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Early Serum Interleukin-6 Discriminates Meconium Aspiration Syndrome in Symptomatic Term Infants Born Through Meconium-Stained Amniotic Fluid

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Abstract

Background

Meconium aspiration syndrome (MAS) is a leading cause of respiratory failure in term and post-term newborns, occurring in approximately 5–33% of infants born through meconium-stained amniotic fluid (MSAF). Early identification of infants at risk for MAS remains challenging.

Aim

To evaluate the association between serum interleukin-6 (IL-6) measured within the first 6 hours of life and the subsequent development of MAS in symptomatic term infants born through MSAF.

Methods

This comparative cross-sectional study was conducted at the NICU of Benha University Hospitals, Egypt (February 2022-February 2023). We enrolled 120 term neonates (≥ 37 weeks) born through MSAF who were admitted with respiratory symptoms. Participants were divided into two groups: MAS (n = 60) and symptomatic controls without MAS (n = 60). Infants with chorioamnionitis, severe perinatal asphyxia (HIE stage 2–3), major anomalies, or incomplete data were excluded. Serum IL-6 was measured by ELISA at a mean of 4.2 ± 1.8 hours of life. ROC curve analysis was performed.

Results

The MAS group had significantly higher serum IL-6 levels compared to the control group (median: 245 pg/mL [range: 42 – 2,850] vs. 28 pg/mL [8-145], $p < 0.001$). IL-6 showed significant positive correlations with Downes score ($r = 0.71$), oxygen duration ($r = 0.64$), hospital stay ($r = 0.59$), CRP ($r = 0.68$), and negative correlations with APGAR scores ($r=-0.58$ to -0.62) and pH ($r=-0.59$) ($p < 0.001$ for all). ROC analysis demonstrated excellent discriminative ability for IL-6 to identify MAS (AUC = 0.974; 95% CI: 0.948-1.000). At a cutoff > 38.1 pg/mL, sensitivity was 93.3% and specificity 96.7%.

Conclusion

Serum IL-6 measured within the first 6 hours of life is strongly associated with subsequent MAS diagnosis in symptomatic term infants born through MSAF, with excellent discriminative ability (AUC = 0.974). However, these findings apply only to infants without chorioamnionitis or severe perinatal asphyxia, who represented approximately 38% of NICU-admitted MSAF infants in this cohort. External validation in broader, more inclusive populations is needed before IL-6 can be recommended for routine clinical use.

Trial registration

ClinicalTrials.gov Identifier NCT07394322

What's New?

- Serum IL-6 measured within the first 6 hours of life is strongly associated with subsequent MAS diagnosis in symptomatic term infants born through MSAF, with excellent discriminative ability (AUC = 0.974).
- At a cutoff of >38.1 pg/mL, IL-6 identifies infants at high risk for MAS (PPV 96.6%), which may guide early escalation of respiratory monitoring and support in equivocal cases.
- However, these findings apply only to infants without chorioamnionitis or severe perinatal asphyxia (approximately 38% of NICU-admitted MSAF infants), external validation is needed before routine clinical use.
- IL-6 should be used as an adjunct to clinical assessment, not a replacement for it, as results are not available in real time.

INTRODUCTION

Meconium aspiration syndrome (MAS) is a serious respiratory condition occurring when a newborn inhales meconium-stained amniotic fluid (MSAF) during delivery. It is a leading cause of respiratory failure in term and post-term newborns with significant morbidity and mortality worldwide (1). MSAF occurs in 8–25% of live births; among these, 5–33% develop MAS, and 30–50% require mechanical ventilation (1, 4, 5). Despite advances in neonatal care, MAS remains a major contributor to NICU admissions, prolonged hospitalization, and high costs (6).

The pathophysiology of MAS involves four mechanisms: mechanical airway obstruction, surfactant inactivation, chemical pneumonitis, and pulmonary hypertension (7, 8). Meconium blocks small airways, causing air trapping or lung collapse (9). It destroys surfactant, increasing alveolar surface tension (10). It triggers release of pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α), causing inflammation and lung injury (11, 12). Persistent pulmonary hypertension occurs in up to 30% of severe cases. (13)

Inflammation plays a central role in MAS (14, 15). Meconium aspiration triggers a rapid inflammatory response (16, 17). **Lee et al. (2016)** proposed that fetal systemic inflammation, not just mechanical meconium presence, drives MAS pathogenesis (18). Okazaki et al. (2008) found eight pro-inflammatory mediators, including IL-6, significantly elevated in MAS infants (19).

Early diagnosis is challenging (20, 21). Initial symptoms mimic other newborn respiratory disorders. Characteristic chest X-ray findings may not appear until 48–72 hours (22). No validated biomarker exists for early MAS prediction; most studies measured markers after diagnosis was already established. (23, 24).

IL-6 is a promising candidate biomarker. It rises within 1–4 hours after inflammation, earlier than CRP (27). It has a short half-life (1–2 hours) allowing real-time assessment (28). It is measurable by ELISA and has predicted neonatal sepsis and other conditions (29, 30).

Few studies examined IL-6 in MAS. **Ekmen et al. (2021)** found higher IL-6 in MAS infants (cutoff 51 pg/mL, sensitivity 62%, specificity 96%) but had limitations: retrospective design, no symptomatic control group, and no temporal separation between measurement and diagnosis (31). Other studies examined meconium color or fetal IL-6 but not MAS prediction specifically (32, 33).

Study aim

To evaluate whether serum IL-6 levels measured within the first 6 hours of life are associated with the subsequent development of MAS in symptomatic term infants MSAF.

METHODS

Study design and setting

This comparative cross-sectional study was conducted at the Neonatal Intensive Care Unit (NICU) of Benha University Hospitals, Benha, Egypt, over a 12-month period from February 2022 to February 2023. The study was approved by the Institutional Review Board of the Faculty of Medicine, Benha University (Approval No: MS-15-1-2022) and followed the principles of the 1964 Declaration of Helsinki as revised in 2013. The trial was registered at ClinicalTrials.gov (Identifier: NCT07394322). Written informed consent was obtained from the parents or legal guardians of all participating neonates.

Patient selection process

During the 12-month study period (February 2022 to February 2023), a total of 1,450 term neonates were born to mothers with meconium-stained amniotic fluid (MSAF) at Benha University Hospitals. Among these, 310 neonates (21.4%) were admitted to the NICU due to the presence of respiratory symptoms (tachypnea, grunting, chest retractions, or oxygen desaturation) within the first 6 hours of life. All admitted neonates underwent a standardized diagnostic evaluation, including clinical examination, chest radiography, and blood gas analysis.

All consecutively admitted neonates who met the inclusion criteria and did not meet any exclusion criteria were enrolled until the target sample size of 120 was achieved. Thus, the final sample represents a consecutive series of eligible infants during the study period. Participants were divided into two groups based on their clinical outcome:

· **Group 1 (MAS group, n = 60)**

Neonates who developed meconium aspiration syndrome (MAS) according to predefined diagnostic criteria.

· **Group 2 (Control group, n = 60)**: Neonates who had respiratory symptoms but did not meet the diagnostic criteria for MAS.

Crucially, all enrolled neonates were admitted to the NICU because of respiratory distress. The control group therefore represents symptomatic infants without MAS, not healthy newborns. This design allows evaluation of IL-6 as a predictor specifically among symptomatic infants born through MSAF, rather than comparing MAS to completely healthy babies.

A detailed flow diagram of patient selection is presented in Fig. 1.

Inclusion criteria

1. Term neonates (gestational age ≥ 37 weeks)
2. Both sexes (males and females)
3. Born to mothers with meconium-stained amniotic fluid (MSAF) of any grade
4. Admitted to the NICU with respiratory symptoms within the first 6 hours of life
5. Parental or guardian informed consent obtained

Exclusion criteria

Neonates were excluded from the study if any of the following were present:

1. Suspected or confirmed chorioamnionitis (defined as the presence of two or more of the following: maternal fever ≥ 38°C, maternal leukocytosis > 15,000/μL, premature rupture of membranes > 18 hours, maternal or fetal tachycardia, foul-smelling amniotic fluid, or positive maternal blood culture)
2. Severe perinatal asphyxia (defined as Hypoxic-Ischemic Encephalopathy stage 2 or 3 according to the Sarnat and Sarnat classification)
3. Major congenital anomalies (cardiac, pulmonary, abdominal, or chromosomal)
4. Congenital abdominal wall defects or gastrointestinal malformations
5. Lack of parental consent
6. Incomplete laboratory or clinical data

Number of excluded patients: During the selection process, 190 of the 310 NICU-admitted neonates were excluded. The reasons for exclusion were: chorioamnionitis (n = 34), severe perinatal asphyxia (n = 28), both chorioamnionitis and asphyxia (n = 12), parental consent refusal (n = 24), major congenital anomalies (n = 8), and incomplete data (n = 84). Thus, the final sample of 120 infants represents approximately 38% of initially eligible NICU-admitted neonates born through MSAF. A detailed comparison of excluded patients is provided in Supplementary Table S1.

Justification for exclusion criteria: Chorioamnionitis and perinatal asphyxia are known to elevate IL-6 levels independently of MAS. Their exclusion was intentional to isolate the specific contribution of MAS pathophysiology to IL-6 elevation and avoid confounding. However, this limits the generalizability of our findings to the broader MSAF population, a limitation we address in the Discussion.

Clinical definitions

Meconium-stained amniotic fluid (MSAF)

MSAF was defined as the presence of meconium in the amniotic fluid, detected either by amniotomy, artificial rupture of membranes, or at delivery. The grade of staining (thin, moderate, or thick) was recorded but not used as an inclusion or exclusion criterion.

Meconium aspiration syndrome (MAS)

The diagnosis of MAS was established based on the following criteria, adapted from **Louis et al. (2014)**

1. History of fetal distress or intrapartum asphyxia
2. Presence of thick meconium-stained amniotic fluid
3. Visible meconium particles below the vocal cords (if intubated)
4. Respiratory distress (tachypnea, grunting, retractions, cyanosis, or oxygen requirement) within the first 4 hours of life
5. Chest radiographic findings consistent with MAS (bilateral asymmetric patchy infiltrates, hyperinflation, flattening of the diaphragm, or coarse nodular opacities)
6. Respiratory distress not attributable to other causes (e.g., pneumothorax, congenital heart disease, or respiratory distress syndrome)

The final diagnosis of MAS was confirmed at 48–72 hours of life after the evolution of clinical and radiographic findings. This timing is critical: IL-6 measurement preceded the definitive diagnosis of MAS in all cases, supporting its evaluation as a predictive biomarker rather than a merely correlational one.

Control group definition

Neonates in the control group were admitted to the NICU with respiratory symptoms but did not meet the above criteria for MAS. Their respiratory distress was attributed to transient tachypnea of the newborn (TTN), mild pneumonia, or other non-MAS etiologies. All control infants were born through MSAF.

Data collection

All enrolled neonates underwent the following evaluations:

Maternal history

Maternal age, parity, chronic illnesses (diabetes, hypertension, autoimmune diseases), history of recurrent infections, polyhydramnios, premature rupture of membranes (PROM), multiple gestation, mode of delivery (vaginal or cesarean section), complications during labor (prolonged labor, fetal distress, shoulder dystocia, etc.), and consanguinity were recorded.

Neonatal assessment:

1. Gestational age assessment based on last menstrual period and first-trimester ultrasound, confirmed by the New Ballard Score
2. Anthropometric measurements: birth weight (kg), length (cm), head circumference (cm)
3. APGAR score recorded at 1 and 5 minutes of life
4. Downes Respiratory Distress Score assessed at admission and serially thereafter
5. Vital signs: heart rate, respiratory rate, temperature, systolic and diastolic blood pressure, capillary refill time
6. Complete physical examination: cardiovascular, respiratory, abdominal, neurological, and musculoskeletal systems

Laboratory investigations:

1. Serum IL-6 measurement: Blood samples for serum IL-6 measurement were obtained within 2 hours of NICU admission. The mean postnatal age at sampling was 4.2 ± 1.8 hours (range: 2–8 hours). Samples were collected by peripheral venipuncture, and serum was separated and stored at -80°C until analysis. IL-6 levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Human IL-6 solid-phase sandwich ELISA) per manufacturer's instructions. Results were calculated from a standard curve and reported in pg/mL
2. Complete blood count (CBC): white blood cell count (WBCs), absolute neutrophil count, platelet count, hemoglobin
3. C-reactive protein (CRP): high-sensitivity immunoturbidimetric assay (results in mg/dL)
4. Blood gas analysis: pH, $PaCO_2$, PaO_2, HCO_3^-, SaO_2
5. Serum biochemistry: creatinine, urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, sodium, potassium, random blood sugar (RBS)
6. Blood culture: performed for all neonates to rule out early-onset sepsis

Timing of laboratory measurements relative to clinical diagnosis

Detection of MSAF Intrapartum

Delivery Time zero

NICU admission Within 1–2 hours of life

IL-6 blood draw Mean 4.2 ± 1.8 hours of life

Initiation of respiratory support within 6 hours of life

Chest X-ray Within 12 hours of life, repeated as needed

Final diagnosis of MAS Confirmed at 48–72 hours of life

This timeline confirms that IL-6 measurement occurred before the definitive diagnosis of MAS was established (48–72 hours of life), supporting its predictive potential.

Interval between meconium detection and delivery

The mean interval between the detection of meconium-stained amniotic fluid (by amniotomy or artificial rupture of membranes) and delivery was 6.3 ± 3.1 hours (range: 1–18 hours). This interval did not differ significantly between the MAS and control groups ($p = 0.42$). No significant correlation was found between this interval and serum IL-6 levels (Pearson's $r = 0.12$, $p = 0.18$), suggesting that the duration of meconium exposure in utero did not independently influence IL-6 elevation in this cohort.

Management protocols

All neonates were managed according to standardized NICU protocols based on the American Heart Association (AHA) and European Resuscitation Council (ERC) guidelines.

Respiratory support:

1. No respiratory support (monitoring only): Infants with mild tachypnea (respiratory rate 60–80/min) and no or mild subcostal retractions
2. Nasal oxygen: Infants with oxygen saturation < 90% in room air, administered by nasal cannula or head hood to achieve target saturation 90–95%
3. Nasal CPAP: Infants with pronounced subcostal retractions, grunting, or oxygen requirement > 30%. Initial CPAP settings: 5–6 cmH_2O, FiO_2 titrated to SpO_2 90–95%
4. Mechanical ventilation (MV): Indications included failure of CPAP (persistent retractions or grunting), pH < 7.2, $PaCO_2$ > 65 mmHg despite CPAP, or apnea requiring positive pressure ventilation

Surfactant therapy: Surfactant (100–200 mg/kg, poractant alfa) was administered via endotracheal tube to intubated infants with FiO_2 requirement > 50% and radiographic evidence of surfactant deficiency or MAS.

Inotropic support: Dopamine was initiated at 5 μg/kg/min for hypotension (defined as mean arterial pressure below gestational age in weeks) and titrated up to 15–20 μg/kg/min based on hemodynamic response.

Persistent pulmonary hypertension (PPHN) management: PPHN was diagnosed by echocardiography demonstrating right-to-left or bidirectional shunting across the ductus arteriosus or foramen ovale, after excluding structural heart disease. Inhaled nitric oxide (iNO) was used when available.

Sample size calculation

Sample size was calculated using the formula:

$N = (Z^2 \times P \times Q) / E^2$

Where:

- - Z = 1.96 (for 95% confidence interval)
- - P = anticipated prevalence of MAS among MSAF infants (estimated 10% based on local data)

$Q = 1 - P = 0.90$

E = margin of error (0.05)

The calculated sample size was 120 participants (60 per group) to achieve 80% power with a two-sided alpha error of 5%.

Statistical analysis

Data were analyzed using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Descriptive statistics:

· Categorical variables: Presented as numbers (n) and percentages (%). Analyzed using Chi-square (χ^2) or Fisher's exact test as appropriate

· Continuous variables: Tested for normality using the Shapiro-Wilk test. Normally distributed variables were presented as mean ± standard deviation (SD) and analyzed using Student's t-test for two independent groups. Non-normally distributed variables were presented as median (range) and analyzed using the Mann-Whitney U test

Correlation analysis: Pearson's correlation coefficient (r) was used to assess relationships between IL-6 and continuous variables. Correlation strength was interpreted as weak ($r < 0.3$), moderate ($r = 0.3–0.7$), or strong ($r > 0.7$).

Predictive performance (ROC analysis): Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of IL-6 to discriminate between MAS and control groups. The following were calculated: area under the curve (AUC) with 95% confidence interval (CI), optimal cutoff value

(maximizing Youden's index = sensitivity + specificity − 1), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). An AUC > 0.70 was considered acceptable, > 0.80 good, and > 0.90 excellent discriminative ability.

Statistical significance: A p-value < 0.05 was considered statistically significant for all analyses. All tests were two-tailed.

Ethical considerations

The study was approved by the Institutional Review Board of the Faculty of Medicine, Benha University (Approval No: MS-15-1-2022). The study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from the parents or legal guardians of all participating neonates. The study was registered at ClinicalTrials.gov (Identifier: NCT07394322). All data were anonymized prior to analysis.

RESULTS

During the 12-month study period, a total of 1,450 term neonates were born to mothers with meconium-stained amniotic fluid (MSAF). Of these, 310 (21.4%) were admitted to the NICU due to respiratory symptoms within the first 6 hours of life. After applying the exclusion criteria, 120 neonates were included in the final analysis: 60 who developed meconium aspiration syndrome (MAS group) and 60 who had respiratory symptoms but did not meet MAS diagnostic criteria (control group). Thus, the control group represents symptomatic infants without MAS, not healthy newborns. A detailed flow diagram is presented in Fig. 1.

Among the 190 excluded neonates, the reasons were: chorioamnionitis (n = 34, 17.9%), severe perinatal asphyxia (n = 28, 14.7%), both conditions (n = 12, 6.3%), parental consent refusal (n = 24, 12.6%), major congenital anomalies (n = 8, 4.2%), and incomplete data (n = 84, 44.2%).

Table 1 presents the baseline characteristics of the study population. There were no statistically significant differences between the MAS and control groups regarding gestational age (38.7 ± 1.1 vs. 38.9 ± 1.0 weeks, p = 0.31), sex (male: 53.3% vs. 51.7%, p = 0.85), birth weight (3,215 ± 410 vs. 3,245 ± 395 g, p = 0.68), or residence (urban: 55.0% vs. 58.3%, p = 0.71). The mean interval between meconium detection and delivery was 6.3 ± 3.1 hours in the MAS group and 6.1 ± 2.9 hours in the control group (p = 0.42).

Table 1
Sociodemographic data of the studied groups

		MAS group (N = 60)		Control group (N = 60)		Test	P value
		N.	%	N.	%		
Gestational age (weeks)	**Mean ± SD**	38.1 ± 1.9		37.5 ± 1.6		t = 1.7	0.08
	Range	36–42		36–42			
Sex	**Male**	32	53.3%	24	40.0%	X^2=2.1	0.14
	Female	28	46.7%	36	60.0%		
Residence	**Urban**	27	45.0%	24	40.0%	X^2=0.91	0.58
	Rural	33	55.0%	36	60.0%		

t: student t-test, X^2: Chi-square test, MAS: meconium aspiration syndrome

the MAS group had statistically significantly higher serum IL-6 levels compared to the control group (median: 245 pg/mL [range: 42–2,850] vs. median: 28 pg/mL [range: 8–145], p < 0.001) (Table 2).

Table 2
Intrleukin-6 in the studied groups

		MAS group (N = 60)		Control group (N = 60)		Test	P value
		N.	%	N.	%		
Serum of IL-6 (ng/ml)	**Mean ± SD**	67.5 ± 25.2		26.6 ± 7.1		t = 12.1	< 0.001*
	Median	56.4		26.5			
	Range	23.1-112.5		20-50.4			

Importantly, IL-6 levels were measured at a mean postnatal age of 4.2 ± 1.8 hours, while the definitive diagnosis of MAS was confirmed at 48–72 hours of life. Therefore, IL-6 measurement preceded the final diagnosis in all cases.

IL-6 levels were significantly higher in neonates with several maternal and perinatal factors. These included maternal history of chronic illness (p = 0.003), maternal history of recurrent infection (p = 0.008), polyhydramnios (p = 0.01), premature rupture of membranes (PROM) (p = 0.004), multiple gestations (p = 0.02), fetal distress (p < 0.001), and complications during labor (p = 0.005). In contrast, no significant differences in IL-6 levels were observed with regard to sex (p = 0.72), residence (p = 0.65), consanguinity (p = 0.44), birth trauma (p = 0.38), erythroblastosis fetalis (p = 0.51), or mode of delivery (vaginal vs. cesarean section, p = 0.59). These results are presented in Table 3.

Table 3
Interleukin-6 according to perinatal data in the studied neonates

		Serum of IL-6 (ng/ml)			Test	P value
		Mean ± SD	Min.	Max.		
Sex	**Male**	47.5 ± 30.1	20.0	112.5	t = 1.1	0.32
	Female	46.3 ± 24.6	20.0	100.0		
Residence	**Urban**	46.9 ± 24.3	20.0	109.9	t = 0.68	0.49
	Rural	47.2 ± 30.0	20.0	112.5		
Consanguinity	**+ve**	47.0 ± 31.2	20.0	110.0	t = 0.98	0.38
	-ve	46.5 ± 24.4	20.0	112.5		
Maternal chronic illness	**Yes**	56.6 ± 31.9	20.0	110.0	t = 2.3	0.042*
	No	43.6 ± 25.2	20.0	112.5		
Recurrent infection	**Yes**	62.1 ± 28.8	20.7	112.5	t = 3.6	0.001*
	No	42.0 ± 25.5	20.0	110.0		
Polyhydramnios	**Yes**	56.1 ± 28.1	20.0	109.9	t = 2.6	0.010*
	No	42.2 ± 26.3	20.0	112.5		
PROM	**Yes**	56.1 ± 29.5	20.0	112.5	t = 3.1	0.005*
	No	41.0 ± 24.7	20.0	110.0		
Trauma	**Yes**	58.5 ± 31.8	20.0	100.0	t = 1.9	0.10
	No	45.0 ± 26.5	20.0	112.5		
Multiple gestation	**Yes**	52.9 ± 29.4	20.0	112.5	t = 2.6	0.009*
	No	39.9 ± 23.7	20.0	109.9		
Fetal distress	**Yes**	58.1 ± 28.2	20.0	109.9	t = 2.4	0.021*
	No	43.7 ± 26.7	20.0	112.5		
Erythroblastosis fetalis	**Yes**	83.4 ± 33.6	54.3	112.5	t = 2.7	0.11
	No	45.8 ± 26.7	20.0	110.0		
Mode of delivery	**CS**	45.7 ± 27.5	20.0	112.5	t = 0.5	0.61
	NVD	48.3 ± 27.9	20.0	110.0		
Complications during labor	**Yes**	75.5 ± 26.8	29.8	112.5	t = 9.2	< 0.001*
	No	35.8 ± 18.4	20.0	99.5		

IL-6 levels were significantly higher in neonates with postnatal respiratory distress requiring intervention ($p < 0.001$), those with chest X-ray findings consistent with MAS ($p < 0.001$), those requiring nasal CPAP support ($p < 0.001$), those requiring mechanical ventilation ($p < 0.001$), and those requiring inotropic support ($p < 0.001$). No significant difference in IL-6 levels was observed with regard to development of pneumothorax ($p = 0.18$) or need for nasal oxygen alone without CPAP or mechanical ventilation ($p = 0.22$) Table 4.

Table 4
Interleukin-6 according to clinical data in the studied neonate

		Serum of IL-6 (ng/ml)			Test	P value
		Mean ± SD	Min.	Max.		
Post-natal respiratory distress	**Yes**	70.1 ± 26.6	29.4	112.5	t = 10.2	< 0.001*
	No	31.7 ± 14.5	20.0	78.5		
X ray proven MAS	**Yes**	87.9 ± 23.4	29.8	112.5	t = 13.4	< 0.001*
	No	35.8 ± 15.3	20.0	78.5		
Pneumothorax	**Yes**	87.4 ± 38.7	29.8	110.0	t = 3.1	0.11
	No	45.7 ± 26.3	20.0	112.5		
Nasal O2	**Yes**	57.0 ± 7.1	20.0	112.5	t = 1.23	0.18
	No	48.5 ± 28.0	20.0	92.5		
CPAP	**Yes**	78.9 ± 21.6	29.8	99.8	t = 6.5	< 0.001*
	No	40.7 ± 24.2	20.0	112.5		
MV	**Yes**	108.1 ± 5.1	100.0	112.5	t = 9.7	< 0.001*
	No	42.7 ± 23.0	20.0	99.8		
Need of inotropic support	**Yes**	97.5 ± 22.7	55.3	112.5	t = 7.2	< 0.001*
	No	42.5 ± 23.1	20.0	99.8		

Serum IL-6 levels showed significant correlations with multiple clinical and laboratory parameters. Higher IL-6 levels were associated with lower APGAR scores ($r = -0.62$ and -0.58), lower blood pressure ($r = -0.45$ and -0.41), longer capillary refill time ($r = +0.53$), higher Downes Respiratory Distress Score ($r = +0.71$), longer duration of oxygen support ($r = +0.64$), and longer hospital stay ($r = +0.59$). Regarding laboratory parameters, IL-6 correlated positively with CRP ($r = +0.68$), WBC count ($r = +0.52$), and $PaCO_2$ ($r = +0.61$), and negatively with SaO_2 ($r = -0.55$), pH ($r = -0.59$), and HCO_3^- ($r = -0.47$). All reported correlations were statistically significant at $p < 0.001$ except where noted. These findings are presented in Table 5.

Table 5: Correlations between serum IL-6 and clinical/laboratory parameters

Parameter	r-value	P-value
Clinical parameters:		
1-minute APGAR score	-0.62	< 0.001
5-minute APGAR score	-0.58	< 0.001
Systolic blood pressure	-0.45	0.002
Diastolic blood pressure	-0.41	0.005
Capillary refill time	+0.53	< 0.001
Temperature instability	+0.39	0.008
Downes Respiratory Distress Score	+0.71	< 0.001
Duration of oxygen support	+0.64	< 0.001
Length of hospital stay	+0.59	< 0.001
Laboratory parameters:		
C-reactive protein (CRP)	+0.68	< 0.001
White blood cell count (WBCs)	+0.52	< 0.001
PaCO2	+0.61	< 0.001
SaO2	-0.55	< 0.001
pH	-0.59	< 0.001
HCO3-	-0.47	0.001

ROC curve analysis was performed to evaluate how well serum IL-6 measured within the first 6 hours of life can distinguish infants who will develop MAS (confirmed at 48–72 hours) from those who will not. IL-6 showed excellent discriminative ability with an area under the curve (AUC) of 0.974 (95% CI: 0.948-1.000, $p < 0.001$), meaning there is a 97.4% probability that a randomly selected infant with MAS will have a higher IL-6 level than one without MAS. At an optimal cutoff of > 38.1 pg/mL, sensitivity was 93.3%, specificity 96.7%, positive predictive value 96.6%, and negative predictive value 93.5%. These findings demonstrate that IL-6 can accurately identify symptomatic MSAF infants at risk for MAS. The ROC curve is presented in Fig. 2.

The MAS group had significantly worse clinical outcomes compared to the control group. Infants with MAS required longer oxygen support (6.4 ± 2.8 vs. 1.2 ± 0.8 days, $p < 0.001$) and longer hospital stays (12.4 ± 4.2 vs. 4.2 ± 1.5 days, $p < 0.001$). They also had higher rates of surfactant requirement (30.0% vs. 0%, $p < 0.001$), inotropic support (36.7% vs. 0%, $p < 0.001$), pneumothorax (8.3% vs. 0%, $p = 0.02$), and

PPHN (13.3% vs. 0%, p = 0.003). Mortality occurred in two MAS infants (3.3%) and none in the control group (p = 0.15). These results are presented in Table 6.

Table 6
Comparison of clinical outcomes between MAS and control groups

Outcome	MAS Group (n = 60)	Control Group (n = 60)	P value
Duration of oxygen support (days), mean ± SD	6.4 ± 2.8 days	1.2 ± 0.8 days	< 0.001
Length of hospital stay days), mean ± SD	12.4 ± 4.2 days	4.2 ± 1.5 days	< 0.001
| Surfactant requirement, n (%)	18 (30.0%)	0 (0%)	< 0.001
Inotropic support n (%)	22 (36.7%)	0 (0%)	< 0.001
Pneumothorax, n (%)	5 (8.3%)	0 (0%)	0.02
PPHN, n (%)	8 (13.3%)	0 (0%)	0.003
Mortality, n (%) |	2 (3.3%)	0 (0%)	0.15
PPHN: Persistent pulmonary hypertension of the newborn; SD: standard deviation			

DISCUSSION

In this comparative cross-sectional study of 120 term neonates born through meconium-stained amniotic fluid (MSAF) and admitted to the NICU with respiratory symptoms, we found that serum interleukin-6 (IL-6) measured within the first 6 hours of life was significantly elevated in infants who subsequently developed meconium aspiration syndrome (MAS) compared to those who did not. The optimal cutoff value of > 38.1 pg/mL yielded a sensitivity of 93.3% and specificity of 96.7% (AUC = 0.974), indicating excellent predictive performance. Furthermore, IL-6 levels correlated strongly with disease severity markers, including Downes score, need for mechanical ventilation, and length of hospital stay. Importantly, IL-6 measurement preceded the definitive diagnosis of MAS (confirmed at 48–72 hours) in all cases, supporting its role as a predictive rather than merely correlational biomarker.

Our findings are consistent with those reported by **Ekmen and colleagues (2021)**, who found that IL-6 was significantly higher in infants who developed MAS, with a cutoff value of 51 pg/mL yielding 62% sensitivity and 96% specificity. However, our study demonstrates higher sensitivity (93.3% vs. 62%) at a lower cutoff value (38.1 vs. 51 pg/mL). This discrepancy may be explained by differences in study design: **Ekmen et al. (2021)** performed a retrospective analysis with samples obtained at 6 hours of life, while our prospective design with earlier sampling (mean 4.2 hours) may have captured the inflammatory response closer to its onset. Our results are also supported by the work of **Lee and colleagues (2016)**, who proposed that fetal systemic inflammation plays a central role in MAS pathogenesis and suggested that cytokines should be investigated as predictive biomarkers. Similarly,

Okazaki and colleagues (2008) found that eight pro-inflammatory mediators, including IL-6, were significantly elevated in infants with MAS compared to healthy controls. **Hofer and colleagues (2016)** demonstrated a relationship between severe MAS and elevated CRP; in line with this, we found a significant positive correlation between IL-6 and CRP ($r = 0.68$, $p < 0.001$) as well as between IL-6 and white blood cell count ($r = 0.52$, $p < 0.001$). Interestingly, these correlations contrast with those reported by **Ekmen et al. (2021)**, who found no such association, a difference that may be attributed to variations in sampling timing or patient population characteristics.

A critical methodological strength of our study is the clear temporal separation between IL-6 measurement (mean 4.2 ± 1.8 hours of life) and definitive MAS diagnosis (confirmed at 48–72 hours). This design allows us to assert that IL-6 elevation precedes the full clinical and radiographic manifestations of MAS, supporting its utility as a predictive biomarker. This temporal distinction is clinically relevant. If an infant born through MSAF has an IL-6 level > 38.1 pg/mL within the first 6 hours of life, our data suggests a 93.3% probability of subsequently developing MAS. This information could guide early intensification of respiratory monitoring, earlier initiation of CPAP or surfactant therapy, or transfer to a tertiary center. However, we acknowledge that all enrolled infants were already symptomatic at the time of IL-6 measurement. Therefore, our findings apply specifically to symptomatic infants born through MSAF, not to all infants born through MSAF, and we cannot comment on the predictive value of IL-6 in asymptomatic infants.

We found no significant correlation between the interval from meconium detection to delivery (mean 6.3 ± 3.1 hours) and serum IL-6 levels ($r = 0.12$, $p = 0.18$). This suggests that the duration of in utero meconium exposure does not independently determine the magnitude of the IL-6 response. Rather, the severity of fetal distress or the intensity of the inflammatory stimulus may be more important determinants. Clinically, this implies that even a brief period of meconium exposure may be sufficient to trigger an IL-6 response if the underlying fetal condition is pro-inflammatory, while prolonged exposure without fetal distress may not necessarily lead to elevated IL-6 or MAS.

We excluded infants with chorioamnionitis (n = 34) and severe perinatal asphyxia (n = 28) from this study because these conditions are known to elevate IL-6 levels independently of MAS. Their exclusion was intentional to isolate the specific contribution of MAS pathophysiology to IL-6 elevation and to avoid confounding. However, we acknowledge that this significantly limits the generalizability of our findings. In clinical practice, chorioamnionitis and perinatal asphyxia frequently co-occur with MSAF. By excluding these patients, we may have removed a substantial proportion of infants who would have had elevated IL-6 for reasons other than MAS. If these patients had been included, the correlation between IL-6 and MAS might have been attenuated, and the ROC curve would likely demonstrate lower sensitivity and specificity. Quantifying this limitation: the number of excluded patients (n = 74) exceeded the number included (n = 120). Our final sample represents only 38% of initially eligible NICU-admitted infants born through MSAF. Therefore, our findings apply to a selected subset of MSAF infants specifically, those without chorioamnionitis or severe asphyxia. We strongly caution against extrapolating our findings to the broader MSAF population without further validation studies that include these excluded subgroups.

We found that while IL-6 was strongly predictive of MAS, other acute phase reactants showed less consistent associations. CRP correlated positively with IL-6 ($r = 0.68$, $p < 0.001$) but is known to peak later (24–48 hours) and may be less useful for early prediction. White blood cells count also correlated with IL-6 ($r = 0.52$, $p < 0.001$), but this is a non-specific marker influenced by many perinatal factors. The discrepancy between our findings and those of **Ekmen et al. (2021)**, who reported no correlation between IL-6 and either CRP or white blood cell count, may be due to differences in sampling timing (6 hours in their study vs. 4.2 hours in ours) or differences in the patient population.

The strengths of our study include its prospective design with clear temporal separation between IL-6 measurement and definitive MAS diagnosis, a well-characterized control group of symptomatic infants without MAS (rather than healthy newborns), detailed documentation of exclusion criteria and patient flow, comprehensive correlation analysis linking IL-6 to clinical severity markers, and reporting of the meconium-to-delivery interval and its lack of correlation with IL-6. However, several limitations must be acknowledged. The exclusion of common co-morbidities (chorioamnionitis and perinatal asphyxia), while necessary to avoid confounding, significantly limits generalizability to the broader MSAF population, as our findings apply to only approximately 38% of eligible NICU-admitted infants. All enrolled infants were symptomatic, so we cannot comment on the predictive value of IL-6 in asymptomatic infants born through MSAF. As a single-center study, our results may not be generalizable to other populations with different demographic characteristics or clinical practices. The relatively small sample size ($n = 120$), while adequately powered for our primary outcome, did not allow for subgroup analyses. Importantly, no validation cohort was used; the predictive cutoff of 38.1 pg/mL was derived from the same dataset in which it was tested, making external validation in an independent cohort urgently needed. Additionally, IL-6 is not a point-of-care test, as ELISA-based measurement requires laboratory infrastructure and may not be available in real time to guide clinical decisions in many settings. Finally, despite excluding known confounders, there remains potential for residual confounding from unmeasured factors such as genetic polymorphisms in the IL-6 pathway, maternal medications, or subclinical infection.

Despite these limitations, our findings suggest that IL-6 measured within the first 6 hours of life may be a useful adjunctive tool for risk stratification in symptomatic term infants born through MSAF. An IL-6 level > 38.1 pg/mL identifies infants at very high risk (PPV 96.6%) of subsequently developing MAS, while a level ≤ 38.1 pg/mL identifies infants at low risk (NPV 93.5%) of developing MAS. Potential clinical applications include considering early transfer to a tertiary NICU, early initiation of CPAP or surfactant therapy, and close monitoring for clinical deterioration when IL-6 is high, while low IL-6 may allow for less intensive monitoring, earlier weaning of respiratory support, and shorter hospital stay. However, we emphasize that IL-6 should not be used in isolation. Clinical assessment (Downes score, oxygen requirement, blood gas analysis) and chest radiography remain essential components of MAS evaluation. IL-6 should be considered an adjunctive tool, not a replacement for clinical judgment.

Several directions for future research are warranted. The cutoff value of 38.1 pg/mL must be validated in an independent, prospective multicenter cohort. Future studies should specifically examine the

predictive value of IL-6 in infants with chorioamnionitis and perinatal asphyxia, as these groups were excluded from our analysis. A study of IL-6 in asymptomatic infants born through MSAF would help determine whether screening is useful for early detection of subclinical MAS. Measuring IL-6 in cord blood could provide even earlier prediction and evaluating whether combining IL-6 with other biomarkers improves predictive accuracy is an important next step. Finally, the economic impact of routine IL-6 screening should be evaluated through cost-effectiveness analysis.

CONCLUSION

Serum interleukin-6 measured within the first 6 hours of life is strongly associated with subsequent meconium aspiration syndrome in symptomatic term infants born through meconium-stained amniotic fluid, with an AUC of 0.974, sensitivity of 93.3%, and specificity of 96.7% at a cutoff value of > 38.1 pg/mL. However, these findings apply only to infants without chorioamnionitis or severe perinatal asphyxia, who represented approximately 38% of NICU-admitted MSAF infants in this cohort. External validation in broader, more inclusive populations is urgently needed before IL-6 can be recommended for routine clinical use. Until such validation is available, IL-6 should be used as an adjunct to clinical and radiographic assessment, not as a standalone diagnostic test.

Abbreviations

ALT
alanine aminotransferase
AST
aspartate aminotransferase
AUC
area under the curve
CBC
complete blood count
CI
confidence interval
CPAP
continuous positive airway pressure
CRP
C-reactive protein
ELISA
enzyme-linked immunosorbent assay
HCO_3^-
bicarbonate
HIE
hypoxic-ischemic encephalopathy
IL-6

interleukin-6
iNO
inhaled nitric oxide
IRB
Institutional Review Board
MAS
meconium aspiration syndrome
MSAF
meconium-stained amniotic fluid
MV
mechanical ventilation
NICU
neonatal intensive care unit
NPV
negative predictive value
$PaCO_2$
partial pressure of carbon dioxide
PaO_2
partial pressure of oxygen
PPHN
persistent pulmonary hypertension of the newborn
PPV
positive predictive value
PROM
premature rupture of membranes
RBS
random blood sugar
ROC
receiver operating characteristic
SaO_2
oxygen saturation
SPSS
Statistical Package for the Social Sciences
TTN
transient tachypnea of the newborn
WBC
white blood cell.

Declarations

Ethics approval and consent to participate: This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments, ClinicalTrials.gov Identifier: NCT07394322 and as revised in 2013. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Benha University, Benha, Egypt, under approval number MS-15-1-2022. Written informed consent was obtained from the parents or legal guardians of all participating neonates prior to enrollment.

Consent for publication: Not applicable. This manuscript does not contain any individual person's data in any form (including individual details, images, or videos) that would compromise anonymity. Written informed consent for publication was therefore not required.

Availability of data and materials: Deidentified individual participant data (including data dictionaries) will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to nashwa.farouk@fmed.bu.edu.eg. The data is available on reasonable request from the authors.

Competing interests: The authors declare that they have no competing interests. No author has received financial support or funding from any commercial entity that could influence the design, conduct, analysis, or reporting of this study. No author holds patents or equity ownership in companies that could benefit from the findings of this study.

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Figures

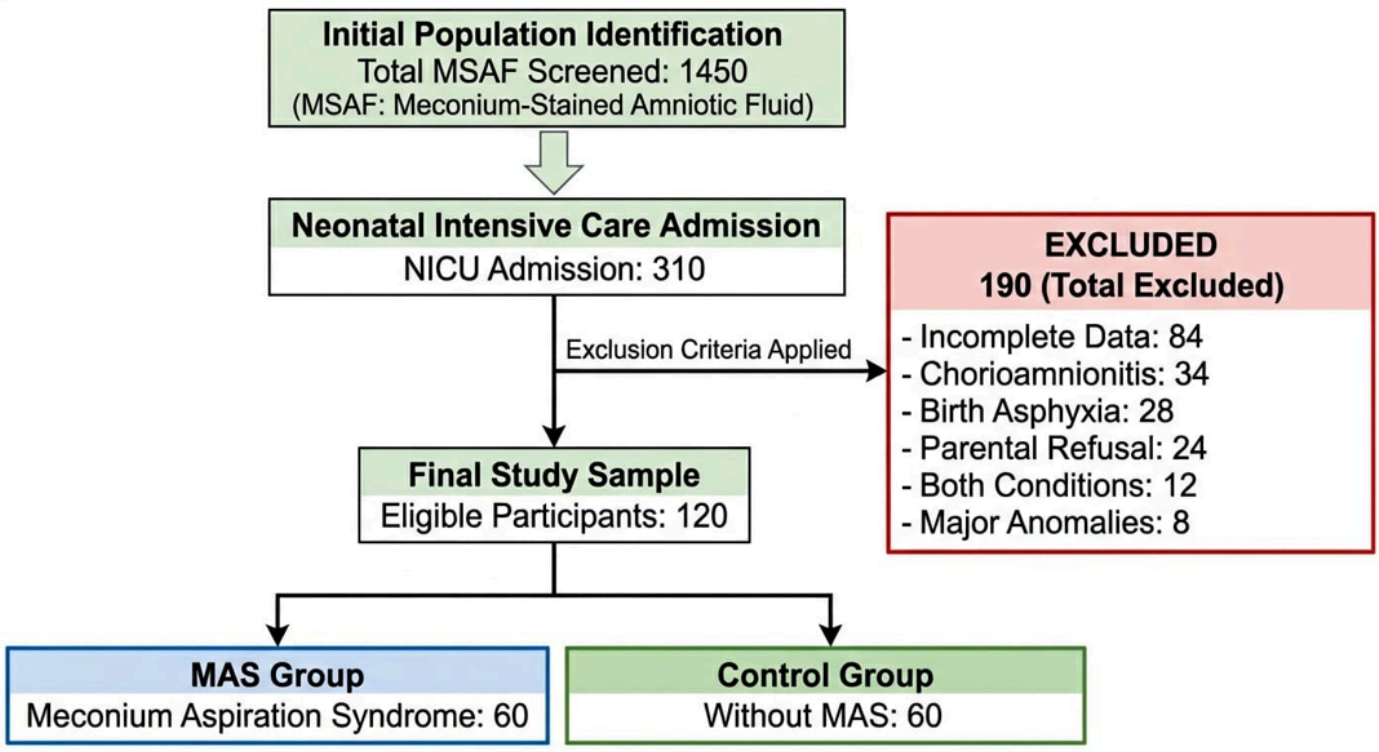


Figure 1

Flow diagram of patient selection

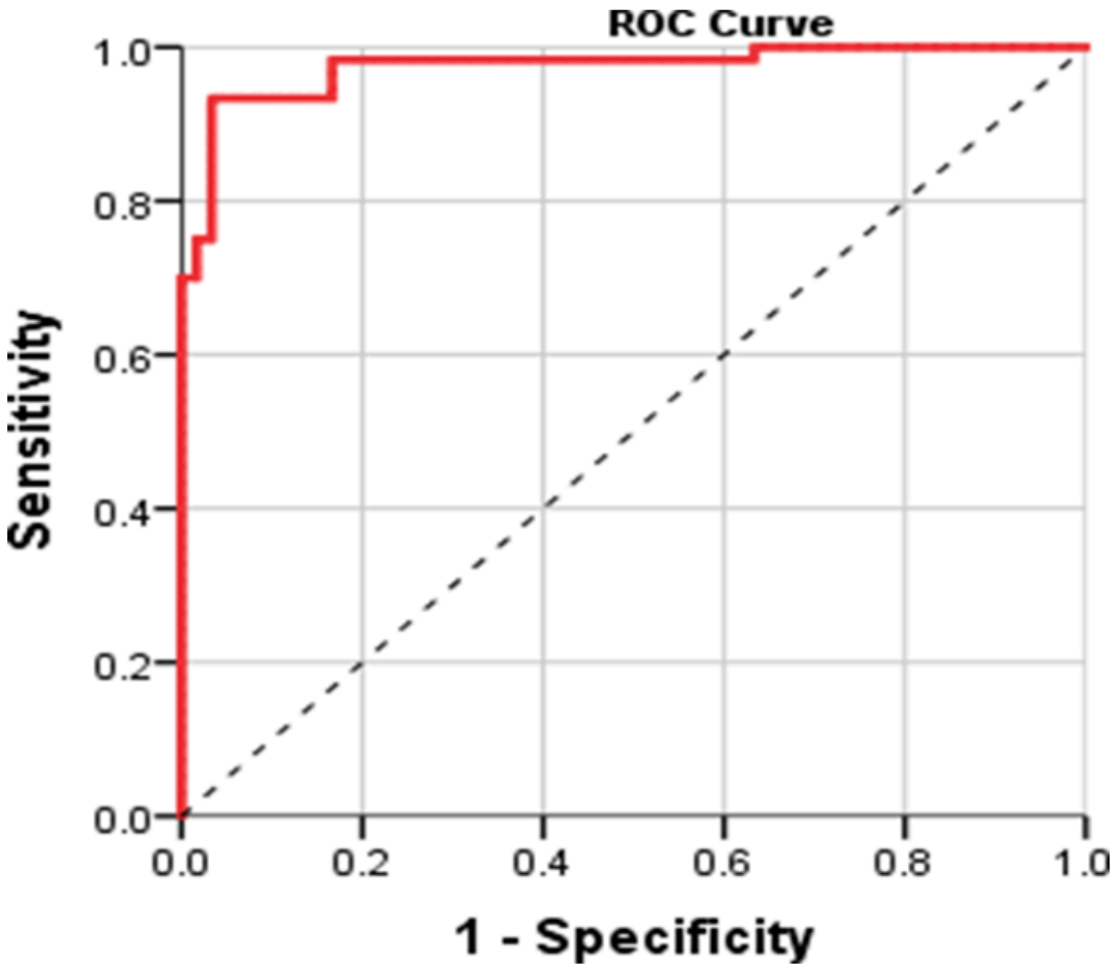


Figure 2

ROC curve of performance of Interleukin-6 in prediction of cases with MAS