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Evaluation of first-trimester PAPP-A and β-hCG levels in isolated single umbilical artery pregnancies and their association with adverse perinatal outcomes

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MAIN POINTS

- First-trimester PAPP-A levels below 0.65 MoM were significantly associated with adverse perinatal outcomes (CAPO) in isolated SUA pregnancies.
- β-hCG MoM levels were significantly higher in SUA cases compared to controls, but were not predictive of adverse outcomes.
- PAPP-A showed moderate predictive value (AUC=0.704) and may aid in risk stratification and closer third-trimester surveillance in isolated SUA cases.

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ABSTRACT

Aim: This study aimed to evaluate the association between first-trimester biochemical markers---pregnancy-associated plasma protein A (PAPP-A) and beta-human chorionic gonadotropin (β-hCG)---and adverse perinatal outcomes in pregnancies complicated by isolated single umbilical artery (SUA).

Materials and Methods: This retrospective case-control study was conducted at atertiary perinatology center between January 2023 and January 2025. The study group included 266 pregnant women diagnosed with isolated SUA, and the control group included 266 healthy singleton pregnancies. First-trimester serum PAPP-A and β-hCG MoM values were compared between groups. Composite adverse perinatal outcome (CAPO) was defined as the presence of at least one of the following: preterm birth, fetal growth restriction (FGR), oligohydramnios, polyhydramnios, intrauterine fetal demise (IUFD) or NICU admission.

Results: Although PAPP-A MoM levels were not significantly different between the SUA and control groups, PAPP-A values were significantly lower in SUA cases that developed CAPO ($p<0.001$). ROC analysis revealed that a PAPP-A cut-off <0.65 predicted CAPO with 71.2% sensitivity and 72.2% specificity (AUC=0.704, $p<0.001$). β-hCG MoM levels were higher in SUA cases than controls ($p<0.001$), but no significant difference was found between SUA cases with and without CAPO ($p>0.05$).

Conclusion: Low first-trimester PAPP-A levels may serve as a moderate predictor of adverse perinatal outcomes in isolated SUA pregnancies. PAPP-A may help guide risk stratification and antenatal surveillance intensity in this population.

Keywords: Single umbilical artery, Pregnancy-associated plasma protein-A, Beta-human chorionic gonadotropin, Pregnancy outcome

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INTRODUCTION

Single umbilical artery (SUA) is a condition in which the umbilical cord, which normally contains two arteries and one vein, contains only one artery and one vein [1]. After diagnosis, a detailed fetal anatomical scan should be performed [1,2]. SUA can occur either without any accompanying fetal anomalies (isolated SUA) or with accompanying anomalies. It is observed in approximately 0.5–1.3% of pregnancies [3,4]. SUA frequently coexists with genitourinary and cardiac anomalies [4,5]. In addition, it may also coexist with chromosomal anomalies [4]. Isolated SUA cases have been associated with perinatal outcomes such as low birth weight, preterm birth, and amniotic fluid abnormalities [3,6,7]. Although it is thought that pregnant women with isolated SUA can be monitored with routine obstetric follow-up in clinical practice, some approaches recommend increased fetal monitoring during the third trimester [7].

Pregnancy-associated plasma protein-A (PAPP-A) and the beta subunit of human chorionic gonadotropin (β-hCG) are important glycoproteins secreted by the placenta in early preg-

nancy [8]. PAPP-A begins to be secreted by trophoblasts after implantation, and its level continues to increase throughout pregnancy. Insufficient PAPP-A levels may reduce the effect of insulin-like growth factor, leading to impaired placental development and restricted fetal growth [8]. β-hCG is also a hormone secreted by syncytiotrophoblasts after implantation. It reaches its highest levels at the end of the first trimester and then gradually decreases [9]. High β-hCG levels are associated with increased trophoblast proliferation and invasion, while low β-hCG levels may indicate trophoblastic insufficiency. This condition may increase the risk of complications such as fetal growth restriction (FGR) in later weeks of pregnancy [9]. Recent studies have shown that PAPP- A and free β-hCG may be meaningful biomarkers for the early detection of various pregnancy complications [8,10,11].

Approximately two-thirds of SUA cases are isolated, with no accompanying structural or chromosomal abnormalities. Although isolated SUA is generally considered to have a better prognosis, recent evidence suggests that even in isolated SUA cases, the risk of certain complications due to placental insufficiency may be increased [3,12]. However, the number of studies specifically examining the relationship between first-trimester PAPP-A and β-hCG values in isolated SUA cases and subsequent perinatal outcomes is extremely limited. Therefore, this study aims to evaluate the perinatal prognostic significance of first-trimester biochemical markers in isolated SUA cases.

MATERIALS AND METHODS

This study is a retrospective case-control design conducted at a tertiary perinatology center where approximately 15,000 births occur annually, between January 2023 and January 2025. The study group consisted of women with singleton pregnancies who were diagnosed with isolated single umbilical artery (SUA) during detailed fetal anomaly screening at 20–24 weeks of gestation. The control group was selected from the database at a 1:1 ratio from healthy, structurally unanomalous singleton pregnancies with similar gestational characteristics following these patients. Ethical approval for the study was obtained from the Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee No. 2 (decision number: AEŞH-BADEK2-2025/069 dated 13/05/2025). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria were defined as being between 18 and 40 years of age, having completed first trimester screening tests between 11+0 and 13+6 weeks, and having complete perinatal records. Maternal systemic diseases, fetal aneuploidy or major congenital malformations, suspected congenital infection, tobacco or alcohol use, discontinuation of hospital follow-up, or incomplete data were accepted as exclusion criteria.

All ultrasound examinations, including the diagnosis of isolated single umbilical artery, were performed by experienced perinatologists at our tertiary center using standardized imaging protocols. Although examinations were conducted by more than one operator, formal interobserver variability analysis was not performed. All maternal, obstetric, and neonatal variables were obtained from the hospital's electronic information management system. In this context, maternal age, body mass index, gravida-parity information, obstetric and medical history, and pregnancy complications such as FGR, preterm delivery, amniotic fluid pathologies, and intrauterine fetal death that developed during pregnancy were recorded. First trimester biomarkers PAPP-A and β-hCG MoM levels were obtained from routine screening tests performed between 11+0–13+6 weeks, in accordance with national screening protocols.

Neonatal data included gestational age at delivery, mode of delivery, birth weight, ultrasound-based estimated fetal weight, 1- and 5-minute Apgar scores, neonatal intensive care unit (NICU) admission, and Composite Adverse Perinatal Outcome (CAPO). CAPO was defined as the presence of at least one of the following: preterm birth (<37 weeks), fetal growth restriction (birth weight <10th percentile), oligohydramnios, polyhydramnios, NICU admission, and intrauterine fetal death.

First-trimester serum PAPP-A and β-hCG levels were obtained from routine prenatal screening tests performed at the institutional laboratory using standardized automated immunoassay systems in accordance with national screening protocols.

The sample size was estimated a priori using G*Power software, assuming an alpha level of 0.05 and a statistical power of 80%, which indicated that a minimum of 116 participants per group would be sufficient. Ultimately, a total of 532 pregnancies were included in the study, comprising 266 isolated SUA cases and 266 healthy controls. The precision of the study findings is reported using effect estimates and their corresponding 95% confidence intervals, rather than post-hoc power calculations.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Macintosh, Version 25.0 (IBM Corp., Armonk, NY, USA). The distribution characteristics of continuous variables were assessed using the Kolmogorov–Smirnov test. Variables showing a normal distribution were defined as mean ± standard deviation, while variables not showing a normal distribution were defined as median (interquartile range). Student's t-test or Mann–Whitney U test was used for intergroup comparisons depending on the distribution characteristics. Categorical variables were expressed as numbers and percentages, and comparisons were made using Pearson's chi-square test or Fisher's exact test when appropriate. ROC curve analysis was performed to evaluate the predictive performance of first-trimester biomarkers, particularly PAPP-A MoM levels, for CAPO development in isolated SUA cases. The cutoff

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Table 1. Demographic and clinical characteristics of the groups.

	SUA group n=266	Control group n=266	p-value
Maternal age (years)	28.9±4.6	28.01±4.9	0.296[a]
Gravidity	2(2)	2(2)	0.256[b]
Parity	2(2)	2(1)	0.165[b]
BMI (kg/m^2)	30.94±4.8	30.05±4.9	0.793[a]
Gestational age at delivery (weeks)	38 (1)	39.1 (1.6)	**<0.001[b]**
Birth weight (g)	3006.9±475.4	3268.5±360.4	**<0.001[a]**
Cesarean section, n(%)	110 (41.3)	119 (44.7)	0.135[c]
Apgar score at 1st minute	9 (1)	9 (0)	**<0.001[b]**
Apgar score at 5th minute	10 (1)	10 (0)	**<0.001[b]**
Fetal growth restriction, n (%)	11 (4.1)	0 (0)	**<0.001[d]**
Preterm labor, n (%)	32 (12.0)	0 (0)	**<0.001[d]**
Oligohydramnios, n (%)	15 (5.6)	0 (0)	**<0.001[d]**
Polyhydramnios, n (%)	20 (7.5)	0 (0)	**<0.001[d]**
IUFD, n (%)	4 (1.5)	0 (0)	**<0.001[d]**
NICU admission, n (%)	25 (9.4)	34 (12.7)	0.226[c]
Composite adverse outcomes, n (%)	91 (34.2)	53 (19.9)	**<0.001[c]**

Data are expressed as n (%), mean ± SD, or median (interquartile range), where appropriate. A p value of <0.05 indicates statistical significance. Statistically significant values are in bold. a: Student's t test, b: Mann–Whitney U test, c: Pearson χ^2 test, d: Fisher's exact test (where appropriate). BMI: body mass index, IUFD: intrauterine fetal demise, NICU: neonatal intensive care unit.

value showing the best discriminatory power was determined using the Youden index. p<0.05 was accepted as the threshold for statistical significance in all analyses. Patients with missing data were not included in the analyses.

RESULTS

The demographic and clinical characteristics of the study population are summarized in Table 1. Maternal age, gravida, parity, and BMI did not differ significantly between the SUA and control groups (p>0.05). However, gestational age at delivery was significantly earlier in pregnancies with SUA (38.0 [1.0] weeks vs. 39.1 [1.6] weeks, p<0.001). Similarly, birthweight was significantly lower in the SUA group (3006.9±475.4 g vs. 3268.5±360.4 g, p<0.001). Several obstetric complications—including fetal growth restriction (4.1% vs. 0%), preterm labor (12.0% vs. 0%), oligohydramnios (5.6% vs. 0%), polyhydramnios (7.5% vs. 0%), and intrauterine fetal demise (1.5% vs. 0%)—occurred more frequently in the SUA group (all p<0.001). The 1st- and 5th-minute Apgar scores were also significantly lower among SUA pregnancies (p<0.001). NICU admission rates were similar between groups (p=0.226). Composite adverse perinatal outcomes were significantly more common in the SUA group (34.2% vs. 19.9%, p<0.001).

Table 2. Comparison of parameters used for first trimester screening in groups.

	SUA group n=266	Control group n=266	p-value
GA at screening (weeks)	12.1 (1)	12.1 (1)	0.996[b]
β-hCG MoM	1.08 (0.84)	0.80 (0.78)	**<0.001[b]**
PAPP-A MoM	0.97 (0.77)	0.97 (0.76)	0.308[b]
NT MoM	0.79 (0.17)	0.71 (0.26)	**<0.001[b]**

[b]: Mann-Whitney U, β-hCG: Beta-human chorionic gonadotropin, PAPP-A: Pregnancy associated plasma protein A, NT: Nuchal translucency, mom: A multiple of the median.

Table 3. Comparison of parameters used for first-trimester screening in SUA cases with andwithout adverse neonatal outcome.

	SUA group n=266	Control group n=266	p-value
GA at screening (weeks)	12 (0)	12 (1)	0.184[b]
β-hCG MoM	1.16 (0.74)	1.18 (1.84)	0.713[b]
PAPP-A MoM	0.63 (0.85)	1.19 (0.82)	**<0.001[b]**
NT MoM	0.77 (0.16)	0.79 (0.17)	0.830[b]

[b]: Mann-Whitney U, β-hCG: Beta-human chorionic gonadotropin, PAPP-A: Pregnancy associated plasma protein A, NT: Nuchal translucency, mom: A multiple of the median.

First-trimester screening parameters are presented in Table 2. The gestational age at the time of screening did not differ between groups (p=0.996). β-hCG MoM levels were significantly higher in the SUA group compared with controls (1.08 [0.84] vs. 0.80 [0.78], p<0.001). PAPP-A MoM values were comparable between groups (p=0.308). Nuchal translucency MoM, however, was significantly higher in the SUA group (0.79 [0.17] vs. 0.71 [0.26], p<0.001), indicating altered early fetal and placental characteristics in SUA pregnancies.

A comparison of SUA cases with and without composite adverse perinatal outcome is shown in Table 3. Screening gestational age and β-hCG MoM levels did not differ significantly between CAPO-positive and CAPO-negative SUA pregnancies (p>0.05). In contrast, PAPP-A MoM values were markedly lower in pregnancies that experienced CAPO (0.63 [0.85] vs. 1.19 [0.82], p<0.001). NT MoM values were similar between the groups (p=0.830). These findings suggest that lower first-trimester PAPP-A levels may serve as an early indicator of adverse perinatal outcomes in isolated SUA cases.

The diagnostic performance of first-trimester PAPP-A MoM

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Table 4. Diagnostic performance of first-trimester PAPP-A MoM levels for predictingcomposite adverse perinatal outcomes in isolated SUA pregnancies.

	Cut-off*	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)	p-value
First trimester PAPP-A (MoM)	<0.65	71.2% (61.8--78.8)	72.2% (64.9--78.7)	63.3% (54.4-71.4)	78.8% (71.4-84.6)	0.704 (0.634-0.774)	**<0.001**

*Cut-off value determined by Youden's index. AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; PAPP-A: pregnancy-associated plasma protein A; β-hCG: betahuman chorionic gonadotropin; CAPO: composite adverse perinatal outcome; SUA: single umbilical artery.

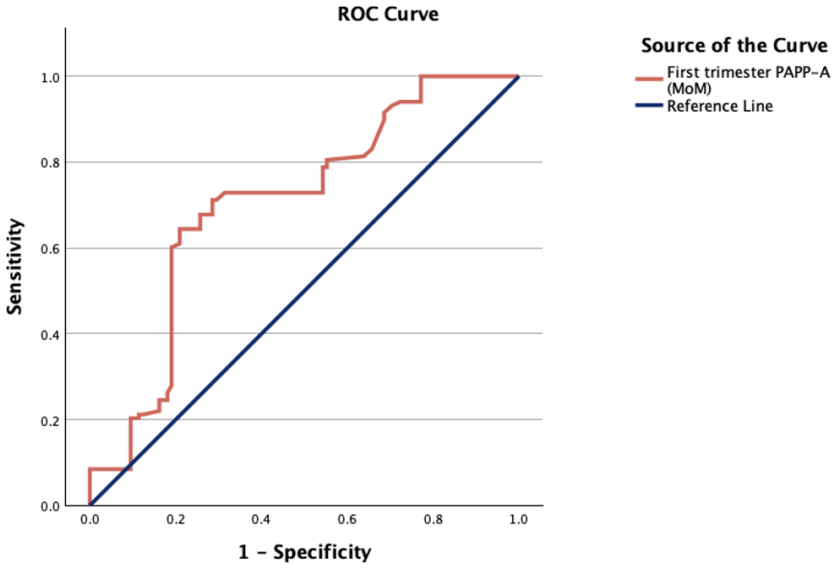

Figure 1. Receiver operating characteristic (ROC) curve for first-trimester PAPP-A levels inpredicting CAPO among pregnancies with SUA.

levels for predicting CAPO is presented in Table 4 and illustrated in Figure 1. ROC analysis demonstrated that a PAPP-A cutoff of <0.65 yielded a sensitivity of 71.2% and a specificity of 72.2%, with an AUC of 0.704 (95% CI: 0.634–0.774, p<0.001). These results indicate a moderate predictive capacity of first-trimester PAPP-A levels for identifying SUA pregnancies at increased risk for adverse perinatal outcomes. At the selected cut-off value (PAPP-A <0.65), the corresponding positive and negative predictive values were 63.3% and 78.8%, respectively.

DISCUSSION

This study investigated the importance of first-trimester screening parameters (β-hCG & PAPP-A) in predicting perinatal outcomes in patients diagnosed with isolated SUA. Isolated SUA usually progresses to delivery without complications. However, predicting which patients are at risk for poor perinatal outcomes can be very helpful to clinicians. In this regard, our study showed that low PAPP-A levels in patients with isolated SUA are associated with the development of CAPO (p<0.001). In the advanced analysis (ROC), it was shown that a PAPP-A MoM below 0.65 can predict CAPO with 71.2% sensitivity and 72.2% specificity (AUC=0.704), indicating that this biomarker has moderate predictive value from a clinical perspective. In contrast, although β-hCG MoM values were higher in isolated SUA cases compared to the control group, no significant difference was found between β-hCG levels in predicting CAPO development (p>0.05). These results suggest that PAPP-A levels in the first trimester may be a stronger marker for perinatal risk classification in isolated SUA pregnancies.

Although a statistically significant difference in NT MoM values was observed between isolated SUA pregnancies and controls, the measured values remained within the normal reference range. Therefore, this finding may not necessarily indicate a clinically relevant abnormality. Mild variations in NT measurements have been reported in association with placental or hemodynamic adaptations in early pregnancy, even in the absence of structural or chromosomal anomalies [13]. In isolated SUA cases, such subtle changes may reflect physiological variability rather than pathological processes. Nevertheless, the clinical implications of this finding are uncertain, and further prospective studies are needed to clarify its significance.

PAPP-A is a placenta-derived glycoprotein secreted by syncytiotrophoblasts and plays a critical role in placental development and fetal growth [14]. Low PAPP-A levels in the first trimester may be associated with insufficient trophoblast invasion and incomplete transformation of the uterine spiral arter-

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ies. These alterations may result in increased resistance in the uteroplacental circulation and chronic placental hypoperfusion. Consequently, reduced placental volume and impaired nutrient exchange may contribute to adverse outcomes such as fetal growth restriction [8,9]. Parallel to this mechanism, Turner et al. found that low PAPP-A levels were associated with preeclampsia, preterm birth, and low birth weight [14]. Similarly, Livrinova et al. also demonstrated a relationship between low PAPP-A and these pregnancy complications [15]. Pummara et al. also emphasized that the risk of preterm delivery is high in patients with low PAPP-A [16].

Morris et al. showed that low PAPP-A levels increased the development of CAPO by 3.31 times. In this large-scale meta-analysis, which included data from more than 175,000 pregnancies, it was emphasized that although low PAPP-A in the first trimester was significantly associated with complications such as preeclampsia and FGR, its positive predictive value alone remained low [17]. In our study, PAPP-A levels did not show a significant difference was observed between the control group and the isolated SUA group. However, when evaluating SUA cases individually, low PAPP-A levels were found to be associated with adverse perinatal outcomes. The AUC value of 0.704 obtained from the ROC analysis in our study is consistent with existing evidence indicating that PAPP-A has limited predictive power when used alone. However, PAPP-A may still be a valuable tool for identifying high-risk pregnancies among patients diagnosed with isolated SUA. Its clinical utility may be enhanced when used in combination with other clinical and biochemical parameters. In this context, first-trimester PAPP-A demonstrates a moderate discriminative performance (AUC = 0.704). Accordingly, PAPP-A may be a valuable adjunct for identifying high-risk pregnancies among patients with isolated SUA, particularly for early risk stratification and tailoring antenatal surveillance rather than serving as a standalone predictor.

In our study, mean first-trimester β-hCG levels in isolated SUA cases tended to be higher than in healthy pregnancies. The number of studies directly comparing first-trimester β-hCG values with SUA cases in the literature is quite limited. A study including 56 patients diagnosed with SUA or velamentous placenta (27 SUA, 29 velamentous placenta) reported that maternal serum β-hCG values may be relatively high compared to the control group [18]. The increase in β-hCG levels observed in isolated SUA cases may reflect enhanced trophoblast activity within the placenta as a compensatory response to the presence of a single umbilical artery [19]. This adaptive mechanism may stimulate syncytiotrophoblast function and lead to increased β-hCG secretion. In contrast, Tulek et al. found isolated SUA cases to be associated with low PAPP-A, but showed no significant difference in β-hCG levels [19]. A study published in 2023 showed that low initial β-hCG levels after transfer in IVF pregnancies were associated with subsequent placental abnormalities, and that the incidence of SUA was significantly higher in this group [20]. However, in that study, β-hCG levels were measured at the time of initial pregnancy detection rather than during the first-trimester screening period. Therefore, the discrepancy between their findings and ours may be attributable to differences in the timing of measurement.

In our study, β-hCG levels were not found to be significantly predictive of adverse perinatal outcomes in cases with SUA. This finding is consistent with the general consensus in the literature; the use of free β-hCG as a predictor of placental problems is unclear and has not been found to be reliable on its own [21]. Parry et al. showed that levels of many placental proteins, including β-hCG, in early pregnancy are associated with adverse pregnancy outcomes. However, they emphasized that these analytes alone are not sufficient to predict CAPO in regression models [22]. Although elevated β-hCG levels may be observed in isolated SUA cases, available data suggest that this finding alone is not indicative of poor perinatal outcomes. In conclusion, the current literature agrees that β-hCG changes observed in isolated SUA cases are largely due to placenta- derived physiological/pathophysiological mechanisms. Prospective studies are needed to better understand these mechanisms.

A strength of this study is that it focused exclusively on pregnancies with isolated single umbilical artery and compared them with a control group of pregnancies without identified structural anomalies. This approach allowed us to evaluate perinatal outcomes associated with isolated SUA while minimizing the influence of major confounding conditions. Previous studies investigating the relationship between isolated SUA and first-trimester biochemical markers such as PAPP-A and β-hCG are limited. In this context, our findings add to the existing literature by providing additional data on the potential association between these markers and adverse perinatal outcomes in isolated SUA pregnancies.

Nevertheless, the retrospective and single-center nature of this study represents an important limitation and may restrict the generalizability of the findings. In addition, although the diagnosis of isolated single umbilical artery was based on standardized ultrasound protocols and performed by experienced perinatologists, ultrasound-based assessment may be operator-dependent, and a formal evaluation of interobserver variability was not conducted. First-trimester biochemical markers were obtained from routine laboratory records, and therefore potential measurement variability related to laboratory conditions and assay performance cannot be entirely excluded. Furthermore, composite adverse perinatal outcome (CAPO) was used as a composite endpoint, and the relative contribution of each individual component may differ. Finally, although data regarding the association between isolated SUA and first-trimester biochemical markers such as PAPP-A and β-hCG remain limited in the literature, the proposed cut-off values derived from this study should be interpreted with caution. Therefore, prospective, multicenter studies with larger and more diverse populations are war-

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ranted to validate these cut-off values, confirm their clinical applicability, and establish robust evidence- based recommendations for the management of isolated SUA pregnancies.

CONCLUSION

This study demonstrates that low first-trimester PAPP-A levels in pregnancies complicated by isolated single umbilical artery are associated with an increased risk of adverse perinatal outcomes. Although the predictive performance of PAPP-A is moderate, it may serve as a useful adjunct for early risk stratification and guiding antenatal surveillance intensity in this population. In contrast, first-trimester β-hCG levels were not predictive of adverse perinatal outcomes in isolated SUA pregnancies. Further prospective, multicenter studies are warranted to validate these findings and clarify their clinical applicability.

Ethics Committee Approval: Ethical approval for the study was obtained from the Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee No. 2 (decision number: AEŞH-BADEK2-2025/069 dated 13/05/2025).

Informed Consent: It was not deemed necessary due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions: MAO: conception, design, materials, data collection and processing, analysis and interpretion, literatüre review, writing, critical review; RD: materials, analysis and interpretion, literatüre review; DDB: materials, analysis and interpretion, literatüre review; FDK: design, data collection and processing, analysis and interpretion; İA: materials, data collection and processing, analysis and interpretion; NVT: conception, design, data collection and processing; ATÇ: conception, design, supervision.

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