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First-Trimester Prediction of Trisomy 21 Using the Nuchal Translucency to Maxillary Length Ratio: Preliminary Observations

Merve Dizdar

mervedizdar@gmail.com

Umraniye Training and Research Hospital

Osman Eren Çetinkaya

Umraniye Training and Research Hospital

İlgi Esen

Bilim University

Serkan Türedi

Umraniye Training and Research Hospital

İbrahim Kale

Umraniye Training and Research Hospital

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Abstract

Background

Increased nuchal translucency (NT) is an established first-trimester marker for trisomy 21, whereas the diagnostic value of fetal maxillary length alone remains uncertain. This study evaluated whether the NT-to-maxillary length ratio could provide additional proportional information for first-trimester prediction of trisomy 21.

Methods

This retrospective matched cohort study included singleton pregnancies assessed at 11 to 14 weeks of gestation between January 2017 and December 2025 at a tertiary referral center. Twelve fetuses with cytogenetically confirmed trisomy 21 were compared with 24 low-risk controls matched 1:2 by maternal age and crown-rump length (CRL). Standard first-trimester ultrasound measurements were reviewed, and maxillary length was measured retrospectively on stored midsagittal fetal profile images. Group comparisons, regression analysis, receiver operating characteristic (ROC) analysis, bootstrap resampling, and logistic regression were performed.

Results

NT and the NT/maxillary length ratio were significantly higher in fetuses with trisomy 21 than in controls, whereas maxillary length alone did not differ significantly. The areas under the ROC curve were 0.905 for NT and 0.927 for the NT/maxillary length ratio. The difference between these AUC values was not statistically significant ($p = 0.522$). The ratio remained associated with trisomy 21 after adjustment for CRL.

Conclusions

The first-trimester NT/maxillary length ratio was increased in fetuses with trisomy 21 and demonstrated good discriminatory performance in this preliminary cohort, but it was not statistically superior to NT alone. Larger prospective studies are required before this ratio can be recommended for clinical use.

Background

Trisomy 21 (Down syndrome) is the most common autosomal trisomy, accounting for approximately 95% of Down syndrome cases and occurring in approximately 1 in 700 to 800 live births. It is associated with a wide spectrum of systemic and structural abnormalities, highlighting the importance of early antenatal detection and risk stratification.1

The characteristic facial phenotype of trisomy 21 was first described by John Langdon Down in 1866.2 These features include epicanthic folds, oblique palpebral fissures, a depressed nasal bridge, an upturned nose, reduced mandibular and maxillary dimensions, midfacial hypoplasia, impaired craniofacial growth, and a relatively short facial profile.3 Although these craniofacial characteristics are well established postnatally, their identification during the first trimester using ultrasonography remains challenging. Consequently, several sonographic soft markers have been developed to improve early screening performance.4

Among these markers, increasing attention has been directed toward fetal facial profile assessment. Previous studies have demonstrated that craniofacial abnormalities in trisomy 21 are closely related to disturbances in maxillary development.5 Shortened maxillary length has been proposed as a first-trimester marker for trisomy 21, and postnatal cephalometric studies also support maxillary underdevelopment in individuals with Down syndrome.6,7

Maxillary length correlates with gestational age and CRL, reflecting its role as a developmental parameter.6,8,9 A relationship between maxillary length and established markers, including NT and nasal bone assessment, has also been reported, with shorter maxillary measurements observed in fetuses with trisomy 21, particularly when the nasal bone is absent.6

Despite these findings, the clinical utility of maxillary length as an isolated marker remains limited because of overlap between affected and unaffected populations. Recent advances in prenatal screening have therefore focused on composite or ratio-based markers that integrate multiple anatomical features to improve diagnostic accuracy. Similar approaches have been applied to other fetal facial markers, including the prenasal thickness-to-nasal bone ratio and the prefrontal space ratio.4

In this context, the NT/maxillary length ratio is a novel parameter that integrates a well-established soft-tissue marker with a craniofacial skeletal measurement. By normalizing NT relative to maxillary size, this ratio may provide additional anatomical context beyond individual measurements alone. This study aimed to evaluate the performance of the NT/maxillary length ratio in predicting trisomy 21 in the first trimester and to assess its potential role as an adjunctive screening marker.

Methods

This retrospective matched cohort study was conducted at a tertiary high volume training and research hospital. The study included singleton pregnancies that underwent first-trimester evaluation in the perinatology unit between 11 and 14 weeks of gestation from January 2017 to December 2025. Data were obtained from the hospital electronic registry system. The study protocol was approved by the Institutional Ethics Committee (approval number 242), and the requirement for informed consent was waived because of the retrospective design.

From an initial cohort of 876 singleton pregnancies with available first-trimester ultrasound records, cases with chromosomal abnormalities were identified through linkage with invasive diagnostic test

results documented in the institutional database. Invasive procedures had been performed because of increased risk identified during first-trimester screening. Among the confirmed trisomy 21 cases, chorionic villus sampling was performed in 11 pregnancies at 13 to 14 weeks of gestation, and amniocentesis was performed in one pregnancy at 17 weeks of gestation. Maternal cell contamination assessment was performed for all 12 trisomy 21 cases in accordance with institutional policy. These 12 fetuses with confirmed trisomy 21 constituted the study group. Pregnancies with other chromosomal abnormalities, multiple gestations, missing ultrasound measurements, or incomplete outcome data were excluded. All pregnancies in the trisomy 21 group were terminated after genetic counseling.

The control group was derived from the same cohort of singleton pregnancies that had no sonographic markers or screening test results suggestive of increased risk for chromosomal anomalies and that did not undergo invasive diagnostic procedures. Only pregnancies resulting in delivery at our institution with healthy neonates and no congenital anomalies or postnatal evidence of chromosomal abnormalities were included. Cases with complete first-trimester ultrasound data, uneventful antenatal follow-up, and confirmed normal postnatal outcomes were eligible for inclusion. Twenty-four low-risk healthy pregnancies were selected as controls using a 1:2 matching ratio based on maternal age and CRL. Because of the preliminary design and the rarity of cytogenetically confirmed trisomy 21 in the eligible cohort, no formal a priori sample size calculation was performed; all eligible trisomy 21 cases during the study period were included.

Ultrasound examination and diagnostic procedures

Invasive diagnostic procedures, including amniocentesis and chorionic villus sampling, were performed in pregnancies identified as high risk for chromosomal abnormalities based on first-trimester screening. Indications for invasive testing included increased NT, abnormal combined screening results including maternal serum biomarkers, the presence of sonographic soft markers, or maternal request after genetic counseling.

All ultrasonographic examinations were performed transabdominally by two experienced perinatology specialists using a high-resolution ultrasound system (Voluson E6; GE Healthcare, Zipf, Austria). Standard first-trimester measurements, including CRL, NT, and nasal bone assessment, were obtained in accordance with established guidelines.10,11 Maxillary length was measured according to the method described by Cicero et al.6

Maxillary length was measured retrospectively from stored ultrasound images. Midsagittal plane images of the fetal profile were reviewed, and only images with adequate visualization of the maxilla and mandible were included. The maxillary bone was identified, and its length was measured as a linear distance along the maxilla, excluding the mandibular ramus and condylar process. Measurements were performed on archived images using the system digital caliper tools (Fig. 1).

Statistical analysis

Statistical analyses were performed using Stata version 17 (StataCorp LLC, College Station, TX, USA). Continuous variables were expressed as mean (standard deviation), and categorical variables were expressed as number (percentage).

Given the relatively small sample size, nonparametric methods were preferred for group comparisons where appropriate. The distribution of continuous variables was assessed using visual inspection and the Shapiro-Wilk test. For comparisons between the trisomy 21 and control groups, the Mann-Whitney U test was used for nonnormally distributed variables, whereas the independent-samples t test was used when the normality assumption was met. Categorical variables were compared using Fisher exact test because of small cell counts.

The association between maxillary length and CRL was evaluated using linear regression analysis within each group. Regression coefficients, 95% confidence intervals (CIs), and coefficients of determination were reported.

ROC curve analysis was performed to assess the diagnostic performance of NT, maxillary length, and the NT/maxillary length ratio. Areas under the curve (AUCs) with 95% CIs were calculated using nonparametric methods appropriate for small sample sizes. Bootstrap resampling with 2000 repetitions was additionally performed to assess the stability of the ROC estimates. ROC comparison analysis was conducted to compare the predictive performance of NT alone and the NT/maxillary length ratio.

Logistic regression analysis was used to evaluate the association between the NT/maxillary length ratio and trisomy 21. To improve interpretability, the ratio was scaled per 0.1-unit increase. Given the limited sample size, models were restricted to a small number of predictors to reduce overfitting. Multivariable analysis was performed with adjustment for CRL. Additional models including NT and maxillary length simultaneously were constructed to assess their independent effects. A two-sided p value < 0.05 was considered statistically significant.

Results

Among 876 singleton pregnancies evaluated during the study period, cases with available first-trimester ultrasound records and documented pregnancy outcomes were screened for eligibility. A total of 458 pregnancies with incomplete ultrasound images or missing outcome data were excluded. Invasive diagnostic test records were then reviewed to identify fetuses with chromosomal abnormalities. Twelve pregnancies with confirmed trisomy 21 constituted the study group. From the remaining low-risk singleton pregnancies, those without invasive testing indications, without sonographic or biochemical markers suggesting increased risk for trisomy 21, and with delivery at our institution without postnatal evidence of trisomy 21 were considered eligible for the control group. Twenty-four controls were selected using a 1:2 matching ratio based on maternal age and CRL (Fig. 2).

Maternal age, gestational age, and CRL were comparable between groups. The mean maternal age was 32.5 (5.0) years in the trisomy 21 group and 32.2 (4.68) years in the control group, with no statistically

significant difference (p = 0.83). Gestational age was similar between groups (12.92 [1.08] vs 12.83 [1.00] weeks; p = 0.82; 95% CI, -0.66 to 0.83), as was CRL (71.7 [12.5] mm vs 71.3 [12.5] mm; p = 0.75; 95% CI, -8.52 to 9.42). NT measurements were significantly higher in the trisomy 21 group than in controls (4.25 [2.18] mm vs 1.48 [0.46] mm; p < 0.001; 95% CI, 1.84 to 3.70). Maxillary length did not differ significantly between groups (7.63 [1.73] mm vs 7.88 [1.84] mm; p = 0.69; 95% CI, -1.55 to 1.04). The NT/maxillary length ratio was significantly higher in the trisomy 21 group (0.576 [0.312] vs 0.196 [0.071]; p < 0.001; 95% CI, 0.25 to 0.51). Categorical comparisons using Fisher exact test showed that nulliparity was less frequent in the trisomy 21 group (0/12 vs 7/24; p = 0.04). Nasal bone presence did not differ significantly between groups (11/12 vs 24/24; p = 0.15) (Table 1).

Table 1
Baseline demographic and sonographic characteristics

Maternal age, years, mean (SD)	**Trisomy 21 group (n = 12)**	**Control group (n = 24)**	**p value‡**	**95% CI†**
	32.5 (5)	**32.2 (4.68)**	**0.83**	**-**
Gestational age, weeks, mean (SD)	12.92 (1.08)	12.83 (1.00)	0.82	-0.66, 0.83
CRL, mm, mean (SD)	71.7 (12.51)	71.3 (12.47)	0.75	-8.52, 9.42
NT, mm, mean (SD)	4.25 (2.18)	1.48 (0.46)	< 0.001	1.84, 3.70
Nulliparous	0/12	7/24	0.04	-
Nasal bone present	11/12	24/24	0.15	-
Maxillary length, mm, mean (SD)	7.63 (1.73)	7.88 (1.84)	0.69	-1.55, 1.04
NT/maxillary length ratio, mean (SD)	0.576 (0.312)	0.196 (0.071)	< 0.001	0.25, 0.51
Values are presented as mean (SD) or n/N, as indicated in the variable column.				
† 95% CIs refer to between-group differences where available; dashes indicate that the interval was not calculated or was not applicable.				
‡ Continuous variables were compared using the Mann-Whitney U test or independent-samples t test, as appropriate; categorical variables were compared using Fisher exact test.				
Abbreviations: CI, confidence interval; CRL, crown-rump length; NT, nuchal translucency; SD, standard deviation.				

Regression analysis demonstrated a positive association between maxillary length and CRL in both groups. In the trisomy 21 group, maxillary length increased by 0.123 mm for each 1-mm increase in CRL (95% CI, 0.080 to 0.167) (Fig. 3), whereas in the control group, the increase was 0.101 mm for each 1-mm increase in CRL (95% CI, 0.053 to 0.148) (Fig. 4).

ROC analysis demonstrated good discriminatory performance for both NT and the NT/maxillary length ratio in predicting trisomy 21 (Fig. 5). The AUC was 0.905 for NT alone and 0.927 for the NT/maxillary length ratio. However, ROC comparison analysis demonstrated that the difference between the two AUC values was not statistically significant (p = 0.522). The empirically derived cutoff value for the NT/maxillary length ratio was approximately 0.19, yielding limited specificity in this sample. Bootstrap resampling with 2000 repetitions was performed to assess the stability of the ROC estimates.

When scaled per 0.1-unit increase, the NT/maxillary length ratio was associated with higher odds of trisomy 21 (odds ratio [OR], 5.78; 95% CI, 1.51 to 22.14; p = 0.010)(Table 2). Owing to the small sample size and wide CI, this estimate should be interpreted cautiously. This association remained significant after adjustment for CRL (OR, 5.73; 95% CI, 1.45 to 22.65; p = 0.013)(Table 2), whereas CRL was not independently associated with outcome (p = 0.96).

Table 2
Regression, logistic regression, and receiver operating characteristic analyses evaluating the association between first-trimester sonographic parameters and trisomy 21

Analysis	**Estimate†**	**95% CI**	**p value**
CRL-maxillary length association in trisomy 21 group	0.123	0.080 to 0.167	< 0.001
CRL-maxillary length association in control group	0.101	0.053 to 0.148	< 0.001
NT AUC	0.905	-	-
NT/maxillary length ratio AUC	0.927	-	-
ROC comparison: NT vs NT/maxillary length ratio	-	-	0.522
Logistic regression: NT/maxillary length ratio and trisomy 21	OR, 5.78	1.51 to 22.14	0.010
CRL-adjusted logistic regression: NT/maxillary length ratio and trisomy 21	OR, 5.73	1.45 to 22.65	0.013
† Regression coefficients (β) represent the change in maxillary length (mm) per 1-mm increase in CRL. Logistic regression estimates are ORs per 0.1-unit increase in the NT/maxillary length ratio. AUC estimates were obtained from ROC analysis.			
Dashes indicate that the measure was not reported or was not applicable for the corresponding analysis.			
Abbreviations: AUC, area under the curve; CI, confidence interval; CRL, crown-rump length; NT, nuchal translucency; OR, odds ratio; ROC, receiver operating characteristic; SD, standard deviation.			

When NT and maxillary length were included in the same model, NT remained significantly associated with trisomy 21 (p = 0.007), whereas maxillary length was not independently associated with trisomy 21 (p = 0.16).

Discussion

This study demonstrates that the NT/maxillary length ratio is significantly elevated in first-trimester fetuses with trisomy 21 and shows good overall discriminatory performance. Although maxillary length alone was not significantly different between groups, the ratio remained associated with trisomy 21 after adjustment for CRL. These findings support the hypothesis that composite markers integrating soft-tissue and skeletal parameters may provide additional anatomical context in first-trimester risk assessment.

Maxillary hypoplasia is a well-recognized feature of trisomy 21 and reflects abnormal craniofacial development.5,7,12 Previous studies have reported shorter maxillary length in affected fetuses, particularly in the first trimester, and have demonstrated its correlation with gestational age and CRL.6,13 However, the clinical utility of maxillary length as a standalone screening marker remains limited because of overlap with unaffected populations and relatively small effect sizes.6,13,14 Our findings are consistent with these observations, as maxillary length alone did not differ significantly between groups.

Previous studies evaluating facial skeletal measurements have reported relatively modest discriminatory performance. Hoopmann et al. demonstrated that although maxillary measurements may be shorter in aneuploid fetuses, only a minority of cases fall below clinically useful thresholds.14 In the present study, no significant difference in absolute maxillary length was observed between groups, further supporting the limited standalone utility of this parameter.

NT remains one of the most robust first-trimester markers for trisomy 21.11 In our cohort, NT demonstrated excellent discriminative performance, with an AUC greater than 0.90, and remained associated with trisomy 21 in multivariable analysis. Although the NT/maxillary length ratio demonstrated a numerically higher AUC than NT alone, ROC comparison analysis showed that this difference was not statistically significant. These findings suggest that NT itself largely drives the ratio predictive performance, whereas maxillary length may provide complementary anatomical information rather than independent discriminatory power.

The concept of combining facial profile markers into ratio-based indices has previously been shown to improve discrimination between chromosomally normal and abnormal fetuses.15,16 The absence of a significant difference in absolute maxillary length despite a significant difference in the NT/maxillary length ratio suggests that relative craniofacial proportionality may be more informative than isolated skeletal measurements alone. This finding supports the concept that trisomy 21 may affect coordinated craniofacial development rather than producing uniformly reduced maxillary dimensions during the first trimester. Normalization approaches that integrate soft-tissue and skeletal parameters may therefore better reflect subtle developmental alterations than single measurements evaluated independently.

Histogram-based comparisons further supported this interpretation. Although CRL distributions were similar between groups because of matching, NT values were shifted toward higher measurements in

trisomy 21, whereas maxillary length showed a tendency toward lower values. The ratio amplified these opposing trends, resulting in improved separation between affected and unaffected populations.

Despite this, the NT/maxillary length ratio should not be interpreted as a replacement for NT. Rather, it may serve as a proportional adjunctive parameter that incorporates anatomical context into the measurement. Similar normalization approaches have been applied in other facial markers, such as the prenasal thickness-to-nasal bone ratio and the prefrontal space ratio, which combine independent features of trisomy 21 to improve detection rates.15,16

From a clinical perspective, the NT/maxillary length ratio may be most relevant for future investigation in borderline or intermediate-risk cases in which additional anatomical context could be useful. However, the limited specificity observed at the empirically derived cutoff limits its immediate clinical applicability. Therefore, this cutoff value should not be used for clinical decision-making without external validation.

The strengths of this study include the matched design, standardized first-trimester measurements, and detailed statistical analysis, including regression and ROC modeling. The relatively small sample size is an important limitation and may reduce statistical power and increase the risk of type II error, particularly for variables such as maxillary length. In addition, maxillary length was assessed only during the first trimester, and the findings may not be generalizable to later gestational ages. Because craniofacial growth is dynamic throughout pregnancy, longitudinal changes in maxillary development could not be evaluated. The retrospective measurement of maxillary length on stored images may also introduce measurement bias and limits assessment of interobserver reproducibility. These findings should therefore be considered preliminary and interpreted with caution.

Future research should focus on larger multicenter studies and should explore whether advanced imaging techniques, such as three-dimensional ultrasonography or automated image analysis, can improve the detection of subtle craniofacial abnormalities. Longitudinal studies may also help determine whether differences in maxillary development become more apparent later in gestation.

Conclusions

The NT/maxillary length ratio was significantly increased in first-trimester fetuses with trisomy 21 and demonstrated good discriminatory performance in this preliminary cohort. However, it was not statistically superior to NT alone. These findings suggest that the ratio may serve as a proportional adjunctive parameter rather than as a replacement for NT. Larger prospective multicenter studies are required to determine whether this ratio provides clinically meaningful incremental value in first-trimester trisomy 21 screening.

Abbreviations

AUC
area under the curve

CI
confidence interval
CRL
crown-rump length
NT
nuchal translucency
OR
odds ratio
ROC
receiver operating characteristic

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Ethics Committee of Umraniye Training and Research Hospital (approval number 242). The requirement for informed consent was waived by the ethics committee because of the retrospective design.

Consent for publication

Not applicable. The manuscript does not contain identifying individual personal data.

Competing interests

The authors declare that they have no competing interests.

Authors' information

Not applicable.

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Author Contribution

MD and IK conceived and designed the study. MD, OEC, IE, ST contributed to data acquisition. MD, IK contributed to data analysis and interpretation. IE and MD drafted the manuscript. OEC, IE, ST and IK

critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Not applicable.

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on request. Upon acceptance, we agree to upload it to a public repository.

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Figures

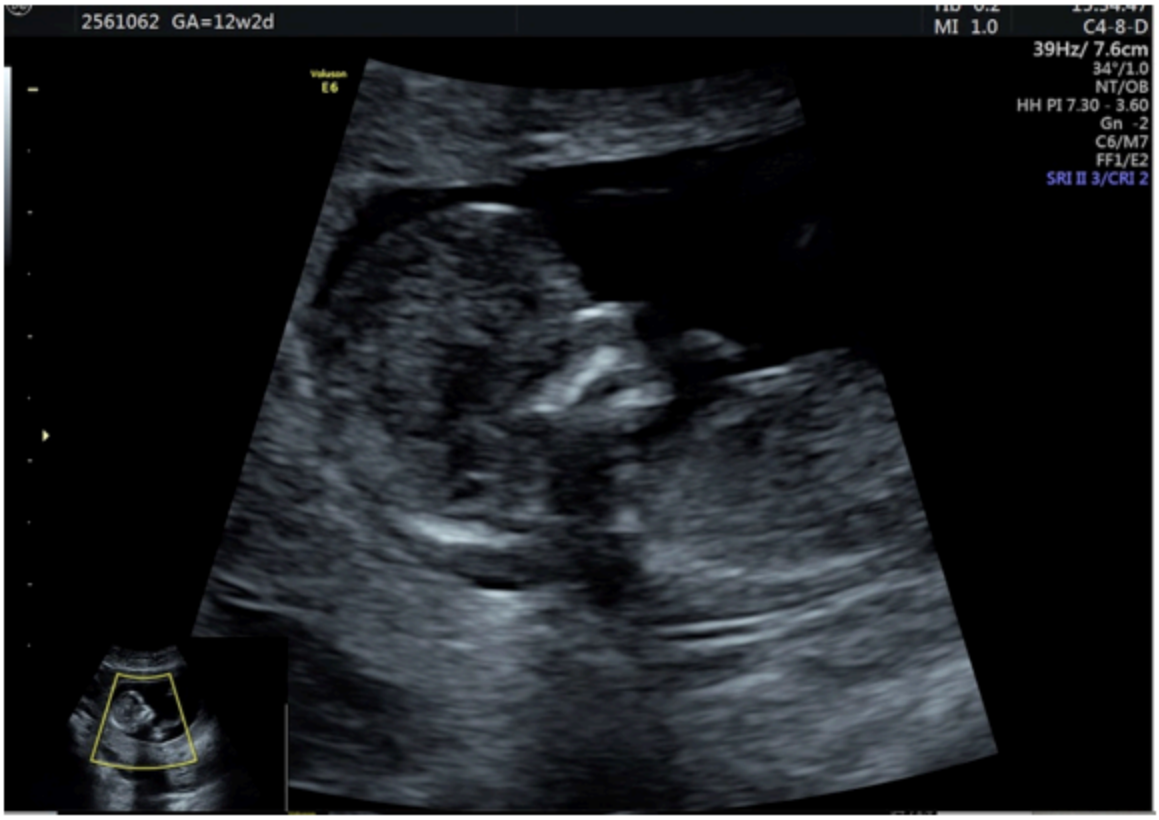


Figure 1

Ultrasound image of a 12-week fetus demonstrating retrospective measurement of maxillary length in the midsagittal plane.

The maxillary bone was measured as a linear distance excluding the mandibular ramus and condylar process.

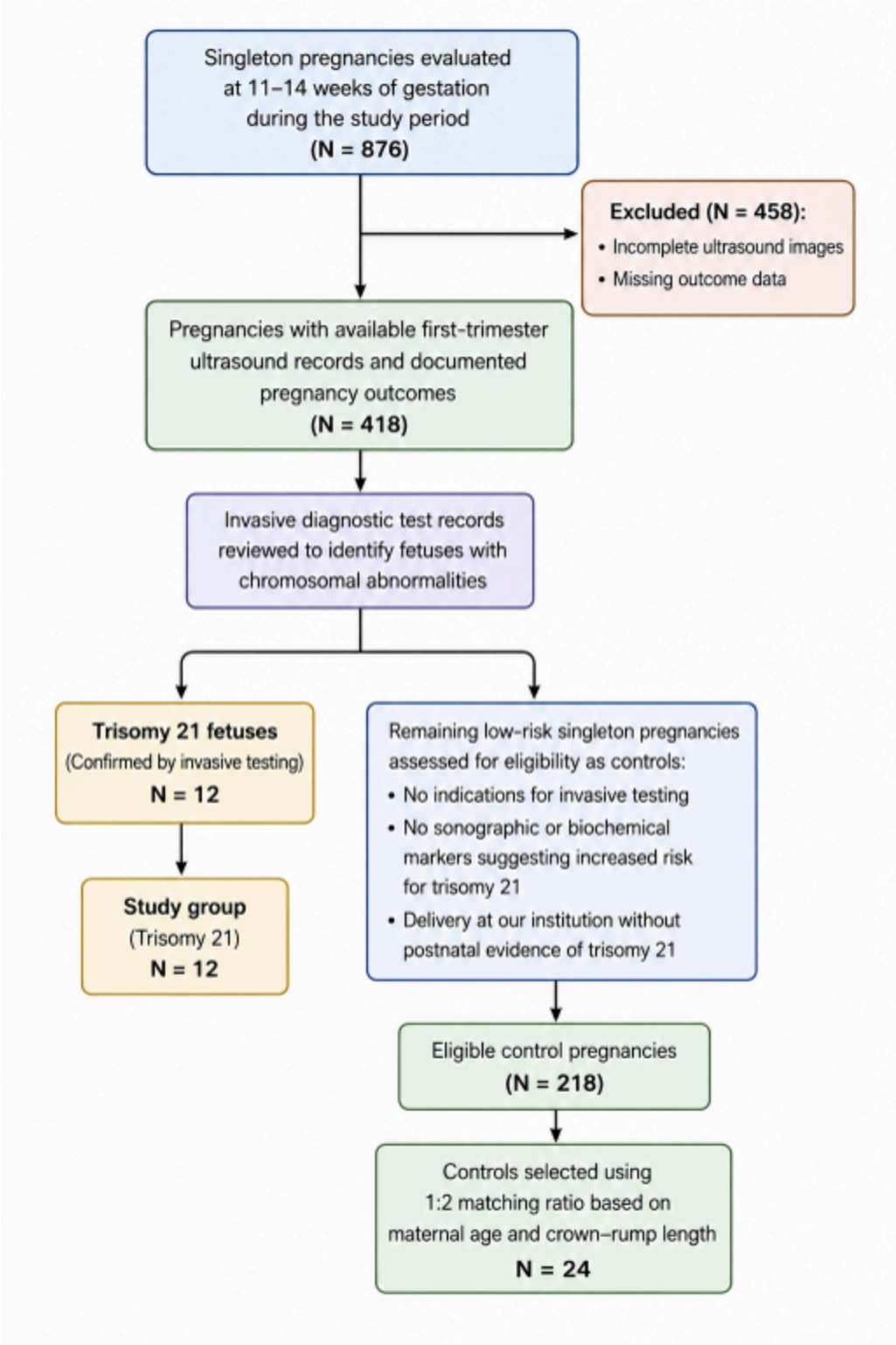


Figure 2

Flowchart demonstrating selection of the study population from singleton pregnancies evaluated between 11 and 14 weeks of gestation.

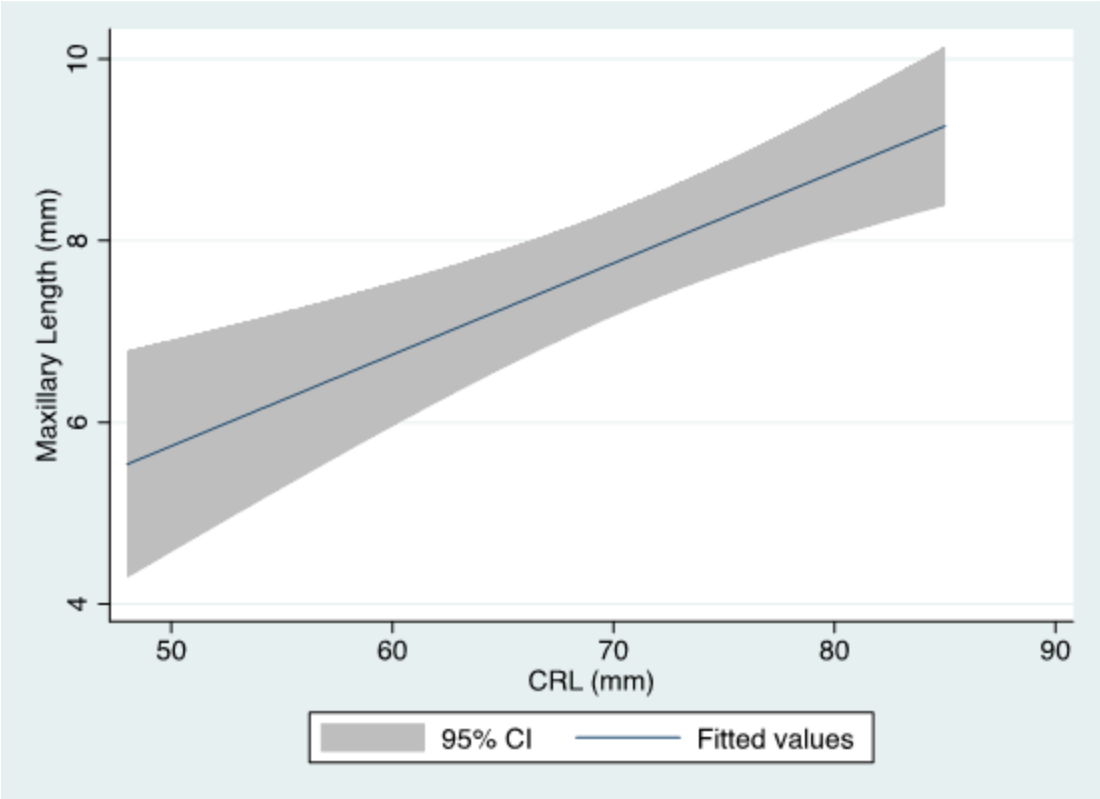


Figure 3

Linear regression analysis demonstrating the association between crown–rump length (CRL) and maxillary length in study group.

The solid line represents the fitted regression line, and the shaded area indicates the 95% confidence interval.

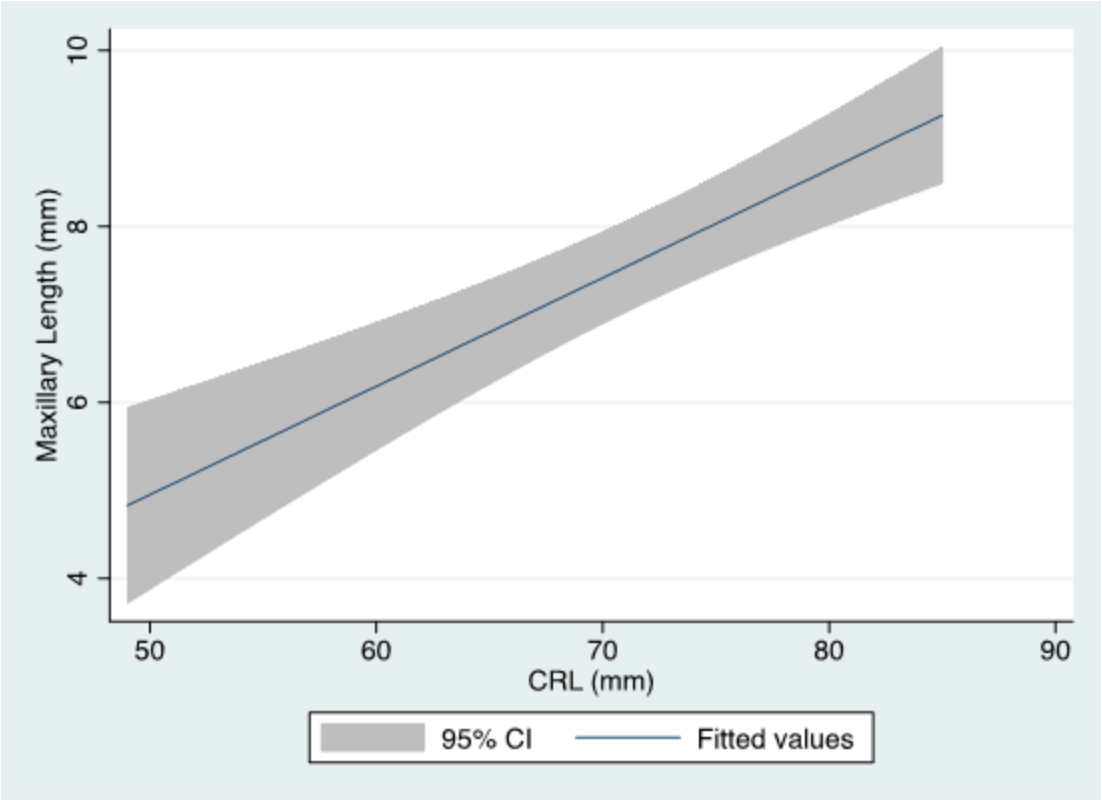


Figure 4

Linear regression analysis demonstrating the association between crown–rump length (CRL) and maxillary length in control group.

The solid line represents the fitted regression line, and the shaded area indicates the 95% confidence interval.

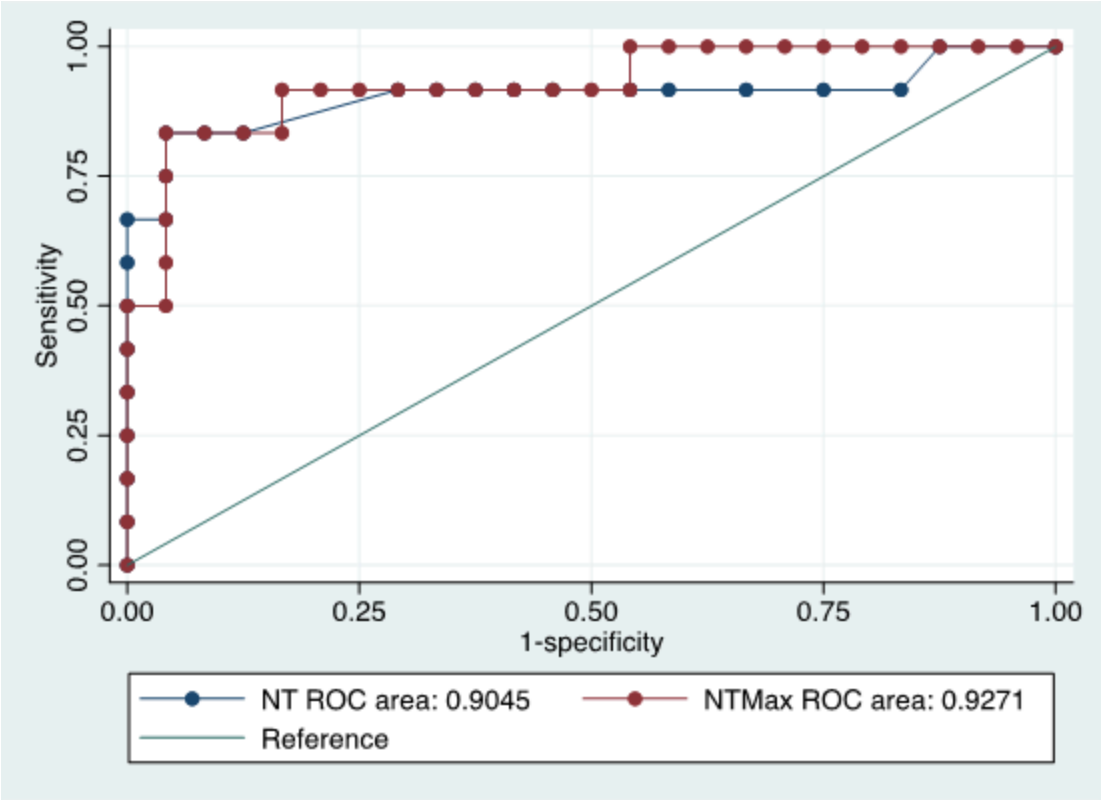


Figure 5

Receiver operating characteristic (ROC) curves comparing the predictive performance of nuchal translucency (NT) and the NT/maxillary length ratio for trisomy 21.

The area under the curve (AUC) was 0.9045 for NT and 0.9271 for the NT/maxillary length ratio.