RESEARCH ARTICLE

Outcomes of severe meconium aspiration syndrome in a resource restricted hospital, South Africa

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ABSTRACT

Meconium aspiration syndrome (MAS) is defined as respiratory distress in a neonate born through meconium-stained liquor (MSAL) whose symptoms cannot be otherwise explained. Mortality and morbidities vary in different resourced health settings. This retrospective study aimed to describe the management strategies, short-term (in-hospital) outcomes and mortality of neonates with severe MAS (defined as those requiring invasive ventilation) at a resource restricted hospital in Cape Town, South Africa.

Ninety-two neonates with suspected MAS were included, of which only 47 were included based on the radiological findings (patchy infiltrates and hyperinflation). The mean gestational age was 39.7±1.4 weeks and mean birth weight was 3246±522g. Most neonates were outborn. High frequency ventilation was the most common initial mode of ventilation (55%). The median duration of invasive ventilation was 3 (IQR 2-4.5) days and total duration of respiratory support was 9 (IQR 4-16) days. Surfactant was administered in 70% of neonates. Pulmonary hypertension (PPHN) developed in 53% and 88% received inhaled nitric oxide. Inotropes were administered to 45% of neonates and steroids were administered

in 64%. Pneumothorax was present in 9%. Neonates were discharged from NICU after a median age of 5 (IQR 3-7) days and had a hospital stay of 12 (IQR 6-21) days. Overall mortality was 8.5% (n=4). Mortality was low and complications (PPHN and sepsis) were high, remaining higher than in high resource countries. Management of PPHN and hypotension, as well as steroid administration were variable. A protocolized management strategy should be adopted, according to resource availability.

IMPACT STATEMENT

Severe MAS, requiring intubation and ventilation, can be treated successfully, using surfactant, high frequency ventilation, inotropes and iNO, resulting in with low mortality in low resources settings, such as South Africa.

KEYWORDS

meconium aspiration syndrome, surfactant, mortality, pulmonary hypertension

INTRODUCTION

Meconium aspiration syndrome (MAS) is defined as respiratory distress in a neonate born through meconium-stained liquor (MSL) whose symptoms cannot be otherwise explained [1]. There is no clear classification for the severity of meconium aspiration, with some studies defining severe MAS (sMAS) as a neonate requiring respiratory support (continuous positive airway pressure and/ or mechanical ventilation) [2], or a neonate requiring mechanical ventilation for more than 7 days, high frequency ventilation or extracorporeal membrane oxygenation (ECMO)[3]. Grading may be also based on FiO2 and management requirements: mild MAS – requiring FiO2<0.4 for less than 48 hours; moderate MAS – requiring FiO2>0.4 for more than 48 hours but with no air leaks and severe MAS – requiring assisted ventilation for more than 48 hours and associated with persistent pulmonary hypertension (PPHN) [1]. Eight to 19% of neonates are born through MSL, of which 5 - 33% develop MAS, and 30 - 50% of those develop sMAS [4]. Studies in high resource countries have shown a 4-fold decrease in the incidence of MAS with a decrease in mortality [1,5,6]. However, in low resource countries, the incidence has not decreased, and mortality remains high [7,8]. A United States population-based study has shown that

neonates born through MSL, with symptoms, have a two-fold increase in length of hospitalization, three-fold increase in hospitalization costs, four-fold increase in risk of mortality, three-fold higher risk of PPHN and a five-fold increase in the risk for hypoxic ischemic encephalopathy (HIE) compared to neonates born through MSL without symptoms[9].

MAS is associated with a variety of complications. These include hypoxic respiratory failure, PPHN, air leak syndromes and asphyxia. Although these are also reported as low in high resource countries [1,5,6], their incidence remains high or unknown in low resource countries [10,11]. The clinical and complications of MAS differs between developing and developed countries and affects management techniques[12].

The management of MAS is mainly supportive and includes maintaining thermoregulation, adequate oxygenation, maintenance of an adequate blood pressure and correction of acidosis and other metabolic or electrolyte disorders. Respiratory support includes surfactant administration [13], ventilatory support [14], management of PPHN [15] and steroid administration [16]. However, in most cases, a wide variety of practices occur, with varying success of treatment, especially in resource-restricted environments[12].

This study aimed to describe the mortality, complications, and management strategies of neonates with severe MAS admitted to a resource restricted hospital in Cape Town, South Africa.

MATERIALS AND METHODS

A retrospective, descriptive study was performed at a tertiary, academic, public health hospital, Cape Town, South Africa between 1st January 2016 and 31st December 2018. All neonates admitted to the neonatal intensive care unit (NICU) requiring invasive ventilation for a presumptive diagnosis of MAS were eligible for inclusion. Neonates were excluded if they required ventilation for other reasons or were diagnosed with chromosomal or congenital abnormalities.

Maternal and neonatal demographic data were collected. Prevalence and management data were collected for specific MAS-complications. Severe meconium aspiration (sMAS) was defined as neonates born through MSL who developed respiratory distress with characteristic radiological findings (hyperinflation and patchy opacity) and requiring invasive mechanical ventilation [2]. Persistent

pulmonary hypertension of the neonate (PPHN) was defined by echocardiography or the need for iNO and/or sildenafil. Hypoxic ischemic encephalopathy (HIE) was defined by the need for therapeutic hypothermia (institutional protocol was in line with the TOBY protocol. [17]). Sepsis was defined as early (<72 hours of age) or late (≥ 72hours of age) onset sepsis and a positive blood culture and/or C-reactive protein (CRP) more than 10nmol/l [18]

Chest XRs (CXR), as performed at admission, were reviewed by a neonatologist and a pediatric pulmonologist, separately, for signs consistent with MAS (hyperinflation and bilateral patchy infiltrates) and air leaks. The pediatric pulmonologist was blinded to the diagnosis.

Statistical analysis

Data were presented as means and standard deviation, or median and interquartile range, depending on normality of data. Categorical data were reported as numbers and percentage. Correlation between investigators was calculated for agreement for diagnosis of MAS on CXR. Data were analyzed using STATA IC15 (Stata Corp, 2017, College Station, TX, USA).

Ethical approval

A waiver of informed consent was approved by Stellenbosch University Health Research Ethics Committee (S20/06/141). Research was performed in accordance with the ethical standards established in the Declaration of Helsinki of 1946.

RESULTS

Ninety-two neonates were admitted with a presumptive diagnosis of sMAS during the study period. Forty-five (49%) neonates were excluded from the study. Four neonates admitted to NICU with a diagnosis of MAS did not require invasive ventilation and a further 41 neonates were excluded as the CXR's did not meet the study definition of MAS. The final study population was 47 neonates. (**Figure 1**) Maternal demographics are described in **Table 1**. The majority of neonates with sMAS were born via cesarian delivery. Meconium-stained liquor (MSL) grading was poorly reported (31/47(66%)) with most cases reported as grade 3 (**Table 1**).

The majority (89%) of neonates with sMAS were outborn. One-third of the included neonates with sMAS required IPPV during resuscitation at delivery and one-quarter required intubation at delivery (**Table 1**).

Radiological diagnosis of MAS

Agreement between a neonatologist and pediatric pulmonologist was high (78%) regarding the radiological diagnosis of MAS. Agreement was high for both evaluated radiological components of MAS (bilateral infiltrates and hyperinflation) as well as for air leaks (**table 2**).

Alternative CXR diagnoses included normal lungs, diffuse alveolar disease, congenital pneumonia, and transient tachypnoea of the newborn. The correlation of alternative diagnoses between the 2 clinicians was low (r=0.115).

Admission parameters

Upon admission, most neonates with sMAS were acidotic and hypoxic: respiratory acidosis (49%), metabolic acidosis (36%) with admission peripheral saturation of 89±9% requiring a fractional inspired oxygen of 0.69±0.27.

Pulmonary indices (OI, PF ratio and OSI), calculated on the first blood gas, are shown in **Table 3**.

Management

High frequency ventilation (HFV) and conventional ventilation (CV) (time cycled, pressure limited assist control (TCPL) mode) were used. HFV was the most common initial mode of ventilation. The primary and sole mode of ventilation was HFV in 15 (32%) and CV in 19 (40%) neonates. Two neonates (4%) were initially started on CPAP but required escalation to HFV within 4 hours of admission. In 5 (10%) neonates CV was escalated to HFV and in 8 (17%) HFV was de-escalated to CV (**Table 3**).

For neonates placed on CV, the mean PIP was 20.9±3.5 cmH2O and PEEP was 4.9±0.8 cmH2O on day 1 of admission. For neonates on HFV, the mean MAP was 16.6±4.3 cmH2O. The mean MAP for the whole study cohort was 13.2±4.3 cmH2O at time of admission.

The majority of infants received intratracheal surfactant - administered as a bolus (**Table 3**).

Non-invasive modes of ventilation, CPAP, and high flow nasal cannula were used as step down respiratory support modes for varying lengths of time (**Table 3**).

Complications and management

Air leaks were found in 11% of the study population on the CXR, with pneumothorax being the most common type (**Table 4**).

PPHN was the most common complication involving more than half of the cohort, mostly diagnosed by echocardiography. iNO was started within 4 hours of life, with the cohort receiving a maximum dose of 20ppm, as per institutional protocol. Sildenafil was used in a third of infants (**Table 4**). The mean dose was 1.4±0.75mg/kg/dose. In 12% (3/25) of neonates, sildenafil was administered primarily due to the unavailability of iNO.

One fifth of neonates were also diagnosed with hypoxic ischemic encephalopathy (HIE) and underwent therapeutic hypothermia (TH) (**Table 4**).

Of the 12 neonates (25%) with sepsis, early onset sepsis occurred in 5 (25%). Late onset sepsis microorganisms included Serratia Marcescens (n=3), Pseudomonas Aeruginosa (n=1), coagulase negative staphylococci (n=1) and Klebsiella Pneumonia (n=2). No neonate had more than one episode of sepsis.

Steroids, mostly dexamethasone, were administered for: weaning of ventilation (13/25(52%)); catecholamine-resistant hypotension (8/25(32%)); hypoglycemia (4/25(16%)), post-extubation stridor (1/25 (4%)) and for management of convulsions (1/25 (4%)). One neonate received a mixture of dexamethasone and hydrocortisone (**Table 4**).

Most neonates required an NICU stay of less than 1 week (median 5 days (IQR 3-7)) and were hospitalized for less than 2 weeks (median 12days (IQR 6-21)). The survival rate was 92% (43/47) with most neonates (77%) being discharged home. Of the 4 neonates that died, 1 (25%) neonate was inborn and 3 (75%) were born outside the hospital. Due to the low mortality, multivariate regression and odds ratio for mortality were not able to be performed as planned.

DISCUSSION

This is the first study performed at our institution, a resource-restricted academic public health hospital, in the Western Cape, South Africa, to determine the morbidity, management and short-term outcomes of severe meconium aspiration syndrome (sMAS). sMAS was defined as the need for intubation and

invasive mechanical ventilation for neonates with radiological signs of MAS (hyperinflation and coarse infiltrates). Mortality was low but morbidities (PPHN, sepsis, HIE) were high.

MAS is traditionally defined as respiratory distress in a neonate born through MSL with characteristic radiological signs whose symptoms cannot be otherwise explained [1]. This study's cohort was comprised only of neonates with severe MAS requiring invasive mechanical ventilation. The cohort also met the requirements of various other study's definitions of sMAS, with most neonates, requiring more than 40% oxygen upon admission, more than half of the cohort diagnosed with PPHN and more than half requiring HFV [1–3].

MSL and respiratory symptoms are often assumed to equate to MAS, and alternative diagnoses may only be found after radiological imaging [19]. Despite a clinical diagnosis of sMAS, nearly 50% of study neonates were excluded based on radiological findings. Abnormal radiological findings are only apparent in 59.9% of neonates born through MSL[20]. Hospital discharge coding data have been shown to be inaccurate [21]. The retrospective nature of the current study, using hospital admission codes and retrospectively reviewed CXR, may have contributed to the high exclusion rate.

The current study showed most neonates were admitted with acidosis, similar to other studies that indicated a pH below 7.25 was associated with sMAS [22,23]. Metabolic acidosis and respiratory failure, both present in this cohort, have been shown to predict mortality[24].

Admission FiO2 in this study was high, similar to another study[23]. An FiO_2 >0.3 at 1 hour after admission has been shown to be associated with prolonged hospitalization[25].In the current study the admission FiO_2 was much higher than 0.3 but no 1-hour values were available. An FiO_2>0.35 and a pH<7.22 have been shown to predict sMAS[23], as also seen in most of this study cohort. Survivors of sMAS had been shown to have a significantly lower FiO_2 with higher mean PaO_2 and SpO_2 at 6,12 and 24 hours as compared to non-survivors[26]. Survivors and non-survivors unable to be compared due to the low mortality rate in this study.

Ventilation

Ventilation in neonates with sMAS is challenging due to airway obstruction with areas of atelectasis and hyperinflation, ventilation-perfusion mismatch, airway compromise, surfactant dysfunction, and is often complicated by PPHN and air leaks [4].

More than half the current study required HFV as primary or step-up mode of ventilation, compared to only one-third in a similar cohort in a previous South African study (2008) [11],with the reason stated as being due to resource constraints at that time. The mean duration of conventional and high frequency ventilation in the current study (2 and 3 days, respectively) was similar to other studies (3 and 5 days, respectively, with duration increasing in those requiring iNO or surfactant) [6].

The most appropriate mode of ventilation for infants with MAS is unknown as there are no comparative studies of high frequency ventilation (HFV) and conventional modes of ventilation. No difference in mortality, need for ventilation, pneumothorax or length of hospitalization has been shown with the use of CPAP compared to mechanical ventilation[27]. In the current study, neonates who required CPAP only, for possible MAS, were not included. CPAP, in conjunction with surfactant, may be an alternative respiratory support strategy to avoid mechanical ventilation, especially in resource-restricted environments[28].

Oxygenation index (OI) has been used to determine the need for extracorporeal membrane oxygenation (ECMO) in neonates with hypoxic respiratory failure (HRF), including MAS, unresponsive to standard management. OI criteria for HRF are: OI<15 mild HRF, 16-25 moderate HRF, 26-40, severe HRF and >40 very severe HRF[29]. OI in this study showed mild HRF, similar to other MAS studies [30]. This may be due to the administration of surfactant [31].

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have been defined using various pulmonary indices: ALI: P/F ratio ≤300, OI 5.3-8.1 and OSI 6.5-7.8. and ARDS: P/F ratio ≤200, OI>8.1 and OSI >7.8 [32]. Our study showed that most neonates had a low PF ratio and a high OSI, indicating ARDS. A P/F ratio ≤200 has been associated with poor outcomes and predict mortality in neonates with MAS [26]. In the current study, most neonates met these criteria, but mortality was low despite significant morbidities. This may be due to the combined management with HFV, surfactant and iNO. OSI, that does not require an arterial line, has been correlated with OI in neonates with HRF[29]. This may offer an alternative to OI calculation in resource restricted environments and requires further research.

Surfactant

In the current study, more than three-quarter of neonates received at least one dose of surfactant (beractant), which may have contributed to the low mortality rate. This is in contrast to the previous South African study (2008) where only 14% of MAS neonates received surfactant, due to resource constraints [11]. This study's surfactant administration rate was similar to a Spanish study (73%) [23] but higher than that used in a Swedish study (53%) [33].

MAS inactivates surfactant [34] and surfactant replacement therapy may decrease the incidence of respiratory failure [35]. Beractant, due to its availability, was used during this study. Although both beractant and poractant alpha have been used in clinical trials, no direct comparison studies are available[36]. Surfactant was administered as a bolus in the current study. No clear clinical differences have been shown to exist between outcomes after bolus vs surfactant lavage [13,36,37].

HFV plus surfactant, as compared to conventional ventilation plus surfactant, has been shown to significantly improve respiratory indices and shortened the duration of ventilation and oxygen use [38]. We were unable to perform a similar comparison due to crossover of ventilation modes in most neonates.

The European Society of Pediatric and Neonatal Intensive Care expert consensus, 2021 supports the use of surfactant in a variety of pediatric and neonatal acute respiratory distress disorders, including MAS [39]. Surfactant could be beneficial in decreasing mortality, air leaks, duration of ventilation, oxygen therapy and hospitalization[40], which may be beneficial in low resource settings[41].

Persistent pulmonary hypertension (PPHN)

PPHN is a leading cause of death in neonates with sMAS.[42] In the current study, more than half of the cohort developed PPHN, lower than in the previous South African study (57%) [11]but significantly higher than a Jamaican (5%) [10] and Indian study(17%) [8]. PPHN has been shown to prolong hospitalization[25].

iNO is the standard therapy for PPHN whilst phosphodiesterase inhibitors (sildenafil and milrinone) may be used as adjuncts[43]. iNO was used in most of the PPHN cases in this cohort with sildenafil as an additional medication, representing the possible one-third of infants that do not respond to iNO[44]. All modalities were used in the current study. HFV combined with iNO may be more successful in treating MAS with PPHN, as compared to ventilation only [45]. The cost of iNO in resource restricted countries

may be prohibitive. Sildenafil may be an alternative and should be investigated as a first-line drug with determination of appropriate dosing[46].

Sepsis

All study neonates received first line antibiotics (ampicillin and gentamicin) upon admission. Two-thirds had a raised CRP whereas only one quarter had a positive blood culture. This is similar to a Spanish study[23]. Sepsis has been shown to be an independent risk factor for mortality in neonates with MAS[24]. Despite this, the mortality in this study was low.

Meconium is a known irritant and causes pulmonary inflammation. Abundant neutrophils and macrophages, with subsequent release of inflammatory cytokines TNF a, IL 1b and IL 8, are present in alveoli within hours [1]. Despite this, MAS has not been shown to increase the incidence of sepsis [47], despite prophylactic antibiotics [48].A raised CRP, possibly due a systemic inflammatory response, is common[49]. Prophylactic antibiotics are therefore not recommended unless there are septic risk factors present[50,51].

Air Leaks

The current study had a slightly lower incidence of air leaks as compared to international literature (9% vs 10-24%[6,11,52]). This may be due to the higher use of HFV use in the study, due to HFV's reduction of local lung overexpansion and repeated alveolar opening and closing [53].

Steroids

Steroids were administered to half of the study cohort to decrease ventilation requirements. Intravenous methylprednisolone and nebulized budesonide may shorten the duration of respiratory distress and oxygen requirement, shorten hospital stay but has shown no effect on mortality in MAS [54] . The early use of steroids, as part of a protocolized management strategy, should be considered and further evaluated.

Hypoxic ischemic encephalopathy

Nearly one fifth of study neonates had HIE meeting criteria for therapeutic hypothermia (TH), similar to Portuguese and Indian studies (30%) [25,55] but higher than in a Jamaican study (6%)[10]. HIE has also been shown to predict prolonged hospitalizations[25]

TH is an accepted therapy for HIE in most developed countries with contradictory evidence in low resource countries.[56] There may be an additive effect of TH and surfactant therapy for neonates with MAS, when other respiratory therapies have been optimized[57]. TH for MAS has shown improved oxygenation, less mechanical ventilation, shorter ICU, and total hospital stay [57,58]. More research is required to determine if TH would be advantageous for sMAS in low resource environments.

Mortality

MAS-associated mortality is low in high resource countries (2.5-4%)[6,22], whilst low resource countries have reported high mortality rates (13-26%) [7,8]. A previous South African study (2004-2006) of neonates requiring mechanical ventilation for MAS reported 33% mortality [11], attributed to infection, PPHN and the low usage of respiratory adjuncts related to various resource constraints [11]. The use of surfactant, HFV and iNO, was 6- 9%, 21-45% and 3-6%, respectively, during the study period [11], much lower than in the current study. Despite being a resource restricted NICU, our study's mortality was 8%, which is slightly higher than in high resource countries but lower than other low resource countries. This may be due to the combined use of surfactant, HFV, iNO and sildenafil, representing higher resource availability more than a decade after the previous South African study. A Spanish study, with a similar cohort and similar management strategy, showed a mortality of 6.6%[23] In a Taiwanese study, MAS was managed according to a standard protocol (CPAP and conventional mechanical ventilation with surfactant (lavage or bolus), HFV and iNO for hypoxic respiratory failure, and dexamethasone for unresponsive hypotension). This protocolized management showed a decrease in morbidity and mortality.[59] Larger studies utilizing a protocolized approach to the management of neonates with severe MAS should be performed.

This study has several limitations. Due to the retrospective nature, not all data were available. Neonates with non-severe MAS (not requiring intubation and invasive ventilation) were not included as this diagnosis was not consistently documented. Many neonates admitted with a suspected diagnosis of sMAS were excluded based on radiological images and were not further investigated.

CONCLUSION

Despite relative resource limitations, our study found that mortality was low despite a high incidence of morbidities (PPHN, HIE and culture-positive sepsis). This may be due to combined use of high frequency ventilation, surfactant and pulmonary vasodilators. Standardized, combined therapies should be investigated for MAS in resource restricted centers.

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AUTHOR CONTRIBUTIONS

JB, LW and PG developed the research question, designed the study and reviewed the ethics submission. JB conducted the literature review and collected the data and LW and PG assisted in the data interpretation. LW performed the data analysis. JB took the lead role in writing the written report. LW and PG supervised JB and provided assistance with literature review, data collection review, report review and auditing. All authors reviewed and approved the final manuscript.

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Figure 1. Flow diagram of patients included in study

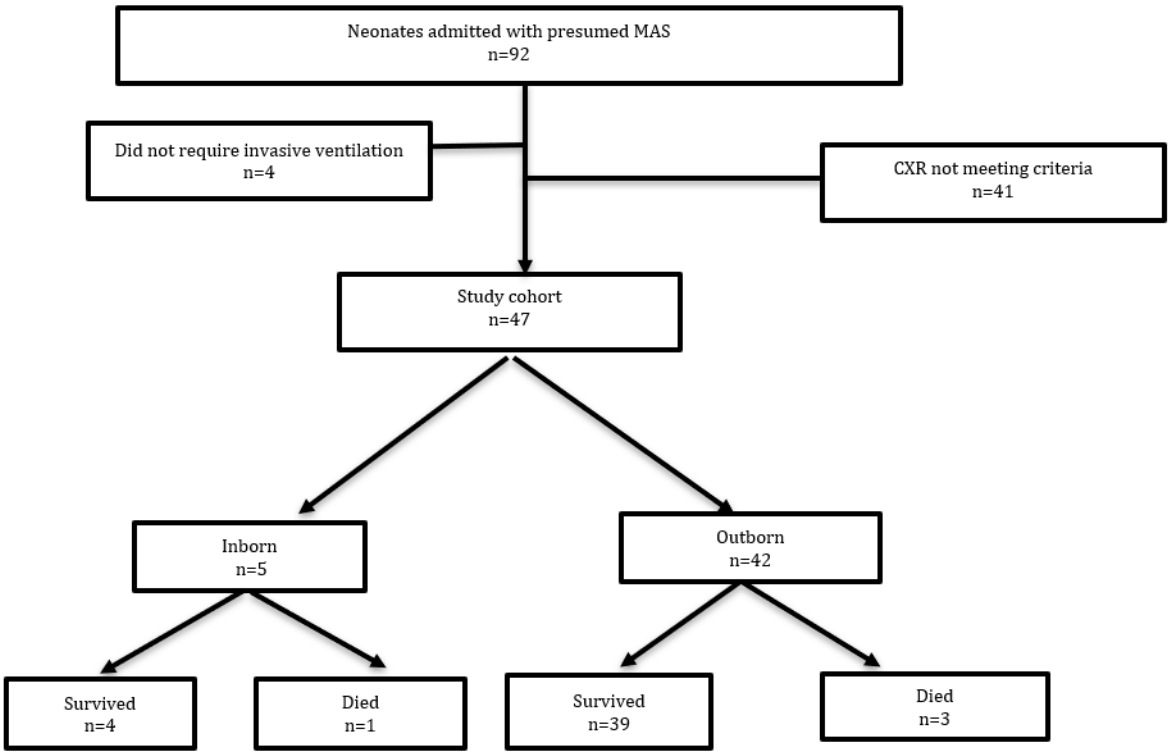

Table 1: Study population demographics

Variable		Data N=47
Maternal Demographics		
Cesarian section, n (%)		32(68)
Normal delivery, n (%)		15(32)
Pre-eclampsia, n (%)		5 (11)
Chorioamnionitis, n (%)		1(2)
Liquor, n (%)	Clear	1(3)
	MSL 1	2(6)
	MSL 2	7(23)
	MSL 3	21(68)
Neonatal Demographics		
Gestational age, weeks, mean ±SD		39.7± 1.4
Birth weight, grams, mean ±SD		3246 ±522
IUGR (<10th centile)		8 (17)
Inborn n (%)		5(11)
Resuscitation at delivery, n (%)	No resuscitation	6(13)
	CPAP	11(23)
	IPPV via T-piece	14(30)
	Intubation	13(28)
	Adrenaline	3 (6)
Apgar 10-min, median (IQR)		8 (7-9)

CPAP - continuous positive airway pressure; IPPV- Intermittent positive pressure ventilation; IUGR -intra-uterine growth restriction; IQR interquartile range-; MSL-Meconium-stained Liquor; MSL 1-Meconium-Stained Liquor Grade 1, MSL 2-Meconium-stained Liquor Grade 2, MSL 3- Meconium-stained Liquor Grade 3; SD – standard deviation.

Table 2: Agreement statistics of CXR for MAS

Parameter	Agreement (%)	Kappa	p-value
Overall CXR diagnosis of MAS	77.5	0.542	<0.001
Bilateral infiltrates	76.4	0.459	<0.001
Hyperinflation	82.0	0.444	<0.001
Pneumothorax	96.6	0.557	<0.001
Pneumomediastinum	96.6	0.709	<0.001

CXR – chest x-ray; MAS meconium aspiration syndrome.

Table 3: Respiratory support modalities

Parameters		**Results**
Admission FiO_2, mean±SD		69±27
Admission OI[#], median (IQR)		6.3 (4.1-16.7)
Admission PF ratio[#], median (IQR)		94.5 (45.7-167.5)
Admission OSI ratio, median (IQR)		9.0 (5.6-16.3)
Conventional ventilation	Total, n (%)	34 (72)
	Duration, days, median (IQR)	2 (1-4)
HFV	Total, n (%)	28(61)
	Duration, days, median (IQR)	3 (2-4.2)
CPAP	Total, n (%)	40(85)
	PNA started, day, median (IQR)	3.5 (2-5)
	Duration, days, median (IQR)	2 (1-3)
High flow nasal cannula	Total, n (%)	16 (34)
	PNA started, days, median (IQR)	6.9 (5-15.5)
	Duration, days, median (IQR)	2 (1-6.5)
NPO_2	Total, n (%)	36 (77)
	PNA started, days, median (IQR)	8 (7-17)
	Duration, days, median (IQR)	2 (1-6.5)
Total duration invasive ventilation, days, median (IQR)		3 (2-4.5)
Total duration non- invasive ventilation, days, median (IQR)		2 (1-5)
Total duration all respiratory support, days, median (IQR)		9 (4-16)
Surfactant administration, n (%)	Any surfactant	38 (81)
	1 dose	33(70)
	2 doses	4(9)
	3 doses	1(2)

CPAP- Continuous positive pressure ventilation; HFV- High frequency ventilation; IQR – interquartile range; NICU- Neonatal intensive care unit; NPO_2- nasal prongs oxygen; OI – oxygenation index; OSI – oxygenation saturation index; PF – partial pressure of oxygen: fraction of inspired oxygen ratio; PNA – postnatal age.

[#] Calculated in 38 neonates who had arterial lines

Table 4: Complications and treatment of complications

Parameters			**Results N=49**
Air leak syndrome	Pneumothorax, n (%)		4(9)
	Pneumomediastinum, n (%)		1(2)
Systemic hypotension	Any inotrope, n (%)		21(45)
	Duration, days, median (IQR)		2 (1-3)
	Initial drug, n (%)	Dobutamine	13(62)
		Dopamine	8(38)
	2nd line, n (%)	Milrinone	5(45)
		Dopamine	3(27)
		Dobutamine	2(18)
		Adrenaline	1(9)
	3rd line, n (%)	Milrinone	2(100)
PPHN	Total, n (%)		25(53)
	Echocardiography diagnosis, n (%)		15(52)
	iNO	administered (%)	22 (88)
		Duration, days, mean ±SD	4.2±2.4
	Sildenafil	Total, n (%)	13(28)
		PNA at start, median (IQR)	1 (0-1)
		Duration, days, median (IQR)	12 (6-22)
HIE received therapeutic hypothermia, n (%)			10(20)
Culture positive sepsis	Total, n (%)		12(25)
	PNA at onset, days, median (IQR)		6.5 (0-8)
Steroids	Total, n (%)		25(64)
	PNA at start, age, median (IQR)		1 (0-3)
	Duration, days, median (IQR)		2 (2-3)
	Type	Dexamethasone, n (%)	16(64)
		Hydrocortisone, n (%)	8(36)

HIE – hypoxic ischemic encephalopathy; iNO – inhaled nitric oxide, IQR – interquartile range; PNA – postnatal age; PPHN – persistent pulmonary hypertension of the newborn; SD – standard deviation.