Obstetrics; *Maternal Fetal Medicine and Perinatology*

The Major Contributors to the Cesarean Section Risk in Nulliparous Women Aged 35 Years and Older

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ABSTRACT

OBJECTIVE: To assess the association between advanced maternal age (AMA) and cesarean section (CS) risk in nulliparous pregnant women aged 35 years and older and examine potential confounders to enhance guidance for pregnant women and healthcare providers.

STUDY DESIGN: This retrospective cohort study of singleton, nulliparous pregnant women with a fetus in the cephalic presentation admitted for delivery was carried out from 1 January 2022 to 31 December 2022. Maternal demographics, medical history, delivery records, and neonatal outcomes were collected from electronic medical records. Univariate and multiple logistic regression analyses identified variables independently associated with CS in AMA cases.

RESULTS: The study included an AMA group (≥35 years, n=52) and a control group (<35 years, n=487). The CS rate was significantly higher in the AMA group (67.3%) compared to the control group (26.1%, p<0.001). Multiple logistic regression revealed that assisted reproductive technology (ART) pregnancies (OR: 39.0), presence of additional maternal disease or pregnancy complication (OR: 5.34), and fetal heart rate (FHR) category III (OR: 3.34) were significantly associated with increased CS risk in AMA women.

CONCLUSION: The risk of CS is significantly elevated in nulliparous women aged 35 and older, particularly among those who conceived through ART, presented with additional maternal diseases, or exhibited FHR category III. These findings provide essential insights for obstetricians to inform AMA patients on CS risks, aiding decision-making.

Keywords: Advanced maternal age; Cesarean section; Contributing factors; Nulliparous pregnant woman

Gynecol Obstet Reprod Med 2025;31(1):16-23

Introduction

The frequency of first childbearing for women aged 35 years and older, also known as advanced maternal age (AMA), has increased steadily worldwide, especially in industrialized countries, during the past decades (1). Birth statistics data from the Turkish Statistical Institute (TSI) in 2019 also confirmed the international trends of increasing first births in all regions of Turkey (2). The growing trend of delaying pregnancy is mainly dependent on cultural and social dynamics, elongated academic years, career prioritization, delayed marriage, widespread use of efficient contraception methods, advancements in assisted reproductive technologies (ART), improvements in the management of pre-existing chronic conditions, and the increased access of these innovations by patients (3,4).

There is a worldwide concern regarding the increasing rates of cesarean section (CS) globally. CS has implications for post-operative short-term maternal adverse outcomes and long-term complications in future pregnancies because of the uterine scar (5,6). The World Health Organization (WHO) has re-assessed the policy about the optimal CS rate. They con-

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Submitted for Publication: 29.10.2024 Revised for Publication: 21.11.2024 Accepted for Publication: 03.02.2025 Online Published: 12.02.2025

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	DOI:10.21613/GORM.2025.1550

How to cite this article: *Oglak SC. Ates Eminoglu HE. Guzel G. Bulut B. Adiguzel O. Yilmaz EZ. Bala M. Haliscelik MA. The Major Contributors to the Cesarean Section Risk in Nulliparous Women Aged 35 Years and Older. Gynecol Obstet Reprod Med. 2025;31(1):16-23*

cluded that this type of delivery should only be carried out when a vaginal delivery is not possible or safe for the mother or the baby and the ideal CS rate may vary worldwide based on the obstetric skills of healthcare providers and the sufficiency of the healthcare services (7). However, women aged 35 years and older commonly consider that their age increases the risk of adverse outcomes for their infants and thus, they have a tendency to opt for a more secure mode of delivery (8). Previous studies have reported that adverse maternal and neonatal outcomes, including gestational hypertensive disorders, gestational diabetes mellitus, placental abnormalities, preterm births, related complications, labor abnormalities, and obstetrical interventions are higher among women aged 35 years or older than among younger women (9,10). In addition to the aforementioned risk factors, a significant concern associated with AMA is the increased risk of antepartum and intrapartum stillbirths and perinatal deaths in pregnant women aged 35 years or older (11). The existing research has reported a linear relationship between increased age at first birth and increased risk of CS (12). However, data surrounding the association between maternal age and the main reasons for CS is limited. Risk-based counseling may significantly influence women's decisions concerning delivery management and interventions, making it crucial to understand the actual risks associated with AMA at first birth.

This study aimed to assess the potential impact of AMA on the risk of CS in nulliparous women to provide better guidance for pregnant women and healthcare providers who manage the delivery process. Additionally, we aimed to investigate the risk estimates of potential confounders to identify whether these variables contributed to the increased risk of CS in nulliparous pregnant women aged 35 years and older.

Material and method

This retrospective cohort study included singleton, nulliparous pregnant women with a fetus in a cephalic presentation who were admitted for delivery at the Obstetrics Department of the Diyarbakır Gazi Yasargil Training and Research Hospital between January 1, 2022, and December 31, 2022. Women who delivered after 24 weeks of gestation, or if gestational age could not be determined, those who gave birth to neonates with a birthweight of ≥500 g during the study period were eligible for inclusion. Participants were divided into two groups: the AMA group and the control group. The study group (AMA group) included all nulliparous singleton pregnant women aged 35 years and older with a fetus in the cephalic presentation without a major congenital abnormality. Control cases were randomly selected using a computer system. The control group included all nulliparous singleton pregnant women younger than 35 years with a fetus in the vertex presentation without a major congenital abnormality. The exclusion criteria for both of the groups were as follows: pregnant women with multiparity, multiple pregnancies, previous history of uterine surgery, contraindications to labor and vaginal delivery, fetuses with malpresentation, suspected macrosomia, prenatally diagnosed major congenital anomalies or aneuploidy. Patients were also excluded if medical records were incomplete or unavailable.

All pregnant women delivered at our hospital and surviving newborns were either admitted to the maternity ward or transferred to our neonatal intensive care unit (NICU). Data on maternal demographic characteristics, medical history, laboratory values at admission, current pregnancy complications, Bishop score at admission, delivery records, and neonatal outcomes were extracted from patients' files and the institutional electronic database. The Ethics Committee of the Gazi Yasargil Training and Research Hospital approved the study (approval date/number: 09.09.2022/165).

At the time of admission of the mother to the labor ward, cervical status was evaluated using the Bishop score. The Bishop score was calculated based on the following components: cervical effacement, dilatation, consistency, position, and the fetal head's station in the pelvis. Each parameter is allocated points, resulting in a total score ranging from 0 to 13 (13). Pregnant women with a Bishop score of ≤6 underwent cervical ripening with vaginal prostaglandins (PGE2). The dose was repeated if the cervix was unfavorable (Bishop score ≤6). Once the Bishop score became favorable, oxytocin infusion was initiated following the removal of vaginal PGE2 if adequate uterine contractions were absent. Pregnant women with a favorable Bishop score (>6) at the time of admission were directly stimulated with intravenous oxytocin perfusion and amniotomy. No induction of labor (IOL) agent was administered if there were decelerations in fetal heart rate (FHR) tracing, or the patient was contracting painfully more than three times in ten minutes on tocometry.

According to our clinical protocol, FHR was continuously monitored during the first and second stages of labor. The FHR tracings from the last hour were classified into three categories based on the ACOG classification (14). Category I included tracings with a baseline FHR of 110-160 beats per minute, moderate variability, and no variable or late decelerations. Category III tracings displayed either a sinusoidal pattern or absent variability, accompanied by any of the following: recurrent variable decelerations, recurrent late decelerations, or bradycardia. Category II encompassed any FHR patterns that did not meet the criteria for Category I or III.

Outcomes for pregnant women aged 35 and older were compared with those of women under the age of 35 years. The primary outcome measured was the CS rate in both of the groups. Pregnant woman of AMA was defined as women aged 35 years and older at the time of delivery (15). A CS was performed in cases of failure to progress, arrest of fetal descent, nonreassuring FHR tracing, the prolonged second stage of labor, fever suggestive of chorioamnionitis, and medical con-

ditions such as uncontrolled high blood pressure, or fetal face presentation. Prolonged labor was defined as the active phase of labor (from 4 cm dilation to delivery) lasting over 12 hours. The prolonged second stage of labor was defined as the duration of the second stage exceeding 2 hours in nulliparous women without epidural analgesia (16). Arrest of descent was defined as the cessation of progress over 1 hour after the active phase of descent has commenced (17). A nuchal cord refers to the umbilical cord being looped around the fetal neck (16). Due to the retrospective nature of the study, it was not possible to determine the presence of a tight nuchal cord.

Statistical analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test the normality. Factors potentially associated with advanced maternal age were analyzed using either Student's t-test or the Mann-Whitney U test, as appropriate. The differences in proportions between groups were compared using the Chi-square or Fisher's exact test. Descriptive statistics were used to summarize the data and were expressed as mean ± standard deviation for normally distributed continuous variables, median (Q1 - Q3) for skewed continuous variables, and count with the percentage of total for categorical variables. To identify the risk factors associated with advanced maternal age, univariate and multiple logistic regression analyses were performed, and adjusted odds ratios with their confidence intervals were calculated. All covariates with missing data in fewer than 20% of observations and a p-value <0.2 in univariate testing were considered for inclusion in the final multiple regression model and retained if the p-value was <0.05 or if they demonstrated evidence of significant confounding (>10% change in effect size). Highly collinear covariates (correlation coefficient >0.6) were not included together in the final multivariable model. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (Armonk, NY: IBM Corp.) and with a p-value <0.05 considered statistically significant.

Results

During the study period, a total of 16903 deliveries occurred, of which 52 nulliparous pregnant women aged ≥35 years were potentially suitable for inclusion in the study. Also, a total of 487 nulliparous pregnant women aged below 35 years at the delivery time constituted the control group. Table I rep-

Table I: *Maternal demographic characteristics, medical history, laboratory values at the time of ad-mission, additional maternal diseases, and complications of current pregnancy*

	Advanced maternal age group (n=52)	Control group (n=487)	P
Maternal age, years	38.17 ± 2.80	22.72 ± 4.30	**<0.001**
Education, n (%)			
Illiterate	12 (23.1%)	240 (49.3%)	**<0.001***
Primary school	11 (21.2%)	185 (38.0%)	
Middle school	10 (19.2%)	3 (0.03%)	
High school	16 (30.8%)	44 (9.0%)	
University	3 (5.8%)	15 (3.1%)	
Smoking, n (%)	3 (5.8%)	13 (2.7%)	0.187*
ART pregnancies, n (%)	3 (5.8%)	2 (0.4%)	**0.007***
Additional maternal diseases and preg-nancy complications, n (%)			
None	42 (80.8%)	466 (95.7%)	**<0.001***
Gestational diabetes	3 (5.8%)	7 (1.4%)	
Type 2 diabetes	1 (2.0%)	0 (0.0%)	
Preeclampsia	1 (2.0%)	13 (2.7%)	
Chronic hypertension	1 (2.0%)	0 (0.0%)	
Gestational hypertension	2 (3.9%)	1 (0.2%)	
Intrahepatic cholestasis of pregnancy	2 (3.9%)	0 (0.0%)	
Hemoglobin, g/dL	11.53 ± 1.34	11.95 ± 1.50	**0.036**
Anemia, n (%)	14 (27.5%)	111 (22.8%)	0.486
Platelet, /mm3 $\times 10^3$	227.0 (178.0 - 260.5)	246.0 (205.0 - 298.0)	**0.009****
Glucose, mg/dL	81.9 (74.9 - 94.3)	83.0 (73.8 - 93.0)	0.990**
Urea, mg/dL	19.46 ± 9.00	18.00 ± 5.34	0.257
Creatinine, mg/dL	0.56 ± 0.11	0.54 ± 0.08	0.372

*Mean ± Std. Dev. and Median (Q1-Q3). *Fisher's Exact test p-value, **Mann-Whitney U test p-value, and all others from Student's t-test*

resents the maternal demographic characteristics, medical history, laboratory values at the time of admission, additional maternal diseases, and current pregnancy complications. The groups were similar regarding smoking and anemia rates. When we analyzed the educational status of the pregnant women, the proportion of illiterate individuals was significantly higher in the control group (49.3%) than in the AMA group (23.1%, p<0.001). AMA group (5.8%) were more likely to have than the control group (0.04%) to have conceived following ART (p<0.001). The presence of at least one additional maternal disease and pregnancy complication (GDM, type 2 diabetes, chronic hypertension, gestational hypertensive disorders, and intrahepatic cholestasis of pregnancy) was significantly higher in the AMA group (19.2%) than in the younger mothers (4.3%, p<0.001).

Table II presents the delivery records and pregnancy outcomes of the participants. No significant differences were detected between the groups regarding the mean gestational age at birth, birth weight, or the proportion of post-term pregnancy, premature rupture of membranes, prolonged labor, the prolonged second stage of labor, meconium-stained amniotic fluid, small for gestational age fetuses, and fetal gender. The rate of cesarean delivery was significantly higher in the AMA group (67.3%) than in the control group (26.1%, p<0.001). Indications for cesarean delivery during labor are shown in Table II. The main reasons for cesarean delivery were fetal distress, failure to progress/cephalopelvic disproportion, and failed induction in both groups. One case in the control group underwent cesarean delivery because of umbilical cord prolapse, and one case suffered from placental abruption. The differences in the cesarean delivery indications demonstrate a variation between the groups (p<0.001), and fetal distress creates this variation. The incidence of Bishop score ≤6 and the need for IOL was significantly higher in the AMA group (59.6% and 98.1%, respectively) compared to the control group (40.9% and 74.1%, p=0.009 and p<0.001, respectively). The incidence of nuchal cord was significantly higher in the

Table II: *Delivery records and pregnancy outcomes of the participants*

	Advance maternal age group (n=52)	**Control group (n=487)**	**p**
Gestational week at birth	38.0 (37.0-39.5)	38.0 (37.0-39.0)	0.455
Birth weight, g	2970.94 ± 452.19	2977.61 ± 475.32	0.923
Post-term pregnancy, n (%)	2 (3.8%)	23 (4.7%)	1.000*
Premature rupture of membranes, n (%)	12 (23.1%)	106 (21.8%)	0.860
Small for gestational age, n (%)	0 (0.0%)	8 (1.6%)	0.357*
Bishop score ≤6, n (%)	31 (59.6%)	199 (40.9%)	**0.009**
Cesarean section (C/S), n (%)	35 (67.3%)	127 (26.1%)	**<0.001**
Reasons for C/S, n (%)			**<0.001**
Fetal distress	27 (51.9%)	63 (12.9%)	
Failure to progress/cephalopelvic disproportion	5 (9.6%)	43 (8.8%)	
Failed induction	3 (5.8%)	19 (3.9%)	
Umbilical cord prolapse	0 (0.0%)	1 (0.2%)	
Placental abruption	0 (0.0%)	1 (0.2%)	
Fetal gender (male), n (%)	28 (53.8%)	249 (51.1%)	0.709
Induction of labor, n (%)	51 (98.1%)	361 (74.1%)	**<0.001**
I**nduction of labor methods**			
Dinoprostone	26 (51.0%)	63 (17.5%)	
Oxytocin	20 (39.2%)	217 (60.1%)	**<0.001**
Dinoprostone + oxytocine	5 (9.8%)	81 (22.4%)	
Prolonged labor, n (%)	1 (4.3%)	8 (2.2%)	0.422*
Prolonged second stage of labor, n (%)	1 (4.3%)	3 (0.6%)	0.334*
Meconium-stained amniotic fluid	5 (9.6%)	27 (5.6%)	0.222*
Nuchal cord, n (%)	4 (7.7%)	6 (1.2%)	**0.011***
Fetal heart rate monitoring, n (%)			
Category I	24 (46.2%)	339 (69.8%)	**<0.001**
Category II	15 (28.8%)	101 (20.8%)	
Category III	13 (25.0%)	46 (9.5%)	
NICU admission, n (%)	5 (9.6%)	53 (11.1%)	0.750
Neonatal death, n (%)	0 (0.0%)	0 (0.0%)	-
1-min Apgar	8.0 (8.0-8.0)	8.0 (8.0-8.0)	0.857
1-min Apgar <7, n (%)	3 (5.8%)	30 (6.2%)	1.000*
5-min Apgar	9.0 (9.0-9.0)	9.0 (9.0-9.0)	0.905
5-min Apgar <7, n (%)	0 (0.0%)	7 (1.4%)	1.000*
Umbilical cord pH <7, n (%)	0 (0.0%)	6 (4.3%)	1.000*
Postpartum hemorrhage, n (%)	3 (5.8%)	7 (1.4%)	**0.028**

*Mean ± Std. Dev. and Median (Q1-Q3). *Fisher's Exact test p-value, **Mann Whitney U test p-value, and all others from Student's t-test*

AMA group (7.7%) than in the control group (1.2%, p=0.011). While FHR category II or III was observed in 53.8% of cases before labor in the AMA group, these FHR tracings were seen in 30.3% of cases before labor in the control group (p<0.001).

Variables such as ART pregnancies, having at least one additional maternal disease and pregnancy complication, Bishop score ≤6, FHR category II or III, and the presence of a nuchal cord were analyzed as risk factors for CS in advanced maternal age using the univariate logistic model. The results of the multiple logistic model, which was established using six of these significant candidate variables, are also presented in Table III. In the multivariable models established with these variables, each evaluated as an independent risk factor, it was observed that ART pregnancies, the presence of at least one of the aforementioned diseases, and FHR category III encompassed the effect of all other variables. Therefore, in the multivariable models, ART pregnancies increase the CS risk approximately 39 times, the presence of additional maternal disease or pregnancy complication increases this risk 5.34 times, and the presence of FHR category III increases the risk 3.34 times in nulliparous mothers with an advanced age compared to the younger counterparts. The relevant confidence intervals and p-values are summarized in Table III.

Discussion

The current study demonstrates that nulliparous pregnant women aged ≥35 years have a significantly higher risk of CS compared to younger nulliparous women. Additionally, multiple logistic regression analysis identified ART pregnancies, the presence of an additional maternal disease or pregnancy complication, and FHR category III as significant factors associated with an increased risk of CS in nulliparous women aged 35 years and older.

The growing prevalence of first childbearing for women aged 35 years and older over recent decades has led to multiple concerns for clinicians and parents, given the maternal and fetal risks linked to this condition. Consistent with our findings, maternal age has been indicated to be a powerful predictor of CS in nulliparous women in previous studies (15,18). The primary reasons associated with the increased rates of CS in nulliparous women with an AMA are controversial. Hypotheses linking AMA to dystocia include reduced myometrial contractility, fewer oxytocin receptors, and placental vessel atherosclerosis. With age, collagen replaces normal muscle in myometrial arteries, restricting blood flow to the placenta, which may contribute to fetal distress and stalled labor. Additionally, declining myometrial function with age may result in less effective uterine contractions (8,19). However, Teal et al. recently found no significant relationship between AMA and the length of induction duration for nulliparous women even among cases who eventually underwent CS (20). In line with this, the incidence of prolonged labor and prolonged second stage of labor were similar between the groups in our study, suggesting that while AMA is a factor, it may not be the sole determinant, and factors beyond age may influence labor outcomes in nulliparous women.

The Bishop score is a pre-labor assessment method utilized to predict successful labor. Determination of the Bishop score is the most frequently used empirical procedure to evaluate the cervix before IOL (21). Kolkman et al. reported that the Bishop score is a poor predictor for the outcome of induced labor at term and should not be used to decide whether to perform IOL or not (22). Studies demonstrated that certain components of Bishop's score provide limited prognostic value in predicting the failure of IOL. A systematic review concluded that examining a modified version of the Bishop's score (potentially excluding some components and considering parity) could be beneficial (23). In our study, the proportion of Bishop scores ≤6 was significantly higher in the AMA group compared to the control group. However, similarly to the literature, when we performed multivariate analysis, we

Table III: *Multivariate logistic regression analysis results*

	Univariate Logistic Results			Multiple Logistic Results		
	B±S.E.	**OR (95%C.I.)**	**p**	**B±S.E.**	**OR (95%C.I.)**	**p**
ART pregnancies	2.698 ± 0.925	14.84 (2.42-91.00)	**0.004**	3.66 ± 1.24	39.22 (3.39-453.03)	**0.003**
Additional maternal diseases and pregnancy complications	1.512 ± 0.451	4.53 (1.87-10.96)	**0.001**	1.667 ± 0.695	5.34 (1.37-20.87)	**0.016**
Bishop score ≤6	0.759 ± 0.297	2.13 (1.19-3.82)	**0.011**			
NST Class Category I						
NST Class Category II	0.741 ± 0.348	2.09 (1.06-4.15)	**0.033**			
NST Class Category III	1.384 ± 0.379	3.99 (1.90-8.38)	**<0.001**	1.207 ± 0.390	3.34 (1.55-7.18)	**0.002**
Nuchal Cord	1.897 ± 0.663	6.66 (1.81-24.44)	**0.004**			

B: Regression Coefficient, S.E.: Standard Error of Regression Coefficient; OR: Odds Ratio; C.I.: Confidence Intervals of Odds Ratio; ART: Assisted Reproductive Technology; NST: Nonstress Test.

found that the Bishop score did not have a significant effect on the failure of IOL and CS rates, indicating a requirement for refined evaluation tools.

Pregnancies achieved by ART are correlated with a higher risk of obstetric complications necessitating cesarean delivery. Although pregnancy and delivery complications are elevated in ART pregnancies, it remains unclear whether these risks originate directly from ART itself or from underlying factors that both increase the likelihood of requiring ART and predispose to pregnancy complications (24). Also, the strong aim to reduce the development of adverse neonatal outcomes of first childbearing for older women achieved by ART is one of the primary reasons why clinicians may opt for a CS if the IOL process does not progress smoothly. Consistently, we found that the risk of CS was approximately 39 times higher in nulliparous women who conceived through ART.

Many studies have reported a higher incidence of additional maternal diseases and pregnancy complications, such as GDM and preeclampsia among pregnant women of AMA (4,15). These pregnancy complications were also correlated with increased CS rates during labor regardless of parity in all age groups. One possible explanation is that these complications lead to placental insufficiency, resulting in a non-reassuring FHR tracing pattern, leading to a higher CS rate (25,26). In our study, additional maternal diseases and pregnancy complications were associated with an approximately 5-fold increase in the likelihood of undergoing CS.

Regardless of the additional co-morbidities, AMA is found to be an independent risk factor for uteroplacental insufficiency which may lead to antepartum and intrapartum complications. Miller concluded that after excluding several obstetric complications such as gestational hypertensive disorders and placenta previa, fetal distress and CS for fetal distress remained significantly more common in women 35 years or older (27). In line with this, we found that FHR category III is a significant independent risk factor for CS and increases the risk about 3 times in nulliparous women. These results underscore the role of AMA as an independent risk factor for fetal distress and increased CS rates, emphasizing the requirement for vigilant monitoring in this population. One possible explanation for the favorable neonatal outcomes in nulliparous women aged 35 and older in our cohort may be the notably high rate of CS in this group.

The main strengths of our study include access to comprehensive electronic medical records and patient files detailing intrapartum events and precise documentation of the Bishop score for all cases. By selecting patients from a single labor and delivery unit, we minimized variations in healthcare throughout the study period. Moreover, our cohort was not restricted to low-risk individuals; it encompassed all nulliparous women aged 35 and older, enhancing the generalizability of our findings to a diverse patient population. The main limitations of our study include its retrospective design, which may not fully capture all factors influencing the managing obstetrician's decision-making process, and a relatively small sample size. Also, although logistic regression analysis was performed to adjust for the potential influence of additional maternal diseases and pregnancy complications, the inclusion of these confounders may still have introduced residual bias, which could affect the interpretation of the results.

Conclusion

The limited evidence available on maternal age and delivery outcomes in contemporary obstetric practice restricts healthcare providers' ability to effectively counsel AMA cases regarding anticipated delivery outcomes. The risk of CS is considerably higher in nulliparous pregnant women aged 35 years and older when compared to younger counterparts. The major contributors to the CS risk in nulliparous AMA women are ART pregnancies, having at least one additional maternal disease or pregnancy complication, and FHR category III. The findings of this study provide basic knowledge to obstetricians that can assist in informing nulliparous pregnant women aged 35 years and older regarding their average risk of CS in the decision-making process.

Declarations

Ethics approval and consent to participate: All participants signed informed written consent for using data before being enrolled in the study. The study was reviewed and approved by the Diyarbakır Gazi Yasargil Training and Research Hospital Clinical Researches Ethics Committee (approval date: 09.09.2022, number: 165). All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable re-quest.

Competing interests: The authors declare that they have no competing interests.

Funding: This study didn't receive any financial support from any organization, institution, or funding agency.

Acknowledgment: We are grateful to all participants and their families who spent precious time participating in this research program. We are also thankful for the tireless efforts of the research team members.

Authors' contributions: Concept: SCO, EZY, MB; Design: SCO, EZY, MAH; Data Collection or Processing: HEAE, GG, BB, OA; Analysis or Interpretation: SCO, HEAE, GG, BB, OA; Literature Review: SCO, HEAE, GG, BB, OA, EZY, MB, MAH; Writing: SCO; Critical Review: SCO.

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