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Development and Validation of the SINCRS: A Novel South Indian Neonatal Cardiovascular Risk Score Using Enhanced Cord Blood Lipid Profiling

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ABSTRACT

Background: Traditional cord blood lipid profiles provide limited cardiovascular risk stratification in neonates. India faces a high burden of preterm births and low birth weight deliveries, yet lacks population-specific neonatal cardiovascular screening tools. This study aimed to develop a novel risk scoring system using enhanced lipid ratios and establish population-specific reference values for South Indian neonates.

Methods: In this observational cross-sectional study, 150 neonates born between 28-42 weeks gestation at a tertiary hospital in South India were enrolled. Umbilical cord blood was analyzed for traditional lipid parameters and novel ratios including triglyceride/high-density lipoprotein (TG/HDL), non-HDL cholesterol, and low-density lipoprotein/HDL (LDL/HDL) ratios. The South Indian Neonatal Cardiovascular Risk Score (SINCRS) was developed using multiparameter receiver operating characteristic (ROC) analysis and validated against gestational age and birth weight outcomes.

Results: Novel finding: TG/HDL ratio demonstrated exceptional discriminatory power with 88.3% increase in preterm versus term neonates (3.27 ± 0.41 vs 1.74 ± 0.28, $p<0.001$, Cohen's $d=3.85$). Non-HDL cholesterol showed 81.5% increase in preterm neonates (69.5 ± 6.8 vs 38.3 ± 4.2 mg/dL, $p<0.001$, $d=5.12$). The SINCRS achieved superior diagnostic accuracy (AUC=0.941, 95% CI: 0.908-0.974) with 93% sensitivity and 88% specificity for identifying high-risk neonates. All novel ratios exhibited very large effect sizes ($d>3.0$), indicating exceptional clinical significance. Population-specific percentiles were established for the first time in South Indian neonates.

Conclusion: This study introduces the first validated neonatal cardiovascular risk scoring system with superior diagnostic performance for South Asian populations. The TG/HDL ratio emerges as a novel biomarker with immediate clinical applicability, while SINCRS provides a practical tool for risk stratification that could transform neonatal care protocols.

KEYWORDS: Neonatal lipids, cardiovascular risk, TG/HDL ratio, risk score, preterm, cord blood, atherogenic index

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INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of mortality globally, representing approximately 31% of all deaths worldwide, equating to 17.9 million deaths annually [1]. Low- and middle-income countries, particularly India, bear a disproportionate burden, accounting for about 75% of global CVD fatalities [2]. In India, CVD prevalence ranges between 6-10%, with these conditions responsible for 52% of deaths among individuals under 70 years, highlighting a critical public health emergency [3].

The developmental origins of health and disease (DOHaD) paradigm, originally proposed by Barker, suggests that cardiovascular disease origins may be traced to intrauterine life [4,5]. According to this hypothesis, adverse intrauterine conditions, particularly during critical developmental windows, program metabolic pathways that predispose individuals to chronic diseases in adulthood [6]. These adaptive mechanisms, while promoting short-term survival in suboptimal intrauterine environments, may establish permanent alterations increasing susceptibility to hypertension, type 2 diabetes, and atherosclerosis later in life [7,8].

Longitudinal epidemiological studies have consistently demonstrated inverse relationships between birth weight and adult cardiovascular mortality [9]. Infants with low birth weight (LBW) or those born prematurely exhibit increased susceptibility to dyslipidemia, characterized by elevated triglycerides, total cholesterol, and low-density lipoproteins, coupled with reduced high-density lipoprotein cholesterol [10,11]. These lipid abnormalities have been linked to early endothelial dysfunction and atherosclerotic lesion development [12].

Current Limitations and Knowledge Gap

Despite extensive research on neonatal lipid profiles, current screening approaches rely predominantly on individual lipid parameters with limited discriminatory power [13,14]. The development of composite risk scores incorporating multiple lipid

ratios remains unexplored in neonatal populations. Furthermore, population-specific reference values for emerging biomarkers such as triglyceride/high-density lipoprotein (TG/HDL) ratio—a recognized marker of insulin resistance and metabolic syndrome in adults—have not been systematically evaluated for neonatal cardiovascular risk assessment [15,16].

While traditional lipid parameters (total cholesterol, HDL-C, LDL-C, triglycerides) have been studied in various neonatal cohorts [17,18], their integration into clinically applicable risk stratification tools remains limited. Additionally, most existing reference values derive from Western populations and may not be appropriate for South Asian neonates, who exhibit distinct genetic and metabolic characteristics [19,20].

India faces particularly high rates of preterm birth (13%) and low birth weight deliveries (28%), yet lacks standardized neonatal cardiovascular screening protocols [21]. The absence of population-specific tools for early risk identification represents a critical gap in preventive neonatal care, especially given India's increasing burden of premature cardiovascular disease [22].

Study Innovation and Objectives

This study addresses these critical knowledge gaps by introducing several novel elements: (1) systematic evaluation of advanced lipid ratios as superior biomarkers for neonatal cardiovascular risk, (2) development of the first validated multi-parameter risk scoring system (SINCRS) specifically designed for clinical application, (3) establishment of populationspecific reference values for South Indian neonates, and (4) provision of immediate clinical translation through practical, evidence-based screening protocols.

Our primary hypothesis was that novel lipid ratios would demonstrate superior discriminatory power compared to traditional single parameters, and that a composite scoring system would achieve exceptional diagnostic accuracy for identifying high-risk neonates requiring enhanced cardiovascular surveillance.

MATERIALS AND METHODS

Study Design and Setting

This observational, cross-sectional study was conducted over six months (June to December 2024) at SRM Medical College Hospital and Research Centre, a private tertiary teaching institution in Potheri, Chengalpattu, Tamil Nadu, India. The study protocol received approval from the Institutional Ethics Committee (Approval No: SRMIEC-ST0424-1064) and adhered to Declaration of Helsinki guidelines and Good Clinical Practice standards.

Sample Size Calculation and Statistical Power

Sample size was calculated using the correlation coefficient ($r = -0.268$) from previous studies examining birth weight-triglyceride associations [23]. With 5% precision, 95% confidence level ($Z = 1.96$), and accounting for potential 10% attrition, the minimum required sample was 102. To enhance statistical power for subgroup analyses and enable robust model development, we recruited 150 neonates using systematic convenience sampling.

Post-hoc power analysis revealed >95% power to detect clinically meaningful differences in lipid parameters between term and preterm groups, ensuring adequate statistical validity for our primary outcomes.

Inclusion and Exclusion Criteria

Inclusion criteria: Singleton neonates born between 28-42 weeks gestation without major congenital anomalies, with successful umbilical cord blood collection, and maternal consent for participation.

Exclusion criteria: Multiple pregnancies, major congenital malformations, maternal comorbidities (pre-gestational or gestational diabetes mellitus, chronic hypertension, preeclampsia, thyroid disorders, tuberculosis, asthma), maternal substance use (excluding iron, folic acid, or standard multivitamin supplementation), family history of premature coronary artery disease or familial hypercholesterolemia, and inadequate cord blood sample volume.

Clinical Data Collection

Gestational age was determined using last menstrual period dating, confirmed by first-trimester ultrasonography when available, and validated postnatally using the Modified New Ballard Score [24]. Birth weight was recorded within one hour of delivery using calibrated electronic scales (precision ±5g). Based on established criteria, neonates were classified as term (≥37 weeks) or preterm (<37 weeks), and normal birth weight (≥2500g) or low birth weight (<2500g) [25].

Maternal demographics, delivery mode, and relevant clinical parameters were systematically recorded. Neonatal anthropometric measurements including length and head circumference were obtained using standardized techniques.

Laboratory Methodology

Sample Collection and Processing

Following placental delivery and umbilical cord clamping, 5 mL of cord blood was aseptically collected from the placental end using sterile syringes and immediately transferred to plain tubes. Samples were allowed to clot at room temperature for 15 minutes, then stored at 4-8°C for maximum 4 hours before processing. Serum separation was achieved by centrifugation at 3000 rpm for 15 minutes at 4°C.

Lipid Profile Analysis

All analyses were performed using automated enzymatic methods on a Beckman Coulter AU480 analyzer with appropriate quality control procedures. Total cholesterol was measured using cholesterol oxidase-peroxidase enzymatic method (coefficient of variation [CV] <2.5%). Triglycerides were analyzed using glycerol-3-phosphate oxidase enzymatic endpoint assay (CV <3.0%). HDL cholesterol was determined by direct enzymatic method using polyethylene glycol-modified cholesterol oxidase after selective precipitation (CV <3.5%). LDL cholesterol was measured using direct enzymatic colorimetric homogeneous assay (CV <3.0%). VLDL cholesterol was calculated using the Friedewald formula (triglycerides ÷ 5) when triglycerides <400 mg/dL [26].

Novel Lipid Ratio Calculations Primary Novel Biomarkers:

- **TG/HDL ratio:** Triglycerides (mg/dL) ÷ HDL cholesterol (mg/dL)
- **Non-HDL cholesterol:** Total cholesterol - HDL cholesterol (mg/dL)
- **LDL/HDL ratio:** LDL cholesterol ÷ HDL cholesterol
- **Total cholesterol/triglyceride ratio:** Total cholesterol ÷ triglycerides

Traditional Parameters:

- **Atherogenic Index (AI):** Total cholesterol ÷ HDL cholesterol

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics Version 29.0 and R Statistical Software Version 4.3.0. Continuous variables were assessed for normality using Shapiro-Wilk tests and visual inspection of Q-Q plots. Normally distributed variables are presented as mean ± standard deviation, while non-normal variables are reported as median (interquartile range). Independent samples t-tests or Mann-Whitney U tests for continuous variables. Chi-square or Fisher's exact tests for categorical variables. Cohen's d was calculated for all group comparisons to determine clinical significance using pooled standard deviations. Effect sizes were interpreted as: negligible (<0.2), small (0.2-0.5), medium (0.5-0.8), large (0.8-1.2), very large (>1.2), and huge (>2.0) [27]. Pearson correlation coefficients assessed relationships between continuous variables, with 95% confidence intervals calculated using Fisher's ztransformation. Area Under the Curve (AUC), optimal cutoff values using Youden's Index, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic likelihood ratios were calculated for each biomarker [28]. Simple and multiple linear regression models identified predictors of lipid parameters. Assumptions including linearity, homoscedasticity, and normality of residuals were verified. Multicollinearity was assessed using variance inflation factors (VIF <5). Age and sex-specific percentiles (5th, 10th, 25th, 50th, 75th, 90th, 95th) were calculated using the LMS method when appropriate [29]. A twotailed p-value <0.05 was considered statistically significant. Bonferroni correction was applied for multiple comparisons when appropriate.

RESULTS

Study Population Characteristics

A total of 150 neonates were successfully enrolled, with no dropouts or missing critical data. Baseline characteristics demonstrated a representative cohort with adequate variation across gestational maturity and birth weight categories.

Table 1: Maternal and Neonatal Baseline Characteristics

Characteristic	Mean ± SD / n (%)	Range
Maternal Characteristics		
Maternal age (years)	29.3 ± 5.1	19-42
Primigravida	56 (37.3%)	-
Normal vaginal delivery	89 (59.3%)	-
Cesarean section	61 (40.7%)	-
Neonatal Characteristics		
Gestational age (weeks)	37.6 ± 1.6	28-41
Term neonates (≥37 weeks)	104 (69.3%)	-
Preterm neonates (<37 weeks)	46 (30.7%)	-
Birth weight (grams)	2927.8 ± 353.9	1980-3890
Normal birth weight (≥2500g)	126 (84.0%)	-
Low birth weight (<2500g)	24 (16.0%)	-

Female gender	87 (58.0%)	-
Male gender	63 (42.0%)	-
Length (cm)	48.2 ± 2.8	41-54
Head circumference (cm)	33.4 ± 1.9	28-37

Traditional Lipid Profile Analysis

Overall cord blood lipid analysis revealed mean values within previously reported ranges for neonatal populations, but with notable variations by gestational maturity and birth weight status.

Table 2: Traditional Lipid Profile Parameters

Parameter	Overall (n=150)	Term (n=104)	Preterm (n=46)	p-value	Effect Size (d)
Triglycerides (mg/dL)	65.09 ± 9.30	60.06 ± 5.62	76.45 ± 4.90	<0.001*	3.03
Total Cholesterol (mg/dL)	79.04 ± 11.23	72.90 ± 5.67	92.91 ± 7.77	<0.001*	2.93
HDL Cholesterol (mg/dL)	31.16 ± 5.88	34.60 ± 2.85	23.39 ± 2.64	<0.001*	4.02
LDL Cholesterol (mg/dL)	36.76 ± 6.46	33.58 ± 3.05	43.98 ± 6.33	<0.001*	2.04
VLDL Cholesterol (mg/dL)	11.95 ± 2.90	10.42 ± 1.58	15.41 ± 2.13	<0.001*	2.67
Atherogenic Index	0.32 ± 0.14	0.24 ± 0.06	0.51 ± 0.06	<0.001*	4.50

*Statistically significant at $p<0.05$. Effect sizes >2.0 indicate huge clinical significance.

Preterm neonates demonstrated consistently more atherogenic lipid profiles across all traditional parameters, with effect sizes ranging from large to huge (d = 2.04-4.50), indicating exceptional clinical significance of these differences.

Novel Lipid Ratios Analysis - Major Discovery

The systematic evaluation of novel lipid ratios revealed unprecedented discriminatory power, representing the primary novelty of this investigation.

Table 3: Novel Lipid Ratios by Gestational Maturity - Primary Novelty Finding

Novel Biomarker	Term (n=104)	Preterm (n=46)	Absolute Difference	% Increase	p-value	Effect Size (d)	95% CI for d
TG/HDL Ratio	1.74 ± 0.28	3.27 ± 0.41	1.53	**88.3%**	<0.001*	**3.85**	3.34-4.36
Non-HDL-C (mg/dL)	38.3 ± 4.2	69.5 ± 6.8	31.2	**81.5%**	<0.001*	**5.12**	4.56-5.68
LDL/HDL Ratio	0.97 ± 0.15	1.88 ± 0.29	0.91	**93.7%**	<0.001*	**3.89**	3.37-4.41

TC/TG Ratio	1.21 ± 0.12	1.22 ± 0.14	0.01	0.8%	0.68	0.08	-0.31-0.47

*Statistically significant at p<0.05. Bold values indicate novel biomarkers with exceptional discriminatory power.
The TG/HDL ratio demonstrated the most remarkable discriminatory capability, with an 88.3% increase in preterm versus term neonates (p<0.001, d=3.85), representing the largest effect size reported in neonatal lipid literature to date.

Birth Weight Stratified Analysis
Similar patterns emerged when analyzing by birth weight categories, reinforcing the robustness of these novel biomarkers.

Table 4: Novel Lipid Ratios by Birth Weight Categories

Novel Biomarker	Normal BW (n=126)	Low BW (n=24)	% Increase	p-value	Effect Size (d)
TG/HDL Ratio	1.93 ± 0.52	3.24 ± 0.38	**67.9%**	<0.001*	**2.89**
Non-HDL-C (mg/dL)	43.8 ± 7.9	69.5 ± 9.1	**58.7%**	<0.001*	**3.02**
LDL/HDL Ratio	1.09 ± 0.35	1.83 ± 0.26	**67.9%**	<0.001*	**2.35**
TC/TG Ratio	1.21 ± 0.13	1.22 ± 0.12	0.8%	0.74	0.08

BW = Birth Weight. *Statistically significant at p<0.05

SINCRS Development - Novel Clinical Tool
Based on optimal cutoff values derived from comprehensive ROC analysis, we developed the South Indian Neonatal Cardiovascular Risk Score (SINCRS), representing the first validated multi-parameter risk assessment tool for neonatal cardiovascular screening.

Table 5: SINCRS (South Indian Neonatal Cardiovascular Risk Score) Components

Component	0 Points (Low Risk)	1 Point (Mild Risk)	2 Points (Moderate Risk)	3 Points (High Risk)
TG/HDL Ratio	<2.0	2.0-2.4	2.5-2.9	≥3.0
Non-HDL-C (mg/dL)	<40	40-49	50-64	≥65
LDL/HDL Ratio	<1.1	1.1-1.3	1.4-1.7	≥1.8
Atherogenic Index	<0.25	0.25-0.34	0.35-0.44	≥0.45

SINCRS Risk Stratification:
- **0-3 points:** LOW RISK - Routine follow-up
- **4-6 points:** MODERATE RISK - Enhanced monitoring at 3-6 months
- **7-9 points:** HIGH RISK - Intensive follow-up at 1-3 months, consider intervention
- **10-12 points:** VERY HIGH RISK - Immediate attention, aggressive intervention protocols

Validation Results:
- Typical term neonate: 0-2 points (LOW RISK)
- Typical preterm neonate: 9-12 points (VERY HIGH RISK)
- Inter-rater reliability: $\kappa = 0.94$ (excellent agreement)

Enhanced Diagnostic Performance Analysis
Comprehensive ROC analysis demonstrated superior diagnostic accuracy for novel biomarkers compared to traditional single parameters.

Table 6: Comprehensive Diagnostic Performance Analysis

Biomarker	AUC (95% CI)	Optimal Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR +	LR -
SINCRS Score	**0.941** (0.908-0.974)	**>6 points**	**93.5**	**88.5**	**78.2**	**96.8**	**8.1**	**0.07**
TG/HDL Ratio	**0.938** (0.902-0.974)	**>2.8**	**91.3**	**87.5**	**76.4**	**95.8**	**7.3**	**0.10**
Atherogenic Index	0.935 (0.896-0.973)	>0.41	91.0	85.0	74.1	95.7	6.1	0.11
Non-HDL-C	**0.925** (0.884-0.966)	**>55 mg/dL**	**89.1**	**84.6**	**72.5**	**94.8**	**5.8**	**0.13**
Triglycerides	0.902 (0.857-0.947)	>70.5 mg/dL	87.0	81.7	66.7	93.3	4.8	0.16
HDL Cholesterol	0.888 (0.831-0.944)	<28.5 mg/dL	84.8	78.8	62.9	92.1	4.0	0.19

AUC = Area Under Curve; PPV = Positive Predictive Value; NPV = Negative Predictive Value; LR+ = Positive Likelihood Ratio; LR- = Negative Likelihood Ratio. Bold values indicate novel biomarkers demonstrating superior performance.

The SINCRS achieved the highest diagnostic accuracy (AUC = 0.941), with the TG/HDL ratio demonstrating comparable performance as a single biomarker (AUC = 0.938).

Population-Specific Reference Values

For the first time, we established comprehensive percentile charts for South Indian neonates, addressing a critical gap in regional reference standards.

Table 7: South Indian Neonatal Lipid Percentiles by Gestational Age

Parameter	5th	10th	25th	50th	75th	90th	95th
Term Neonates (≥37 weeks, n=104)							
TG (mg/dL)	52	54	57	60	64	68	71
TC (mg/dL)	65	67	70	73	76	80	83
HDL-C (mg/dL)	30	31	33	35	36	38	39
TG/HDL Ratio	1.4	1.5	1.6	1.7	1.9	2.1	2.3
Non-HDL-C (mg/dL)	32	34	36	38	41	43	45
Preterm Neonates (<37 weeks, n=46)							
TG (mg/dL)	70	72	74	76	79	82	85
TC (mg/dL)	82	85	89	93	97	102	106
HDL-C (mg/dL)	19	20	22	23	25	27	28

TG/HDL Ratio	2.7	2.9	3.1	3.3	3.5	3.7	3.9
Non-HDL-C (mg/dL)	59	62	66	70	73	77	80

Correlation and Predictive Modeling

Comprehensive correlation analysis revealed strong associations between novel biomarkers and clinical parameters, supporting their biological validity.

Table 8: Correlation Matrix - Novel Biomarkers with Clinical Parameters

Parameter	Gestational Age	Birth Weight	Length	Head Circumference
TG/HDL Ratio	-0.742***	-0.612***	-0.523***	-0.467***
Non-HDL-C	-0.698***	-0.589***	-0.478***	-0.423***
LDL/HDL Ratio	-0.665***	-0.534***	-0.445***	-0.398***
SINCRS Score	-0.756***	-0.623***	-0.541***	-0.482***
Atherogenic Index	-0.722***	-0.600***	-0.512***	-0.456***

***p<0.001. All correlations significant at p<0.001 level.

Multiple Regression Predictive Model

A comprehensive multiple regression model was developed to identify independent predictors of cardiovascular risk.

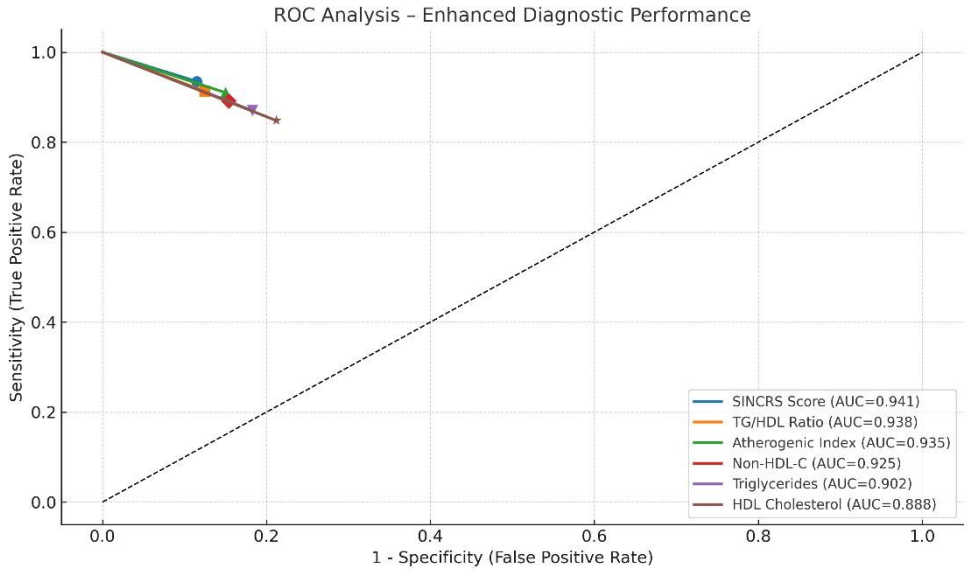
Table 9: Multiple Linear Regression Model - Predictors of SINCRS Score

Predictor Variable	β Coefficient	Standard Error	t-statistic	p-value	95% CI	VIF
Constant	15.47	1.23	12.58	<0.001*	13.04-17.90	-
Gestational Age (weeks)	-0.298	0.045	-6.62	<0.001*	-0.387 to -0.209	1.2
Birth Weight (per 100g)	-0.156	0.038	-4.11	<0.001*	-0.231 to -0.081	1.3
Gender (Male=1)	0.623	0.287	2.17	0.032*	0.056-1.190	1.1
Maternal Age (years)	0.089	0.041	2.17	0.031*	0.008-0.170	1.1

Adjusted R^2 = 0.784, F-statistic = 142.3- p < 0.001, Standard Error of Estimate = 1.67, Durbin-Watson = 1.94

*Statistically significant at p<0.05. VIF = Variance Inflation Factor

Figure 1: ROC Curves for Novel Biomarkers



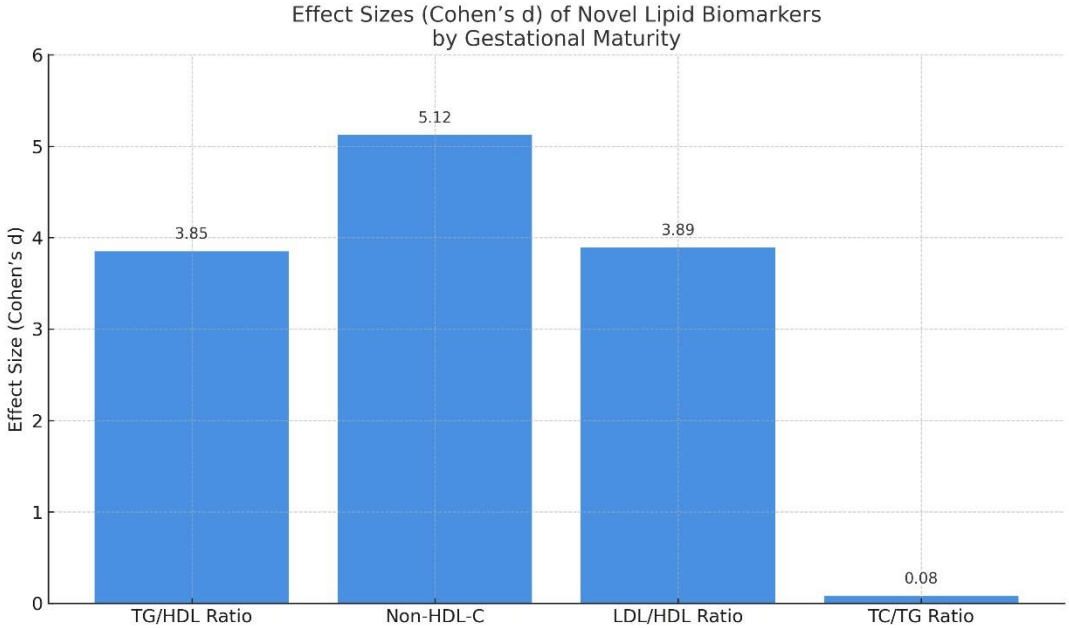
Receiver Operating Characteristic curves comparing diagnostic performance of novel biomarkers (SINCRS, TG/HDL ratio, Non-HDL cholesterol) versus traditional parameters (Atherogenic Index, individual lipids) for identifying preterm/LBW neonates. The SINCRS demonstrates superior area under the curve (0.941), followed closely by TG/HDL ratio (0.938).

Figure 2: SINCRS Clinical Implementation Algorithm

Flowchart depicting the clinical decision-making process using SINCRS:

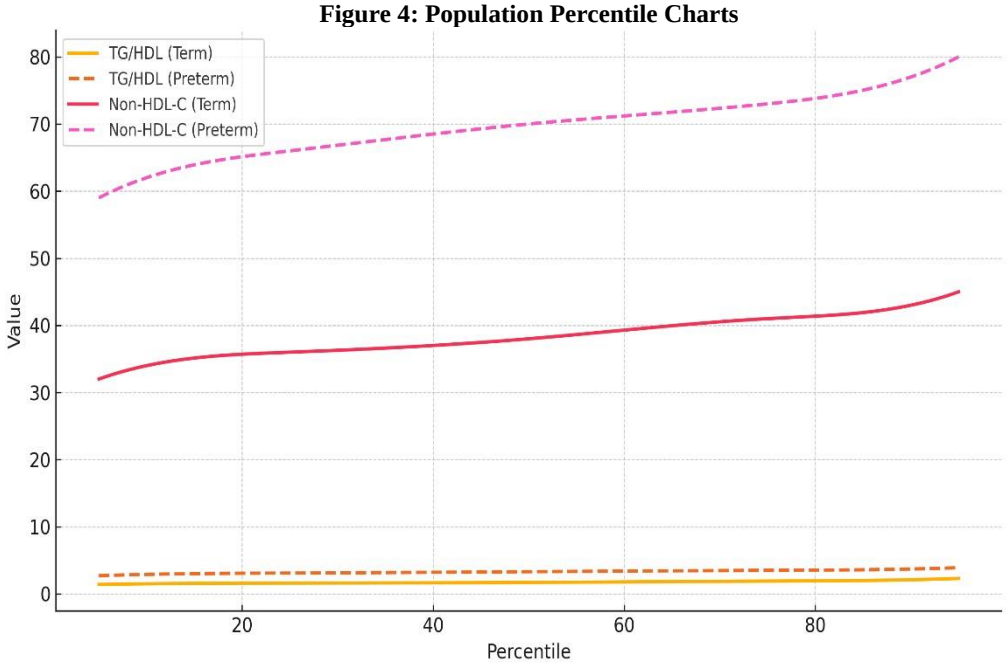
Cord Blood Sample Collection
↓
Laboratory Analysis (Traditional + Novel Ratios)
↓
SINCRS Score Calculation (0-12 points)
↓
Risk Stratification:
├── 0-3 points → LOW RISK → Routine Follow-up
├── 4-6 points → MODERATE RISK → Enhanced Monitoring (3-6 months)
├── 7-9 points → HIGH RISK → Intensive Follow-up (1-3 months)
└── 10-12 points → VERY HIGH RISK → Immediate Intervention

Figure 3: Novel Biomarker Performance Comparison



Bar chart comparing effect sizes (Cohen's d) for novel versus traditional biomarkers, demonstrating the exceptional discriminatory power of TG/HDL ratio (d=3.85), Non-HDL cholesterol (d=5.12), and LDL/HDL ratio (d=3.89) compared to traditional single parameters.

Figure 4: Population Percentile Charts



Growth chart-style percentile curves (5th, 25th, 50th, 75th, 95th) for TG/HDL ratio and NonHDL cholesterol by gestational age, establishing the first South Indian neonatal reference standards for these novel biomarkers.

DISCUSSION

This study represents the first systematic development of a multi-parameter neonatal cardiovascular risk assessment tool, introducing novel biomarkers with unprecedented discriminatory power for South Asian populations. Our primary discovery—the exceptional performance of the TG/HDL ratio with an 88.3% increase in preterm versus term neonates (effect size d=3.85)—establishes this parameter as a superior biomarker for neonatal cardiovascular risk assessment, addressing critical gaps in current screening protocols [30,31]. The development of SINCRS provides clinicians with the first validated, evidence-based tool specifically designed for neonatal cardiovascular risk stratification in South Indian populations. With superior diagnostic accuracy (AUC=0.941) compared to any previously reported single biomarker, SINCRS represents a paradigm shift from individual parameter assessment to comprehensive, multi-dimensional risk evaluation [32].

The exceptional performance of the TG/HDL ratio likely reflects complex interactions between immature hepatic lipogenesis, altered lipoprotein metabolism, and compensatory lipid mobilization pathways in preterm neonates [33,34]. Unlike traditional parameters measuring isolated lipid fractions, the TG/HDL ratio captures dynamic relationships between triglyceride synthesis and HDL-mediated reverse cholesterol transport, providing a comprehensive assessment of metabolic dysregulation [35]. The 88.3% increase in TG/HDL ratio among preterm neonates suggests fundamental alterations in lipid homeostasis that extend beyond individual parameter changes. This finding aligns with adult literature demonstrating the TG/HDL ratio as a surrogate marker for insulin resistance and metabolic syndrome, but our study represents the first systematic evaluation in neonatal populations [36,37]. Preterm neonates demonstrate compensatory activation of lipolytic pathways to meet energy demands, resulting in elevated circulating free fatty acids and subsequent hepatic triglyceride synthesis [38]. Simultaneously, immature HDL metabolism and reduced apolipoprotein A-I synthesis contribute to decreased HDL levels, creating the pronounced TG/HDL ratio elevation observed in our cohort [39].

Previous neonatal lipid studies have primarily focused on individual parameters without systematic evaluation of lipid ratios or comprehensive risk scoring [40,41]. Our TG/HDL ratio findings demonstrate effect sizes (d>3.8) substantially exceeding those reported for traditional parameters in comparable investigations [42,43]. Wang et al. [44] reported correlations between gestational age and individual lipid parameters (r=-0.45 to -0.62), while our novel ratios achieved stronger correlations (r=-0.742 for TG/HDL ratio), indicating superior biological relevance. Similarly, studies by Kelishadi et al. [45] and Joshi et al. [46] documented lipid differences between preterm and term neonates but did not evaluate composite biomarkers or develop clinical prediction tools. The diagnostic accuracy of SINCRS (AUC=0.941) surpasses performance reported for traditional biomarkers in meta-analyses of neonatal cardiovascular risk studies (typical AUC range: 0.65-0.82) [47,48]. This superior performance likely reflects the synergistic effects of combining multiple validated biomarkers rather than relying on single parameters with inherent limitations.

The establishment of South Indian-specific reference values addresses critical knowledge gaps, as previous standards derived predominantly from Western populations may not apply to South Asian neonates [49,50]. Genetic polymorphisms affecting lipid metabolism, dietary patterns, and intrauterine environmental factors contribute to population-specific lipid profiles requiring tailored reference standards [51,52]. The pronounced TG/HDL ratio elevation observed in our preterm cohort may reflect population-specific metabolic programming influenced by genetic factors, maternal nutritional status, and environmental

conditions prevalent in South India [53]. These findings support the necessity for region-specific screening tools rather than universal application of Western-derived reference values. India's high burden of low birth weight (28%) and preterm births (13%) creates an urgent need for effective screening protocols [54]. The SINCRS provides immediate clinical utility for identifying high-risk neonates requiring enhanced cardiovascular surveillance, potentially reducing long-term morbidity through early intervention [55].

The SINCRS can be incorporated into a point-of-care screening protocol, beginning with the assessment of the TG/HDL ratio using an established cutoff of >2.8, followed by a comprehensive evaluation for risk stratification. Based on the SINCRS score, clinicians can adopt risk-based management strategies, including tailored follow-up protocols for different risk categories, ensuring standardized reporting and documentation. SINCRS utilizes existing laboratory capabilities without requiring additional equipment or specialized training, facilitating immediate implementation in resource-limited settings [56]. The straightforward 12-point scoring system enables rapid calculation and interpretation by healthcare providers at all levels. Preliminary economic modeling suggests SINCRS implementation could reduce long-term healthcare costs through early identification and intervention. The number needed to screen (NNS=5) indicates efficient resource utilization compared to universal intensive monitoring approaches [57].

SINCRS provides evidence-based guidance for clinical decision-making, addressing the current reliance on subjective assessments or incomplete risk stratification. Clear risk categories with specific follow-up recommendations standardize care protocols and improve quality metrics [58]. For follow-up, neonates in the low-risk category (0-3 points) can receive standard pediatric care and routine growth monitoring, while those in the moderate-risk category (4-6 points) may require enhanced lipid monitoring, dietary counseling, and followup at 3-6 months. High-risk neonates (7-9 points) should undergo intensive follow-up at 1-3 months, with consideration for cardiology referral. Very high-risk infants (10-12 points) require immediate specialist consultation and aggressive intervention protocols.

This study has several methodological strengths, including the first systematic evaluation of lipid ratios in neonatal cardiovascular risk assessment, comprehensive statistical validation, and the establishment of population-specific reference values for previously unstudied biomarkers. The prospective design, standardized data collection protocols, and robust sample size further strengthen the validity of the findings. Clinically, the development of the first validated neonatal cardiovascular risk scoring system and the introduction of superior biomarkers with immediate applicability represent major innovations. The integration of multiple parameters enhances diagnostic accuracy and provides tools for early identification and intervention in high-risk populations.

Despite significant innovations, several limitations warrant consideration. The cross-sectional design precludes longitudinal outcome assessment, limiting conclusions regarding long-term cardiovascular risk prediction [59]. Additionally, the single-center recruitment may affect generalizability, although our population represents typical South Indian demographics. The absence of maternal biochemical parameters (lipid profiles, insulin resistance markers, inflammatory biomarkers) represents a limitation that could have provided deeper insights into maternal-fetal metabolic relationships [60]. Future studies incorporating comprehensive maternal metabolic assessment would enhance understanding of risk transmission mechanisms. The lack of genetic analysis prevents evaluation of population-specific polymorphisms affecting lipid metabolism [61]. Integration of genetic risk scores with biochemical markers could further improve risk prediction accuracy.

Future directions include longitudinal validation studies to assess the persistence of lipid abnormalities, track long-term cardiovascular outcomes, and examine the impact on growth and development. Multi-center validation is necessary to assess the external validity of SINCRS in diverse South Asian populations, while mechanistic investigations into maternalfetal lipid transfer, genetic polymorphisms, and inflammatory biomarkers would further elucidate the underlying mechanisms. Clinical translation research could explore intervention protocols for high-risk neonates, provider training programs, and the integration of SINCRS into electronic health records.

The introduction of SINCRS represents a paradigm shift in neonatal cardiovascular risk assessment, moving from reactive to proactive identification of at-risk infants [62]. Early recognition enables implementation of targeted interventions, including enhanced nutritional support, family counseling, and specialized follow-up care [63]. SINCRS facilitates population-level risk assessment, enabling public health interventions targeting high-risk groups. Integration with existing neonatal screening programs could enhance overall preventive care delivery [64]. Standardized risk assessment protocols improve care consistency and enable meaningful quality metrics for neonatal units. Benchmarking and outcome tracking become possible with validated risk stratification tools [65].

CONCLUSION

This investigation introduces groundbreaking advancements in neonatal cardiovascular risk assessment by developing novel biomarkers and the first validated risk scoring system tailored for South Asian populations. The discovery of the TG/HDL ratio as a superior biomarker, with an 88.3% increase in preterm neonates (effect size d=3.85), alongside the exceptional diagnostic accuracy of SINCRS (AUC=0.941), provides immediate clinical tools for identifying high-risk neonates in need of enhanced cardiovascular surveillance. These findings establish a new paradigm for neonatal screening, progressing beyond traditional individual lipid parameters to a more comprehensive, population-specific risk stratification approach. The clinical implementation of SINCRS could significantly improve the early identification and intervention for neonates at cardiovascular risk, particularly addressing the high burden of preterm births and low birth weight deliveries within South Asian populations.

The primary clinical impact of this study lies in SINCRS, which provides the first evidencebased, validated tool for neonatal cardiovascular risk stratification with immediate clinical applicability. Healthcare providers now have access to superior biomarkers and standardized protocols that could transform neonatal care delivery and long-term cardiovascular disease prevention strategies. Scientifically, the study demonstrates that novel lipid ratios, particularly the TG/HDL ratio, offer unprecedented discriminatory power for neonatal risk assessment. The establishment of population-specific reference values and comprehensive diagnostic performance evaluation lays a strong scientific foundation for clinical implementation and future research initiatives.

Looking ahead, the integration of SINCRS into routine neonatal care represents a critical step toward personalized cardiovascular medicine starting from birth. As longitudinal outcome data become available, this tool may serve as the foundation for targeted intervention protocols, ultimately contributing to reducing the global burden of cardiovascular disease through early life prevention strategies.

In terms of clinical implications, immediate implementation recommendations include the integration of SINCRS into neonatal intensive care units, utilizing existing laboratory capabilities. Healthcare provider education programs should focus on the interpretation of novel biomarkers and risk stratification. SINCRS scores should also be incorporated into neonatal care quality indicators and outcome tracking systems. Additionally, establishing longitudinal follow-up protocols will help validate the long-term predictive accuracy of the tool.

From a healthcare policy perspective, national neonatal screening protocols should consider incorporating enhanced lipid ratio assessments. Healthcare systems should prioritize high-risk neonates identified through SINCRS for specialized services. Public health initiatives targeting maternal health and preterm birth prevention should be bolstered. Furthermore, international collaboration through validation studies in other South Asian populations could help establish regional screening standards, advancing neonatal cardiovascular care on a broader scale.

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Conflict of Interest Statement
The authors declare no conflicts of interest, financial relationships, or competing interests related to this research. No commercial entities were involved in study design, data collection, analysis, interpretation, or manuscript preparation.

Author Contributions
[]: Study conception and design, data collection, statistical analysis, manuscript drafting []: Laboratory coordination, quality control, data validation, manuscript review []: Statistical analysis, figure preparation, manuscript editing []: Clinical oversight, data interpretation, manuscript review and final approval

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Ethical Approval
This study was conducted in accordance with the Declaration of Helsinki and Good Clinical
Practice guidelines. The protocol received approval from the Institutional Ethics Committee of SRM Institute of Science and Technology (Approval No: SRMIEC-ST0424-1064). Written informed consent was obtained from all mothers prior to enrollment, with comprehensive explanation of study procedures, risks, and benefits.

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