Epidemiology and risk factors for acquiring and predicting disease severity in meconium aspiration syndrome

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Background. Meconium aspiration syndrome (MAS) occurs in approximately 5% of babies born through meconium-stained amniotic fluid. Risk factors associated with severity of MAS in neonates from developing countries has been infrequently described.
Objective. To identify incidence and risk factors associated with the severity of MAS in a lower middle-income country.
Method. A retrospective descriptive analysis was conducted on records of neonates diagnosed with MAS at four regional hospitals in the eThekwini district of KwaZulu-Natal, South Africa, between 1 January 2015 and 31 December 2017.
Results. A total of 187 neonates had been diagnosed with MAS, of whom 157 survived. The overall incidence of MAS was 2 per 1 000 live births. All the neonates were born through thick meconium. The majority (n=119, 63.6%) of patients were male. Asphyxia was documented in 97 cases (51.9%) and was significantly associated with severe disease (p<0.001). Seizures were noted in 91patients (48.7%), of which 86 (94.5%) occurred in neonates with asphyxia. A quarter of the sample (n=47, 25%) were outborn, with severe disease associated significantly with this group (p=0.025). Multiple logistic regression showed that the occurrence of seizures was significantly associated with severe MAS, (adjusted odds ratio = 23.7, 95% confidence interval 7.58 - 97.7; p<0.001).
Conclusion. Neonates born through thick meconium, with moderate to severe asphyxia that is associated with seizures are at increased risk of developing severe MAS. Close monitoring of labour in the intrapartum period, early recognition of fetal distress and timely obstetric intervention are crucial to prevent asphyxia.
Keywords: meconium-stained amniotic fluid, meconium aspiration syndrome, asphyxia, Apgar score

S Afr J Child Health 2022;16(4):239-244. https://doi.org/10.7196/SAJCH.2022.v16i4.1856

Meconium aspiration syndrome (MAS) is characterised by early onset of respiratory distress in a neonate born through meconium-stained amniotic fluid (MSAF) with poor lung compliance and clinical hypoxaemia presenting radiographically as patchy opacification and hyperinflation.[1]

Few studies from Africa have investigated MAS, with most seeming to focus on risk factors for mortality and maternal factors associated with MSAF.[2,3] This is the first study from Africa looking at predictors of risk factors associated with disease severity of MAS.

A complete understanding of the epidemiology of MAS has been hampered by the lack of population-based studies and the lack of large numbers of neonates with confirmed disease. The incidence of MAS varies from country to country, based on available resources. Incidence has decreased over the years owing to better fetal monitoring of term and post-term babies and dealing with a neonate born through MSAF.

In developed countries, incidence of MAS ranges between 0.4 and 1 per 1 000 deliveries,[4-6] whereas the incidence is approximately 10 times higher (4 - 11 per 1 000 births) in developing countries.[2,7,8] The overall incidence of MAS and severe MAS increases with increasing gestational age.[4,6] Fischer *et al.*[6] found MAS incidences of 11% (i.e. 1.1 per 1 000 live births) at 37 - 38 weeks of gestation, 0.20% at 39 - 41 weeks and 0.49% at 42 - 43 weeks. The risk was higher in post-term neonates (42 - 43 weeks), with a 4-fold and 27-fold risk at 42 and 43 weeks gestation, respectively.

The lower incidence of MAS in developed countries is attributed to post-maturity being avoided and more aggressive management of fetal distress.[5]

Risk factors for acquiring MAS in neonates born through MSAF include gender, place of birth, mode of delivery, gestational age and condition at birth (as indicated by the 5-minute Apgar score).[4] Advanced gestational age, lower rates of caesarean section, thick meconium, birth in a tertiary centre, non-reassuring fetal heart rate tracing, acute tocolysis and planned home birth have also been associated with increased risk of MAS.[4,9] In neonates with MAS, higher birthweight reduced the odds of dying.[10]

Low Apgar scores at 1 and 5 minutes appear to be strongly associated with severity of MAS.[4,11,12] (A low Apgar score at 5 minutes has been shown to have an odds ratio of 52 (45 - 59) for developing severe MAS.[4])

Place of birth is also a risk factor that determines the severity of MAS. Neonates born in tertiary centres had a higher risk of acquiring MAS owing to high-risk pregnancies being delivered at these centres.[4] Results on mode of delivery as a risk factor for MAS vary, with some studies showing an increased risk,[4,13] some reporting no risk,[14] and others showing reduced risk of acquiring MAS with caesarean section.[15] The higher risk could be related to the fetus already being compromised.

The current study aimed to establish the incidence of MAS among neonates born at four regional hospitals in KwaZulu-Natal, South

Africa (SA), and to identify risk factors associated with severity of the condition.

Method

In this retrospective study, the medical records of neonates with a diagnosis of MAS were obtained from four regional hospitals (King Edward VIII Hospital, RK Khan Hospital, Mahatma Gandhi Memorial Hospital and Prince Mshyeni Memorial Hospital) for the period 01 January 2015 to 31 December 2017.

Risk factors for the condition and its severity analysed in this study included: mode of delivery; place of delivery; gender; Apgar score, gestational age; asphyxia; seizures; HIV exposure; persistent pulmonary hypertension of the newborn (PPHN); and air-leak syndrome.

The severity of MAS was assigned based on the classification by Cleary and Wiswell.[1]

- Mild MAS: Disease in which the patient requires <40% oxygen for <48 hours
- Moderate MAS: Disease in which the patient requires >40% oxygen for longer than 48 hours, with no pulmonary air leak
- Severe MAS: Disease in which the patient requires assisted ventilation for >48 hours and which is often associated with PPHN.

Diagnosis of asphyxia/hypoxic ischaemic encephalopathy (HIE) was based on an Apgar score of <7 at 5 minutes, associated with seizures and altered level of consciousness. Classification of asphyxia/HIE as mild, moderate or severe was based on the classification of Sarnat and Sarnat.[16]

Diagnosis of PPHN was determined mostly based on clinical grounds, as there was no resident cardiologist at the regional hospitals. Signs of PPHN were taken as differential oxygen saturation >10 mmg Hg between the pre-ductal and post-ductal oxygen saturation and a difference of 10 - 20 mmHg between partial pressure of oxygen in the right upper limb and that of the lower limbs.[17]

Statistical analyses

Descriptive and inferential statistical analyses were used. Descriptive statistics included summary measures such as minimum and maximum values, quartiles, interquartile range, means, standard deviation and coefficient of variation. Categorical variables were described as counts and percentage frequencies. Student's *t*-test was used to compare two groups when data were normally distributed and the rank–sum test was used if data were not normally distributed.

Pearson's chi-squared (χ^2) or Fisher's exact test (in the case of small frequencies) was used to determine association between categorical variables. Binary logistic regression was applied to determine factors associated with severity, including univariate analysis (unadjusted), multiple logistic regression (adjusted) and stepwise backward regression to remove irrelevant variables in the model. Results are presented as odds ratios and the associated 95% confidence intervals (CIs).

All inferential statistical analyses used a significance level of $p<0.05$.

Ethical considerations

Ethics approval for the study was received from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (ref. no. BE022/17) and gatekeeper permission was obtained from the respective hospitals and the provincial Department of Health.

Results

A total of 91 518 live births were recorded from the four regional hospitals during the study period, with 4 237 neonates born through thick MSAF (Grade 3). Fig. 1 shows the selection process of neonates with MAS, resulting in 351 files noting a diagnosis of MAS in the admission record being requested.

Files could not be found for 35 (9.9%) of the patients. From the retrospective chart review, 187 of the 4 237 neonates were identified with a primary diagnosis of MAS; 129 cases were excluded as they did not meet the criteria for MAS (no indicative features on chest X-ray) despite being born through MSAF.

Table 1 shows the breakdown of the live births, MSAF-associated births and MAS-diagnosed neonates from the four regional hospitals. A high number of births were recorded from Prince Mshyeni Memorial Hospital, likely as there is no district hospital or midwife obstetric unit in the hospital's drainage area.

The incidence of MAS in neonates born through thick meconium was 2 per 1 000 live births. In total, 4.6% of the live births were through thick meconium and 4.4% of these neonates developed MAS.

Baseline characteristics

Of the 187 neonates diagnosed with MAS, 131 cases (70.05%) were severe and 56 (29.9%) were characterised as mild. Most of the MAS-diagnosed neonates were male (*n*=119, 65%), 77 (42.8%) were HIV exposed and close to two-thirds of the neonates (*n*=114, 62%) were delivered by caesarean section (Table 2). An Apgar score <7 at 5 minutes was recorded in 35 cases (19.1%). Median and mean Apgar scores were 8 and 7.8, respectively.

Growth was appropriate for gestational age in a large proportion of the neonates (*n*=167, 89.8%). Three-quarters of the sample were inborn (*n*=140, 74.9%). Mean (SD) gestational age was 39.3 (1.52) weeks; the median age was 40 weeks (range: 34 - 43 weeks). Mean (SD) birthweight was 3 160 (483) g.

The median maternal age was 25 (IQR: 20 - 29 years). Gestational age was between 41 and 43 weeks for 25 cases (13.3%). Of these, 21 were born at 41 weeks, with three and one neonate being born at 42 and 43 weeks, respectively. The median duration of hospital stay for

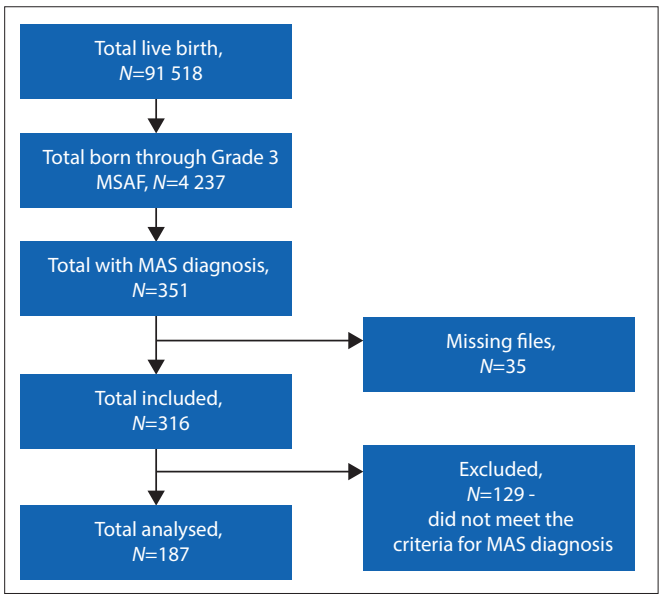

Fig. 1. Flow diagram for sample selection
MAS = meconium aspiration syndrome; MSAF = meconium-stained amniotic fluid

neonates with severe MAS was 9 days and 5 days for those with mild disease ($p<0.001$).

Risk factors associated with severity of MAS

Of the 56 neonates diagnosed with mild MAS, 10 (18%) demised; 20 of the 131 severe cases (15.3%) demised. In the group with mild disease, 11 cases (19.6%) had a low 5-minute Apgar score, compared with 24 (18.9%) in the severe group.

Twenty-nine (51.8%) of the cases with mild disease were born by caesarean section compared with 85 (66.4%) in the severe group.

Higher maternal age appeared to be associated with increased disease severity (26 years v 23 years for the severe group v mild group) ($p=0.08$).

In the group with severe disease, 60 neonates (47.2%) were HIV exposed compared with 17 (32.1%) in the mild group ($p=0.061$). Of the severe cases, 39 (29.8%) were outborn compared with eight (14.3%) of the mild cases ($p=0.025$).

A low Apgar score, gender, birthweight, gestational age and mode of delivery did not appear to be associated with severity of disease.

Documented positive blood cultures were noted in seven cases across the total sample (*Escherichia coli*: 3; Group B *Streptococcus*: 2; *Listeria monocytogenes*: 1; *Klebsiella pneumonia*: 1). All seven these cases were from the group with severe disease. Elevated C-reactive protein levels were noted in 17 of 72 cases; of these, 16 neonates had severe MAS.

Asphyxia was documented in 97 cases (52.7%), of which 8 were mild, 76 were moderate and 10 were classified as severe. Seizures were reported in 91 cases (49.2%), of which 10 (17.9%) were from the group with mild MAS and 81 (62.8%) were from the group with severe disease.

Intubation and chest compression, as part of resuscitation, were similar in both groups. On univariate analysis, both asphyxia and seizures were associated with severe disease at statistically significant levels ($p<0.001$). Of the neonates with a diagnosis of asphyxia ($n=97$), 86 (88.7%) also had seizures. Of those who did not have asphyxia ($n=87$), 5.7% ($n=5$) had seizures. This suggests that the majority of the neonates who had seizures also presented with underlying asphyxia.

PPHN was a complication in 55 of the 131 neonates (42%) with severe disease ($p<0.001$); four of these cases were diagnosed on echocardiography and the remaining diagnoses were based on clinical criteria. Air-leak syndrome was noted for 14 cases; this complication was noticed in 12 (9.2%) neonates with severe MAS although it was not statistically significant ($p=0.23$).

Backward stepwise regression analysis (Table 3) showed that, after adjusting for all the variables, the presence of seizures (adjusted odds ratio (aOR) = 23.74, 95% CI: 7.58 - 97.71; $p<0.001$) and the need for bag mask ventilation (aOR = 0.30, 95% CI: 0.10 - 0.82; $p=0.025$) were significant risk factors for severe MAS.

Discussion

This study highlights the main risk factors for disease severity, which included asphyxia, seizures and being outborn.

All the neonates in this study with MAS were born through thick meconium. Gupta *et al.*[18] reported MAS only for thick meconium in their analysis. The number of neonates born through other grades of MSAF was not reported in our study.

The incidence of MAS in our study was 2 per 1 000 live births. This incidence is higher than what has been reported in an earlier study conducted at a tertiary SA hospital (1.43 per 1 000 live births).[19] Adhikari and Gouws[2] reported an MAS incidence of 4 - 11 per 1 000 births in a retrospective study from 11 institutions in SA. Our results show a lower incidence of MAS than what has been reported from other developing countries (9 - 10 per 1 000 live births).[7,8]

Almost two-thirds of MAS cases in our study were male (63.6%), but this was not statistically significantly associated with disease severity. Similar results were found in other studies, as, for example, in a study by Dargaville *et al.*,[4] who found 52.4% of MAS cases being male and 42% born by caesarean section. Mean birthweight in our study was similar to that found by Oliveira *et al.*[12]

In an earlier SA study, Velaphi and Van Kwawegen[19] found 31% of the MAS cases to have been HIV exposed. In our study, HIV exposure was 41% although it was not associated with disease severity.

Advanced gestational age (>41 weeks) was not found to be risk factor for disease severity in our study, although other studies have found this to be a risk factor for severe MAS.[6,13,15,19] Our finding may be due to the small number of neonates born after 41 weeks in our sample. Preventing gestation to progress beyond 41 weeks has been shown to decrease the risk of acquiring MAS in developed countries.[5]

Almost two-thirds (61%) of births in our sample were through caesarean sections, but mode of delivery was not found to be a risk factor for disease severity. Our finding is similar to that of Khazardoost *et al.*,[14] although other researchers have noted caesarean section as a risk factor for severe disease[4,6,11,13] or that it could even reduce the risk of MAS.[15] Our study did not evaluate indications for caesarean section.

Neither birthweight nor maternal age was found to be significantly associated with disease severity, similar to findings reported in other studies.[6,7,11] However, Dargaville *et al.*[4] reported a doubling of MAS in growth-restricted neonates.

Unlike previous reports,[4,7,9,11,14] our findings did not show a low Apgar score at 5 minutes to be a risk factor for disease severity. However, more patients were diagnosed with asphyxia and required resuscitation than those documented with a low Apgar score (18.5%) at 5 minutes, suggesting an over-interpretation of Apgar scores. This finding is similar to what has been reported by Velaphi and Van Kwawegen.[19] Accurate documentation of the Apgar score needs to be emphasised in the delivery room.

We found asphyxia to be significantly associated with severe disease on univariate analysis. In utero asphyxia could lead to gasping respiration, which could result in aspiration of meconium.

Occurrence of post-natal seizures was identified as a risk factor for severe disease based on univariate and multivariate analyses.

Table 1. Breakdown of births at the four regional hospitals (N=91 518)

Variable	King Edward VIII	Mahatma Gandhi Memorial	RK Khan	Prince Mshyeni Memorial
Live births, *n*	18 463	21 107	18 357	33 591
MSAF-associated births, *n*	1 018	648	576	1 995
MAS-diagnosed neonates, *n* (%)	60 (5.9)	51 (7.9)	35 (6.1)	41 (2.1)

MAS = meconium aspiration syndrome; MSAF = meconium-stained amniotic fluid

Table 2. Characteristics of sample and risk factors associated with disease severity

Variable	Total (*N*=187), *n* (%)	Mild disease (*N*=56), *n* (%)	Severe disease (*N*=131), *n* (%)	*p*-value*
Birthweight (g), mean (SD)	3 156.7 (482.8)	3 142.3 (490.3)	3 162.9 (481.3)	0.791
GA (weeks), median (IQR)	40 (39 - 40)	40 (38.5 - 40)	40 (39 - 40)	0.881
Maternal age (years), median (IQR)	25 (20 - 29)	23 (18 - 29)	26 (21 - 29.5)	0.084
HIV status (*N*=180)†				0.061
Unexposed	103 (57.2)	36 (67.9)	67 (52.8)	
Exposed	77 (42.8)	17 (32.1)	60 (47.2)	
Growth (*N*=186)†				0.132
Appropriate for GA	167 (89.8)	48 (85.7)	119 (91.5)	
Large for GA	8 (4.3)	5 (8.9)	3 (2.3)	
Small for GA	11 (5.9)	3 (5.4)	8 (6.2)	
Male	119 (65)	38 (67.9)	81 (63.8)	0.594
Mode of delivery (*N*=184)†				0.079
Caesarean	114 (62)	29 (51.8)	85 (66.4)	
Normal vaginal delivery	68 (37)	27 (48.2)	41 (32)	
Born before arrival	2 (1.1)	0 (0)	2 (1.6)	
Apgar score at 5 min (*N*=183)†				0.906
Normal	148 (80.9)	45 (80.4)	103 (81.1)	
Low (<7)	35 (19.1)	11 (19.6)	24 (18.9)	
Bag mask ventilation (*N*=172)†				0.199
No	104 (60.5)	30 (53.6)	74 (63.8)	
Yes	68 (39.5)	26 (46.4)	42 (36.2)	
Intubation (*N*=172)†				0.599
No	147 (85.5)	49 (87.5)	98 (84.5)	
Yes	25 (14.5)	7 (12.5)	18 (15.5)	
Chest compression (*N*=172)†				0.716
No	164 (95.3)	53 (94.6)	111 (95.7)	
Yes	8 (4.7)	3 (5.4)	5 (4.3)	
Place of delivery				0.025
Inborn	140 (74.9)	48 (85.7)	92 (70.2)	
Outborn	47 (25.1)	8 (14.3)	39 (29.8)	
Persistent pulmonary hypertension				<0.001
No	132 (70.6)	56 (100)	76 (58)	
Yes	55 (29.4)	0 (0)	55 (42)	
Seizures (*N*=185)†				<0.001
No	94 (50.8)	46 (82.1)	48 (37.2)	
Yes	91 (49.2)	10 (17.9)	81 (62.8)	
Asphyxia (*N*=184)†				< 0.001
No	87 (47.3)	37 (66.1)	50 (39.1)	
Yes	97 (52.7)	19 (33.9)	78 (60.9)	
Duration of stay (days), median (IQR)	7 (4 - 11)	5 (3 - 6.5)	9 (5 - 13)	<0.001
Hypoxic ischaemic encephalopathy (*N*=183)†				<0.001
None	89 (48.6)	35 (62.5)	54 (42.5)	
Grade 1	8 (4.4)	6 (10.7)	2 (1.6)	
Grade 2	76 (41.5)	8 (14.3)	68 (53.5)	
Grade 3	10 (5.5)	7 (12.5)	3 (2.4)	

**p*-values based on non-missing cases only (rank–sum test; Kruskal–Wallis test; Pearson's chi-squared test; Fisher's exact test)
†Missing data
SD = standard deviation; IQR = interquartile range; GA = gestational age

Seizures were noted in neonates with moderate to severe asphyxia in 88.6% of the cases, suggesting that asphyxia complicated by seizures is associated with severe MAS. Asphyxia (both moderate and severe) has been described as being significantly associated with severe MAS before.[9]

PPHN was found in 42% (55/131) of neonates with severe MAS, similar to findings by Velaphi and Van Kwawegen.[19] PPHN could be present in utero in fetuses that experience chronic hypoxia. Several studies have shown increased musculature of the distal pulmonary arteriole in autopsies of neonates who died of severe MAS

Table 3. Predictors of severe disease among patients with MAS*

Characteristic	OR (95% CI), (*N*=187)	*p*-value	aOR (95% CI), (*N*=187)	*p*-value†	Backward stepwise OR (95% CI), (*N*=187)	*p*-value†
Died	1.59 (0.52 - 5.92)	0.444	0.99 (0.14 - 8.35)	0.989	-	
Birthweight (2500 -3 999 g)	1.00 (1.00 - 1.00)	0.263	1.00 (1.00 - 1.00)	0.326	-	
Gestational age (34 -42 wks)	1.10 (0.88 - 1.39)	0.387	1.11 (0.76 - 1.65)	0.582	-	
Maternal age (18 -40 yr)	1.05 (0.99 - 1.13)	0.121	1.01 (0.92 - 1.11)	0.828	-	
HIV exposed	1.75 (0.81 - 3.89)	0.158	2.06 (0.72 - 6.17)	0.182	-	
Large for GA	1.31 (0.16 - 27.04)	0.817	0.88 (0.02 - 52.95)	0.946	-	
Small for GA	1.31 (0.29 - 9.26)	0.747	1.23 (0.08 - 19.92)	0.879	-	
Female	1.25 (0.57 - 2.81)	0.586	1.51 (0.53 - 4.44)	0.443	-	
Apgar score at 5 min <7	1.35 (0.51 - 4.02)	0.560	0.58 (0.07 - 4.51)	0.595	-	
Suction (	2.11 (0.74 - 5.85)	0.152	2.06 (0.51 - 8.59)	0.312	-	
Bag mask ventilation	0.66 (0.30 - 1.46)	0.306	0.22 (0.05 - 0.83)	0.031	0.30 (0.10 - 0.82)	0.025
Intubation	1.32 (0.43 - 5.00)	0.646	3.50 (0.23 - 82.43)	0.400	-	
Chest compression	0.63 (0.10 - 4.92)	0.618	0.29 (0.01 - 9.65)	0.473	-	
Outborn	2.01 (0.68 - 7.38)	0.240	1.74 (0.36 - 10.66)	0.513	-	
Seizures	15.14 (5.44 - 54.18)	0.001	32.52 (5.87 - 259.11)	0.001	23.74 (7.58 - 97.71)	<0.001
Asphyxia	4.75 (2.11 - 11.45)	0.001	0.75 (0.11 - 4.18)	0.750	-	
Early onset sepsis						
Confirmed	1.55 (0.49 - 5.90)	0.478	1.05 (0.18 - 6.24)	0.955	-	
Suspected	2.93 (0.90 - 13.22)	0.106	5.20 (1.03 - 36.13)	0.064	-	

*Reference condition for severity is No/Moderate.
†Based on non-missing cases only.
CI = confidence interval; GA = gestational age.

within 48 hours of birth.[20] Pulmonary air leak as a complication of MAS was found in 14 (7.5%) neonates in our study, of whom nine presented with severe disease; the incidence was lower than what has been reported by Velaphi and Van Kwawegen.[19] (24%), but similar to that reported by Dargaville *et al.*[4] (9.6%) Other studies have reported an incidence ranging from 8 to 20%.[21,22]

Study limitations

This was a retrospective study and information regarding maternal factors such as complications during pregnancy and the intrapartum period was not obtained. Diagnosis of MAS was based on radiological findings documented in patient charts. Neonates who did not have chest X-rays before they died may have been missed, which may have resulted in an under-reporting of MAS.

All the MAS-diagnosed neonates in this study were born through thick meconium. Data regarding lower grades of meconium consistency causing MAS were not documented in the admission records of all the hospitals. Apgar scores, although well documented, may have been over-estimated. There was poor documentation of the method of suctioning of neonates born through MSAF.

Conclusion

This study offers useful insight regarding the risk factors associated with severity of MAS. Incidence was lower than what has been reported from other developing countries. Neonates born through thick MSAF and who present with moderate to severe asphyxia associated with seizures appear to be at an increased risk of acquiring severe MAS. PPHN and air-leak syndrome were common complications associated with severe MAS. Intensive fetal monitoring during labour could allow for earlier recognition of fetal distress, which could potentially prevent intrapartum asphyxia. HIV was not a risk factor for disease severity. There was a wide discrepancy between neonates who had a low Apgar score at 5 minutes and neonates diagnosed with asphyxia.

We recommend that the classification of MAS severity proposed by Cleary and Wiswell[1] be reassessed as it currently addresses severity based only on respiratory interventions. Severity should also include risk factors. Accurate estimation of Apgar score needs to be emphasised.

Declaration

Acknowledgements. We thank the staff from the medical records departments at all the participating hospitals for assisting with file retrieval.
Author contributions. RS was involved in study conceptualisation and design, and collection, analysis and interpretation of data. MA and PMJ contributed to the discussion and literature review. PT assisted with data analysis and interpretation of data. All authors critically reviewed the article prior to submission and approved the final version to be published.
Funding. None.
Conflicts of interest. None.

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Accepted 2 August 2021