Comparison of the Efficiency of Induction and Adjuvant Chemotherapy in Patients with Locally Advanced Nasopharyngeal Cancer

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ABSTRACT

Objective: To make a comparative evaluation of induction chemotherapy (ICT) or adjuvant chemotherapy (ACT) added to standard concurrent chemoradiotherapy in patients diagnosed with locally advanced nasopharyngeal cancer (LANPC) (Stage 3-4a patients, except T3N0).

Study Design: Observational study.

Place and Duration of the Study: Department of Medical Oncology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey, from April 2009 to June 2021.

Methodology: Clinicopathological features of adult patients diagnosed with LANPC were recorded from the hospital's patient registry database. Patients without the medical records were excluded. An assessment of the effectiveness of induction or ACT added to standard definitive chemoradiotherapy (CRT) was performed, and the application cycles were evaluated.

Results: Seventy-four patients (71.6% male, mean age 50.8±11.7) with LANPC were included in the study. There is no statistical difference in progression-free survival (PFS) between patients who applied ICT (before CRT) and ACT (after CRT) ($p = 0.61$). Female patients and patients aged ≤50 years had better PFS as independent factors (HR=3.82, 95% CI 1.14-12.74, $p = 0.029$; HR: 1.06 95% CI 1.02-1.10, $p = 0.002$, respectively). Also, patients aged 50 years and younger and female patients had a statistically longer overall survival (OS) ($p = 0.045$, and $p = 0.012$, respectively). While there was statistically no significant difference in PFS according to the number of cycles for EBER-positive patients received adjuvant Cisplatin-5FU (CF); 3 cycles compared to 2 showed a statistically higher OS ($p = 0.06$, and $p = 0.022$, respectively).

Conclusion: LANPC patients were found to have a positive survival if they were young and females. There was a positive impact on survival of intensified adjuvant CF in EBER-positive nonkeratinising, undifferentiated LANPC patients.

Key Words: *Locally advanced nasopharyngeal cancer, EBER, Induction chemotherapy, Adjuvant chemotherapy.*

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INTRODUCTION

Considering that head and neck cancers are generally associated with alcohol and smoking, nasopharyngeal cancer (NPC) differs from other epithelial head and neck cancers since it is endemic due to the effects of genetic, environmental, and ethnic factors. Epstein-Barr virus (EBV) infection in particular, which is caused by the environmental factors, is directly related to the pathogenesis of NPC.[1] Although NPC is not very common in many regions, it is a real health problem in East and Southeast Asia; more than 70% of the world average of 129,000 cases in 2018 were recognised in this region.[2,3]

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EBV-related nonkeratinizing subtype accounts for more than 95% of cases in the endemic region while the keratinizing subtype makes up for less than 20% of all cases world-wide.[3] Surgery is not the first preferred treatment due to the anatomic localisation of NPC; however, radiotherapy (RT) has become an unrivalled method of treatment for the non-metastatic disease since it is a radiosensitive tumour.[1] The 5-year OS in the early-stage NPC patients is above 90% with RT alone. On the other hand, due to the disease's localisation, atypical clinical symptoms, and high invasiveness, 60-70% of the patients are in the locally advanced stage at the time of diagnosis, and the 5-year survival of these patients decreases to 67-77% with RT alone.[4,5] Platinum-based concurrent chemoradiotherapy (CRT) therefore became the standard treatment for LANPC following many clinical trials.[6-8] Still, despite the CRT, the local recurrence or distant metastasis is observed in 30% of patients.[9,10] Thus, the addition of ICT or ACT to CRT in the treatment of these patients has been accepted as a more rational clinical approach for the disease control.[11]

According to the international guidelines, there is still no adequate standardisation for additional treatment to CRT for Stage 3-4a (except T3N0) LANPC patients. Therefore, this study was conducted to investigate the survival advantages of the ICT and ACT over each other in LANPC patients.

METHODOLOGY

Patients aged 18 years and over with Stage 3-4a (except T3N0) LANPC, presented at the Department of Medical Oncology at Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between April 2009 and June 2021, were included in the study. Patients who were previously diagnosed at other medical centres were also accepted. The study was prepared in compliance to the Declaration of Helsinki. Patients' information were recorded by retrospectively scanning the hospital database. Patients with missing or no medical record, patient who were younger than 18-year, patients with distant metastasis and unsuitable for CRT were excluded from the research. The study was approved by the Ethics Board (Number: 2022-08/2018 dated 07.09.2022).

Cases diagnosed with Stage 3-4a (except T3N0) LANPC received 2 or 3 cycles of induction (before CRT) or adjuvant (after CRT) CT in addition to total 70 gy RT (5 days a week; daily 2.0-2.12 gy for 7 weeks) concurrent standard 40mg/m^2 cisplatin. Patients were administered either DCF (docetaxel 70 mg/m^2 day 1, cisplatin 75 mg/m^2 day 1, 5-FU 1000mg/m^2/day day 1-4 IV infusion; every 3 weeks, 2 or 3 cycles, for both ACT and ICT) or CF (cisplatin 100mg/m^2 day 1, 5-FU 1000mg/m^2/day day 1-4, every 3 weeks, 2 or 3 cycles, for induction administration; cisplatin 80mg/m^2 day 1, 5-FU 1000mg/m^2/day day 1-4 IV infusion, every 4 weeks, 2 or 3 cycles, for adjuvant administration) protocols. The analyses were made for survival in terms of both ICT *vs.* ACT and 2 *vs.* 3 cycles according to the administered protocols of treatment. Additionally, factors influencing prognosis in all study patients were determined.

SPSS version 24.0 was used to perform the statistical analysis. Categorical variables were expressed as counts and percentages with Pearson's Chi-square and Fisher's exact tests. In survival analysis, the Kaplan-Meier curve was used, and comparisons were made with the log-rank test. Moreover, variables found to be statistically significant in univariate analysis were evaluated in multivariate cox regression analysis. The value of $p<0.05$ was accepted as significant in all statistical tests.

RESULTS

Fifty-three patients out of 74 included in the study were males (71.6%) while 21 of them (28.4%) were females. The mean age was 50.8 ±11.7 years, and 36 of them (48.6%) were ≤50 while 38 (51.4%) were >50 years of age. Sixteen patients (21.6%) received ICT whereas 58 (78.4%) got ACT. An evaluation of the administered CT protocols showed that 62 patients (83.8%) had CF protocol and 12 (16.2%) had DCF protocol.

Table I: Comparison of patients' characteristics.

	ICT (n=16)	ACT (n=58)	p-value
Age			
≤50	9(56.2%)	27(46.5%)	
>50	7(43.7%)	31(53.4%)	0.49[a]
Sex			
Female	4(25%)	17(29.3%)	
Male	12(75%)	41(70.6%)	>0.99[b]
Stage			
3	9(56.2%)	48(82.7%)	
4a	7(43.7%)	10(17.2%)	0.04[b]

a: Pearson Chi-square, b: Fisher's exact.

Table II: Clinicopathological features of the patients.

	n (%) (n=74)
Gender	
Female	21 (28.4)
Male	53 (71.6)
Age mean ± SD (50.8±11.7)	
≤50	36 (48.6)
>50	38 (51.4)
Smoking	
Yes	54 (73.0)
No	20 (27.0)
Alcohol	
Yes	14 (18.9)
No	60 (81.1)
ECOG	
0	12 (16.2)
1	62 (83.8)
T	
1	17 (23.0)
2	29 (39.2)
3	16 (21.6)
4	12 (16.2)
N	
1	8 (10.8)
2	60 (81.1)
3	6 (8.1)
Stage	
3	57 (77)
4a	17 (23)
CT*	
Induction	16 (21.6)
Adjuvant	58 (78.4)
CT Protocol	
CF**	62 (83.8)
DCF***	12 (16.2)
Total Patient CT Cycle	
2	23 (31.1)
3	51 (68.9)
Pathological Types	
Nonkeratinizing	64 (86.5)
Keratinizing	6 (8.1)
Anaplastic	3 (4.1)
Lymphoepithelioma	1 (1.4)
EBER	
Positive	57 (77.0)
Negative	17 (23.0)
Recurrence	
No	52 (70.3)
Yes	
Bone	8 (10.8)
Local	6 (8.1)
Liver	3 (4.1)
Lungs	3 (4.1)
Liver + Bone	2 (2.7)

CT: Chemotherapy,CF: Cisplatin/5-Fluorouracil,***DCF: Docetaxel/Cisplatin/5-Fluorouracil.*

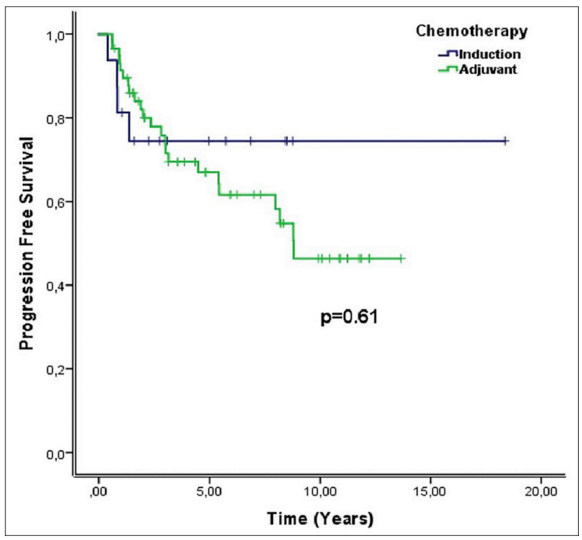

Figure 1(a): Progression free survival between ICT and ACT patients.

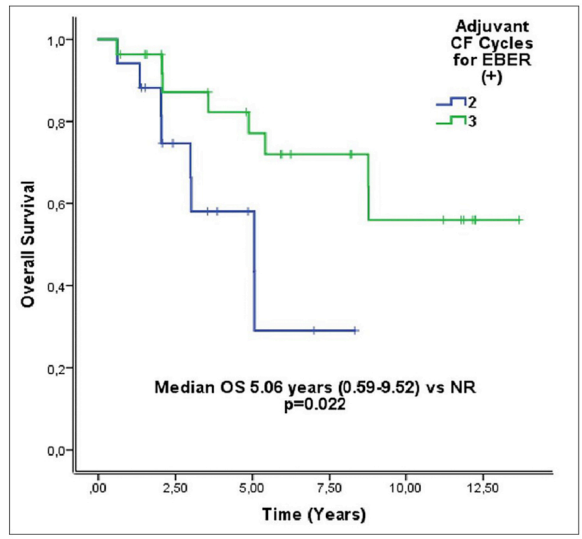

Figure 1(b): Overall survival.

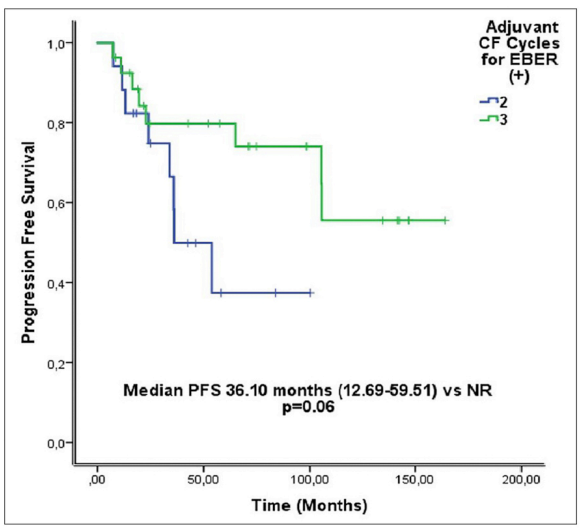

Figure 1(c): Adjuvant CF cycles in EBER (+) patients (PFS).

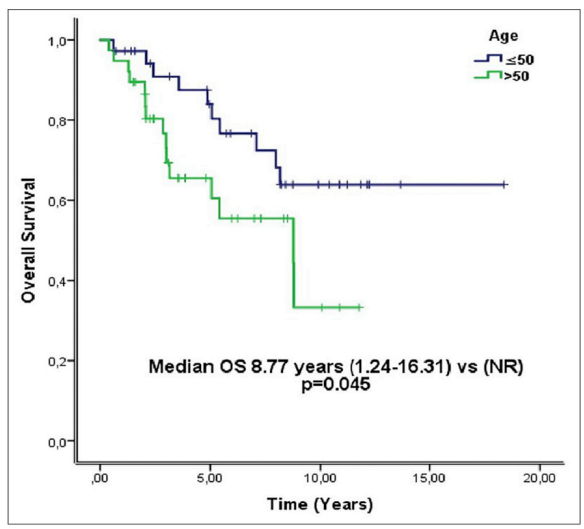

Figure 1(d): Overall survival by age.

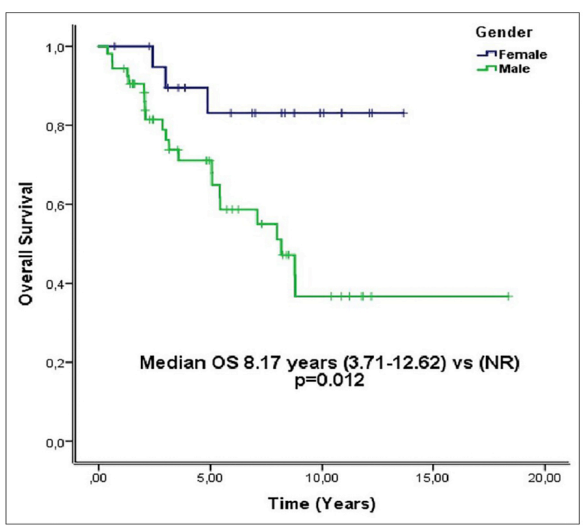

Figure 1(e): Overall survival by gender.

Table III: Progression free survival analyses.

Progression free survival	Univariate cox regression		Multivariate cox regression	
	HR (CI 95%)	p-value	HR (CI 95%)	p-value
Induction CT 2 *vs.* 3 cycles	1.50 (0.15-14.49)	0.72		
Induction CT CF *vs.* DCF	1.38 (0.14-13.36)	0.77		
Induction CT Stage 3 *vs.* 4a	4.13 (0.43-39.78)	0.21		
Adjuvant CT 2 *vs.* 3 cycles	0.50 (0.20-1.24)	0.13		
Adjuvant CT CF *vs.* DCF	2.16 (0.28-16.25)	0.45		
Adjuvant CT Stage 3 *vs.* 4a	0.68 (0.20-2.31)	0.54		
1 = Female *vs.* 2 = Male	4.27 (1.28-14.25)	0.01	3.82 (1.14-12.74)	0.029
1 = ≤50 age *vs.* 2 = >50 age	1.06 (1.02-1.10)	0.001	1.06 (1.02-1.10)	0.002

In the comparison of categorical variables according to the timing of chemotherapy applied in terms of age (≤50 *vs.* >50 years), gender (male *vs.* female) and stage (3 *vs.* 4a) of the patients, no statistically significant difference was found between the age groups and gender according to the timing of the chemotherapy applied (p = 0.49 by Pearson's Chi-square test; p: >0.99 by (Fisher's exact test, respectively). A statistically significant difference was found in the timing of CT applied in 9 (12.2%) Stage 3 patients received ICT, 48 (64.9%) Stage 3 patients received ACT, 7 (9.5%) Stage 4a patients received ICT, and 10 (13.5%) Stage 4a patients received ACT (p = 0.04, Table I).

Fifty-seven patients (77%) were detected to be EBER-positive through the use of *in situ* hybridization (ISH) from tumour tissue, and the remaining 17 patients (23%) were EBER-negative. The clinicopathological features of the patients are summarised in Table II.

In Kaplan-Meier analysis, no statistical difference was found in PFS between ICT and ACT patients (p=0.61, Figure 1a). Forty four patients out of 57 (77%) who were EBER-positive, which indicates EBV-RNA positivity, were administered adjuvant CF protocol (this group accounts for 59.4% of the whole study sample). In these patients, 3 cycles of adjuvant CF compared to 2 cycles were not statistically significant (p = 0.06) in PFS (Figure 1c) but 3 cycles compared to 2 cycles contributed significantly positivıty to OS (median OS: 5.06 years *vs.* NR, p = 0.022, Figure1b). When all patients included in the study were evaluated, those aged 50 years and younger compared to participants over 50 years of age and female patients compared to males demonstrated statistically significantly higher OS (8.77 years *vs.* NR, p = 0.045; 8.17 years *vs.* NR, p = 0.012, respectively, Figure 1d and e).

Patients were tested with the univariate Cox regression analysis based on the number of cycles (2 *vs.* 3), the applied CT protocols (DCF *vs.* CF), and the stage (3 *vs.* 4a). There was no significant difference in any comparison in PFS (for ICT 2 *vs.* 3 cycles p = 0.72, DCF *vs.* CF p = 0.77, Stage 3 *vs.* 4a p = 0.21; for ACT 2 *vs.* 3 cycles p = 0.13, DCF *vs.* CF p=0.45, Stage 3 *vs.* 4a p = 0.54). The multivariate Cox regression analysis carried out for variables influencing PFS in all groups that were determined by univariate Cox analysis and found to be significant demonstrated that females compared to males and patients aged 50 and younger compared to those over 50 had better PFS (HR: 3.82, 95% CI 1.14-12.74, p = 0.029; HR: 1.06, 95% CI 1.02-1.10, p = 0.002, respectively) (Table III).

DISCUSSION

The current literature does not contain enough studies showing which treatment modality is more effective in LANPC from among ICT+CRT *vs.* CRT+ACT combinations.[12] The use of ICT offers two potential benefits; the first one is facilitating the planning of RT by shrinking the tumour and the second one is allowing the completion of CT doses that are aimed to be administered before the emergence of CRT-related toxic effects.[13]

Intergroup study 0099 was terminated earlier than its determined period because the interim analysis demonstrated that compared to RT alone, CRT (with cisplatin) followed by 3 cycles of adjuvant CF therapy ensured higher survival.[14] Furthermore, 20 studies and a meta-analysis including 5144 patients in total published by Ribassin-Majed *et al.* established that adding adjuvant CT to CRT contributes to PFS compared to CRT alone, and the authors asserted that adding more CT to CRT may reduce recurrences.[15] A meta-analysis containing 27 studies performed with 7940 patients by You *et al.* argued that ICT before CRT is the best treatment option for OS, PFS, and distant metastasis-free survival although it was not compared head-to-head with other therapy modalities (including adjuvant CT after CRT).[16]

The joint guideline recently published by the American Society of Clinical Oncology (ASCO) and Chinese Society of Clinical Oncology (CSCO) recommends ICT+CRT for LANPC Stage 3-4a (excluding T3N0) patients and it recommends for patients that could not receive ICT should be considered for ACT after CRT.[17] According to the latest National Comprehensive Cancer Network (NCCN) guideline, CT should be added to CRT in LANPC patients (especially in Stage 3-4a patients) in line with the currently available evidence. However, there is still no clear evidence as to whether CT should be added before or after CRT in these patients.[12] In accordance with the information summarised here, this study aimed to perform a comparative evaluation for survival, after the treatment schemes applied on patients diagnosed with LANPC, considering the stage, number of cycles and CT protocols.

In this study, there was no statistically significant PFS compared of patients who received ICT and those who received ACT (p = 0.61). The uneven number of patients in the relevant groups and the differences in the CT protocols and the number of cycles between the patients are some of the limitations of this study. Also, the analysis of the ICT-receiving patients for PFS showed that the number of cycles (2 *vs.* 3), the CT protocol (DCF *vs.* CF), and different stages (Stage 3 *vs.* 4a) were not statistically significant (p = 0.72, p = 0.77, and p = 0.21, respectively). Similar to the ICT results, the analysis of the ACT-receiving patients for PFS demonstrated that there was no statistically significant difference between 2 *vs.* 3 cycles, DCF *vs.* CF, and Stage 3 *vs.* 4a (p = 0.13, p = 0.45, and p = 0.54, respectively).

The incidence of nasopharyngeal cancer is 2-3 times higher in men than in women, and the incidence peaks between 50 and 59 years of age in population with high incidence and declines in advancing ages. In low-risk populations, a small incidence peak is observed in young and adolescent population, but this rate increases with age.[18] In large-scale studies with Asian samples where NPC is observed heavily, the female gender is found to be statistically significantly advantageous regarding OS,[19,20] disease-free survival,[19] and distant metastasis.[19,21] Furthermore, studies in this field documented that younger patients have better OS.[19,21] In this study, the number of male patients was approximately 2.5 times higher than female patients, and the mean age was 50.8, similar to the patient population in endemic regions. Also, considering all the patient groups in this study, in parallel with the studies conducted in high population regions, PFS in the males was approximately 4 times worse than females, and patients aged >50 years had 1.06 times worse PFS than patients aged ≤50 years as independent variables (HR=3.82, 95% CI 1.14-12.74, p = 0.029; HR:1.06, 95% CI 1.02-1.10, p = 0.002, respectively). In addition to these, analyses in this study supported the current literature since it was determined that females compared to males and patients aged 50 and younger compared to those over the age of 50 were statistically significantly advantaged on OS (median OS 8.17 years *vs.* NR, p = 0.012; median OS 8.7 years *vs.* NR, p = 0.045, respectively).

Unlike other head and neck cancers, in NPC, approximately 1/3 of high-risk patients experience recurrence and/or distant metastasis. In order of frequency, bones, liver, and lungs are the most common distant metastasis sites.[22] Recurrence or distant metastasis was observed in 29.8% of the patients in the study, which is close to the literature, and the bones (10.8%) were found to be the highest distant metastasis site.

Tests for EBV detection can be performed from both blood and tissue, and EBV positivity is usually seen in the nonkeratinized, undifferentiated group. The tests performed for the detection of EBV from tumour tissue are EBV-RNA (EBER) *in situ* hybridisation (ISH) and LMP-1 detection by immunohistochemical staining, and EBER is the more sensitive method.[23] EBV-DNA load can be measured with real-time PCR on serum or plasma, and it has 53% to 96% sensitivity and 88% to 100% specificity.[24] A meta-analysis containing 13 heterogenous studies by Zhang *et al.* identified pre-treatment EBV-DNA levels are an independent risk factor for mortality and distant metastasis.[25] However, EBV-DNA testing is currently available only in selected centres.

The current ongoing NRG-HN001 (NCT02135042) study investigates the role of ACT therapy after CRT in LANPC patients. The aim of this phase 2/3 study is to investigate whether ACT administration should be eliminated or intensified based on EBV-DNA plasma levels.[12]

Since EBV-DNA testing on plasma or serum was not possible due to insufficient technical infrastructure at the study centre, the ISH EBER method was used to detect EBV-related NPC. Fifty-seven patients (77%) were diagnosed to be EBER-positive nonkeratinizing undifferentiated LANPC, and 44 out of 57 participants (59.4% of all patients) received adjuvant CF. The CF protocol was preferred instead of the DCF protocol, which is more toxic in terms of tolerability since the patients had previously received CRT. The number of cycles to be administered was determined based on patients' tolerability and treatment compliance during the initial CRT and ACT cycles. In this study, 3 cycles of CF in EBER-positive patients compared to 2 cycles were numerically significant in PFS and statistically significant in OS (median PFS 36.1 months *vs.* NR, p = 0.06; median OS 5.06 years *vs.* NR, p = 0.022). In line with this information, an important finding in this study was the survival advantage provided by intensified ACT administration to EBV-related LANPC patients. Other limitations of the study are the following: being a retrospective study, including patients from a single centre, inability to examine EBV-DNA levels at the centre where the study was implemented, and failure to evaluate patients for acute and chronic toxicities.

The results obtained in the study are important because the study sample is similar, in terms of distribution, to the patients in regions where NPC is common and the sample consists of the patient group for whom guidelines recommend ICT or ACT in addition to CRT (Stage 3-4a patients, excluding T3N0); however, it requires more comprehensive studies to be applicable in a clinical practice. One of the important contributions of this study is the demonstration of better survival with intensified systemic treatment in addition to CRT in EBV-related LANPC patients, which is another topic of discussion.

CONCLUSION

LANPC patients were found to have a positive survival if they were young and female. There was a positive impact on survival of intensified adjuvant CF in EBER-positive nonkeratinising, undifferentiated LANPC patients.

ETHICAL APPROVAL:
An approval was received from the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Training and Research Hospital (Number 2022-08/2018, dated September 7, 2022).

PATIENTS' CONSENT:
Due to the retrospective nature of the study, patients' consent was waived.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
MB, FT, AK, OA: Carried out the conception and design of the research, drafted the manuscript, carried out the analysis and interpretation of data.
MB, FT: Performed the statistical analysis and participated in data acquisition.
All authors approved the final version of the manuscript to be published.

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