Prediction score for prolonged hospital stay in Meconium aspiration syndrome: A Multicentric collaborative cohort of South India

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Abstract

Background and Objective: With improved survival in neonates with meconium aspiration syndrome (MAS), the focus is currently on mitigating the morbidities. The objective of this study was to predict factors determining prolonged hospital stay in neonates with MAS. **Materials and methods:** It was a retrospective cohort from five centres of south India between 2018 and 2020. Neonates [?]35 weeks of gestation admitted to NICU with the diagnosis of MAS and requiring oxygen beyond 24 hours of life were included in the study. The morbidities in the neonates with stay [?]7 days (short stay) were compared with >7 days (prolonged stay). Logistic regression by the backward stepwise method was used for predictive score creation. **Results:** Out of 347 neonates with MAS discharged home, 103 (29%) had a short stay and 244 (71%) had prolonged stay. The primary support beyond O2 (CPAP/MV) (42% vs 83%, p<0.001), FiO2 at 1hr>30% (45% vs 87%, p<0.001), HIE stage 2 or 3 (2% vs 27%, p<0.001), moderate-severe PPHN (3% vs 31%, p<0.001) were independent factors associated with prolonged stay on logistic regression. A prediction model was devised using weighted scores of these four associated morbidities. The clinical score thus developed had 83% sensitivity, 68% specificity for the prediction of prolonged stay [AUC- 82, 95% CI (78-87), p<0.001]. **Conclusion:** More than two-thirds of neonates with MAS had prolonged stay. The primary support beyond oxygen, Fio2 requirement >30%, Moderate to severe PPHN, HIE stage 2 or 3 were predictive of prolonged stay in neonates with MAS.

Introduction:

Meconium aspiration syndrome (MAS) is a common cause of morbidity and mortality in neonates born at or beyond term gestation. Meconium stained amniotic fluid occurs in 4-22% of all pregnancies. About 3-12% of neonates born by meconium-stained amniotic fluid develop respiratory distress requiring NICU admissions[1]. The mortality of MAS ranged from 25-40% in developing countries in the last decade[2,3]. The last decade also witnessed the addition of novel management strategies like avoiding routine ET suction in the delivery room, CPAP as primary support, surfactant administration etc. With improvement in supportive care combined with the above strategies, the outcomes of MAS are improving[4, 5, 6, 7]. Thus currently, there is a need to focus on reducing morbidities associated with MAS.

The median stay of neonates with moderate to severe MAS has ranged between 4-29 days with a median of 8 days[8, 9, 10, 11]. Prolonged hospital stay is one of the vital morbidity associated with MAS. Prolonged stay adds to both direct and indirect costs. Few studies have evaluated the predictors of severe MAS[9-10]. Although the length of stay was assessed in these studies, the predictors of long-stay were not assessed specifically. In this study, we aimed to evaluate the associated morbidities of MAS and predict factors determining prolonged hospital stay in such neonates.

Material & Methods:

This retrospective study was conducted in five tertiary care neonatal intensive care units (NICU) of South India over 29 months (January 2018 to May 2020). All neonates (both inborn and outborn) above 35 weeks of gestation born by meconium-stained amniotic fluid with the onset of distress within 12 hrs of life, requiring respiratory support beyond 24 hrs of life and chest x-ray showing features of MAS ((hyper-inflated lung fields with diffuse non-homogenous opacity or reticulonodular pattern or low volume lungs with reticulogranularity and air-bronchograms)[12] were eligible for enrolment. Newborns with major life-threatening congenital malformations were excluded. The Institutional Ethics committee approved the study at all the centres.

Of the five centres participated, two centres were private sector hospitals, one was public sector hospital, two were trust hospitals. All the centres catered to sick term and preterm infants, both intra and extra mural. The five centres had similar protocols in the respiratory management of neonates with MAS. The primary respiratory support was defined as the highest respiratory support required within the first 6 hours of admission. Surfactant was administered if FiO2 was above 40% on CPAP or mechanical ventilation. Only one centre had access to inhaled nitric oxide. The data was retrieved with the discharge diagnosis of "Meconium aspiration syndrome" from the computerized database or admission registers. The data was collected with respect to respiratory support, timing of initiation of CPAP, timing of surfactant administration, number of doses of surfactant, severity of PPHN, vasodilators usage , antibiotic usage, indication for antibiotic usage and number of days, length of stay in hospital till discharge and survival outcomes were collected. The primary support beyond oxygen included either CPAP or mechanical ventilation. The data were entered into a web database and coded for each centre separately.

The prolonged hospital stay was arbitrarily defined as a stay beyond 7 days of life for the study purpose as there was no clear definition from previous studies. Neonatal sepsis was diagnosed if the blood culture was positive. Hypoxic Ischemic Encephalopathy (HIE) was classified using Sarnat and Sarnat staging[13]. Persistent pulmonary hypertension was diagnosed based on 2D-Echocardiographic findings of elevated pulmonary artery systolic pressure (PASP). The PASP greater than three quarters of systolic pressure was defined as moderate-severe PPHN[14]. The hypoxemia in PPHN was stratified based on the Oxygen saturation index (OSI). The OSI values correspond to half of the oxygenation index (OI)[15], and severity of hypoxemia in PPHN was graded as mild < 7.5, moderate [?] 7.5- 12.5, and severe >12.5.

The primary outcome measure was to identify morbidities predicting prolonged length of stay (>7days). The secondary outcome was to evaluate the proportion of associated morbidities in our cohort.

Statistical analysis:

Categorical outcomes were analyzed by chi-square test with continuity correction or Fisher's exact test, wherever one or more expected cell size was less than 5. Numerical variables were tested for normality using the test for normality (Kolmogorov–Smirnov). Normally distributed variables were compared by unpaired t-test after evaluating equality of variance by Levene's test (F test), whereas skewed variables were analyzed with the Mann–Whitney U-test. Univariate analysis was done to identify predictors of long stay. Logistic regression with backward stepwise elimination was done to identify independent predictors of long stay and a p-value of less than .05 was taken as significant. A weighted prediction score was devised using beta coefficients of independent variables derived from the logistic model (multiplied by 10 and rounded off to nearest integer)[16]. The discriminatory power and calibration of the prediction score was evaluated using area under Receiver Operating Characteristic (ROC) curve. The optimal cut-off for the weighted score was calculated using the ROC curve and estimated sensitivity, specificity and positive predictive value of the cut off[17]. The analysis was done using statistical software packages IBM-SPSS v.25 (SPSS Inc, NY, USA).

Results:

Out of the total 6007 admissions, 434 (7%) neonates had meconium stained liquor and respiratory distress at birth. The respiratory distress settled within 24 hours in 40 neonates. In the remaining 384 neonates, 347

were discharged home and were enrolled for the study. A total of 10 neonates died, 24 were categorised as Leave against medical advice (LAMA) and 3 were repatriated to the referral hospitals for the continuation of care and outcome data were not available. The mortality including the neonates sent LAMA with grave outcomes was 23 (5.9%). The flow of the patients is summarized in figure 1.

About 35% of neonates required resuscitation at birth. At admission, 163 (47%) neonates had significant distress, evidenced by Downes score [?]4. 184 (53%) were stabilized on CPAP as primary respiratory support. The neonates in the cohort had associated morbidities of HIE stage 2 or 3 in 67 (19%), surfactant requirement 94 (27%), PPHN in 80 (23%). The median length of hospital stay (IQR) was 10 (7-14) days. The baseline characteristics of enrolled neonates are outlined in table 1.

Amongst 347 neonates, 103 (29%) were discharged before 7 days and remaining 244 (71%) had prolonged stay. On univariate comparison of short stay versus long stay (table 2), Positive pressure ventilation (PPV) at birth (27% vs 38%, p=0.05), intubation at birth (2% vs 19%, p<0.001), HIE stage 2 or 3 (2% vs 27%, p<0.001), Fio2 at 1hr>30% (45% vs 87%, p<0.001), Downe's score at admission [?]4 (64% vs 90%, p<0.001), primary support beyond O2 (CPAP or MV) (42% vs 83%, p<0.001), CPAP as primary support after admission (36% vs 60%, p<0.001), invasive mechanical ventilation (6% vs 23%, p<0.001), surfactant requirement (1% vs 38%, p<0.001), moderate-severe PPHN (3% vs 31%, p<0.001) were statistically significant factors seen in the prolong stay group. Although CPAP as primary support was seen as a statistically significant risk factor in the prolonged stay, CPAP initiation was delayed by a mean difference of 21 hrs (-32 to -10) in the prolonged stay group compared to short stay.

On multivariate analysis, 4 parameters, namely primary support beyond oxygen, FiO2 more than 30% one hour post admission, presence of moderate-severe PPHN, HIE stage 2 or 3, were found to be independent predictors of prolonged stay in hospital (Table 3). These 4 variables were used to devise a scoring system predictive of prolonged stay in MAS. The beta coefficients obtained from the logistic regression were used to calculate the weights of these parameters. The final weighted score is as follows: 9 (Primary support beyond oxygen) + 15 (FiO2 more than 30% 1hour after admission) + 20 (moderate-severe PPHN) + 29 (HIE stage 2 or 3), with each variable being assigned a value as '1' if present and '0' if absent. The ROC curve was plotted to evaluate the predictive ability of the weighted score. The Area under curve (AUC) was 82% (95% CI 78-87%), p<0.001 and thus had excellent model discriminatory power. Based on the distribution of the neonates in both the groups for the weighted score and ROC curve analysis (Table 3) (figure 2), the optimal cutoff for prolonged stay was determined. The optimal cutoff was $\geq$ 21 had sensitivity, specificity, positive predictive value and negative predictive value of 83%, 68%, 86% and 62%, respectively. The positive and negative likelihood ratios were 2.6 and 0.25, respectively.

Discussion:

In the current multicentre collaborative study on 384 neonates with MAS, 347 were discharged home successfully. Previous studies have made efforts to identify predictors of mortality [2,3]. With improved survival there is limited evidence on length of stay in the hospital based on associated morbidities, although few studies have addressed the predictors of severe MAS[9-11]. The present collaborative study attempted to devise a predictive model/ scores to predict prolonged stay. To our knowledge, this is the first study to determine the predictors of prolonged stay in the hospital in MAS neonates.

The requirement of primary support beyond O2, FiO2 beyond 30% by 1 hour of admission, moderate-severe PPHN and HIE stage 2 or 3 were predictive of prolonged hospital stay (>7 days) in our cohort. The final weighted score in the model was obtained from beta-coefficients and is known to be superior to the traditional way of devising using odds ratio[18]. The final score thus obtained from the regression had excellent discriminatory power to predict the outcome [AUC 0.82, 95% CI (78-87%)], figure 2. The optimal cutoff (J-point) >21 with varying combinations of any of the 4 predictors had a positive predictive value of 2.6, i.e. 2.6 times more likely to have prolonged hospital stay. The OSI was used to classify the severity of PPHN in the study. The OSI, as evidenced in previous studies, correlates with OI when SpO2>70% and is a non-invasive reliable marker allowing for continuous monitoring for oxygenation status[15,19]. The

conventional definition proposed by Cleary and Wiswell to define severity of MAS involves: (a) mild MAS, requires <40% oxygen for <48 hours, (b) moderate MAS, requires >40% oxygen for >48 hours with no air leak, and (c) severe MAS, requires assisted ventilation for >48 hours and is often associated with PPHN[20]. The conventional definition has been in use for more than two decades. The severity is primarily based on respiratory support and does not provide guidance on mortality or length of stay in hospital. Moreover with the increasing use of CPAP as primary support[8] in the current era, the applicability of the classification is a debatable. The index study identified additional morbidities in the current era with better management of MAS and moreover determined the predictive scores for prolonged stay.

The predictors of severe MAS had varied with previous two published studies[9-10]. Hofer et al. studied 55 neonates with severe MAS from a cohort of 205 MAS neonates and found acute tocolysis, fetal distress and moderate birth asphyxia as significant risk factors associated with severe MAS on univariate analysis. The independent predictors by regression analysis were not available. The majority of neonates had a long stay with a median stay of 12.5 (1-144) days. Another retrospective cohort by Oliveira et al. enrolled 15 neonates with severe MAS from a cohort of 29 MAS neonates and found the need for surfactant therapy as a predictor of severity. These neonates had a hospital stay of a median (range) of 8 (2-29) days. Previous studies were limited by smaller samples and thus limited predictors of severity. Although the length of stay was similar to the index study, predictors of prolonged stay were not specifically addressed.

The associated morbidities in the current study were similar to other published studies[5, 9, 10-12] in MAS, except Oliveira et al[10] who had higher surfactant requirement in the sample of 29 neonates. CPAP is increasingly used as the primary respiratory support in MAS[5,8]. A randomized trial by Pandita et al.[5] evaluated the role of CPAP as primary respiratory support in MAS and found a reduction in the need for mechanical ventilation, sepsis, shock and PPHN in the CPAP group. CPAP as primary respiratory support was used in 184 (53%) neonates with invasive ventilation in 64 (19%) in our study. The current study also had a lower incidence of late-onset sepsis in 2 (0.6%). Despite the use of CPAP as primary support, there was no increased incidence of air leaks compared to similar studies[5, 8]. Antibiotics are commonly prescribed empirically in neonates with MAS owing to the sickness. However, antibiotics have not affected the duration of hospital stay or mortality in MAS as per meta-analysis of 4 RCTs[22]. The current study had 7 (2%) neonates with early-onset sepsis and 2 (0.6%) neonates with late-onset sepsis. However, antibiotics were started for 322 (93%) neonates empirically. Considering the low incidence of sepsis, there is a need for quality improvement strategies for optimizing antibiotic usage in MAS. Steroids reduce pulmonary inflammation on histology and improve oxygenation in animal studies[23, 24]. Two recently published systematic reviews[25, 26] have evaluated the role of steroids in MAS. There was no mortality benefit, but reduced hospital stay with nebulised budesonide was observed (low certainty of evidence). The current study used dexamethasone in post-extubation settings, and nebulised steroids or methylprednisolone were not used. There is a need for further large well-designed study evaluating the role of steroids in severe MAS.

The strengths of the study are large sample size from a multicentric cohort, standardized criteria for respiratory management and devising a simple clinical prediction score. Difference in the level of nursing care, doctor:staff ratio, different patient demographics could have altered outcomes in MAS at each centres. Despite these limitations, the study has proposed a prediction score for a prolonged stay in MAS applicable across low and middle-income countries. This scoring could help in optimizing the strategies for treating MAS in the initial few hours. Validation of the scoring would be required in different settings before broader application of the scoring. The prediction score can serve as a tool for risk stratification for future clinical trials. There is a need for QI strategies on optimizing antibiotic use and respiratory management. To conclude, more than two-thirds of neonates with MAS had prolonged stay. The primary support beyond oxygen, Fio2 requirement >30%, Moderate to severe PPHN, HIE stage 2 or 3 were predictive of prolonged stay in neonates with MAS.

References

1. Vain NE, Batton DG. Meconium "aspiration" (or respiratory distress associated with meconium-stained amniotic fluid?). Semin Fetal Neonatal Med 2017;22:214-219.

2. Qian L, Liu C, Zhuang W, Guo Y, Yu J, Chen H, Wang S, Lin Z, Xia S, Ni L et al. Neonatal respiratory failure: a 12-month clinical epidemiologic study from 2004 to 2005 in China. Pediatrics 2008;121:e1115-24.
3. Louis D, Sundaram V, Mukhopadhyay K, Dutta S, Kumar P. Predictors of mortality in neonates with meconium aspiration syndrome. Indian Pediatr 2014;51:637-40.
4. Nangia S, Thukral A, Chawla D. Tracheal suction at birth in non-vigorous neonates born through meconium-stained amniotic fluid. Cochrane Database Syst Rev 2021;6:CD012671.
5. Pandita A, Murki S, Oleti TP, Tandur B, Kiran S, Narkhede S, Prajapati A. Effect of Nasal Continuous Positive Airway Pressure on Infants With Meconium Aspiration Syndrome: A Randomized Clinical Trial. JAMA Pediatr 2018;172:161-165.
6. El Shahed AI, Dargaville PA, Ohlsson A, Soll R. Surfactant for meconium

aspiration syndrome in term and late preterm infants. Cochrane Database Syst Rev 2014;(12):CD002054.

1. Natarajan CK, Sankar MJ, Jain K, Agarwal R, Paul VK. Surfactant therapy and antibiotics in neonates with meconium aspiration syndrome: a systematic review and meta-analysis. J Perinatol 2016;36 Suppl 1:S49-54.
2. Bhagwat P, Murki S, Mehta A, Oleti T, Gannavaram D. Continuous positive airway pressure in meconium aspiration syndrome: an observational study. J Clin Neonatol 2015;4:96.
3. Hofer N, Jank K, Resch E, Urlesberger B, Reiterer F, Resch B. Meconium aspiration syndrome–a 21-years' experience from a tertiary care center and analysis of risk factors for predicting disease severity. Klin Padiatr 2013;225:383-8.
4. Oliveira CPL, Flôr-de-Lima F, Rocha GMD, Machado AP, Guimarães Pereira Areias MHF. Meconium aspiration syndrome: risk factors and predictors of severity. J Matern Fetal Neonatal Med 2019;32:1492-1498.
5. Thornton PD, Campbell RT, Mogos MF, Klima CS, Parsson J, Strid M. Meconium aspiration syndrome: Incidence and outcomes using discharge data. Early Hum Dev 2019;136:21-26.
6. Dargaville PA, Copnell B. The epidemiology of meconium aspiration syndrome: incidence, risk factors, therapies, and outcome. Pediatrics 2006;117:1712–1721.
7. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol 1976;33:696-705.
8. Dhillon R. The management of neonatal pulmonary hypertension. Arch Dis Child Fetal Neonatal Ed 2012;97:F223-8.
9. Rawat M, Chandrasekharan PK, Williams A, Gugino S, Koenigsknecht C, Swartz D, Ma CX, Mathew B, Nair J, Lakshminrusimha S. Oxygen Saturation Index and Severity of Hypoxic Respiratory Failure. Neonatology 2015;107:161–6.
10. Makdisse M, Ramos L. A risk score for predicting peripheral arterial disease in individuals 75 years or older. Arq Bras Cardiol 2007; 88:555-61.
11. Pillai MS, Sankar MJ, Mani K, Agarwal R, Paul VK, Deorari AK. Clinical prediction score for nasal CPAP failure in pre-term VLBW neonates with early onset respiratory distress. J Trop Pediatr 2011;57:274-9.
12. Moons KG, Harrell FE, Steyerberg EW. Should scoring rules be based on odds ratios or regression coefficients?. J Clin Epidemiol 2002;55:1054-5.
13. Muniraman HK, Song AY, Ramanathan R, Fletcher KL, Kibe R, Ding L, Lakshmanan A, Biniwale M. Evaluation of Oxygen Saturation Index Compared With Oxygenation Index in Neonates With Hypoxemic Respiratory Failure. JAMA Netw Open 2019;2:e191179.
14. Cleary GM, Wiswell TE. Meconium-stained amniotic fluid and the meconium aspiration syndrome: an update. Pediatric Clinics of North America 1998;45:511–529.
15. Swarnam K, Soraisham AS, Sivanandan S. Advances in the management of meconium aspiration syndrome. Int J Pediatr 2012;2012:359571.
16. Kelly LE, Shivananda S, Murthy P, Srinivasjois R, Shah PS. Antibiotics for neonates born through meconium-stained amniotic fluid. Cochrane Database Syst Rev 2017 Jun;6:CD006183.

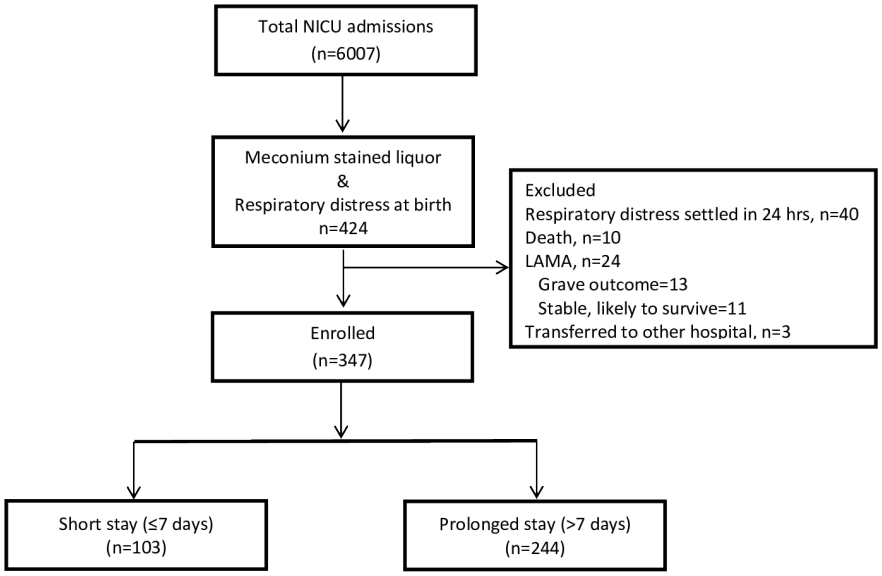
17. Lin C, Jeng M, Yang Y, Hsiao Y, Kou YR. Comparison of different dosing strategies of intratracheally instilled budesonide on meconium injured piglet lungs. Pediatr Pulmonol 2017;52:891-899
18. Mokra D, Mokry J, Drgova A, Petraskova M, Bulikova J, Calkovska A. Intratracheally administered corticosteroids improve lung function in meconium-instilled rabbits. J Physiol Pharmacol 2007;58:389-98
19. Phattraprayoon N, Ungtrakul T, Tangamornsuksan W. The Effects of Different Types of Steroids on Clinical Outcomes in Neonates with Meconium Aspiration Syndrome: A Systematic Review, Meta-Analysis and GRADE Assessment. Medicina (Kaunas). 2021;57(11):1281.
20. Yeung T, Jasani B, Shah PS. Steroids for the Management of Neonates With Meconium Aspiration Syndrome: A Systematic Review and Meta-analysis. Indian Pediatr 2021;58:370-376.

Figure legends

Figure I: Flow of study patients

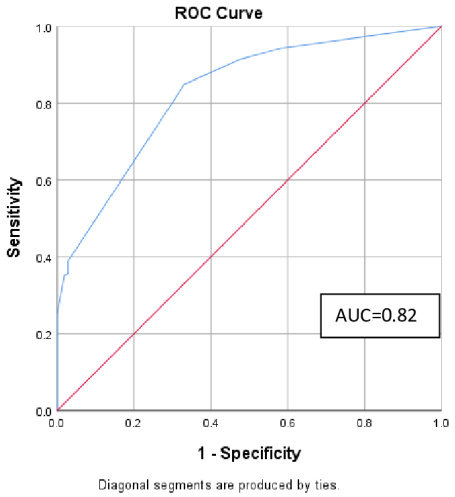
Figure II: Receiver Operating Characteristic Curve for the discriminatory ability of Prediction score for prolonged stay in Meconium aspiration syndrome

Figure l: Flow of study patients



Abbreviation: LAMA- Leave Against Medical Advice

Figure ll: Receiver Operating Characteristic Curve for the discriminatory ability of Prediction score for prolonged stay in Meconium aspiration syndrome



Abbreviation: AUC- Area Under Curve

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