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Investigation of the predictive effect of hematologic indices in patients with intracerebral hemorrhage

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Abstract

Aim: This study aimed to investigate the role of systemic inflammatory markers in predicting mortality in patients with intracerebral hemorrhage (ICH). ICH is a severe stroke subtype with high mortality and disability rates.

Methods: Researchers analyzed data from patients who underwent surgery, including decompressive craniectomy, between 2015 and 2023. This study examined demographic data, comorbidities, observation periods, mortality rates, hemograms, and biochemical parameters. Patients were divided into survivor (n=1205) and non-survivor (n=440) groups.

Results: Results showed non-survivors had lower hemoglobin levels and significantly higher C-reactive protein (CRP) levels compared to survivors. Inflammatory indices, such as the Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and Platelet-to-Lymphocyte Ratio (PLR), were also elevated in the non-survivor group. Cut-off values were determined to predict the outcomes. For example, the SII cut-off was 1793.62 (65,4% sensitivity, 58,9% specificity), and the SIRI cut-off was 4.81 (63,4% sensitivity, 58% specificity).

Conclusion: The study concluded that elevated white blood cell counts, SIRI, SII, and CRP levels are associated with increased mortality risk in ICH patients.

Keywords: Intracerebral hemorrhage, hematological indices, SIRI, mortality, decompression

Introduction

Intracerebral hemorrhage (ICH) is a severe form of stroke characterized by bleeding within brain tissue, leading to high rates of mortality and disability. In recent years, systemic inflammatory markers, such as the Systemic Inflammation Response Index (SIRI) and Systemic Immune-Inflammation Index (SII), have been investigated for their potential roles in predicting outcomes and complications in ICH patients. The SIRI, a composite index calculated using peripheral neutrophil, monocyte, and lymphocyte counts, has demonstrated its capacity to predict diverse outcomes in patients with ICH. For instance, a study by Li et al. demonstrated that SIRI is an independent predictor of 3-month functional outcomes and 1-month mortality in patients with spontaneous ICH, with a stronger prognostic ability than neutrophil-to-lymphocyte ratio (NLR) (1-4).

Concurrently, Zhao et al. discovered that elevated SIRI levels on the third postoperative day were associated with severe pneumonia in patients with cerebral hemorrhage, suggesting their utility in predicting severe complications post-surgery (5). In the context of stroke-associated pneumonia (SAP), a prevalent complication following ICH, the SIRI has also been emphasized as a valuable predictive marker. Yu and Wang demonstrated that elevated SIRI levels serve as a significant independent predictor of SAP in patients with spontaneous ICH. This finding was supported by a notable area under the curve (AUC) value, which signifies the diagnostic utility of SIRI. (2). The present finding is corroborated by Wang et al., who, in their study, compared various inflammatory indices and ascertained that, while the neutrophil-to-lymphocyte ratio (NLR) exhibited the optimal predictive capacity for dialysis (SAPI), SIRI nevertheless exerted an influence on the inflammatory response subsequent to ICH (3). The SII, an additional inflammatory marker calculated using platelet, neutrophil, and lymphocyte counts, has also been examined for prognostic value in ICH. Li et al. reported that the SII, particularly when measured on the first-day post-ICH, was associated with poor 90-day functional outcomes, indicating its potential as a prognostic tool (6). Trifan and Testai further corroborated the predictive capability of the SII by demonstrating that it functions as an independent predictor of unfavorable outcomes at hospital discharge in patients with supratentorial spontaneous ICH (7). While both SIRI and SII are valuable in predicting outcomes and complications of ICH, their specific applications may vary. SIRI appears to be more directly associated with immediate complications, such as SAP and severe pneumonia, while SII is more focused on long-term functional outcomes. The incorporation of these indices into clinical practice holds the potential to facilitate the early identification of high-risk patients, thereby enabling more targeted interventions. In summary, both SIRI and SII show great promise as inflammatory markers for predicting outcomes in ICH patients (6-8). SIRI has been shown to have particular utility in the prediction of complications, such as SAP and severe pneumonia, while SII has been found to be more indicative of long-term functional outcomes. When used in conjunction with conventional clinical assessments, these indices have the potential to enhance the management and prognosis of ICH patients. Future research endeavors should prioritize the validation of these findings through large-scale, multicenter studies. These studies should aim to establish standardized cut-off values and integrate these markers into standard clinical practice (3-8). In these studies, new parameters and the usefulness of inflammatory parameters such as SIRI and SII for mortality in patients with ICH were used.

The aim of this study was to investigate the predictive effect of hematological indices in patients with intracerebral hemorrhage.

Materials and Methods

Ethics committee approval was received for this study from the Non-Interventional Clinical Research Ethics Committee of Antalya Training and Research Hospital with the approval number 2024/6-15.

The objective of this study was to examine the outcomes of patients admitted to a single-level tertiary education and research hospital with intraspinal hematoma following hematoma diagnosis. The study will concentrate on the management of the hematoma, encompassing the evacuation of the hematoma and the potential necessity for decompressive craniectomy. Furthermore, the necessity for decompressive craniectomy is evident in patients who underwent surgery between January 1, 2015, and January 1, 2023. The dataset under consideration comprises patients who presented at the emergency department of our hospital on the relevant date and underwent hematoma evacuation and/or decompressive craniectomy. These patients were included in the study. Conversely, patients with incomplete data, including all patients under the age of 18, were excluded from the study. Individuals with a documented history of oncological or hematological chronic diseases, along with those who used steroids or comparable medications that could potentially influence blood parameters, were included in the study.

Furthermore, subjects who presented with an infection upon initial assessment or those who were hospitalized at a different facility were included in the study. The following context is provided for additional clarification. A thorough review of the hospital information system and the associated documentation was conducted. A thorough examination of the demographic data, additional illnesses, observation periods, and mortality rates of the patients was conducted. Concurrently, a comprehensive evaluation of the hemogram and biochemical parameters was performed. The hemogram parameters recorded included white blood cell count, monocyte, lymphocyte, platelet, immature granulocyte, mean platelet volume, and C-reactive protein (CRP) levels. The correlation

between these parameters and mortality was also evaluated. Furthermore, the ratios of the aforementioned parameters, calculated using the total number of monocytes, neutrophil count, lymphocyte count, and neutrophil-to-lymphocyte ratio, were used to determine SIRI. The formulation of the SII is based on the calculation of thrombocyte count, neutrophil count, and lymphocyte count ratios. Patients were stratified into two groups: those who succumbed and those who did not. Groups were compared based on their respective parameters. A graphical illustration of the study is shown in Figure 1.

Statistical analysis

Analyses were performed using the SPSS software (IBM SPSS Statistics version 27.0, IBM Inc., Armonk, NY, USA).

The data were categorized accordingly. Categorical variables were expressed as frequencies and percentages. A distribution analysis was performed for numerical data. Variables with a normal distribution were presented as mean ± standard deviation, whereas those not following a normal distribution were described using median and interquartile range. For the analysis of numerical variables, the t-test was applied for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. Multiple linear regression analysis was employed to assess the dependent variable, while the Receiver Operating Characteristic (ROC) curve analysis was used to evaluate the predictive power of the independent variable.

A *p*-value of less than 0.05 was considered statistically significant.

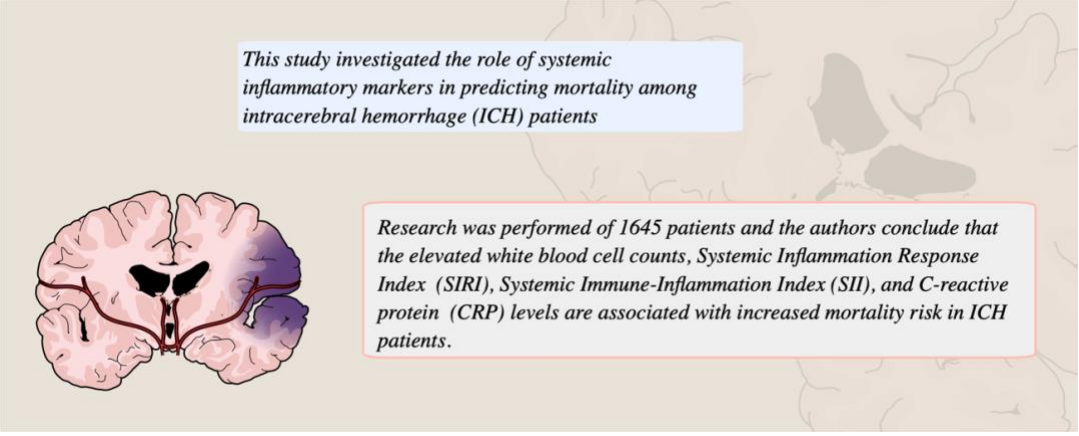

Figure 1. Graphical illustration of the study

Results

The study comprised two groups: survivors (n = 1205) and non-survivors (n = 440). A statistically significant difference was observed in sex distribution, with a higher percentage of females in the non-survivor group (45,9%) than in the survivor group (31,3%). The average age was also higher in the non-survivor group (76,91 years) than in the survivor group (69.06 years). Furthermore, hypertension (HT) manifested at a significantly higher frequency in the survivor group (10,5%) than in the non-survivor group (0,5%) (Table 1). The follow-up settings exhibited no significant disparities between the two groups, with no substantial differences observed in the proportion of patients undergoing follow-up in the service or intensive care unit (ICU). However, a range of significant differences in various blood parameters was identified between the two groups (Table 2).

Non-survivors exhibited elevated white blood cell (WBC) counts (13.47) in comparison to survivors (11.02) and diminished red blood cell (RBC) count (3.65) relative to survivors. Furthermore, a significant decrease in hemoglobin levels was observed in non-survivors compared to that in survivors. Concurrently, C-reactive protein (CRP) levels exhibited a marked increase in non-survivors compared with survivors. Other inflammatory indices, namely the Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and Platelet-to-Lymphocyte Ratio (PLR), were elevated in non-survivors (Table 3). The study identified cut-off values for various indices to predict outcomes. For instance, the SII cut-off was determined to be 1793.62 with a sensitivity of 65,4% and specificity of 58,9%. A similar outcome was observed with the SIRI cut-off, which was registered at 4.81 with a sensitivity of 63,4% and specificity of 58% (Tables 4 and 5). The ROC curves are shown in Figures 2 and 3. Moreover, the results of the analyses conducted to ascertain the independent variable are presented in Table 6.

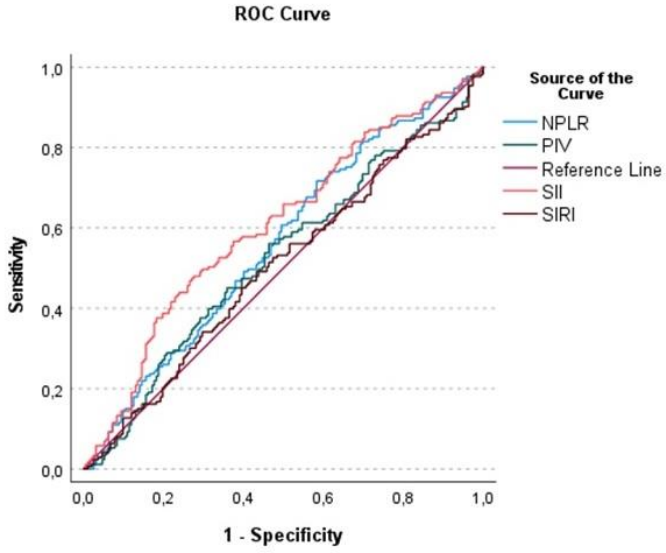

Figure 2. ROC analysis according to mortality

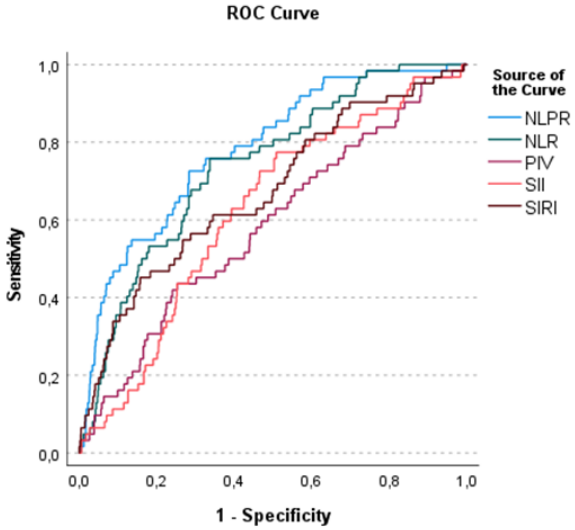

Figure 3. ROC analysis according to the operation

Table 1. Demographics comparison

	Live (n=1239)	Ex (n=471)	*p*-value	Observational (n=1645)	Surgery (n=65)	*p*-value
Gender (Female) (n,%)	389 (31.4%)	215 (45.6%)	<0.001	579 (35.2%)	25 (38.5%)	0.338
Age (mean±SD)	68.65±14.6	76.38±9.89	<0.001	71.16±13.69	61.26±15.95	<0.001
Hypertension (n,%)	137 (11.1%)	7 (1.1%)	<0.001	129 (7.8%)	15 (23.1%)	<0.001
Cerebrovascular event (n,%)	546 (44.1%)	193 (41%)	0.136	728 (44.3)	11 (16.9%)	<0.001
Decomptaion (n, %)	34 (2.7%)	31 (6.6%)	<0.001			
Follow-up (n,%)						
Service	684 (55.2)	244 (51.8%)	0.114	928 (56.4%)	0	<0.001
Intensive Care Unit	555 (44.8%)	227 (48.2%)		717 (43.6%)	65 (100%)	

Table 2. Comparison of biochemical data

	Live (n=1239)	Ex (n=471)	*p*-value	Observational (n=1645)	Surgery (n=65)	*p*-value
White blood cells (mean±SD)	11.08±4.11	13.55±5.92	<0.001	11.66±4.69	14.06±6.49	<0.001
Red Blood Cells (mean±SD)	4.02±0.85	3.64±7.79	<0.001	3.93±0.85	3.67±0.89	0.422
Hemoglobin (mean±SD)	11.23±2.36	10.18±2.13	<0.001	10.96±2.34	10.43±2.39	0.812
Platelets (mean±SD)	288.03±132.5	297.62±162.25	0.226	293.23±141.34	225.70±121.01	0.193
MPV (mean±SD)	10.31±1.40	10.30±1.42	0.073	10.3±1.41	10.68±1.16	0.016
PCT (mean±SD)	0.30±0.13	0.30±0.15	<0.001	0.29±0.13	25.1±0.11	0.113
Neutrophil (mean±SD)	8.49±3.89	11.12±5.24	<0.001	9.08±4.35	11.89±0.82	<0.001
Lymphocyte (mean±SD)	1.50±0.79	1.29±0.90	<0.001	1.46±0.82	1.04±0.85	0.148
Monocyte (mean±SD)	0.79±0.36	0.78±0.50	<0.001	0.78±0.38	0.88±0.82	<0.001
Eozonophile (median, IQR)	0.17 (0.31)	0.07 (0.18)	<0.001	0.76 (0.43)	0.81 (0.49)	<0.001
Basophil (median, IQR)	0.04 (0.03)	0.03 (0.04)	<0.001	0.04 (0.04)	0.02 (0.03)	0.026
IG% (median, IQR)	0.6 (0.6)	1.3 (1.7)	0.001	0.7 (1)	0.6 (0.65)	0.643
IG (median, IQR)	0.06 (0.07)	0.16 (0.25)	0.001	0.07 (0.12)	0.07 (0.10)	0.172
CRP (median, IQR)	53.6 (104.4)	101.5 (127)	0.001	74.4 (112.75)	89.50 (100.38)	0.162

Ig: Immature granulocyte, CRP: C-reactive protein

Table 3. Comparison of hematological indices

	Live (n=1239)	Ex (n=471)	p-Value	Observational (n=1645)	Surgery (n=65)	p-Value
SII (median, IQR)	1509.98 (2175,87)	2556 (3360,82)	0.001	1711,38 (2525,82)	2739,12 (2204,37)	0.001
SIRI (median, IQR)	4.09 (5,49)	6.45 (7,75)	<0.001	4,58 (5,86)	8,07 (13,83)	<0.001
PIV (median, IQR)	1026.05 (1866,53)	1927,47 (2430,72)	<0.001	1229,35 (2078,36)	1672,1 (2779,36)	0.025
NPLR (median, IQR)	0.021 (0.03)	0.033 (0,05)	0.001	0,23 (0,03)	7 (0,01)	<0.001
NLR (mean±SD)	5.64 (5,78)	8.57 (11,37)	0.001	6,23 (6,93)	13,91 (13,54)	<0.001

Table 4. ROC analysis according to mortality

	AUC±SD	p-Value	Cut-Off	Sensitivity	Specificity
SII	0.646±0.016	0.001	1793.62	66	58.3
SIRI	0.633±0.016	0.001	4.808	64.8	57.8
PIV	0.618±0.016	0.001	1257.75	66.2	56.1
NPLR	0.651±0.016	0.001	0.286	57.6	63.4
NLR	0.670±0.015	0.001	5.767	74.6	51.1

Table 5. ROC analysis according to operation

	AUC±SD	p-Value	Cut-Off	Sensitivity	Specificity
SII	0.622±0.033	0.001	1663.37	77.4	49.1
SIRI	0.672±0.037	0.000	10.99	45.2	84.1
PIV	0.584±0.037	0.027	2592.61	43.5	74.7
NPLR	0.781±0.029	0.001	0.039	100	0.7
NLR	0.739±0.030	0.001	8.408	75.8	66.3

Table 6. Multiple linear regression analysis according to mortality and operation status

Mortality	Estimate	95% CI (profile likelihood)	Odds ratios	95% CI (profile likelihood)	*p*-value
SII	0.0003	0.0001371 to 0.0005466	1	1.000 to 1.001	0.001
SIRI	0.0088	-0.04072 to 0.05998	1.009	0.9601 to 1.062	0.727
PIV	-0.00002	-0.0001887 to 0.0001427	1	0.9998 to 1.000	0.797
NPLR	26.01	17.13 to 35.58	$19x10^{12}$	27505566 to 2.826e+015	<0.001
NLR	-0.142	-0.2331 to -0.05523	0.867	0.7921 to 0.9463	0.001
Operation					
SII	-0.0001045	-0.0004721 to 0.0002154	0.9999	0.9995 to 1.000	0.546
SIRI	0.05513	-0.01351 to 0.1290	1.057	0.9866 to 1.138	0.127
PIV	-7.962e-005	-0.0003815 to 0.0002019	0.9999	0.9996 to 1.000	0.590
NPLR	4.655	-5.176 to 13.11	105.2	0.005648 to 492596	0.293
NLR	0.02773	-0.08072 to 0.1434	1.028	0.9225 to 1.154	0.625

Discussion

The implementation of novel parameters as markers of mortality serves to underscore the significance of physicians and facilitate their decision-making process. The treatment plan and the patient can serve as a guide during the follow-up process. In the present study, the efficacy of parameters such as the SIRI, SII, and PLR was demonstrated.

Recent research findings indicate that patients with acute intracerebral hemorrhage (ICH) who presented with systemic inflammatory response syndrome (SIRS) at the time of admission had an elevated risk of mortality at one-month, three-month, and one-year follow-up, with hazard ratios ranging from 2.030 to 2.532. The findings of this study suggest a heightened

association between the presence of SIRS at the time of admission and an elevated mortality risk in older patients or those with larger hematoma volumes. This observation indicates a more pronounced relationship between SIRS and ICH mortality in these specific subgroups (9). Lee et al. found that admission Systemic Inflammation Response Index (SIRI) was an independent predictor of 3-month functional outcome and 1-month mortality in patients with spontaneous intracerebral hemorrhage (ICH). The SIRI was determined to be a stronger prognostic indicator compared to the neutrophil-to-lymphocyte ratio (NLR) in predicting outcomes of patients with ICH, as indicated by receiver operating characteristic analyses and predictive models (10). Zhu et al. discovered that systemic inflammatory response syndrome (SIRS) exhibited a strong correlation with the propensity for hematoma expansion (HE) in patients suffering from ICH (11). Boehme et al. found that patients with systemic inflammatory response syndrome (SIRS) upon admission for ICH were younger than those without SIRS. Although SIRS was associated with ICH score on admission and infection, it was not found to be an independent predictor of poor functional outcomes after ICH (12). Godoy et al. found that higher baseline white blood cell (WBC) counts were associated with larger hematoma volume at admission and greater severity of spontaneous intracerebral hemorrhage (sICH) as assessed by the Glasgow Coma Scale. While WBC count was initially predictive of higher 30-day mortality rates, this association reversed when adjusted for other confounding variables and C-reactive protein (CRP) concentration quartiles, suggesting that WBC count may only serve as a surrogate biomarker of sICH severity (13). Pressman et al. found that patients who underwent decompressive craniectomy (DC) after symptomatic intracerebral hemorrhage (sICH) did not show improved functional outcomes at 90 days based on multivariable analysis. The analysis revealed that younger age and absence of a prior history of cancer were associated with enhanced functional outcomes in patients who underwent DC following sICH (14). Ridha et al. found that premorbid blood pressure control, especially untreated hypertension, may influence the relationship between diffusion-weighted imaging (DWI) lesions and acute blood pressure reduction after intracerebral hemorrhage. Ridha et al. (2023) found that, while systolic blood pressure reduction was not directly associated with diffusion-weighted imaging (DWI) lesions, there was an interaction effect observed between systolic blood pressure reduction and chronic hypertension status. This indicates a potential modification of risk based on premorbid blood pressure control (15). Zhao et al. found that the study focused on comparing the predictive efficacy of inflammatory and nutritional indices for stroke-associated pneumonia (SAP) in patients with ICH, with the objective of determining their clinical utility in the early detection of pneumonia. Among the inflammatory and nutritional markers studied, the Controlling Nutritional Status (CONUT) index was identified as the most reliable predictor of SAP in patients with ICH, with an area under the curve (AUC) of 0.6743 and a significant association with the occurrence of SAP (16). Zhu et al. discovered a novel parameter: serum secretoneurin levels were considerably elevated in patients with intracerebral hemorrhage (ICH) compared with healthy controls. Zhu et al. discovered that serum secretoneurin levels were elevated in patients with ICH compared with healthy controls. This elevated level of secretoneurin in the serum was independently found to predict poor prognosis 90 days after ICH. Levels of secretoneurin exceeding 22.8 ng/mL were able to distinguish patients at risk of poor prognosis with a sensitivity of 66.2% and a specificity of 81.0% (17). In the present study, a lower hemoglobin level was observed in non-survivors than in survivors. Concurrently, CRP levels exhibited a marked increase in non-survivors compared with survivors. Concurrently, other inflammatory indices, namely SII, SIRI, and PLR, exhibited elevated levels in non-survivors.

Limitations

The retrospective nature of the study may have introduced bias and limited the ability to establish causality. This research was conducted at a single center, which may impact the generalizability of the findings to a broader population. This study highlights the challenge of developing specific therapeutic targets for inflammation in patients with ICH, suggesting a limitation in the current understanding and treatment options for post-hemorrhagic secondary brain injury. The study did not investigate the long-term outcomes of patients beyond the time of hospital discharge; therefore, the impact of the SII Index on outcomes after discharge was not addressed. This study focused specifically on patients with supratentorial spontaneous intracerebral hemorrhage, limiting the generalizability of the findings to other types of intracerebral hemorrhage or neurological conditions. This study did not investigate the specific mechanisms through which SIRS contributes to an increased risk of mortality and disability in patients with acute ICH. Further research is required to understand the underlying pathways. Another limitation highlighted in the paper is the need for further research to fully understand the complex signaling pathways involved in intercellular communication within the brain after a hemorrhagic event.

Conclusion

Higher white blood cell (WBC) counts, in conjunction with the systems of the inflammatory response (SIRI and SII) and the C-reactive protein (CRP) levels, have been demonstrated to be associated with an elevated risk of mortality in patients with intracerebral hematoma.

Disclosures

Ethical Approval: Ethics committee approval was received for this study from the Non-Interventional Clinical Research Ethics Committee of Antalya Training and Research Hospital, in accordance with the World Medical Association Declaration of Helsinki, with the approval number: 2024/6-15.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – U.O.M.; Design – U.O.M.; Supervision – Ö.Z.; Materials – U.O.M.; Data collection &/or processing – U.O.M.; Analysis and/or interpretation – Ö.Z.; Literature search – U.O.M, Ö.Z.; Writing – U.O.M.; Critical review – Ö.Z.

Conflict of Interest: There is no any conflict of interest.

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