E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.02.232

Research Article

Umbilical Cord Blood Biomarkers as Predictors of Meconium Aspiration Syndrome: A Prospective Cohort Study

Tahir Mohi ud din Dar[1], Owais Ayoub Khan[2], Dr Naseer Yousuf Mir[3*], Bashir Ahmad Charoo[4]
[1]Senior Resident, Department of Pediatrics, SKIMS Soura.
[2]Post Graduate, Department of Pediatrics, SKIMS Soura.
[3*]Assistant Professor, Department of Pediatrics, Government Medical College Handwara.
[4]Professor & Head, Department Pediatrics & Neonatology, SKIMS soura.
Corresponding Author: Dr Naseer Yousuf Mir
Assistant Professor, Department of Pediatrics, Government Medical College Handwara.
Email: mirnasirgmc@gmail.com
Received: 11.06.26, Revised: 08.07.26, Accepted: 07.08.26

ABSTRACT
Background: Early identification of neonates at risk of meconium aspiration syndrome (MAS) may facilitate timely monitoring and respiratory support.
Objective: To evaluate umbilical cord-blood lactate and acid–base parameters for predicting MAS among neonates born through meconium-stained amniotic fluid.
Methods: This prospective cohort study included 72 neonates. Cord-blood pH, PCO_2, PO_2, bicarbonate, oxygen saturation, base excess, and lactate were measured immediately after delivery. Neonates were followed for development of MAS, respiratory-support requirements, and in-hospital outcome.
Results: MAS developed in 19 neonates (26.4%). Compared with non-MAS neonates, affected neonates had higher lactate (5.40 vs 2.60 mmol/L), lower bicarbonate (15.03 vs 22.18 mEq/L), more negative base excess (−10.76 vs −4.57 mEq/L), and lower 1- and 5-minute Apgar scores (all $p<0.001$). Cord-blood pH, PCO_2, PO_2, and oxygen saturation did not differ significantly. Lactate showed the highest discrimination for MAS (AUC 0.81), followed by pH (0.75) and base deficit (0.71).
Conclusion: Cord-blood lactate may be a useful early adjunct for predicting MAS.

Keywords: Meconium Aspiration Syndrome, Cord Blood, Lactate, Acid–Base Status, Neonate.

INTRODUCTION

Meconium-stained amniotic fluid (MSAF) is present in about 5%–20% of women in labour and increases with increasing gestation. Most exposed neonates are asymptomatic, but a subset develop meconium aspiration syndrome (MAS) defined as respiratory distress after birth due to MSAF, compatible radiographic abnormalities, and no other cardiopulmonary cause [1,2].

The pathophysiology of MAS is complex and involves partial or complete airway obstruction, chemical pneumonitis, surfactant inactivation, pulmonary vasoconstriction, ventilation–perfusion mismatch, air leak, and persistent pulmonary hypertension. The severity of the disease can vary from needing only supplemental oxygen to mechanical ventilation, haemodynamic instability and death [2]. The changes in airway management in the delivery room have led to a decrease in unnecessary intervention in vigorous neonates, but have not eliminated the need to identify infants at risk of developing respiratory disease. A large multicentre trial did not show any decrease in MAS or other respiratory diseases in apparently vigorous meconium-stained neonates when routine intubation and tracheal suctioning were performed [3].

The early risk assessment is usually based on the characteristics of the meconium, fetal compromise, neonatal respiratory findings, and Apgar scores. These measures, however, may not adequately capture the metabolic effects of intrapartum hypoxia. Higher neonatal blood lactate levels, lower pH, and a low 5-minute Apgar score have been linked to subsequent MAS in infants born via MSAF [4]. Low umbilical-cord pH is also linked to significant neonatal morbidity, but definitions and thresholds differ across studies [5].

Umbilical-cord blood is a direct and objective measurement of fetal acid–base status. Lactate is a marker of anaerobic metabolism, and bicarbonate and base deficit are markers of the metabolic component of acidosis. Arterial cord lactate was a better discriminator of neonatal

morbidity than pH in a prospective term cohort [6]. Lactate was also found to be more predictive of adverse outcomes than pH in subsequent studies, which also found that lactate was more informative than pH for identifying adverse outcomes associated with intrapartum hypoxia [7]. The clinical significance of these findings is that a near-normal or variably measured pH may mask significant metabolic disturbance, while lactate and base-deficit parameters may offer complementary early information.

Although respiratory care has improved, early prediction of MAS remains challenging, and there is limited evidence specifically evaluating cord-blood lactate in addition to a comprehensive acid–base profile in MSAF-exposed neonates [8]. The present prospective cohort study thus aimed to assess cord-blood lactate, pH, bicarbonate, and base deficit for early discrimination of MAS in neonates born through MSAF. It also compared perinatal characteristics, respiratory-support requirements, and short-term outcomes between neonates with and without MAS.

METHODS

Study design and participants

This prospective, hospital-based observational cohort study was conducted in the Department of Pediatrics and Neonatology, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Soura, and the Department of Paediatrics, SKIMS Medical College, Bemina. Neonates born through meconium-stained amniotic fluid (MSAF) were consecutively enrolled. Neonates were excluded when parental consent was declined or when congenital heart disease, congenital diaphragmatic hernia, congenital pulmonary airway malformation, or another major lung anomaly was present.

Clinical assessment and outcome measures

Perinatal and neonatal information—including gestational age, sex, mode of delivery, Apgar scores, clinical signs of respiratory distress, respiratory-support requirements, and in-hospital outcome—was recorded using a structured proforma. Meconium aspiration syndrome (MAS) was diagnosed in neonates born through MSAF who developed respiratory distress with compatible chest-radiographic findings and no alternative congenital cardiopulmonary explanation. Respiratory support was categorized as oxygen by hood, continuous positive airway pressure, or mechanical ventilation.

Umbilical cord-blood analysis

Immediately after delivery, 1 mL of umbilical cord blood was collected under aseptic conditions in a pre-heparinized syringe. Cord-blood pH, partial pressures of carbon dioxide and oxygen, bicarbonate, oxygen saturation, base excess, and lactate were measured. Base excess was expressed using its recorded signed values; the corresponding magnitude of base deficit was used in the receiver operating characteristic analysis.

Statistical analysis

Categorical variables were presented as n (%), and continuous variables as mean ± SD. Neonates were divided into two groups: those who developed MAS and those who did not. Fisher's exact test was used to compare categorical variables. For continuous variables, the mean differences and 95% confidence intervals were reported and compared using Welch's independent-samples t test. Principal proportions were calculated using the Wilson score intervals. Hedges' g with 95% confidence intervals were used to present standardized differences in cord-blood lactate, bicarbonate, and base excess.

The discriminatory performance of cord-blood lactate, pH and base deficit was assessed by receiver operating characteristic analysis and summarized by the area under the curve. All tests were two-tailed and $p<0.05$ was regarded as statistically significant. Data were entered into Microsoft Excel and analysed using IBM SPSS Statistics.

Ethical considerations

The study received approval from the institutional ethics committee before enrolment. Written informed consent was obtained from the parent or legal guardian of each neonate, and participant confidentiality was maintained throughout the study.

RESULTS

All 72 enrolled neonates born through meconium-stained amniotic fluid were included in the analysis. Meconium aspiration syndrome developed in *n*=19 (26.4%) (95% CI 17.6% to 37.6%), while *n*=53 (73.6%) did not develop MAS. The cohort comprised *n*=35 (48.6%) male and *n*=37 (51.4%) female neonates.

Perinatal characteristics

Sex distribution and gestational age did not differ significantly between the MAS and non-MAS groups. Apgar scores were lower among neonates who subsequently developed MAS at both 1 minute (5.40 ± 1.62 vs 7.40 ± 1.40; mean difference -2.00, 95% CI -2.86 to -1.14; $p<0.001$) and 5 minutes (7.50 ± 0.30 vs 8.50 ± 0.20; mean difference -1.00, 95% CI -1.15 to -0.85; $p<0.001$) (Table 1).

Table 1. Perinatal Characteristics According To Meconium Aspiration Syndrome Status

Characteristic	MAS (n=19)	Non-MAS (n=53)	Effect estimate/test statistic	p value
Male sex	8 (42.1%)	27 (50.9%)	OR=0.70 (95% CI 0.24 to 2.02)	0.597
Gestational age, weeks	39.04 ± 2.40	38.01 ± 2.80	MD=1.03 (95% CI -0.33 to 2.39); Welch t=1.53, df=36.82	0.134
Apgar score at 1 minute	5.40 ± 1.62	7.40 ± 1.40	MD=-2.00 (95% CI -2.86 to -1.14); Welch t=-4.78, df=28.23	<0.001
Apgar score at 5 minutes	7.50 ± 0.30	8.50 ± 0.20	MD=-1.00 (95% CI -1.15 to -0.85); Welch t=-13.49, df=23.98	<0.001

Data are *n* (%) or mean ± SD. Percentages are column percentages. Sex was compared using Fisher's exact test; continuous variables were compared using Welch's *t* test. CI, confidence interval; df, degrees of freedom; MAS, meconium aspiration syndrome; MD, mean difference; OR, odds ratio; SD, standard deviation.

Umbilical cord-blood parameters

Cord-blood lactate was higher in the MAS group than in the non-MAS group (5.40 ± 2.40 vs 2.60 ± 2.00 mmol/L; mean difference 2.80 mmol/L, 95% CI 1.54 to 4.06; Welch $t=4.55$, $p<0.001$). In contrast, bicarbonate was lower (15.03 ± 5.17 vs 22.18 ± 4.78 mEq/L; mean difference -7.15 mEq/L, 95% CI -9.92 to -4.38; $p<0.001$), and base excess was more negative (-10.76 ± 5.69 vs -4.57 ± 4.47 mEq/L; mean difference -6.19 mEq/L, 95% CI -9.15 to -3.23; $p<0.001$) (Table 2).

Cord-blood pH was numerically lower in the MAS group (7.16 ± 0.40 vs 7.26 ± 0.20), but the difference was not statistically significant (mean difference -0.10, 95% CI -0.30 to 0.10; $p=0.308$). PCO_2, PO_2, and oxygen saturation also did not differ significantly between groups (all $p>0.05$) (Table 2).

Table 2. Umbilical Cord-Blood Parameters According To Meconium Aspiration Syndrome Status

Cord-blood parameter	MAS (n=19)	Non-MAS (n=53)	Mean difference (95% CI)	Welch t (df)	p value
pH, dimensionless	7.16 ± 0.40	7.26 ± 0.20	-0.10 (-0.30 to 0.10)	-1.04 (21.31)	0.308
PCO_2, mmHg	47.49 ± 11.65	47.25 ± 12.98	0.24 (-6.28 to 6.76)	0.07 (35.17)	0.941
Bicarbonate, mEq/L	15.03 ± 5.17	22.18 ± 4.78	-7.15 (-9.92 to -4.38)	-5.27 (29.76)	<0.001
PO_2, mmHg	26.79 ± 17.73	32.48 ± 24.79	-5.69 (-16.38 to 5.00)	-1.07 (44.50)	0.289
Oxygen saturation, %	37.28 ± 23.67	43.13 ± 26.01	-5.85 (-19.05 to 7.35)	-0.90 (34.71)	0.374
Base excess, mEq/L	-10.76 ± 5.69	-4.57 ± 4.47	-6.19 (-9.15 to -3.23)	-4.29 (26.40)	<0.001
Lactate, mmol/L	5.40 ± 2.40	2.60 ± 2.00	2.80 (1.54 to 4.06)	4.55 (27.49)	<0.001

Values are mean ± SD. Mean differences are MAS minus non-MAS. pH is dimensionless. CI, confidence interval; df, degrees of freedom; MAS, meconium aspiration syndrome; PCO2, partial pressure of carbon dioxide; PO2, partial pressure of oxygen; SD, standard deviation.

The largest standardized separation was observed for bicarbonate (Hedges' $g=-1.45$, 95% CI -2.02 to -0.87), followed by lactate ($g=1.31$, 95% CI 0.75 to 1.88) and base excess ($g=-1.27$, 95% CI -1.84 to -0.71) (Figure 1).

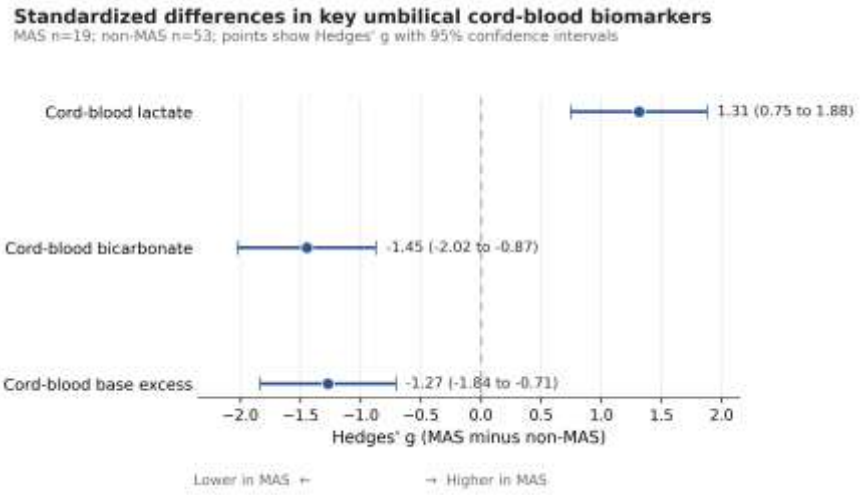

Figure 1. Standardized Mean Differences in Selected Umbilical Cord-Blood Biomarkers between Neonates with and Without Meconium Aspiration Syndrome. Points Represent Hedges' G And Horizontal Bars Represent 95% Confidence Intervals. Positive Values Indicate Higher Mean Levels In The MAS Group; Negative Values Indicate Lower Mean Levels.

Discriminatory performance

Receiver operating characteristic analysis showed that cord-blood lactate had the greatest discrimination for subsequent MAS (AUC 0.81), followed by cord-blood pH (AUC 0.75) and base deficit (AUC 0.71) (Figure 2).

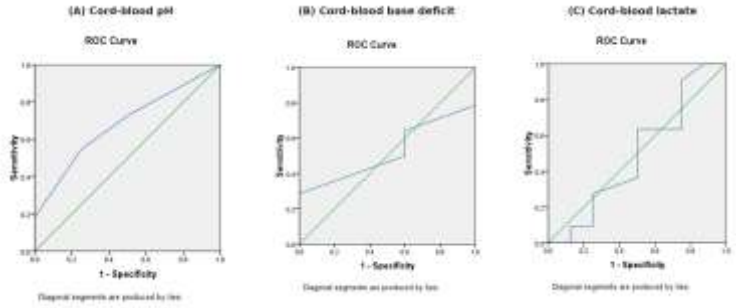

Figure 2. Receiver Operating Characteristic Curves for Umbilical Cord-Blood Ph, Base Deficit, and Lactate in Discriminating Subsequent Meconium Aspiration Syndrome. Panels A-C Correspond To Ph, Base Deficit, And Lactate, Respectively, With Areas Under The Curve Of 0.75, 0.71, And 0.81. The Diagonal Line Represents No Discrimination.

Respiratory course and short-term outcome

Respiratory distress occurred in 26/72 neonates (36.1%). Among these, 7/26 (26.9%) settled within 2 hours without respiratory support, 8/26 (30.8%) received oxygen by hood, 7/26 (26.9%) required continuous positive airway pressure, and 4/26 (15.4%) required mechanical ventilation. Among the 19 neonates with MAS, 17 (89.5%) were discharged alive and 2 (10.5%) died during hospitalization. (table3)

Table 3. Respiratory Course and Short-Term Outcomes

Domain	Treatment/Outcome	N/N	Percentage
Study outcome	Meconium aspiration syndrome	19/72	26.4% (95% CI 17.6%–37.6%)
Respiratory course	Any respiratory distress	26/72	36.1% (95% CI 26.0%–47.6%)
Treatment among neonates with respiratory distress	Settled within 2 hours without respiratory support	7/26	26.9%
	Oxygen by hood	8/26	30.8%

	Continuous positive airway pressure	7/26	26.9%
	Mechanical ventilation	4/26	15.4%
Outcome among neonates with MAS	Discharged alive	17/19	89.5%
	In-hospital death	2/19	10.5% (95% CI 2.9%–31.4%)

DISCUSSION

Of the 72 neonates in this prospective cohort, 19 (26.4%) developed meconium aspiration syndrome (MAS). Neonates who developed MAS had significantly higher cord-blood lactate, lower bicarbonate, more negative base excess, and lower 1- and 5-minute Apgar scores. Lactate had the highest discrimination for subsequent MAS (AUC 0.81) compared to pH (AUC 0.75) and base deficit (AUC 0.71). However, there were no significant differences between groups for pH, PCO_2, PO_2, or oxygen saturation. These results indicate that metabolic markers, especially lactate, may be better able to detect clinically significant intrapartum compromise than individual pH or respiratory gas measurements.

The present results are similar to Bhat et al. who studied 231 MSAF complicated deliveries, with 25 neonates (10.8%) developing MAS. They evaluated cord pH, base deficit, and lactate by ROC analysis and concluded that metabolic acid–base abnormalities were helpful in identifying neonates who were at risk for developing subsequent MAS [9]. This increased incidence of MAS in our cohort could be due to differences in referral patterns, severity of meconium, diagnostic criteria, and obstetric risk. However, both studies suggest that cord blood should be collected before clinical respiratory deterioration is complete.

Lactate is not only predictive of the occurrence of MAS, but also of its prognosis. Mazouri et al. investigated neonates with established MAS, and found that 40% received thick MSAF and 60% received thin MSAF. Lactate levels in the cord blood were correlated with pulmonary haemorrhage, persistent pulmonary hypertension, intraventricular haemorrhage and respiratory failure requiring ventilatory support [10]. Their findings support our observation of a mean lactate difference of 2.80-mmol/L between MAS and non-MAS neonates, and indicate that cord lactate levels may be a marker of disease risk as well as of the severity of cardiopulmonary and neurological disease.

Our finding of significantly lower Apgar scores in neonates with MAS is in agreement with Oliveira et al. In their NICU cohort, MAS represented 0.66% of admissions, non-reassuring or abnormal cardiotocography and low 1-minute Apgar score were associated with MAS, and surfactant requirement predicted greater disease severity [11]. In our study, the mean Apgar scores were 2 points lower at 1 minute and 1 point lower at 5 minutes. Cord lactate and bicarbonate could thus serve as objective biochemical markers of the physiological compromise that is clinically evident as a low Apgar score.

Clinical observation alone may not be enough as respiratory distress can occur after a reassuring transition. Singh et al. specifically assessed vigorous neonates born by MSAF and showed that respiratory disease, such as MAS, may manifest after birth. At a cut-off of 9, their clinical prediction score had a sensitivity of 74.1%, specificity of 84.6%, a positive predictive value of 71.6%, and a negative predictive value of 86.2% [12]. The lactate AUC of 0.81 is similar to the overall discrimination and suggests that biochemical markers may be used in addition to early clinical scoring, especially if the neonate is initially vigorous.

Hernández et al. created a model to predict ventilation in neonates with MAS based on fetal tachycardia, time from meconium detection to delivery, low 5-minute Apgar score, delivery room intubation, and caesarean delivery. The model had a sensitivity of 72% and a specificity of 64%, but misclassified around 32% of cases [13]. These results show the shortcomings of clinical and obstetric variables. Our study did not develop a multivariable prediction model, but the large standardized differences for bicarbonate, lactate, and base excess indicate that adding cord-blood biochemistry to the prediction model may enhance risk stratification beyond perinatal characteristics.

Another known risk factor is the consistency of the meconium. Berkus et al. reported that moderate or thick meconium was associated with an adverse neonatal outcome, independently of fetal heart-rate abnormalities and maternal medical disease (RR 3.2, 95% CI 2.0–5.2) [14]. Usta et al. also found a set of intrapartum and neonatal risk factors for MAS,

with 92% sensitivity and 56% specificity and 8% positive predictive value [15]. These studies collectively suggest that exposure to meconium and routine clinical parameters are good indicators of exposure, but do not have high positive discrimination. Cord lactate could provide further specificity as it is a direct measure of anaerobic metabolism.

The epidemiological study by Dargaville et al. highlights the clinical significance of early stratification. MAS-related mortality was relatively rare, but was seen in 2.5% of affected infants, with the median duration of intubation being 3 days and prolonged oxygen therapy and hospitalization being significant burdens [16]. In our smaller group, 15.4% of neonates with respiratory distress needed mechanical ventilation, and mortality in MAS cases was 10.5%. The broad confidence interval for mortality and the small number of deaths does not allow for direct comparison, but the results do indicate that clinically significant respiratory morbidity is still occurring due to MAS.

It is interesting that there is no significant difference in pH, although there are differences in lactate, bicarbonate and base excess. Cord pH is a combination of respiratory and metabolic factors and can be relatively preserved if there are compensatory mechanisms. Lactate is a more direct measure of anaerobic metabolism, while bicarbonate depletion and more negative base excess reflect the buildup of metabolic acid. The precision of pH estimates may also have been reduced by sampling variability, arterial or venous admixture, and the relatively small size of the MAS group. Therefore, pH should not be used alone to assess neonates exposed to MSAF.

The strength of this study is that it included prospective enrollment, that cord blood was sampled immediately, that the outcome of MAS was clinically and radiographically defined, and that several acid–base parameters were directly compared. Reporting effect sizes and ROC areas further confirms that there was clinically meaningful separation in addition to statistical significance.

The main drawbacks are the small single-centre sample (n = 19 MAS events), and the lack of externally validated biomarker thresholds. Arterial and venous cord samples were not analysed separately and meconium thickness, fetal heart-rate patterns, duration of labour, timing of cord clamping and maternal risk factors were not included in multivariable analysis. The results of the ROC should therefore be considered exploratory. Further multicentre studies are required to determine if lactate contributes to the predictive value of Apgar scores, meconium grade and intrapartum clinical variables and to determine thresholds associated with respiratory-support requirements and mortality.

Overall, cord-blood lactate, bicarbonate, and base excess were more strongly associated with subsequent MAS than isolated pH or respiratory gas parameters. Lactate provided the best discrimination and may be a useful early adjunct for identifying MSAF-exposed neonates who require closer observation and timely respiratory support.

CONCLUSION

Cord-blood lactate, bicarbonate, and base excess were significantly associated with subsequent meconium aspiration syndrome, with lactate showing the best discriminatory performance. These readily available parameters may support early identification and closer monitoring of at-risk neonates born through meconium-stained amniotic fluid.

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