Original Article

Eur J Breast Health 2026; 22(1): 66-71
DOI: 10.4274/ejbh.galenos.2025.2025-8-1

Ultra-Hypofractionated Radiotherapy Plus Boost for T1-2 Breast Cancer Patients: Early Results of a Prospective Study Based on the Fast-Forward Scheme

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ABSTRACT

Objective: Hypofractionated radiotherapy (RT) is the standard adjuvant treatment for breast cancer patients after surgery. The recent results of the FAST-FORWARD trial on ultra-hypofractionated RT, delivered over one week, support a viable alternative regimen for early-stage breast cancer. Whether the addition of a tumor bed boost could further improve patient outcomes is still under investigation.

Materials and Methods: We report the results of a single-center prospective study involving 26 early-stage (T1, 2N0) breast cancer patients treated with whole-breast RT consisting of five daily fractions of 5.2 Gy (FAST-FORWARD regimen) followed by a tumor-bed boost of three daily fractions of 3 Gy.

Results: Grade 1 early breast toxicity (skin changes and altered breast consistency) was documented in 20% of patients within the first 3 months after treatment completion. No events of acute pneumonitis were reported. Whole-breast and tumor-bed boost volumes did not affect the occurrence of breast toxicity. Minimal radiation-induced lung injury (grade 1) was noted in 95.8% of patients, while one patient (4.2%) developed grade 2 lung toxicity, which was later downgraded to grade 1 at the 12-month post-RT time point. With a median follow-up of 72 months, none of the patients presented with locoregional recurrence or distant metastases.

Conclusion: The present study highlights the safety of a hypofractionated RT boost to the tumor bed after ultra-hypofractionated whole-breast RT. No clear evidence exists to date regarding the superiority of delivering a tumor bed boost after ultra-hypofractionated RT or the specific patient subgroups to which a boost should be prescribed.

Keywords: Breast cancer; radiotherapy; ultra-hypofractionation; toxicity; prospective trial; boost

Cite this article as: Kypraiou E, Koukourakis IM, Platoni K, Patatoukas G, Kollaros N, Efstathopoulos E, et al. Ultra-hypofractionated radiotherapy plus boost for T1-2 breast cancer patients: early results of a prospective study based on the fast-forward scheme. Eur J Breast Health. 2026; 22(1): 66-71

Key Points

- Ultra-hypofractionated radiotherapy (ultra-hypo-RT) for early-stage breast cancer has shown promising results.
- A hypo-RT boost to the tumor bed after whole-breast ultra-hypo-RT appears to be safe and effective.
- Radiobiological analysis of the radiotherapy dose delivered to the whole breast and to the booster field area further supports the excellent cosmetic results.

Introduction

Breast cancer is the most commonly diagnosed malignancy, accounting for approximately 315.000 new cases per year in the United States of America. It is also the fourth leading cause of cancer deaths (1). Breast conserving surgery (BCS) and mastectomy are central components of breast cancer treatment, while neoadjuvant and/or adjuvant systemic therapy and adjuvant radiotherapy (RT) are routinely applied according to tumor and patient characteristics and the surgical procedure utilized. Regarding RT, irradiation of the breast and regional lymph nodes (in cases of nodal involvement) is prescribed after BCS, whereas RT to the chest wall and nodal areas is reserved for patients with large tumors, nodal metastases, or positive surgical margins on pathological evaluation (2). The Early Breast Cancer Trialists' Collaborative Group meta-analysis cemented the importance of adjuvant RT post-BCS, reporting reductions of 16% and 4% in the 10-year risk of locoregional and distant recurrence and the Fifteen-year risk of breast cancer death, respectively (3).

Standard RT to the breast and lymph nodes originally consisted of 25 daily fractions of 2 Gy each, delivered over 5 weeks, with or without a tumor bed boost (4, 5). However, during the past 20 years, an improved

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Received: 01.09.2025
Accepted: 13.11.2025
Online Publication Date: 25.12.2025

understanding of tumor and normal tissue radiobiology has paved the way for randomized trials assessing the efficacy of hypofractionated RT (hypo-RT) schedules, which comprise daily RT doses >2 Gy and aim to achieve a significant reduction in overall treatment time, providing greater convenience for patients and busy RT departments. In 2008, the START B randomized trial demonstrated that adjuvant RT delivered as 15 daily fractions of 2.66 Gy conferred 5-year locoregional relapse rates of 2.2% in women with early-stage breast cancer, similar to the rate with standard fractionation (3.3%). In addition, late adverse RT events reported by patients were fewer in the hypofractionated arm (6). Similar to the START B trial, Whelan et al. (7) [Ontario Clinical Oncology Group (OCOG)] reported no difference in the 10-year local recurrence rates of women with node-negative, early-stage breast cancer who underwent hypo-RT (42.5 Gy/2.65 Gy/f in 22 days) versus standard RT (6.7% *vs.* 6.2%) (77. Further hypofractionation in the range of 5–6 Gy per fraction was originally tested in the UK FAST trial, which compared standard daily RT with once-weekly RT of 5.7 or 6 Gy for five weeks in early-stage (N0) breast cancer, and showed that once-weekly schedules (including 28.5 Gy delivered in five weekly fractions) produced local control and toxicity outcomes similar to those of standard fractionation (8, 9).

In 2020, the results of the FAST-FORWARD phase III trial, comprising 4,096 breast cancer patients (pT1–3, pN0–1) previously treated with BCS or mastectomy, were published (10). Patients were randomly assigned to adjuvant RT directed to the breast and/or nodal areas: 40 Gy in 15 daily fractions over 3 weeks (START B fractionation), 27 Gy in 5 daily fractions of 5.4 Gy, or 26 Gy in 5 daily fractions of 5.2 Gy (overall treatment time of 1 week for the ultra-hypo-RT arms). It was shown that RT of 26 Gy delivered over 1 week conferred outcomes comparable to those with 40 Gy irradiation (0.7% difference in 5-year local relapse rates; 2-year moderate-to-marked arm and hand swelling rates were 10% with 40 Gy versus 7% with 26 Gy) (11). A tumor-bed RT boost (10 or 16 Gy, delivered in 2-Gy fractions) was optional and was not part of the randomization protocol; approximately 75% did not receive an RT boost. This was also the case for patients enrolled in the START B trial, whereas a tumor-bed boost was omitted in the FAST and OCOG studies. The authors of the FAST-FORWARD trial suggested that a study focusing on a sequential or synchronous RT boost alongside hypo-RT should be conducted.

In this prospective study, we investigated the safety of a sequential RT tumor-bed boost in breast cancer patients undergoing adjuvant RT (FAST-FORWARD).

Materials and Methods

In this single-center prospective study conducted in the Department of Clinical Radiation Oncology at ATTIKON University Hospital, 26 patients with early-stage breast cancer were treated with adjuvant hypofractionated, accelerated RT (hypo-ART) according to the FAST-FORWARD RT scheme after BCS between 2018 and 2019. The study continues to recruit patients. Since assessing late radiation effects in hypofractionated regimens is crucial, we decided to submit this interim report, which includes patients with more than five years' follow-up. Patient and disease characteristics are displayed in Table 1. The study was approved by the local Ethics and Research Committee (approval number: A1.4.17-4-2018, date: 24.05.2018). Inclusion criteria were patients older than 18 years who had a pathological diagnosis of epithelial breast cancer, with pathological stage pT1-2/pN0 without distant metastasis, and who were treated with BCS as primary treatment. Patients with locally advanced disease, nodal involvement on pathological evaluation, a synchronous diagnosis of another malignancy, a history of autoimmune disease, known genetic susceptibility to increased radiation sensitivity, or pregnancy were excluded. All patients gave written informed consent to participate in the study and to allow their laboratory and clinical data to be used anonymously for research purposes. One patient was lost to follow-up immediately after RT completion, and another patient was lost after three months of follow-up. Thus, 25 and 24 patients were available to assess acute and late toxicity, respectively.

Radiotherapy

The prescribed RT schedule incorporated 5 daily fractions of 5.2 Gy delivered over 1 week via a linear accelerator (VitalBeam, Varian). 6 MV was the standard energy applied, although higher-energy 10 MV fields were also required to achieve better dose homogeneity in patients with large breasts. A sequential tumor-bed boost was delivered in three fractions of 3 Gy each. The clinical target volume (CTV) consisted of breast tissue, as defined by the area between the pectoralis major muscle and 3 mm below the skin surface. A margin of 10 mm beyond the CTV was applied to define the planning target volume (PTV), accounting for patient setup errors and respiratory motion. A 3D-conformal RT (3D-CRT) technique with tangential fields was used. The CTV of the tumor bed boost was defined as the area encompassed by surgical clips placed during lumpectomy; a 1 cm margin was applied for PTV delineation. A 3D-CRT technique – with anterior/oblique fields – was also used for the sequential boost. Daily cone-beam computed tomography (CT) was performed on all patients.

Regarding PTV coverage goals, the lower dose limit was set so that 95% of the PTV volume receives at least 95% of the administered dose. Regarding the upper dose limit, less than 5% and less than 2% of the PTV should receive ≥105% and ≥107% of the administered dose, respectively, with a maximum dose <110%. Dose constraints for the heart and ipsilateral lung were V_EQD2 (25 Gy) <10% for the cumulative RT plan.

Radiobiological Considerations

To clearly portray the biological effects of this ultra-hypofractionated, accelerated regimen, we calculated the equivalent dose delivered in 2-Gy fractions (EQD2) using the linear-quadratic model. We used the α/β values of 3, 4, and 10 Gy for late normal tissue effects, breast cancer, and early normal tissue toxicity, respectively. Treatment acceleration was also taken into account: λ values of 0.2 Gy/day and 0.6 Gy/day (daily dose required to compensate for cell repopulation) were considered for slow-proliferating normal tissues and for breast cancer and rapidly-proliferating normal tissues, respectively. Treatment acceleration ($\Delta\tau$) was defined as the number of days needed to deliver the EQD2 dose minus the 5 or 10 days required for the FAST-FORWARD and the FAST-FORWARD plus boost regimens, respectively (12-15). The mathematical formulas applied are as follows:

$$EQD2 = \text{Total dose} \times ([\alpha/\beta + \text{dose per fraction}]/[\alpha/\beta + 2])$$

$$EQD2\text{-}T = EQD2 + (\lambda \times \Delta T)$$

Toxicity Evaluation

Acute breast toxicity was evaluated at completion of breast RT, at one week, and at three months, or at any time patients reported signs or symptoms involving the skin, breast, or arm. Late breast toxicity was assessed clinically 1 year after treatment completion, acute and late lung

Table 1. Patient, disease and treatment characteristics

No pts	26
Age	
Median	57
Range	39–76
Menopausal status	
Pre	7
Post	19
PS	
0	26
Location	
Left breast	10
Right breast	16
Histology	
NOS (*)	26
Lymphovascular invasion	
Yes	3
No	23
T-stage	
T1	21
T2	5
Node involvement	
N0	26
Grade	
1	11
2	12
3	3
ER status	
Negative	2
Positive	24
Positivity range (%)	50–100
PgR status	
Negative	4
Positive	22
Positivity range (%)	3–100
HER-2 status	
Negative	22
Positive	4
Ki-67	
<14%	12
≥14%	14
Molecular status	
Luminal A	10
Luminal B	14
HER2-enriched	2
Triple negative	0
Surgery (invasive tumors)	
Conservative	26
SLNB (**)	25
Axillary dissection	1
Resection margins (mm)	
Range	2–10
Median	2.5
Chemotherapy	
None	21
Postoperative	5
Hormone therapy	
Yes	24
No	2
During radiotherapy	13

(*)NOS: Non-otherwise specified; (**)SLNB: Sentinel lymph node biopsy; HER2: Human epidermal growth factor receptor 2; ER: Estrogen receptor

toxicities were assessed with high-resolution CTs at 3- and 12-months post-irradiation, respectively. Late toxicity was evaluated annually. Acute toxicity grading of dermatitis, breast edema, and pneumonitis was conducted using the Common Terminology Criteria for Adverse Events version 5.0 (16). Late RT adverse events were graded using the Radiation Therapy Oncology Group/ European Organisation for Research and Treatment of Cancer Late Radiation Morbidity scale (17). In addition, radiation-induced lung toxicity was assessed using a grading scale previously proposed by our group (Supplemental Table 1) (18).

Follow-up

Patients were assessed for ipsilateral breast tumor recurrence or regional recurrence every 6 months during the first 2 years and annually thereafter. Physical examination and mammography or ultrasound were performed at each visit, while CT of the chest and abdomen was required to evaluate potential nodal and distant metastases.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism version 8.0 (GraphPad Software Inc., La Jolla, CA, USA). The Mann-Whitney non-parametric test was used for intergroup analysis.

Results

The majority of patients (73%) were postmenopausal, and 62% of tumors were located in the right breast. Histologically, all tumors were ductal adenocarcinomas (no special type), had no nodal involvement, and were locally staged as T1 (81%) and T2 (19%). Ninety-two percent of tumors (92%) were estrogen receptors (ER)-positive, while human epidermal growth factor receptor 2 expression was noted in 15% of cases. BCS was performed with negative resection margins in all patients. Adjuvant chemotherapy was administered to 19% of patients, and all ER-positive patients received hormonal therapy. Fifty-four percent of them received hormonal therapy during RT. The Median follow-up was 72 months (range, 61–86 months).

Dosimetric Data

Regarding whole-breast irradiation, the average conformity and homogeneity indices were 1.3 and 0.26, respectively. The breast volumes receiving 105% and 107% of the prescribed dose were 32.39 cc and 2.65 cc, respectively. The average dose to 95% of the breast volume (D95%) was 25.42 Gy.

Breast/Arm Toxicity

Early grade 1 breast toxicity (skin and breast consistency) was noted in 5 of 25 patients (20%) during the first 3 months of follow-up. Figure 1 presents a typical image of a patient's breast before and one week after treatment completion. No patients (0%) experienced late breast or arm toxicity of any grade (edema, breast fibrosis, lymphedema). Figure 2a illustrates the progression of breast toxicity during the first year after RT. With a median follow-up of 72 months, no further deterioration in late toxicity was observed.

Breast Volume and Toxicity

Breast toxicity was further analyzed by breast volume (CTV-breast) and by the volume of the breast included in the boost field (PTV-boost). Overall, the breast CTV ranged from 200.8 to 1,510 cc (median 663.8 cc; mean 661.8 cc). Among the five patients who developed grade 1 toxicity, the median CTV-breast was 733.8 cc, compared with 643.3 cc in the remaining patients; this difference was not statistically significant (p = 0.65). The PTV-boost volume ranged from 37.9 to 246.5 cc (median 100.3 cc, mean 112.2 cc). The median PTV-boost volumes were 125.3 cc and 89 cc in patients with grade 1 and 0 toxicity, respectively (p = 0.34).

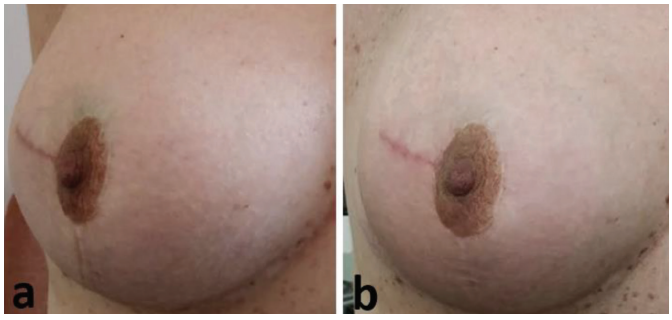

Figure 1. Typical images of a patient's breast before and one week after treatment completion, showing lack of any toxicity

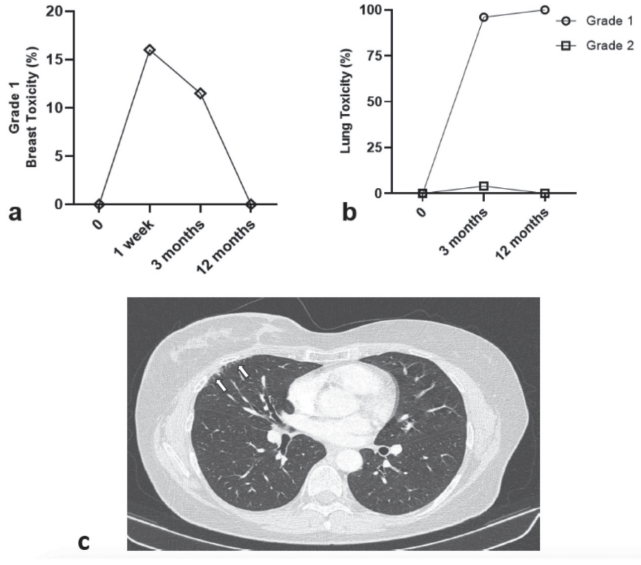

Figure 2. Toxicity in time: (a) Percentage of patients developing grade 1 breast toxicity (skin and breast consistency) during the first year after radiotherapy, (b) Percentage of patients developing lung grade 1 and 2 toxicity during the first year after radiotherapy (time zero corresponds to the start of treatment), (c) Typical computed tomography image of a grade 1 lung toxicity 12 months after radiotherapy (white arrows)

Lung Toxicity

None of the patients developed acute pneumonitis. Grade 1 lung toxicity (ground-glass opacities without obscuration of the subjacent pulmonary vessels within the tangential fields) was noted in 23 of 24 patients (95.8%) on CT scans performed 3 months after RT. One additional patient (4.2%) developed grade 2 lung toxicity (limited consolidations), which had regressed by the 12-month follow-up. All patients were asymptomatic. Figure 2b shows the time course of lung toxicity during the first year after RT. During a median follow-up of 72 months, no additional cases of lung fibrosis were recorded. Figure 2c presents a representative CT image showing grade 1 lung toxicity 12 months after RT.

Radiobiological Analysis

Table 2 shows the EQD2 for the FAST-FORWARD RT regimen and for the regimen used in our study (FAST-FORWARD plus boost), compared with a conventionally fractionated RT scheme across the previously mentioned α/β and λ values (with and without time correction). Appendix I presents an example of detailed calculations.

Local, Regional and Distant Control

Over a median follow-up of 72 months, none of the patients developed local, regional, or distant metastases.

Discussion and Conclusion

Standard fractionation of RT is a well-established and effective approach for patients with cancer. However, it became evident early on that multiple visits to RT departments can reduce compliance—especially among patients with low performance status and those who must commute long distances to the hospital—or even lead to refusal to undergo RT (19, 20). In addition, accelerated RT schedules facilitate the treatment of more patients per year in busy RT departments. The FAST-FORWARD trial established the efficacy and safety of ultra-hypofractionated and accelerated RT in early-stage breast cancer patients after BCS or mastectomy. In this prospective study, we evaluated the safety and efficacy of 26 Gy of adjuvant RT delivered in 5 daily fractions followed by a tumor bed boost of 9 Gy (3 Gy/fraction) in 26 patients with early-stage breast cancer.

The role of an RT tumor-bed boost after whole-breast irradiation has been debated since RT established its role in the adjuvant treatment of patients with breast cancer. A strong indication for prescribing higher radiation doses to the surgical cavity is the presence of positive surgical margins on pathological evaluation, a finding that suggests an increased probability of tumor recurrence and distant metastases (21, 22). Nevertheless, Bartelink et al. (23) assessed the efficacy and safety of a 16 Gy boost given to 2,658 breast cancer patients after whole-breast RT. Although a survival benefit was not observed, there was a statistically significant decrease in local recurrence rates in the RT-boost arm of the study, with 20-year ipsilateral breast tumor recurrence rates of 16.4% versus 12% in the no-boost and boost groups, respectively. However, a significant increase in the 20-year incidence of breast fibrosis was observed in the group receiving the boost (5.2% *vs.* 1.8%).

A subgroup analysis by patient age revealed that patients younger than 40 experienced the greatest reduction in local recurrence compared

Table 2. Equivalent dose delivered in 2 Gy fractions, with and without time correction (EQD2 and EQD2-T), for conventional radiotherapy (RT) and the FAST-FORWARD and FAST-FORWARD plus boost regimens

α/β (Gy)	Radiotherapy regimens				
	Conventional RT	FAST-FORWARD		FAST-FORWARD plus boost*	
	EQD2 and EQD2-T (Gy) + boost	EQD2 (Gy)	EQD2 – T (Gy)	EQD2 (Gy)	EQD2-T (Gy)
3	50+10 (60)	42.64	47.44	42.64+10.8 (53.44)	47.44+11.4 (58.84)
4	50+10 (60)	39.87	52.47	39.87+10.5 (50.37)	52.47+11.7 (64.17)
10	50+10 (60)	32.93	43.13	32.93+9.75 (42.68)	43.13+10.95 (54.08)

*: Breast tissue within the booster dose area

with other age groups, leading the authors to suggest that the tumor-bed boost could be safely omitted in breast cancer patients older than 60 years. In addition, patients with high-grade, hormone-receptor-negative disease have been shown to benefit from an additional radiation dose (24), which should also be considered across all age groups. In the import high trial, patients were randomized to receive a sequential boost (16 Gy in 8 fractions after 40 Gy hypo-RT) or a concomitant boost (48 or 53 Gy in 15 fractions to the surgical cavity) (25). Boost sequencing had no effect on treatment outcome; however, a higher boost dose was associated with a 4%–5% higher incidence of moderate-to-marked breast induration compared with the other trial arms. A phase III randomized trial (HI-RISE) is ongoing, comparing hypo-RT (40 Gy in 15 fractions) with a simultaneous integrated boost (SIB) to the tumor bed and standard fractionated RT with a sequential boost of 10 Gy in 5 fractions (26).

Approximately 25% of patients in the FAST-FORWARD trial received an RT boost of 10-16 Gy, delivered in 2-Gy fractions (10). To date, no publications have focused on this patient subgroup. Zanoguera et al. (27) reported on 126 breast cancer patients (<60 years old, with high-grade disease, or with lymphovascular or perineural invasion) who were treated with adjuvant RT (FAST-FORWARD) and a SIB of 3 Gy (29 Gy/5.8 Gy per fraction to the tumor bed). During a median follow-up of 6.25 months, no significant adverse events were documented. Acute skin toxicity post-RT was minimal: only nine patients presented with grade 1-2 dermatitis. Similarly, Montero et al. (28) assessed the efficacy and safety of an SIB in breast cancer patients: 29 Gy (5.8 Gy/fraction) to the tumor bed in 272 patients, or 30–31 Gy (6–6.2 Gy/fraction) in 111 patients with close/positive margins. No patients developed locoregional recurrence or distant metastasis during the median follow-up of 18 months. Grade 1 and grade 2 dermatitis were noted in 48% and 4% of patients, respectively; minimal late RT sequelae (grade 1 or 2) were also reported in less than 5% of patients. Breast and boost volumes were associated with increased skin toxicity.

In the current study, we demonstrated that a sequential boost of 3 fractions of 3 Gy after ultra-hypo-RT was well tolerated, as no increase in toxicity was documented in our patient cohort. Moreover, the volume of the whole breast and the volume of the breast included in the boost area did not affect the occurrence of breast toxicity. This has also been confirmed by radiobiological analysis. According to the EQD2-T values to the whole breast, the FAST-FORWARD regimen appears to be associated with far less early toxicity compared to conventionally fractionated RT, in accordance with a subanalysis of the FAST-FORWARD trial (29). Our analysis further suggests that this improved toxicity profile also applies to breast tissue within the boost field. Moreover, predicted late toxicity from EQD2-T analysis indicates a slightly lower burden with the FAST-FORWARD plus boost regimen. Regarding the efficacy of the RT scheme applied in this study, the EQD2-T values predict a higher biological anti-tumor dose to the breast tissue within the boost area.

The aforementioned data indicate the safety of a hypo-RT boost to the tumor bed following ultra-hypofractionated whole-breast RT. No clear evidence exists as of yet about the superiority of delivering a tumor bed boost after ultra-hypo-RT, or the specific patient subgroups to which a boost should be prescribed. Certain limitations exist in our study. A larger patient cohort would permit drawing more reliable conclusions, while the inclusion of a control arm could further shed light on the necessity of an RT boost. The prospective nature and novelty of this report, however, could form the basis for future trials.

Ethics

Ethics Committee Approval: The study was approved by the local Ethics and Research Committee (approval number: A1.4.17-4-2018, date: 24.05.2018).

Informed Consent: All patients gave written informed consent to participate in the study and to allow their laboratory and clinical data to be used anonymously for research purposes.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.K., I.M.K., K.P., G.P., N.K., E.E., N.K., A.Z., V.K.; Concept: E.E., N.K., A.Z., V.K.; Design: E.E., N.K., A.Z., V.K.; Data Collection or Processing: E.K., I.M.K.; Analysis or Interpretation: E.K., I.M.K., K.P., G.P., N.K., E.E., N.K., A.Z., V.K.; Literature Search: E.K., I.M.K.; Writing: E.K., I.M.K., K.P., G.P., N.K., E.E., N.K., A.Z., V.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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