The Effect of Fluid Challenge Test on Optic Nerve Sheath Diameter

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ABSTRACT

Objective: To investigate the effect of the fluid challenge test on the optic nerve sheath diameter (ONSD) change.

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Anesthesiology and Reanimation, Ondokuz Mayis University Hospital, Samsun, Turkey, from January to November 2021.

Methodology: A fluid challenge was defined as a 500 mL crystalloid infusion administered over 10 minutes, and fluid responsiveness was defined as a subsequent increase in stroke volume of at least 15% administered to the ICU patients. The ONSD and hemodynamic variables were measured by ultrasonography before (T_0), at the end (T_1), and 30 min after the fluid challenge (T_2). The primary outcome of the study was the change in ONSD measurements associated with the fluid challenge, and the secondary outcome was the relationship between fluid responsiveness and the change in ONSD.

Results: A total of 60 patients were included. The ONSD (mm) value was significantly higher at T_1 compared to T_0 (mean ± standard deviation: 5.12±0.30 mm *vs.* 5.10±0.32 mm; p=0.011). However, at T_2, the ONSD was similar to that at T_0 (5.10±0.31 mm *vs.* 5.10±0.32 mm; p=0.662). The stroke volume (mL) was also significantly higher at T_1 and T_2 compared to T_0 [median IQR 60 (6) mL *vs.* 60 (4.7) mL *vs.* 52 (5) mL, respectively, p <0.01]. No significant relationship was found between the ONSD and the change in fluid responsiveness (p=0.621).

Conclusion: The fluid challenge test increases ONSD and may cause an increase in intracranial pressure.

Key Words: *Fluid therapy, Stroke volume, Intracranial pressure, Ultrasonography, Optic nerve sheath diameter.*

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INTRODUCTION

The fluid challenge is a simple volume resuscitation evaluation method that provides an indication of the patient's likelihood of benefiting from an increase in intravenous fluid volume. Both the fluid challenge and fluid responsiveness are evaluated by interpreting the change in hemodynamic parameters after 500 mL of crystalloid (or 250 mL of colloid) solution is infused over 10–15 minutes.[1] This is done in an attempt to regulate the fluid therapy of hemodynamically unstable patients in order to prevent fluid overload. However, the fluid challenge test that is applied to prevent fluid overload and to predict fluid response, may also cause tissue oedema by causing fluid overload, especially in critically ill patients.[2]

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Previous studies have shown that fluid overload is associated with negative outcomes and increased mortality.[3] The main pathophysiology of fluid extravasation is capillary endothelial damage, which results in only 5% of intravenously administered fluids remaining in the vessel after one hour.[4] Fluid overload is also associated with the development of cerebral oedema and impaired cognitive functions.[5] In addition to inappropriate fluid replacement in the intensive care unit (ICU) patients, many other factors, including impaired hemodynamics, organ failure, inotropic medications, and positive pressure mechanical ventilation contribute to the development of cerebral oedema and thus increased intracranial pressure.[6] The current gold standard method used to detect increased intracranial pressure is an invasive procedure that involves the insertion of an intracranial catheter into the ventricles or the cerebral parenchyma. However, routine use of this method in patients that do not have a traumatic brain injury is not recommended due to the potential complications.[7] In recent years, the optic nerve sheath diameter (ONSD) measured by ultrasonography (USG) has been frequently used to detect increase in the intracranial pressure.[8] The hypothesis of the study was that the fluid challenge test may increase ONSD. In this study, the aim was to investigate the effect of the fluid challenge test on ONSD change in ICU patients with hemodynamic instability using optic nerve sheath USG.

METHODOLOGY

This prospective quasi-experimental study was registered in the Protocol Registry and Results System (ClinicalTrail.gov NCT04928040) following the approval of the local ethics committee (OMU/KAEK 2020/436), and was conducted in accordance with the principles of the Declaration of Helsinki. After obtaining written informed consent from the patients' representatives, patients over the age of 18 without known intracranial pathology who were monitored on mechanical ventilator support in the tertiary care ICU of the Ondokuz Mayis University, between January 18, 2021 and November 16, 2021, and who underwent a fluid challenge to determine their fluid needs, were included in the study. The fluid challenge test was applied to the patients who met at least one of the following criteria: systolic blood pressure < 90 mmHg; mean blood pressure < 65 mmHg; tachycardia [*i.e.* heart rate (HR) of 100 beats/min]; mottled skin; oliguria (*i.e.* urine output of 20 mL/h or <0.5 mL/Kg/h for two hours); acute renal failure [according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria]; or arterial lactate concentration >2 mMol/L. Patients, who met any of the following criteria: known intracranial hypertension; severe mitral or aortic regurgitation; cardiac arrhythmia; those in the early postpartum period; and patients who could not be evaluated due to the poor echogenicity, were excluded.

The patients' gender, age, weight, body mass index (BMI), acute physiology and chronic health evaluation (APACHE) II score, the last sequential organ failure assessment (SOFA) score before the fluid challenge test, c-reactive protein (CRP) level, haemoglobin level, plasma osmolarity (P_{osm}) [according to the formula $P_{osm} = 2\,[Na(+)] + glucose\ (mg/dL)/18 + blood\ urea\ nitrogen\ (mg/dL)/2.8)$], concomitant systemic diseases, the reason for ICU admission, mechanical ventilator support during the fluid challenge [mode, positive index respiratory pressure (PEEP) and plateau pressure (Pplat)], and total fluid balance were recorded.

The patients' ONSD, mean arterial pressure (MAP), HR, stroke volume (SV), and cardiac output (CO) measurements were recorded before the fluid challenge (T_0), at the end of the fluid challenge (T_1), and 30 min later (T_2). The fluid challenge test was performed by infusing 500 mL of crystalloid solution (0.9% NaCl) over 10 min at a constant rate (50 mL/min). ONSD measurement was performed by an experienced anesthesiologist who had previously performed at least 50 ONSD measurements. The ultrasound measurements were recorded and images stored. Briefly, the patients' eyes were closed, and a sterile transparent cover was placed over the eyelids. A thick conductive ultrasound gel was then applied, and a linear USG probe (GE Logiq V1, 8–13 MHz, General Electric Co, Jiangsu, China) was placed gently (without applying pressure) on the eyeball transversely with the diameter on the horizontal plane. The distance, between the outer borders of the optic nerve and 3 mm posterior to the point where the optic nerve enters the eyeball, was measured on the transverse plane (Figure 1). To minimise observational variables, the ONSD was measured three times in the both eyes, and the mean value was recorded as the ONSD. Fluid responsiveness was defined as an increase of SV >15% from baseline. The SV measurements were performed using the Vivid S6 echocardiograph (GE Medical Systems, Milwaukee, WI, USA) with the transthoracic echocardiograph in the parasternal long axis view. The SV was calculated using the following formula: the left ventricular outflow tract (LVOT) area = (mean LVOT diameter/2)^2 × 3.14. To reduce variability, the average of the three measurements was recorded as the LVOT diameter. The aortic blood flow was measured from the apical five-chamber view [mean of the five consecutive velocity time integrals (VTIs)], using the formulas SV = LVOT area × VTI and CO = SV× HR.

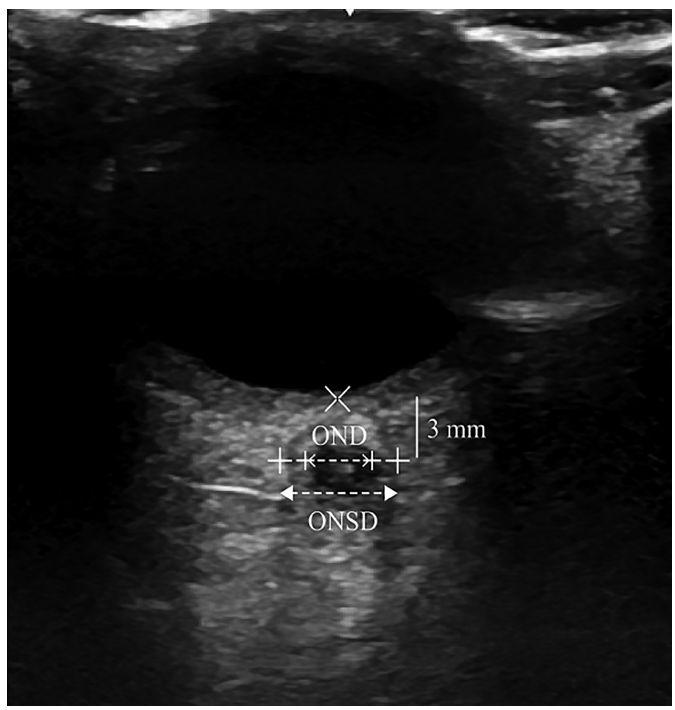

Figure 1: Measurement of the optic nerve sheath diameter by ultrasonography. ONSD: Optic nerve sheath diameter; OND: Optic nerve diameter.

After the fluid challenge test, the change in intracranial pressure according to the ONSD measurements (primary outcome) and the fluid responsiveness associated with the change in ONSD measurements (secondary outcome) were assessed.

The data of the pilot study were conducted with 20 patients by measuring ONSD before and at the end of the fluid challenge (mean ± SD; 5.14 ± 0.108 *vs.* 5.19 ± 0.108) were evaluated with the G*Power 3 (Version 3.1.9.4) program. With an effect size of 0.46, a type 1 error was 0.05, and a test power of 0.90, the minimum number of cases was determined as 54. Considering the possibility of data loss by the researchers, a total of 60 patients were decided as the studied number. The data were analysed using IBM SPSS v26.0 (IBM, New York, USA). To assess the normality of the group distribution, the Kolmogorov-Smirnov test was used; however, the Shapiro-Wilk test was used for subgroup analyses with a sample size ≤30. Normally distributed variables were described by their mean and standard deviations; whereas, non-normal variables were described by their

median and inter-quartile range (IQR). Nominal variables were expressed as frequencies and percentages. The change in ONSD following the fluid challenge manoeuver was categorised into three groups (increasing, decreasing, and unchanged). Kruskal-Wallis H test was used depending on the normality test results for the comparisons among the groups. Paired samples t-test or Wilcoxon test was applied depending on the normality test results for the variables measured before and after the fluid challenge manoeuver. Factors affecting ONSD increased after the fluid challenge were evaluated with binary logistic regression analysis. According to the normality test results, the correlation between the changes in SV and ONSD was evaluated using the Spearman's correlation test, fluid responsiveness and ONSD change were assessed with the Mann-Whitney U-test, and p-value <0.05 was considered significant for all the tests.

RESULTS

The fluid challenge test was performed on 92 patients during the study period. Twenty patients with a traumatic brain injury and 12 patients, who could not undergo a transthoracic echocardiographic evaluation due to the poor echogenicity, were excluded from the study. A total of 60 patients were included in the study and analysed. The patients' demographic data, laboratory values, APACHE II and SOFA scores, concomitant systemic diseases, reasons of ICU admission, mechanical ventilator support during the fluid challenge test, and total fluid balance are shown in Table I.

Table I: Demographic and clinical characteristics of the patients.

	Study Patients (n = 60)
Female/Male n (%)	29 (48.3) / 31 (51.7)
Age (years) median (IQR)	67.5 (23.2)
Body weight (kg) (mean ± SD)	74.1 ± 16.7
BMI (kg/m^2) (mean ± SD)	26.3 ± 4.2
APACHE II median (IQR)	20 (8.5)
SOFA Score median (IQR)	6 (2)
CRP (mg/L) median (IQR)	80.5 (106.2)
Hb (gr/dL) median (IQR)	9.5 (1.6)
P_{osm} (mOsm/kg) (mean ± SD)	298.7 ± 9.1
Systemic diseases n (%)	
Diabetes mellitus	35 (58.3)
Hypertension	37 (61.7)
Coronary artery disease	10 (16.7)
COPD	13 (21.7)
Chronic renal failure	6 (10)
Cause of ICU admission n (%)	
Postoperative	28 (46.7)
Trauma	20 (33.3)
Sepsis	12 (20)
Mechanical ventilator mode n (%)	
P SIMV	34 (56.7)
V SIMV	8 (13.3)
CPAP	18 (30)
PEEP (cm H_2O) median (IQR)	6 (3)
Pplat (cm H_2O) median (IQR)	22 (6)
Total fluid balance (mL) median (IQR)	2850 (2300)

APACHE II, Acute physiology and chronic health evaluation score; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CPAP: Continuous positive airway pressure; CRP: C-reactive protein; Hb: Hemoglobin; IQR: Interquartile range; PEEP: Positive end expiratory pressure; Pplat: Plateau pressure; P-SIMV: Pressure synchronised intermittent mandatory ventilation; SOFA: Sequential organ failure assessment; V-SIMV: Volume synchronised intermittent mandatory ventilation.

The ONSD measured by USG at T_1 compared to T_0 had increased in 39 patients (65%), decreased in 11 patients (18.3%), and remained unchanged in 10 patients (16.7%). When all the patients were evaluated, it was determined that the mean ONSD (mm) at T_1 had significantly increased compared to T_0 (5.10±0.32 mm *vs.* 5.12±0.30 mm; p=0.011). A significant relationship was found among the ONSD (increased at T_0), the patients' CRP (mg/L) (p=0.048), and calculated P_{osm} (mOsm/Kg) (p=0.001). The ONSD measured at T_2 and T_0 were found to be similar (5.10±0.32 mm *vs.* 5.10±0.31 mm; p=0.662).

The variables affecting the change in ONSD after the fluid challenge manoeuver are shown in Table II. The ONSD and hemodynamic variables of the patients at T_0, T_1, and T_2 are shown in Table III.

According to the binary logistic regression analysis, it was seen that the increase in ONSD, after the fluid challenge, was associated with CRP value and sepsis.

Following the fluid challenge test, 40% of the patients were determined to be responsive to the fluid, according to the SV measurements. No correlation was found between the increase in ONSD and the increase in SV (p=0.489). There was also no relationship between fluid responsiveness and ONSD change (p = 0.621).

DISCUSSION

This study revealed that the ONSD diameter increased at the end of the fluid challenge and returned to its normal diameter 30 minutes after the test. The increase in ONSD after the fluid challenge was associated with the patients followed up in the intensive care unit due to sepsis and patients with high CRP levels. No association was found between the changes in ONSD and LV or fluid response.

Fluid boluses cause temporary improvements in hemodynamic parameters and determine the treatment procedures. However, the diffusion of crystalloid fluids into the extravascular space intensifies due to secondary causes, such as the inflammatory response and endothelial damage, especially in the ICU patients.[9] Many studies have shown that an increase in the inflammatory response causes an increase in the intracranial pressure.[10] Given that the ICU admits the patients after trauma, sepsis, and surgery. The increase in the ONSD seen in this study may be associated with the intracranial tissue oedema that develops due to the endothelial permeability secondary to increased inflammatory cytokines. The high CRP levels (94.5 ± 61.1mg/L) seen during the fluid challenge test supports this view. An increase in the CRP value, which is an acute inflammatory protein, was also associated with an increase in the ONSD.

Vasoconstriction that develops due to the tissue hypoperfusion leads to capillary endothelial damage, which contributes to extravasation.[11] Perfusion that improves following fluid resuscitation may reduce this adverse effect.

Table II: ONSD change and patient characteristics (T_1 *vs.* T_0).

	ONSD Unchange (n = 10)	ONSD Decreasing (n =11)	ONSD Increasing (n = 39)	p
Gender (female) n (%)	7 (70)	4 (36.4)	18 (46.2)	0.275
Age (years) (mean ± SD)	66.1 ± 11.4	61.3 ± 12.4	60.3 ± 16.6	0.620
Body weight (kg) (mean ± SD)	83.1 ± 21.8	77.8 ± 15.1	70.8 ± 15	0.136
BMI (kg/m^2) (mean ± SD)	28.2 ± 4.9	26.6 ± 4.4	25.7 ± 3.9	0.269
APACHE II (mean ± SD)	21.4 ± 5.5	21 ± 7	21.2 ± 5.9	0.978
SOFA Score (mean ± SD)	5.9 ± 1.2	5.3 ± 1.1	6.3 ± 2.2	0.468
MAP (mmHg) mean ± SD	54.3 ± 4.1	54.6 ± 4.4	54.6 ± 4.2	0.967
SpO2 (%) mean ± SD	96.4 ± 1.8	95.7 ± 2.1	97 ± 2	0.239
CRP (mg/L) (mean ± SD)	64.2 ± 32.5	74.9 ± 65.4	107.8 ± 62.3	0.048
Hb (gr/dL) (mean ± SD)	10.2 ± 1.3	9.7 ± 1.3	9.6 ± 1	0.485
P_{osm} (mOsm/kg) (mean ± SD)	299.7 ± 6.1	307.4 ± 6.3	296 ± 8.9	0.001
Systemic diseases n (%)				
Diabetes mellitus	7 (70)	6 (54.5)	22 (56.4)	0.710
Hypertension	6 (60)	7 (63.6)	24 (61.5)	0.995
Coronary artery disease	1 (10)	1 (9.1)	8 (20.5)	0.552
COPD	2 (20)	3 (27.3)	8 (20.5)	0.882
Chronic renal failure	1 (10)	1 (9.1)	1 (10.3)	0.994
Cause of ICU Admission n (%)				0.749
Postoperative	5 (50)	4 (36.4)	19 (48.7)	
Trauma	2 (20)	5 (45.5)	13 (33.3)	
Sepsis	3 (30)	2 (18.2)	7 (17.9)	
Mechanical ventilator n (%)				0.282
P-SIMV	6 (60)	6 (54.5)	22 (56.4)	
V-SIMV	3 (30)	2 (18.2)	3 (7.7)	
CPAP	1 (10)	3 (27.3)	14 (35.9)	
PEEP (cm H_2O) (mean ± SD)	6.2 ± 1.5	6.4 ± 1.7	6.7 ± 1.7	0.523
Pplat (cm H_2O) (mean ± SD)	22.6 ± 3.3	22.1 ± 4.1	22.9 ± 3.4	0.841
Fluid balance (L) (mean ± SD)	3.95 ± 2.32	3.22 ± 1.37	3.25 ± 1.80	0.737

APACHE II: Acute physiology and chronic health evaluation score, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, CPAP: Continuous positive airway pressure, MAP: Mean arterial pressure, PEEP: Positive end expiratory pressure, Pplat: Plateau pressure, SpO2: Saturation of pulse oximetry, P-SIMV: Pressure synchronised intermittent mandatory ventilation, Posm: Plasma osmolarity, SOFA: Sequential organ failure assessment, V-SIMV: Volume synchronised intermittent mandatory ventilation, T_0: Start of fluid challenge; T_1: End of fluid challenge.

Table III: Change in ONSD and hemodynamic parameters after the fluid challenge.

	T_0	T_1	T_2	p
ONSD (mm) (mean ± SD)	5.10 ± 0.32	5.12 ± 0.30	5.10 ± 0.31	T_0-$T_{1=}$ .011
				T_0-T_2 =.662
MAP (mmHg) median (IQR)	55 (6)	58 (6.7)	60 (5)	T_0-T_1 <.001
				T_0-T_2 <.001
HR (pulse/min) (mean ± SD)	108.1 ± 14.9	105.4 ± 14.4	105.2 ± 13	T_0-T_1 <.001
				T_0-T_2 <.001
SV (mL) median (IQR)	52 (5)	60 (6)	60 (4.7)	T_0-T_1 <.001
				T_0-T_2 <.001
CO (mL) (mean ± SD)	5684.8 ± 762.9	6211.2 ± 848.1	6167.3 ± 782.2	T_0-T_1 <.001
				T_0-T_2 <.001

ONSD: Optic nerve sheath diameter; MAP: Mean arterial pressure; HR: Heart rate; IQR: Interquartile range; SV: Stroke volume; CO: Cardiac output; T_0: Start of fluid challenge; T_1: End of fluid challenge; T_2: Fluid challenge 30 minutes. For within group comparison, paired data were analysed using paired samples t-test or Wilcoxon-signed rank test.

Although the ONSD increased after the fluid challenge in the present study, the fact that it returned to baseline values after 30 minutes post-procedure suggests that the increase may have been associated with decreased tissue hypoperfusion given that the MAP, SV, and CO values all increased 30 min after the fluid challenge.

To reduce the risk of any secondary damage and brain oedema which may develop in patients with traumatic brain injury, the hypertonic fluid treatments are used to increase the P_{osm}. Obtaining a target P_{osm} of 320 mOsm/Kg in patients with cerebral oedema is recommended.[12] A significant correlation was found between low P_{osm} and an increase in ONSD, following the fluid challenge test in the present study. The ONSD increased further in patients with low P_{osm}. However, this relationship between P_{osm} and ONSD increase could not be demonstrated in the logistic regression analysis.

The appropriate fluid-loading time for the fluid challenge is yet to be clarified. In the study conducted by Vincent *et al*., the authors argued that a 20–30 minutes time interval is the correct loading interval.[13] However, Toscani *et al*. showed in their meta-analysis that there was no difference between fluid loading performed under 15 minutes and fluid-loading performed between 15–30 minutes in terms of determining fluid responsiveness.[14] In the present study,

which was conducted using the duration previously defined for the fluid challenges, fluid-loading applied in a time as short as 10 minutes may have caused the increase in the ONSD.

The rapid fluid infusion due to hypovolemia may cause peripheral and pulmonary oedema.[2] Therefore, a mini fluid challenge test has been proposed where a 100 mL colloid infusion is administered, after which hemodynamic parameters are evaluated to determine fluid responsiveness. There are also studies proposing a modification of the amount of crystalloid according to the body weight to reduce fluid extravasation instead of using the standard 500 mL crystalloid solution.[15] In the present study, no relationship could be demonstrated between the ONSD change and BMI after the 500 ml fluid challenge.

Fluid responsiveness is interpreted based on preload; therefore, there is a change in SV following the fluid challenge.[14,16] In the present study, an increase in the SV of at least 15% occurred in 24 patients following the fluid challenge, suggesting that these patients needed fluid. Based on fluid responsiveness, the change in ONSD was found to be similar between the patients who needed and those who did not need fluid following the fluid challenge. This result suggests that the fluid challenge-related increase in the ONSD cannot be explained by fluid overload. To the authors' knowledge, this study is the first to examine the effect of the fluid challenge test on the ONSD. The most recent SSC guidelines have recommended the use of at least 30 mL/Kg (ideal body weight) of intravenous crystalloids for initial fluid resuscitation.[17] However, the use of a fixed volume for initial resuscitation is based on observational evidence.[18] In the present study, a significant increase in the ONSD was seen after the administration of 500 mL of fluid, which is an amount much lower than that recommended in the sepsis guidelines. In addition, the increase in ONSD was more prominent in the study, especially in sepsis patients. Therefore, prospective studies are needed to evaluate the potential side effects of the recommended fixed volume for initial resuscitation in hemodynamically unstable ICU patients, such as those with sepsis or in septic shock.

This study has several limitations. First, the authors assumed that an increase in ONSD is suggestive of an increase in intracranial pressure. While most studies support this view, other studies have asserted that the ONSD is not suggestive of an increase in intracranial pressure.[19] Most of the studies that investigated ONSD and intracranial pressure have compared the ONSD with a different intracranial pressure measurement method. No previous study has investigated the correlation between the extent of an increase in the ONSD and an increase in the intracranial pressure. Therefore, the extent of the increased ONSD observed in the present study, cannot said to be linked to an increase in intracranial pressure. Secondly, the brain perfusion pressure could not be calculated usually by subtracting the intracranial pressure value from the mean arterial pressure (which determines the intracranial perfusion), changes due to the non-similar increase in both parameters following a fluid challenge. Thirdly, a complete standardisation could not be achieved due to the different diseases of the patients and the support treatment requirements such as different mechanical ventilation support.

CONCLUSION

The fluid challenge test, which is frequently used to determine the fluid requirements of the ICU patients, may increase ONSD for a short time. Increased ONSD may be associated with increased intracranial pressure. The effects of any kind of rapid fluid resuscitation on the critically ill population, who may suffer an increase in intracranial pressure for many reasons, should be investigated with prospective randomised controlled trials.

ETHICAL APPROVAL:
The study was approved by the Institutional Ethics Committee of the University of Ondokuz Mayis (OMU/KAEK 2020/436).

PATIENTS' CONSENT:
Informed consents were obtained from all the patients / relatives prior to the study began.

COMPETING INTEREST:
The authors declared no potential competing interest with respect to the research, authorship, and/or publication of this study.

AUTHORS' CONTRIBUTION:
OK: Methodology, supervision and wrote original draft.
BD: Supervision, review writing, and editing.
NUAK: Data curation, supervision, and writing the original draft.
FU: Writing a review and editing.
All the authors have actively contributed to the production of the manuscript and approved the final version for publication.

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