respectively. A total of 399 patients (66.3%) had at least one comorbidity in their medical history, and the most frequent comorbidity was hypertension (201patients, 33.4%). A total of 476 patients (79.1%) were hospitalized in the ward unit, and 126 (20.9%) were admitted to the ICU. In-hospital mortality occurred in 96 patients (15.9%) and did not occur in 506 (84.1%). Table 1 shows the detailed data of the cases.

The median BUN value in the non-survivor group was significantly higher than that in the survivor group (non-survivor: 24.76 mg/dl [17.38–38.31]; survivor: 14.43 mg/dl [10.84–20.42]; $p < 0.001$). As for the mean albumin value, that in the non-survivor group was significantly lower than that in the survivor group (non-survivor: 3.60 ± 0.58 g/dl; survivor: 4.13 ± 0.51 g/dl; $p < 0.001$). For the median BAR value, that in the non-survivor group was significantly higher than that in the survivor group (non-survivor: 6.7 mg/g [4.7–10.1]; survivor: 3.4 mg/g [2.5–5.2]; $p < 0.001$). For the median creatinine value, that in

Table 1
Features of participants.

Number of Persons		602(100%)
Age[a]		63(49–73)
Gender[b]	Male	312(51.8%)
	Female	290(48.2%)
Vital Signs	Fever (C°)[c]	36.67 ± 0.73
	Pulse (per minute)[c]	92.98 ± 17.19
	Systolic Blood Pressure (mmHg)[c]	131.38 ± 21.57
	Diastolic Blood Pressure (mmHg)[c]	74.96 ± 11.67
	MAP (mmHg)[c]	93.78 ± 13.25
	Saturation (%)[a]	94(90–96)
Complaints[b]	Fever	309(51.3%)
	Cough	321(53.3%)
	Shortness of Breath	286(47.5%)
Laboratory Results	BUN (mg/dl)[a]	15.51 (11.49–22.39)
	Albumin (g/dl)[c]	4.05 ± 0.55
	BAR (mg/g)[a]	3.7(2.7–5.8)
	Creatinine (mg/dl)[a]	1.02(0.87–1.26)
	BUN>16,05 (mg/dl)[b]	290(48.2%)
	Albumin<4.01 (g/dl)[b]	263(43.7%)
	BAR>3.9 (mg/g)[b]	287(47.7%)
Medical History[b]	Comorbidity[d]	399(66.3%)
	Hypertension	201(33.4%)
	Diabetes Mellitus	156(25.9%)
	Cardiovascular Disease	104(17.3%)
	Asthma-COPD	100(16.6%)
	Malignancy	65(10.8%)
	Cerebrovascular Disease	16(2.7%)
Length of Hospital Stay (Day)[a]		8(5–13)
Emergency Service Outcome[b]	Ward Unit	476(79.1%)
	ICU	126(20.9%)
Hospital Outcome[b]	Discharged	506(84.1%)
	Ex	96(15.9%)
In-hospital mortality[b]	Survivor	506(84.1%)
	Nonsurvivor	96(15.9%)

COPD: Chronic Obstructive Pulmonary Disease, MAP: Mean Arterial Pressure, ICU: Intensive Care Unit.

[a] Data are presented as median (25%–75%).

[b] Data are presented as n (%).

[c] Data are presented as mean ± standard deviation.

[d] Having at least one additional disease in his/her medical history.

Table 2
Evaluation of participants by in-hospital mortality.

	Nonsurvivor(96)	Survivor(506)	*p* value
Age[a]	75(67–81)	60(46–71)	<0.001[e]
Fever (°C)[b]	36.84 ± 0.82	36.64 ± 0.7	0.015[f]
Pulse (per minute)[b]	94 ± 19.54	92.79 ± 16.72	0.577[f]
SBP (mmHg)[b]	131.1 ± 26.21	131.43 ± 20.62	0.907[f]
DBP (mmHg)[b]	72.16 ± 12.97	75.48 ± 11.35	0.023[f]
MAP (mmHg)[b]	91.7 ± 15.92	94.16 ± 12.67	0.161[f]
Saturation (%)[a]	89(80–93)	94(92–96)	<0.001[e]
BUN (mg/dl)[a]	24.76 (17.38–38.31)	14.43 (10.84–20.42)	<0.001[e]
Albumin (g/dl)[b]	3.60 ± 0.58	4.13 ± 0.51	<0.001[f]
BAR (mg/g)[a]	6.7(4.7–10.1)	3.4(2.5–5.2)	<0.001[e]
Creatinine (mg/dl)[a]	1.23(0.95–1.62)	1(0.85–1.22)	<0.001[e]
Length of hospital stay (days)[a]	13(8–23)	7(5–12)	<0.001[e]
Gender[c]			
Male	63(65.6%)	249(49.2%)	0.003[g]
Female	33(34.4%)	257(50.8%)	
Fever(complaint)[c]	40(41.7%)	269(53.2%)	0.039[g]
Cough[c]	50(52.1%)	271(53.6%)	0.791[g]
Shortness of Breath[c]	68(70.8%)	218(43.1%)	<0.001[g]
Comorbidity[c,d]	80(83.3%)	319(63%)	<0.001[g]
Hypertension[c]	48(50%)	153(30.2%)	<0.001[g]
Diabetes Mellitus[c]	32(33.3%)	124(24.5%)	0.070[g]
Cardiovascular Disease[c]	26(27.1%)	78(15.4%)	0.006[g]
Asthma-COPD[c]	19(19.8%)	81(16%)	0.361[g]
Malignancy[c]	17(17.7%)	48(9.5%)	0.017[g]
Cerebrovascular Disease[c]	6(6.3%)	10(2%)	0.029[h]

COPD: Chronic Obstructive Pulmonary Disease, MAP: Mean Arterial Pressure.
[a] Data are presented as median (25%–75%).
[b] Data are presented as mean ± standard deviation.
[c] Data are presented as n (%).
[d] Having at least one additional disease in his/her medical history.
[e] Mann–Whitney U test was used.
[f] Student's t-test was used.
[g] Chi square test was used.
[h] Fisher's exact test was used.

the non-survivor group was significantly higher than that in the survivor group (non-survivor: 1.23 mg/dl [0.95–1.62]; survivor: 1 mg/dl [0.85–1.22]; $p < 0.001$). Table 2 shows the detailed intragroup comparisons by in-hospital mortality.

We performed ROC analysis to determine the in-hospital COVID-19 mortality predictive power of the BUN, albumin, and BAR levels. The AUC value of the BUN level was found to be 0.771 (Fig. 1), and 83.3% sensitivity, 58.5% specificity, 27.6% positive predictive value (PPD), and 94.9% negative predictive value (NPD) were reached with the cut-off BUN value of 16.5 mg/dl. As for the albumin level, its AUC value was found to be 0.765 (Fig. 1), and 79.2% sensitivity, 63% specificity, 28.9% PPD, and 94.1% NPD were reached with the cut-off albumin value of 4.01 g/dl. For BAR, its AUC value was found to be 0.809 (Fig. 1), and 87.5% sensitivity, 59.9% specificity, 29.3% PPD, and 96.2% NPD were reached with the cut-off BAR value of 3.9 mg/g. The AUC value of BAR was significantly higher than the AUC value of BUN ($p < 0.001$). The detailed results of the ROC analysis are given in Table 3.

In terms of predicting in-hospital COVID-19 mortality, the patients with BUN>16.5 mg/dl had an odds ratio of 7.048; those with albumin<4.01 g/dl had an odds ratio of 6.482; and those with BAR>3.9 mg/g had an odds ratio of 10.482. The detailed odds ratio results are given in Table 4.

4. Discussion

In this study, we wanted to predict the in-hospital mortality of COVID-19 patients using the BUN, albumin, and BAR parameters. According to the results of this study, BAR was found to be more valuable than the BUN and albumin levels in predicting the in-hospital mortality of COVID-19 patients. As far as we know, our study was the first to have predicted the in-hospital mortality of COVID-19 patients using BAR.

In this study, the BUN levels were significantly higher in the non-survivor group than in the survivor group. In addition, the BUN levels

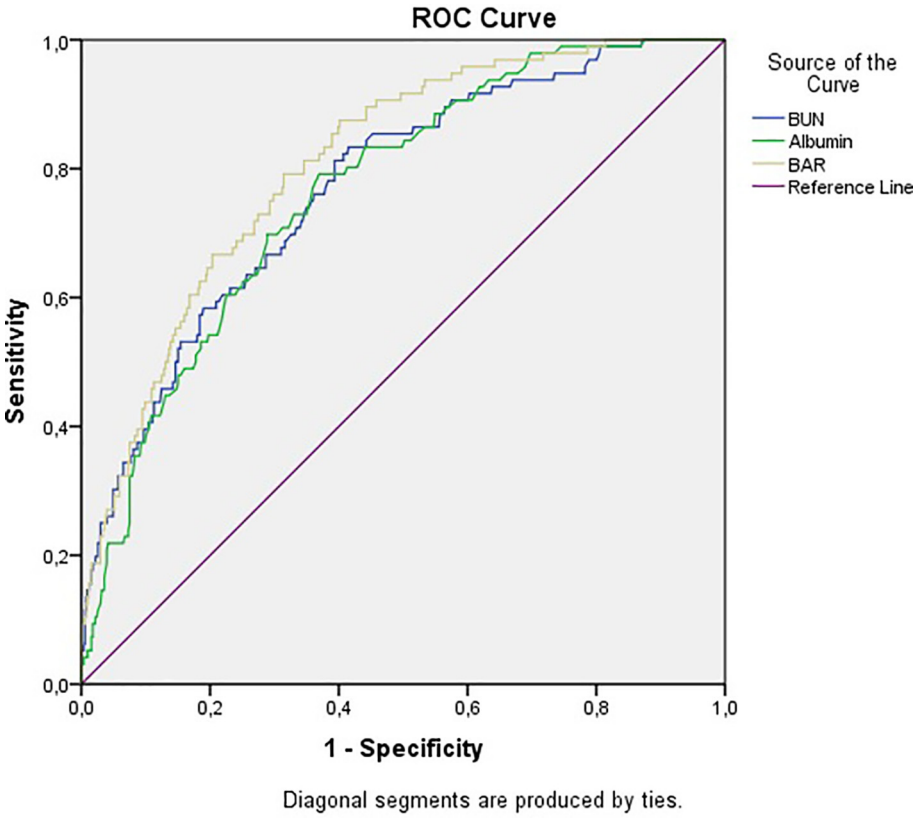

Fig. 1. ROC curve by in-hospital mortality.

Table 3
ROC Analysis result by in-hospital mortality status.

		BUN	Albumin	BAR
In-hospital mortality	AUC (95% CI)	0.771 (0.721–0.821)	0.765 (0.718–0.813)	0.809 (0.765–0.852)
	p value	0.868*	0.099**	<0.001***
	Cut-off level	>16.05 mg/dl	<4.01 g/dl	>3.9 mg/g
	Sensitivity	83.3%	79.2%	87.5%
	Specificity	58.5%	63%	59.9%
	PPV	27.6%	28.9%	29.3%
	NPV	94.9%	94.1%	96.2%

CI: Confidence interval; AUC: Area under the curve.
* *p* values are obtained from the paired comparisons of the AUCs of BUN and the AUC of Albumin.
** *p* values are obtained from the paired comparisons of the AUCs of Albumin and the AUC of BAR.
*** *p* values are obtained from the paired comparisons of the AUCs of BAR and the AUC of BUN.

Table 4
Odds ratio results obtained according to optimum cut off values.

		Odds rate	95% CI
In-hospital mortality	Bun>16.05 mg/dl	7.048	4.005–12.402
	Bun<16.05 mg/dl	1	
	Albumin<4.01 g/dl	6.482	3.836–10.954
	Albumin>4.01 g/dl	1	
	BAR>3.9 mg/g	10.448	5.562–19.626
	BAR<3.9 mg/g	1	

CI: Confidence interval.

reached a 0.771 AUC value according to the result of the ROC analysis performed to predict in-hospital mortality. The BUN level above 16.05 mg/dl had an odds ratio of 7.048 in predicting the in-hospital mortality of COVID-19 patients. Cheng et al. carried out a study with 305 COVID-19 patients (85 of whom had died) and found that the BUN levels were significantly higher in the non-survivor group than in the survivor group [16]. In addition, they found that the BUN level with a 0.88 AUC value was able to predict in-hospital mortality [16]. Ok et al. carried out a study with 139 COVID-19 patients and found that the BUN level with a 0.790 AUC value was able to predict the severity of the disease [24]. Many factors may explain the relationship between a high BUN level and COVID-19 mortality. The relationship between a high BUN level and the presence of pneumonia is one possible explanation. According to many studies, a high BUN level is an indicator of the severity of pneumonia [9]. It is even used as a parameter in the CURB-65 scoring system [8]. There have been studies in which 100% pulmonary damage occurred in mortal cases of COVID-19 [25]. In fact, in some studies on COVID-19 mortality, respiratory failure was shown as the cause of death in approximately 70% of the cases [25]. Frequent lung involvement in severe COVID-19 patients may explain the relationship between BUN level and COVID-19. Kidney injury is also common among patients hospitalized with COVID-19, and is associated with high mortality [26]. Thus, the use of the BUN level to evaluate kidney function [6] may also explain the relationship between the BUN level and COVID-19 mortality.

In this study as well, the albumin levels were significantly lower in the non-survivor group compared to the survivor group. In addition, according to the result of the ROC analysis performed to predict in-hospital mortality, they reached a 0.765 AUC value. The albumin level below 4.01 g/dl had an odds ratio of 6.482 in predicting in-hospital COVID-19 mortality. Violi et al. carried out a study with 319 hospitalized COVID-19 patients (64 of whom had died) and found that the albumin levels were significantly lower in the non-survivor group than in the survivor group [23]. In addition, they found that the albumin level below 3.2 g/dl had an odds ratio of 2.48 in predicting in-hospital mortality. In Aziz et al.'s meta-analysis study including 11 studies, the relationship between hypoalbuminemia and COVID-19 severity was demonstrated [27]. There may be many reasons for the relationship between low albumin levels and COVID-19 mortality. Malnutrition is a risk factor for in-hospital mortality [28], and there is a higher rate of malnutrition in elderly patients [28]. Also, albumin is used to assess malnutrition [18]. The fact that high age is a risk factor for COVID-19 mortality [4] and there is a high prevalence of malnutrition in elderly patients with COVID-19 [29] can be among the reasons for the relationship between the albumin level and COVID-19 mortality. The risk of arterial and venous thromboembolic events increases with the decrease in albumin level [23]. There is a relationship between COVID-19 patients with respiratory failure in the ICU and severe hypercoagulability [30]. It can thus also be shown as a reason for the relationship between the albumin level and COVID-19 mortality.

Finally, the BAR levels in this study were significantly higher in the non-survivor group than in the survivor group. In addition, according to the result of the ROC analysis performed to predict in-hospital COVID-19 mortality, the BAR level reached a 0.809 AUC value. The BAR level above 3.9 mg/g had an odds ratio of 10.448 in predicting in-hospital COVID-19 mortality. As mentioned earlier, we did not come across any other COVID-19 study that used BAR. In this study, the AUC and odds ratio values obtained by BAR for predicting in-hospital COVID-19 mortality were higher than the values obtained by the BUN and albumin levels. In the study conducted by Dundar et al. with 1253 geriatric patients to predict the mortality of geriatric patients, they found that the AUC value and odds ratios obtained by BAR were higher than those obtained by the BUN and albumin levels [15]. In the study conducted by Ryu et al. with 443 aspiration pneumonia patients to predict mortality, they found that the AUC and odds ratio values obtained by BAR were higher than those obtained by the albumin level [7].The BUN and albumin parameters are accessible parameters in emergency services, but evaluating them together by proportioning them is more valuable than evaluating them separately.

This study had some limitations. The exclusion of patients who were not hospitalized due to COVID-19 was one limitation because we do not know how much it would have affected the results of this study if such patients were included in it for evaluating COVID-19 patients as a whole, both those who were hospitalized and those who were not. The fact that the treatment protocols were not evaluated in this study was another limitation of the study because throughout the course of the pandemic, the treatment protocols for the disease have constantly changed. We do not know how much it would have affected the results of this study if the treatment protocols were standardized. CRF patients were also not included in this study to reduce the effect of such condition on the BUN level. However, as the design of the study was retrospective, we were able to exclude only the CRF patients who were undergoing dialysis. The inclusion of pre-dialysis CRF patients and the retrospective method employed by the study also constitute study limitations as we do not know how much it would have affected the results of the study if the pre-dialysis CRF patients were not included in it. Lastly, the fact that this study was a single-center study was likewise a limitation.

5. Conclusion

In this study, the BUN, albumin, and BAR levels were significantly higher in the non-survivor group than in the survivor group. It was found that all three could reliably predictin-hospital COVID-19 mortality. The AUC values and odds ratios obtained by BAR for predicting in-hospital COVID-19 mortality, however, were higher than those obtained by the BUN and albumin levels. Thus, BAR was found to be more valuable than the BUN and albumin levels in predicting in-hospital COVID-19 mortality.

Ethics committee approve

Necmettin Erbakan University Meram Medical Faculty Pharmaceutical and Non-Medical Device Studies Ethical Committee by the decision number of 2021/3022.

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Human rights

During the research, the World Medical Association(WMA) Declaration of HELSINKI and/or the World Psychiatric Association HAWAII Declaration of Good Clinical Practice rules were complied with.

Declaration of Competing Interest

The authors declare no conflict of interest.

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