PaO_2/FiO_2 Ratio as Predictor of Mortality in Neonates with Meconium Aspiration Syndrome

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Abstract

Objectives Partial arterial pressure of oxygen/fraction of oxygen in inspired air (PaO_2/FiO_2) ratio has been used as a predictor of outcome in some neonatal conditions, but has not been used in meconium aspiration syndrome (MAS). This study was conducted with the objective to study if the PaO_2/FiO_2 ratio of < 200 at 6, 12, and 24 hours of life can predict mortality in neonates with MAS.

Study Design Two hundred neonates with MAS were included in the study. PaO_2/FiO_2 ratio was calculated at 6, 12, and 24 hours of life. Sensitivity, specificity, predictive values, and likelihood ratio at cut-off < 200 to predict mortality was calculated.

Results PaO_2/FiO_2 ratio at cut-off of < 200 was found to predict mortality in neonates with MAS with 94.1% sensitivity and 96.6% specificity. It was also able to predict development of severe MAS.

Conclusion PaO_2/FiO_2 at < 200 can predict all-cause mortality in neonates with MAS. It can be used as vital tool in identifying newborns at high risk, thus helping in focused care.

Keywords

- PaO_2/FiO_2 ratio
- MAS
- neonates

Meconium aspiration syndrome (MAS) is one of the main causes of neonatal mortality and morbidity. About 5% of neonates born with meconium-stained amniotic fluid (MSAF) develop MAS.[1] MAS has been reported to have mortality as high as 26%.[2,3] Morbidity in MAS is seen in the form of increased duration of hospital stay, prolonged stay on intravenous (IV) fluids, and sepsis.[4] Owing to its high morbidity and mortality, it becomes pertinent to study the risk factors, outcomes, and factors predicting mortality, morbidity, and outcomes in these neonates, although the studies are limited.[5,6] Singh et al observed fetal distress and absent/poor cry to be predictors of respiratory distress in neonates born through MSAF.[7] Lin et al observed asphyxia, pneumothorax, and persistent pulmonary hypertension of newborn (PPHN) to be the most important risk factors of mortality in MAS.[8]

Louis et al[5] reported higher initial oxygen requirement apart from myocardial dysfunction and birth weight to be independent predictors of mortality in neonates with MAS. Parameters that have been studied as a measure of higher oxygen demand in different studies include partial arterial pressure of oxygen (PaO_2), fraction of oxygen in inspired air (FiO_2), PaO_2/FiO_2 ratio (ratio of PaO_2 to FiO_2), SpO_2/FiO_2 ratio (ratio of percentage oxygen saturation to FiO_2), oxygenation index (OI), and oxygen saturation index (OSI).[5,9,10] Some of these like OI and OSI can be done only in ventilated neonates.[10–12] PaO_2/FiO_2, also called as the Carrico index, that is, ratio of PaO_2 to FiO_2 is being shown to be a reliable predictor of mortality and morbidity in congenital diaphragmatic hernia and periventricular hemorrhage.[13,14] The ratio has also been used as a component of neonatal and pediatric prediction mortality scores.[10,15] It is an invasive parameter but it has the advantage of being a bed side investigation and can be done in ventilated and nonventilated neonates as well. Considering the high mortality associated with MAS in neonates, this study was performed with the primary objective to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR) of PaO_2/FiO_2 ratio of < 200 at 6, 12,

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and 24 hours of life in predicting mortality in full neonates with MAS. Our secondary objectives were to determine the sensitivity, specificity, PPV, NPV, and LR of PaO_2/FiO_2 ratio of < 200 in predicting outcome in terms of development of severe MAS, establishment of full breastfeeding, duration of IV fluids, and duration of hospital stay. Also, we compared the relative performances of PaO_2/FiO_2 ratio at cut-offs of 150, 200, 250, and 300 in predicting mortality.

Methods

This diagnostic accuracy study was conducted in the department of pediatrics of a tertiary care teaching hospital after obtaining approval from institutional ethical committee. The study was conducted from November 2015 to April 2017. All neonates ≥ 37 completed weeks of gestation admitted in the neonatal intensive care unit (NICU) with diagnosis of MAS were enrolled in the study after taking written informed consent from parent/guardian. MAS was defined as neonates born through MSAF, having respiratory distress, and chest X-ray findings suggestive of MAS.[16] Respiratory distress was scored using Downes score in study participants[17] and neonates with score of $> 1/10$ were labeled to have respiratory distress. Neonates with ≥ 2 risk factors for early-onset sepsis, infant of diabetic mother, neonates of mother suffering from tuberculosis, human immunodeficiency virus, or other chronic diseases, and neonates with associated congenital anomalies or clinical suspicion of chromosomal diseases were excluded from study. FiO_2 was recorded and PaO_2 was measured in all neonates at 6 ± 2, 12 ± 2, and 24 ± 2 hours. Neonates were monitored and managed in the NICU as per standard unit protocol. Severe MAS was defined as disease requiring assisted ventilation for > 48 hours, often associated with PPHN.[1]

All the details were recorded in a predesigned case record form.

Methods of Assessment of PaO_2 and FiO_2

PaO_2 was measured using arterial blood gas (ABG) estimation by ABG analyzer (Nova Biomedical). Modified Allen's test was done in all neonates before taking arterial blood sample. Preductal arterial sample, from right radial artery, was taken under all aseptic precautions in 1 mL preheparinized syringe and evaluated for blood gas.

Estimation of FiO_2

FiO_2 was measured using the FiO_2 monitor (InMed).

Sample Size

There was no previous study that had used PaO_2/FiO_2 ratio as predictor of mortality in neonates with MAS. Considering that PaO_2/FiO_2 ratio of < 200 at 6 ± 2 hours, can determine mortality with 85% sensitivity, with 15% relative precision on either side, and 95% confidence level, we needed a sample size of 30, that is, the patients who did not survive. Data from our NICU showed a mortality of 15% in neonates admitted with MAS. To get nonsurvivor number of 30, we needed to enroll 200 neonates with MAS in our study.

Statistical Analysis

Statistical analysis was performed by the SPSS program for Windows, version 20.0 (SPSS, Chicago, IL). Continuous variables were presented as mean $\pm$ standard deviation (SD), and categorical variables were presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired *t*-test, whereas Mann–Whitney *U*-test was used for non normally distributed variables. Categorical variables were analyzed using either chi-square test or Fisher's exact test. Receiver operating characteristics (ROC) curve were drawn and area under the curve (AUC) was calculated to compare the diagnostic accuracy of PaO_2/FiO_2 ratio at cut-offs of < 150, < 200, < 250, and < 300 at 6, 12, and 24 hours. For all statistical tests, a *p*-value of < 0.05 was considered as significant.

Results

In our study, out of 200 neonates enrolled, 178 (89%) survived and 22 (11%) neonates did not. We had a male: female ratio of 2.1:1 in our study. Among the survivors and nonsurvivors, there was predominance of males. Mean gestational age and other baseline parameters were comparable in both survivors and nonsurvivors as shown in ►**Table 1**, except the Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score. Survivors had a significantly higher mean $\pm$ SD APGAR scores than nonsurvivors at 1, 5, and 10 minutes (8.7 ± 0.6, 8.9 ± 0.43, and 8.9 ± 0.18 vs. 7.3 ± 1.8, 7.8 ± 1.3, and 8.0 ± 1.3; *p*-value of < 0.05). Median APGAR score of survivors was 9, 9, and 9, which was higher than that of nonsurvivors, that is, 7, 8, and 8.5 at 1, 5, and 10 minutes, respectively. Downes score at birth in survivors was 1.9 ± 0.78 and in nonsurvivors was 2.9 ± 1.02. Downes score gradually decreased in neonates who survived over the course of 24 hours, whereas an increasing pattern was seen in Downes score who did not survive.

Enrolled neonates were provided oxygen support by means of oxygen hood, nasal prongs, continuous positive airway pressure, nasal intermittent positive pressure ventilation, or ventilator. Eight out of 178 survivors and all the 22 nonsurvivors required mechanical ventilation. Among the survivors, 11 had birth asphyxia, and out of these 1 had hypoxic ischemic encephalopathy (HIE)-I, 2 HIE-II, and 1 neonate developed HIE-III. Out of the nonsurvivors, 10 neonates had birth asphyxia and the number of neonates in this group with HIE-I, HIE-II, and HIE-III were 0, 1, and 2, respectively. Mean $\pm$ SD of ABG parameters, namely, PaO_2, SpO_2, FiO_2, partial arterial pressure of carbon dioxide ($PaCO_2$), PaO_2/FiO_2, and SpO_2/FiO_2 ratio were compared among survivors and nonsurvivors (►**Table 2**). It was observed that survivors had significantly higher mean PaO_2, SpO_2, and lower FiO_2 and $PaCO_2$ values as compared with nonsurvivors at all 6, 12, and 24 hours of life. Also, it was observed that the mean PaO_2/FiO_2 ratio and SpO_2/FiO_2 ratio were significantly higher in survivors as compared with nonsurvivors at all 6, 12, and 24 hours.

Table 1 Baseline demographic profile of survivors and nonsurvivors

Variables	Survivors $N = 178$ (%)	Nonsurvivors $N = 22$ (%)	*p*-Value
Gender			
Male	117 (65.7)	18 (81.8)	
Female	61 (34.2)	4 (18.1)	
Gestation			
37–39 wk	142 (79.8)	18 (81.8)	0.831
40–41 wk	36 (20.2)	4 (18.2)	
AGA	152 (85.4)	16(72.7)	0.212
SGA	24(13.4)	6(27.3)	
LGA	2(1.12)	0	
Anthropometric parameters	**Mean ± SD**		
Birth weight (g)	2,703.21 ± 434.83	2,654.7 ± 459.41	0.561
Length (cm)	47.5 ± 1.79	47.4 ± 1.67	0.732
Head circumference (cm)	33.5 ± 0.85	33.5 ± 0.93	0.904
Gestational age (wk)	38.2 ± 1.53	38.5 ± 1.41	0.378
Downes score			
At birth	1.9 ± 0.78	2.9 ± 1.02	< 0.001[a]
6 h	1.7 ± 0.83	3.5 ± 1.47	< 0.001[a]
12 h	1.2 ± 0.98	3.9 ± 1.63	< 0.001[a]
24 h	0.7 ± 1.0	4.3 ± 1.70	< 0.001[a]
APGAR score			
APGAR score – 1 min	8.7 ± 0.6 9.0 (0)[b]	7.3 ± 1.8 7.0 (2.0)[b]	0.001[a]
APGAR score – 5 min	8.9 ± 0.43 9.0 (0)[b]	7.8 ± 1.3 8.0 (2.0)[b]	0.002[a]
APGAR score –10 min	8.9 ± 0.18 9.0 (0)[b]	8.0 ± 1.3 8.5 (2.0)[b]	0.003[a]

Abbreviations: AGA, appropriate for gestational age; APGAR score, Appearance, Pulse, Grimace, Activity, and Respiration score; IQR, interquartile range; LGA, large for gestational age; SD, standard deviation; SGA, small for gestational age.
[a]*p*-Value of < 0.05 is considered significant.
[b]Median (IQR).

Table 2 Comparison of ABG parameters among survivors and nonsurvivors

	Survivors ($n = 178$) (mean ± SD)	Nonsurvivors ($n = 22$) (mean ± SD)	*p*-Value
PaO_2			
6 h	108.07 ± 35.7	69.37 ± 20.9	< 0.001
12 h	104.6 ± 34.3	72.8 ± 27.2	< 0.001
24 h	106.1 ± 37.2	79.3 ± 41.8	< 0.001
SpO_2			
6 h	95.8 ± 4.5	80.3 ± 16.04	< 0.001
12 h	96.6 ± 3.1	80.4 ± 13	< 0.001
24 h	96.3 ± 6.8	73.9 ± 21.2	< 0.001
FiO_2			
6 h	0.33 ± 0.06	0.54 ± 0.21	< 0.001
12 h	0.30 ± 0.07	0.61 ± 0.25	< 0.001
24 h	0.26 ± 0.07	0.65 ± 0.26	< 0.001
$PaCO_2$			
6 h	23.7 ± 4.6	31.1 ± 7.3	< 0.001
12 h	23.3 ± 4.5	33.5 ± 10.5	< 0.001
24 h	23.5 ± 4.4	31.7 ± 6.9	< 0.001
PaO_2/FiO_2 ratio			
6 h	327.9 ± 97.0	144.8 ± 51.4	< 0.001
12 h	355.1 ± 114.1	150.4 ± 74.8	< 0.001
24 h	412.5 ± 135.5	139 ± 45.4	< 0.001
SpO_2/FiO_2 ratio			
6 h	299.2 ± 63.46	171.3 ± 60.46	< 0.001
12 h	340.0 ± 89.43	153.4 ± 66.41	< 0.001
24 h	388.9 ± 92.87	125.7 ± 57.80	< 0.001

Abbreviations: ABG, arterial blood gas; FiO_2, fraction of oxygen in inspired air; $PaCO_2$, partial arterial pressure of carbon dioxide; PaO_2, partial arterial pressure of oxygen; SD, standard deviation; SpO_2, oxygen saturation.

PaO_2/FiO_2 ratio at cut-off of < 200 at 6, 12, and 24 hours was used to predict mortality in the studied neonates. The ratio had maximum sensitivity (94.1%) and specificity (96.6%) with AUC of 0.95 at 24 hours of life. The maximum NPV (98.8%) was seen at 24 hours and PPV (74.1%) was at 6 hours with a maximum LR (27.68%) at 24 hours (►**Table 3**). Cut-off of 150, 250, and 300 were also used to predict mortality. PaO_2/FiO_2 cut-off of < 200 turned out to be the best predictor statistically (►**Table 3**).

Comparing these ratios among themselves, it can be seen that PaO_2/FiO_2 < 300 was found to be highly sensitive and PaO_2/FiO_2 < 150 to have high specificity in predicting outcome. But none of these were both sensitive and specific at the same time. Ratio of < 200 at 6, 12, and 24 hours of life had both the best sensitivity and specificity with AUC ranging from 0.92 to 0.95 (►**Table 3**).

ROC curve was also dawn to assess the diagnostic performance of PaO_2/FiO_2 ratio at cut-off of < 200 for predicting mortality in neonates with MAS. AUC at 6 hours was 0.89 and at 24 hours was 0.95, concluding that the PaO_2/FiO_2 ratio at 24 hours is a better predictor of mortality in neonates with MAS (►**Fig. 1A**, **B**).

PaO_2/FiO_2 < 200 was also assessed to predict secondary outcomes, namely, development of severe MAS, establishment of breastfeeding by day 5, duration of IV fluids for ≥ 5 days, and duration of hospital stay for ≥ 8 days (►**Table 4**). It was found to significantly predict development of severe MAS in these neonates with a sensitivity of 88.8% and specificity of 92.5% in this study.

Sensitivity and specificity of PaO_2 was estimated at 6, 12, and 24 hours of life and it was found to have maximum sensitivity of 79.2% and specificity of 81.8% at PaO_2 < 83.1 at 6 hours of life. At 12 hours, at PaO_2 < 85.7, sensitivity was 75.8% and specificity was 77.3%, and at 24 hours, at a PaO_2 < 79.5, sensitivity was 78.1% and specificity was 64.7%.

Table 3 Sensitivity, specificity, PPV, NPV, and LR of PaO_2/FiO_2 ratio < 200, 150, 250, and 300 at 6, 12, and 24 hours in predicting mortality

	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR	AUC	*p*-Value
$PaO_2/FiO_2 < 200$								
6 h	90.9%	96.1%	74.1%	98.8%	23.31	0.09	0.94 (0.85–1.00)	< 0.001
12 h	90.9%	92.7%	60.6%	98.8%	12.45	0.10	0.92 (0.85–1.0)	< 0.001
24 h	94.1%	96.6%	72.7%	99.4%	27.68	0.06	0.95 (0.000–1.0)	< 0.001
$PaO_2/FiO_2 < 150$								
6 h	50.0	90.4	91.7	94.1%	5.21	0.55	0.75 (0.611–0.88)	< 0.001
12 h	50.0	100.0	100.0	94.2%		0.50	0.75 (0.613–0.89)	< 0.001
24 h	58.8	99.4	90.9	96.2%	98.00	0.41	0.79 (0.644–0.94)	< 0.001
$PaO_2/FiO_2 < 250$								
6 h	95.5%	80.3%	37.5%	99.3%	4.85	0.06	0.88 (0.81–0.94)	< 0.001
12 h	90.9%	83.7%	40.8%	98.7%	5.58	0.11	0.87 (0.79–0.95)	< 0.001
24 h	100.0%	93.3%	58.6%	100.0%	14.93	0.00	0.97 (0.94–0.99)	< 0.001
$PaO_2/FiO_2 < 300$								
6 h	100.0%	53.4%	21.0%	100.0%	2.15	0.00	0.77 (0.69–0.84)	< 0.001
12 h	95.5%	64.0%	24.7%	99.1%	2.65	0.07	0.80 (0.72–0.87)	< 0.001
24 h	100.0%	82.6%	35.4%	100.0%	5.75	0.00	0.91 (0.87–0.95)	< 0.001

Abbreviations: AUC, area under the curve; FiO_2, fraction of oxygen in inspired air; LR, likelihood ratio; NPV, negative predictive value; PaO_2, partial arterial pressure of oxygen; PPV, positive predictive value.

We estimated the sensitivity and specificity of SpO_2/FiO_2 ratio and found that at $SpO_2/FiO_2 < 236.6$ at 24 hours had sensitivity of 94.9% which is comparable to the sensitivity of $PaO_2/FiO_2 < 200$ (94.1%). Specificity of $SpO_2/FiO_2 < 236.6$ at 24 hours was 100% which is higher against the specificity of $PaO_2/FiO_2 < 200$ (96.6%) at 24 hours. ►**Fig. 2** shows the ROC curve of SpO_2/FiO_2 at 24 hours of life for predicting mortality in neonates with MAS.

Discussion

We observed that the PaO_2/FiO_2 ratio of < 200 was able to predict mortality in term neonates with MAS. It was also able to predict development of severe MAS in these neonates.

Few previous studies have reported certain predictors of mortality in MAS. Vora and Nair studied 90 neonates admitted with MAS and reported abnormal fetal heart rate to be significantly associated with the neonates' outcome.[18] A large cohort of neonates with MAS was studied for Australian and New Zealand population, and the authors reported low APGAR score and fetal distress to be significantly associated with mechanical intubation due to MAS.[6] We also found low APGAR scores to be associated with poor neonatal outcome in our study. Presence of tracheal meconium was another risk factor to be associated with the presence of MAS.[19] Fischer et al reported thick meconium amniotic fluid, fetal tachycardia, APGAR score of ≤ 3 at 1 minute, and birth in a level III facility to be independently associated with severe MAS.[20] Other clinical predictors of morbidity in MAS were reported to be the need for mechanical ventilation in the first hour of life, shock, renal failure, asphyxia, and PPHN.[19–22] Apart from these factors, presence of high OI, high alveolar arterial oxygen tension gradient at admission, and at 2 hours to be risk factors of mortality in MAS neonates.[5] PaO_2/FiO_2 ratio gives an objective assessment of the pulmonary status and was also used as a predictor of outcome in patients after congenital diaphragmatic hernia, periventricular hemorrhage, and cardiac surgery and was found to be a good predictor of mortality in all the conditions.[9,13,14] Our results in MAS were in line with other studies. Louis et al assessed initial oxygen requirement (FiO_2), maximum oxygen requirement, duration of oxygen supplementation, and initial PaO_2 between survivors and nonsurvivors in MAS and found a significant difference in initial oxygen requirement and maximum oxygen requirement.[5] We also found the PaO_2/FiO_2 ratio to be an early predictor of mortality in MAS.

SpO_2/FiO_2 ratio has also shown to have a high specificity and sensitivity at 24 hours and can be used as a noninvasive parameter in predicting mortality; however, due to limitations of SpO_2 like dyshemoglobinemias and hyperbilirubinemia, more studies need to be done for its validation in MAS. Morbidity was also assessed in terms of development of severe MAS, duration of hospital stay, duration of IV fluids, and establishment of breastfeeding. It was seen that the PaO_2/FiO_2 ratio of < 200 could predict development of severe MAS in these neonates. In the study by Louis et al,[5] median duration among survivors was 168 hours (7 days) and among nonsurvivors was 24 hours. In our study, we also had a shorter duration

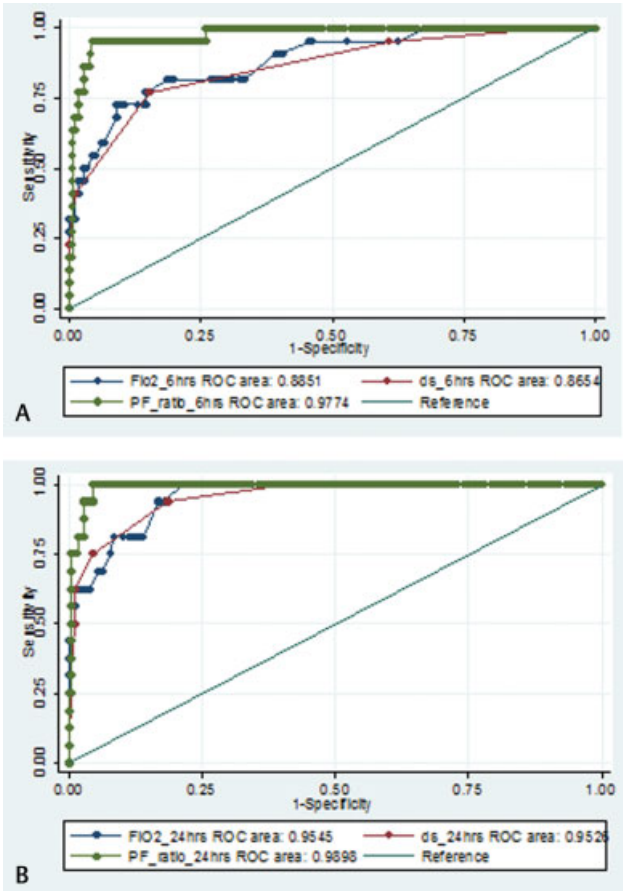

Fig. 1 (**A**, **B**) Receiver operating characteristics (ROC) curve of partial arterial pressure of oxygen (PaO_2)/fraction of oxygen in inspired air (FiO_2) < 200 at 6 and 24 hours of life.

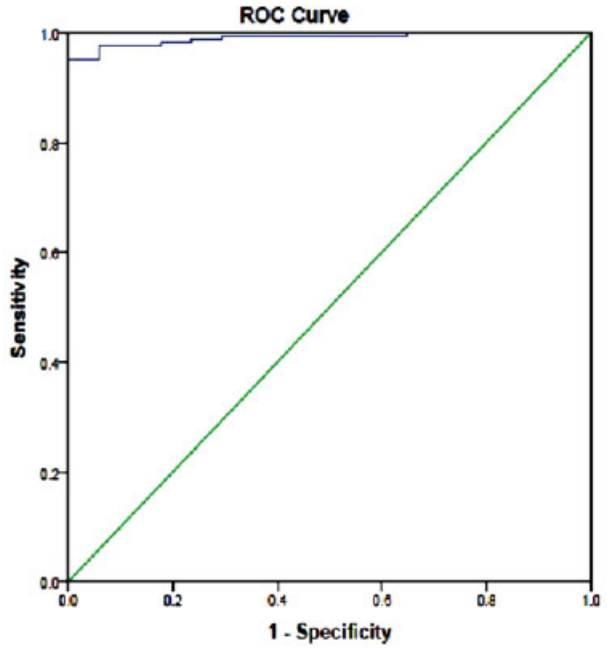

Fig. 2 Receiver operating characteristics (ROC) curve of oxygen saturation (SpO_2)/fraction of oxygen in inspired air (FiO_2) < 236.6 at 24 hours of life.

of hospital stay among nonsurvivors, that is, 3.5 days, as against 8.57 days among survivors. In another study on MAS-intubated neonates, duration of hospital stay was seen to be 17 days.[6]

The strength of this study is that the PaO_2/FiO_2 ratio was prospectively assessed at multiple time points in neonates with MAS within an early and crucial period of 24 hours. In our setup of limited resources and increased burden on newborn emergency health care, this ratio can be used as a vital tool and point of care investigation in identifying newborns at high risk, thus helping in triage and more focused care of those neonates.

We assessed all-cause mortality in our study. More studies may be conducted to assess cause-specific mortality taking care of confounders like birth asphyxia, sepsis, and shock so that the specific role of PaO_2/FiO_2 in predicting mortality in MAS can be studied.

To conclude, PaO_2/FiO_2 ratio can be used in neonates with MAS to predict at-risk neonates and can be used for early intervention.

Funding
None.

Conflict of Interest
None.

Table 4 Sensitivity, specificity, PPV, NPV, and LR of PaO_2/FiO_2 ratio < 200 at 24 hours in predicting secondary outcomes

PaO_2/FiO_2 < 200	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR	AUC	*p*-Value
Development of severe MAS	88.80	92.50	36.40	99.4	11.84	8.25	0.91	< 0.001
Establishment of breastfeeding by day 5	4.90	98.20	85.70	32.0	2.72	1.03	0.52	0.44
Duration of IV fluids ≥5 days	5.30	83.2.0	22.70	48.60	0.32	0.88	0.44	0.11
Duration of hospital stay ≥8 days	30.00	89.70	13.60	96.00	2.91	1.28	0.56	0.09

Abbreviations: AUC, area under the curve; FiO_2, fraction of oxygen in inspired air; IV, intravenous; LR, likelihood ratio; MAS, meconium aspiration syndrome; NPV, negative predictive value; PaO_2, partial arterial pressure of oxygen; PPV, positive predictive value.

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