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Umbilical cord arterial and venous gases, ionogram, and glucose level for predicting neonatal morbidity at term

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Introduction

During labor, the fetus can be exposed to hypoxia because of umbilical cord compression and reduction in placental flow during uterine contractions. Hypoxia can lead to fetal and subsequent neonatal acidemia, which is associated with severe morbidity and/or mortality.¹⁻³ The assessment of intrapartum hypoxia at birth has 2 main goals. The first is to increase understanding of its association with adverse neonatal outcomes as part of primary prevention, and the second is to be able to predict neonates at risk for morbidity and mortality and to ensure appropriately focused interventions.^{4,5}

Umbilical cord blood gas provides an objective assessment of the newborn's metabolic status.⁶ The standard definition of severe acidemia includes an umbilical arterial pH <7.00 and a base deficit (BD) ≥ 12 mmol/L.^{7,8} One study reported that a cutoff value of 7.00 for pH has a sensitivity of 57.8% and a specificity of 85.9% for global morbidity.⁹ In the same study, in the fetus population with pH ≤ 7.00 , 79.6% were discharged in the absence of neurological symptoms. Measurement of umbilical cord lactate concentration is another approach for identifying acidosis and hypoxia. : its sensitivity and specificity for predicting neonatal neurological outcome, were 69.7% (95% confidence interval (CI) 23.8–94.4%) and 93% (95% CI 86.8–96.3%), respectively.¹⁰ These observations may lead to inappropriate and disproportionate management of newborns because of excessive vigilance induced by poor gas blood results.

In addition to assessment of umbilical cord gas, other simple analyses could be performed such as the ionogram (including sodium, potassium, calcium, bicarbonate concentrations) and measurement of glucose level. New markers of the fetal response to hypoxia may provide useful measures of fetal physiology during labor. For example, hyponatremia has been reported to occur in mothers and their infants during labor¹¹ and can be worsened by oxytocin administration.¹² High potassium concentration in the infant during labor may be a

consequence of anaerobic metabolism, as seen in adults^{13,14} but can also lead to electrocardiogram modifications, which are known to appear during distress in labor.¹⁵

Adrenergic activity is increased by hypoxia during labor and can influence potassium and glucose level regulation.^{13,16} Our hypothesis is that hyperkalemia may be encountered in poor fetal outcomes, associated or not with hyponatremia, and glucose level modifications.

Indeed, the objective of this study was to assess whether umbilical cord blood gas parameters, ionogram, and glucose level values can be used to predict adverse neonatal outcomes.

Materials and Methods

Cohort

This was a 15-month (October 2016 to December 2017) retrospective cohort study in a single center in Lille, France. All deliveries of live singletons after 37 weeks, regardless of the presentation and mode of delivery were included. We excluded all deliveries of neonates with major congenital abnormalities.

Measurements

In our center, after delivery, a paired cord acid–base analysis is routinely performed. We validated our cord blood gas values according to the methods of Westgate et al ¹⁷ to obviate: (i) inadvertently sampling from the same vessel twice or (ii) transposing the vessels when taking the samples, on introduction into the analyzer, or when entering data. Therefore, we excluded all samples for which only one sample was taken, the values were nonphysiological, or the arterial–venous pH difference was <0.02 . The cord was double clamped 1 min after delivery at a minimum length of 10 cm with the placenta in situ, and both the artery and vein were sampled using preheparinized glass capillaries and analyzed within 15 min (Instrumentation ABL90FlexPlus (Radiometer), Brønshøj, Denmark). Routine calibrations were run 8 times a day. Umbilical cord measurements included the arterial and venous ionogram (potassium, sodium, calcium), glucose level, and gas (pH, lactate concentration, partial pressure of oxygen (pO_2), pCO_2 , HCO_3^- , and base deficit). Distribution of umbilical cord gas, ionogram and glycemia values at term from this study has been published ¹⁸.

Outcomes

The primary outcome of the study was global composite morbidity (GCM) including neurological composite morbidity (NCM) and systemic composite morbidity (SCM). The NCM included all neonates with one or more of the following: encephalopathy (grade I, II, or

III), need for hypothermic therapy, abnormal electroencephalogram, abnormal imaging (cranial ultrasound or magnetic resonance imaging), seizures, or abnormal tone or movement. SCM included neonates with one or more of the following: intubation, need for ventilation, meconium aspiration syndrome, coagulopathy, or need for inotropes. Admission to the neonatal intensive care unit and neonatal death were also analyzed.^{9,19,20} The secondary outcome was NCM.

Statistics

The statistical analyses were performed using SAS software (SAS Institute Inc, Cary, NC, version 9.4). The data are expressed as mean, standard deviation, median and interquartile range (IQR) for continuous variables, and as frequencies and percentages for categorical variables. The normality of each distribution was assessed graphically and using the Shapiro–Wilk test.

Bivariate comparisons of composite morbidity groups were performed using Student's *t* test for quantitative variables. The Mann–Whitney *U* test was used for non-Gaussian distributions, the chi-squared test was used for categorical variables, and Fisher's exact test was used when the expected cell frequency was <5.

Receiver-operating characteristic (ROC) curves were generated to assess the ability of each umbilical cord parameter to predict GCM. The discriminatory powers were determined by calculating the area under the curve (AUC) with 95% CIs, and optimal cutoff values were determined by maximizing the Youden index. The sensitivity, specificity, and positive and negative predictive values were calculated for optimal cutoff values and previously established cutoff values. For arterial umbilical cord parameters with an AUC >0.70, we performed pairwise comparisons of discriminatory powers using the Delong test. Statistical significance was defined as $P < .05$.

Ethics

This study was approved by the local committee of the French Data Protection Authority (CNIL # DEC16-208). Every patient gave their consent thanks to a written document.

Results

During the study period, 5557 live singletons were born at or after 37 weeks of gestation (Figure 1). Of these, 5161 had paired and valid samples, and were included in the study. Fifty-two (1.01%) newborns presented with GCM, including 17 (0.33%) with NCM.

Characteristics of the population are detailed in Table 1. Maternal factors that were significantly associated with the neonatal composite variable GCM were body mass index, higher in GCM group; previous cesarean section, higher in GCM group; and induction of labor, also higher in GCM group. A higher percentage of infants small for gestational age was also observed in GCM group, and the mode of delivery was more frequently operative vaginal or cesarean in GCM group. No other differences in maternal and labor characteristics between groups were observed. Excluded patients for missing blood samples (n=396) differed from studied populations for previous for maternal age, gestational age, previous diabetes, birth weight and mode of delivery, but not for other characteristics, especially for NICU admissions (Table S1).

The incidence of the composite morbidity factor GCM was 1.01% (Table 2): 12 neonates required only respiratory support, 42 were transferred to the neonatal unit, and 4 required hypothermic therapy. Only 1 neonatal death occurred after retroplacental hematoma.

Table 3 presents the data for cord samples according to GCM. Levels of potassium (arterial or venous), calcium (arterial or venous), sodium (arterial or venous), glucose (arterial), and HCO_3^- (venous) did not differ significantly between groups with or without GCM. Venous glucose level was higher in the GCM group ($P=.003$), and the arterial HCO_3^- level was lower in the GCM group ($P<.0001$). pH, pCO_2 , pO_2 , BD, and lactate levels (arterial or venous) differed significantly between the neonates with and without GCM. Similar results were found for NCM (Table S2).

Sixty (1.16%) neonates had an arterial pH <7. In this group, 13 (25.0%) were in the GCM group and 8 (47.1%) were in the NCM group.

The predictive abilities of the significant umbilical cord parameters for identifying GCM are shown in Table 4. Three arterial parameters (pH, lactate concentration, and BD) and 2 venous parameters (pH and pCO₂) had an AUC >0.70. As shown in supplementary figure (Figure S1), the predictive ability of arterial pH did not differ significantly from that of arterial lactate concentration ($P=.25$) or BD ($P=.79$). Similarly, the AUC values did not differ between the 2 venous parameters ($P=.24$). For predicting NCM, the AUC values for arterial pH, arterial lactate concentration, and arterial BD were 0.885 (0.81 to 0.86), 0.845 (0.72 to 0.97), and 0.85 (0.74 to 0.96), respectively.

The optimal cutoff values for predicting GCM were 7.144 for arterial pH, 7.236 for venous pH, 6.5 mmol/L for arterial lactate, and -8.1 mmol/L for arterial BD.

Comment

Principal Findings

This cohort study, including all births and not only those with adverse neonatal outcome, provides new information on the relationship between umbilical cord samples at birth and neonatal outcomes. Median values of pH, pCO₂, pO₂, BD, and lactate concentration differed significantly between groups with and without GCM and between groups with and without NCM., whereas the ionogram values were similar. The cutoff for predicting a worse neonatal outcome was 7.144 for arterial pH, 6.5 mmol/L for lactate concentration, and 8.1 mmol/L for BD. No component of the biochemical analyses was able to predict GCM or NCM.

Interpretation of results

Little is known about the biochemical and glyceemic composition and its relationship with fetal physiology. Potassium is a key regulator in the placenta, such for vascular exchanges, where potassium channels contribute to the adaptation of the placenta to chronic hypoxia.¹⁶ We hypothesized that, during acute hypoxia, potassium ion level would increase in the GCM group because it increases under anaerobic conditions in adults.^{13,14} However, our data gave some context to the rejection of our hypothesis. For sodium level, tolerance to a water load is diminished during labor. Intake of even moderate fluid volumes may cause hyponatremia in both the maternal and fetal compartments, and this trend can be exacerbated by oxytocin administration. Some authors have reported that hyponatremia is linked to poor neonatal outcomes.^{11,12} We did not observe hyponatremia in our series, and this difference between other studies may reflect differences in maternal management of oxytocin administration and fluids.

The ionic form of calcium serves as a universal intracellular messenger involved in the modulation of many processes such as neurotransmission, enzyme and hormone secretion, and many biological processes, such as cell cycle regulation and programmed cell death.²² In

our study, we found no clinical differences in the umbilical cord ionogram values at birth, which may reflect the continuous imbalance between the cord blood and maternal compartment during labor. Glucose level reflects the imbalance between glucose consumption during labor and adrenergic activity during hypoxia.^{22,23} In term infants delivered by caesarean section, the glucose level is strongly associated with the maternal glucose level, cord pO₂, and lactate level.²⁴ In our series, only venous glucose level was differed slightly between groups and is more likely to have reflected the maternal status than fetal physiology.

Acidosis status during labor has been studied thoroughly. Andres et al reported that ‘pathologic’ fetal acidemia seems to be indicated by an umbilical artery pH<7 with a metabolic component (i.e., BD and HCO₃⁻), whereas the umbilical artery pO₂ has no apparent clinical utility.²⁵ Malin et al reported outcomes for 481,753 infants with known cord gas values and concluded that low arterial pH was strongly associated with long-term adverse outcomes.²⁶ Prior studies that compared the predictive ability of pH, BD, and lactate concentration concluded that lactate concentration was at least as good as BD and pH for predicting poor neonatal outcomes^{19,27,28}; our results are consistent with those of these studies.

The pH cutoff values differ between studies: 7.0, 7.05, or 7.10. In a cohort study of 51,519 singleton, term, nonanomalous live neonates with validated umbilical cord arterial pH values, Yeh et al²⁹ found that the absolute risk of an adverse neurological outcome was significantly increased at pH <7.10 (0.36%) and was lowest in those with pH 7.26–7.30 (0.16%). Even with a pH <7.00, the risk was only 2.95%. However, more than 75% of neonates with adverse neurological outcomes, including seizures within 24 hours of birth, had a pH >7.10. In our study, the pH threshold for best predicting global morbidity was similar: 7.144.

The international consensus for ascribing cerebral palsy to intrapartum hypoxia states that the arterial pH must be <7.00.³⁰ Graham et al³¹ used a cutoff of 7.0 for ascribing the cause of

neonatal encephalopathy. In our study, we found a small positive predictive value of a pH <7, in that only 21.7% of neonates exhibited global morbidity.

pH information is important for the neonatologist and for legal issues. However, even though pH is the best predictive tool at present, it remains imperfect. This idea is strengthened by studies of the long-term developmental outcomes. For example, Hafström et al studied 234 neonates with umbilical arterial pH <7.05 and BD in extracellular fluid >12.0 mmol/L, and who had appeared healthy at birth. The outcome measures at 6.5 years of age shown no differences in neurologic or behavioral problems in these children compared with control children.³²

Clinical implications

Routine cord blood sampling that includes measurement of pH, lactate concentration, and BD is useful for predicting neonatal morbidity.^{17,33} Measuring ionogram values or glucose level does not appear to improve this predictive ability. This may be explained by an imbalance between the placenta and maternal blood, which results in similar cord blood values regardless of the morbidity risk of the fetus. Arterial pH remains the best available tool, even if its positive predictive value is only 21.7% with a cutoff of 7 or 3.0% with a cutoff of 7.144.

Research implications

Knutzen et al attempted to find associations between different parameters of cord blood by using a formula but did not find any improvement in predicting morbidity than pH alone.³⁴ It would be interesting to study a composite parameter that includes cord blood values with clinical assessment, such as the Apgar score or known risk factors. It would also be interesting to evaluate the long-term adverse neonatal outcomes in a larger cohort.

Strengths and limitations

The main strength of our study is the systematic sampling of arterial and venous cord blood, which allowed us to include 92.8% of our initial population and avoid selection bias for pathological events. Even if our studied population differed from excluded cases, it did not concern NICU admissions, but mostly maternal factors with differences with no clinical value i.e a difference of only 0.09 weeks of gestation or 76 grams for birthweight. In previous studies, Yeh et al²⁹ included only 52.4% of all births and Graham et al³¹ included only 10% of all births, and did not compare excluded vs included populations. The main limitations are the size of our population, the rare occurrence of poor neonatal outcomes in term fetuses, and the absence of long-term follow-up.

Conclusions

Umbilical cord blood analysis can reliably predict adverse neonatal outcomes in term fetuses. The best predictors were arterial pH and lactate concentration. Ionogram and glucose level values were not significant predictors of global or neurological morbidity. The optimal pH threshold was 7.144. These results should be confirmed in a larger cohort with neonatal follow-up.

None of the authors have any conflicts of interest or financial ties to disclose.

Contribution to authorship: RV, LG, CG wrote this article. RV, PM collected data. VD manage the statistical analysis. VHD, TR, LS, CG helped with study elaboration, and made corrections.

Details of ethics approval: This study was approved by the local committee of the French Data Protection Authority (CNIL # DEC16-208). Every patient gave their consent thanks to a written document for using their medical record in database.

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Figure captions

FIGURE 1 Flow chart of the study participants.

SUPPLEMENTAL FIGURE S1 part A ROC curves of arterial pH, lactate, and BD for predicting composite global morbidity. ROC, receiver-operating characteristic curve.;

SUPPLEMENTAL FIGURE S1 part B ROC curves of venous pH and pCO₂ for predicting composite global morbidity. ROC, receiver-operating characteristic curve.

+FIGURE 1 Flow chart of the study participants

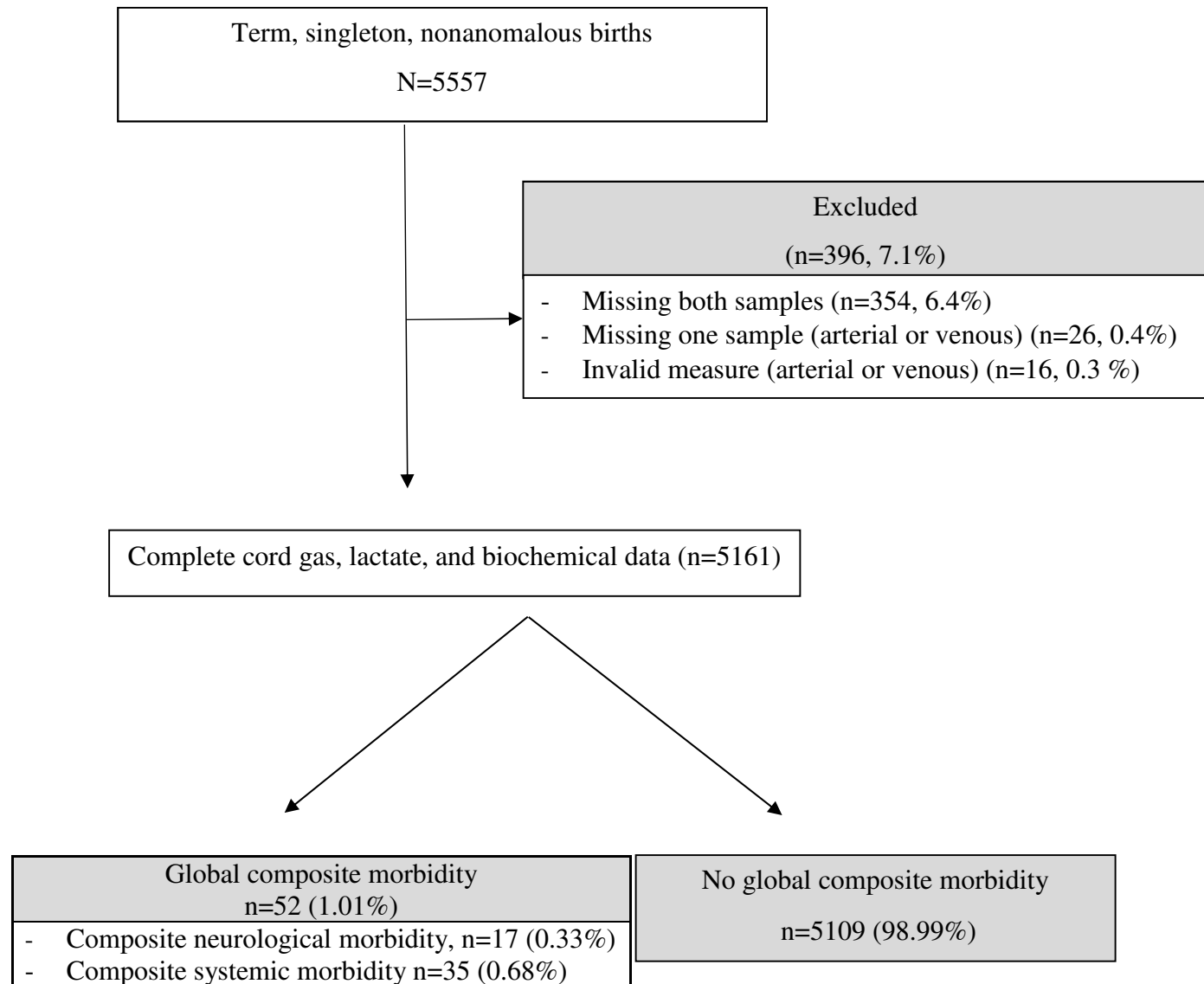


TABLE 1 Baseline characteristics of the study participants

	Entire cohort (n=5161)	No neonatal composite morbidity GCM (n=5109)	Neonatal composite morbidity GCM (n=52)	<i>P</i>
Maternal age (years)	30.9±5.4 31 (27.3 to 34.6)	30.9±5.4 37 (27.3 to 34.6)	30.8±5.2 31.5 (27.6 to 34.1)	.94
Body mass index (kg/m ²)	24.4±5.6 23.1 (20.5 to 26.9)	24.4±5.5 23.1 (20.5 to 26.9)	26.8±6.4 26.3 (21.3 to 30.4)	.014
Gestational age (weeks)	39.4±1.2 39 (39 to 40)	39.4±1.2 39 (39 to 40)	39.21±1.38 39 (38 to 40)	.25
Late term pregnancy	643 (12.5)	634 (12.4)	9 (17.3)	.29
Nulliparity	2722 (52.7)	2691 (52.8)	31 (59.6)	.32
Previous diabetes	49 (0.9)	48 (0.9)	1 (1.9)	.39
Gestational diabetes	812 (15.7)	802 (15.7)	10 (19.2)	.49
Previous hypertension	41 (0.8)	40 (0.8)	1 (1.9)	.34
Gravid hypertension	50 (1)	48 (0.9)	2 (3.9)	.09
Preeclampsia	56 (1.1)	56 (1.1)	0 (0)	1
Previous caesarean section	469 (9.1)	458 (9.0)	10 (19.2)	.024
Induction of labor	1624 (31.5)	1600 (31.3)	24 (46.1)	.022
Birth weight (g)	3405±464 3400 (3093 to 3710)	3406±462 3400 (3100 to 3710)	3371±656 3470 (2720 to 3870)	.72
Small for gestational age	209 (4.1)	203 (4.0)	6 (11.5)	.018
Male infant	2673 (51.8)	2651 (51.9)	27 (42.3)	.17
Mode of delivery				<.001
Spontaneous vaginal	3482 (67.5)	3467 (67.9)	16 (30.8)	
Operative vaginal	832 (16.1)	821 (16.1)	11 (21.1)	
Cesarean	846 (16.4)	821 (16.1)	24 (48.1)	
Apgar <7 at 5 min	30 (0.6)	10 (0.2)	20 (38.5)	<.001

The data are presented as mean±SD and median (interquartile range) or number and percentage n (%) of participants having a given categorical characteristic. Significant results (p<0.05) are in bold.

TABLE 2 Distribution of components of neonatal composite morbidity (n=52)

Component	n (%)
Composite neurological morbidity	
Hypoxic encephalopathy	17 (32.7)
Abnormal imagery	9 (17.3)
Electroencephalogram anomalies	
Stage 1	8 (15.3)
Stage 2	7 (13.5)
Stage 3	2 (3.8)
Seizures	4 (7.7)
Hypothermic therapy	4 (7.7)
Composite systemic morbidity	
Respiratory assistance	
Mechanical ventilation	46 (88.5)
Endotracheal intubation	12 (23.1)
Meconium aspiration syndrome	3 (5.8)
NICU admission	42 (80.8)
Neonatal death	1 (1.9)

TABLE 3 Umbilical cord blood samples according to neonatal global composite morbidity

		No global composite morbidity (n=5109)	Global composite morbidity (n=52)	<i>P</i>
K ⁺ (mmol/L)	Arterial	6.53±1.71 6.0 (5.3 to 7.4)	6.49±1.78 6.2 (5.1 to 7.0)	.75
	Venous	5.77±1.16 5.50 (4.9 to 6.3)	5.85±1.20 5.4 (4.9 to 6.6)	.72
Na ⁺ (mmol/L)	Arterial	133.5±4.34 134 (132 to 136)	134.2±4.63 135 (132.5 to 137)	.065
	Venous	133.4±3.37 134 (132 to 135)	133.4±3.06 134 (131 to 135.5)	.95
Ca ₂ ⁺ (mmol/L)	Arterial	1.37 ±0.16 1.41 (1.33 to 1.47)	1.41±0.15 1.44 (1.34 to 1.51)	.068
	Venous	1.40 ±0.12 1.42 (1.37 to 1.47)	1.41±0.14 1.42 (1.37 to 1.48)	.82
Glucose level (mg/dL)	Arterial	66.7 ±14.7 65 (57 to 75)	68.90±21.51 64.5 (53.5 to 79.5)	.58
	Venous	82.1±13.86 80 (73 to 90)	87.98±14.86 85.5 (79 to 98)	.003
pH	Arterial	7.20±0.07 7.21 (7.15 to 7.25)	7.08±0.15 7.11 (7 to 7.19)	<.0001
	Venous	7.32±0.07 7.33 (7.29 to 7.37)	7.23±0.13 7.25 (7.16 to 7.32)	<.0001
pCO ₂ (mmHg)	Arterial	63.39±9.42 62.7 (57 to 69)	75.12±17.55 71.0 (60.15 to 90.4)	<.0001
	Venous	44.10±7.71 43.1 (39.1 to 47.9)	53.81±16.03 48.9 (44.2 to 56.65)	<.0001
pO ₂ (mmHg)	Arterial	18.27±12.75 16.8 (11.9 to 22.3)	17.01±26.21 10.2 (5.35 to 17.7)	<.0001
	Venous	26.67±9.92 26.4 (21.6 to 30.9)	22.61±8.01 23.35 (17.2 to 27.5)	<.0001
Lactate (mmol/L)	Arterial	4.92 ±1.83 4.7 (3.6 to 6)	7.74±3.48 7.35 (4.7 to 9.1)	<.0001
	Venous	3.94±1.57 3.1 (2.3 to 4.3)	5.137±3.16 4.9 (2.6 to 7.2)	<.0001
HCO ₃ ⁻ (mmol/L)	Arterial	24.57 ±2.45 24.7 (23.0 to 26.3)	22.62±2.85 22.8 (20 to 24.95)	<.0001
	Venous	22.69 ±2.22 22.8 (21.2 to 24.2)	21.90±2.66 22.4 (19.8 to 23.8)	.071
Base deficit (mmol/L)	Arterial	4 ±3.05 3.8 (1.9 to 6.0)	7.46±4.07 7.25 (4.15 to 10.4)	<.0001
	Venous	3.28 ±2.38 3.1 (1.6 to 4.8)	5.63±3.63 4.9 (2.6 to 9.0)	<.0001

* *P*<.05; #*P*<.001. The data are presented as mean±SD and median (interquartile range). Significant results (*p*<0.05) are in bold.

TABLE 4 Ability of significant umbilical cord parameters to predict global composite morbidity

		AUC (95% CI)	Cutoff	PPV	NPV	Se	Sp
pH	Arterial	0.76 (0.68 to 0.84)	7	21.7	99.2	25.0	99.1
			7.1	5.3	99.4	50.0	90.9
			7.144*	3.0	99.6	65.4	78.4
	Venous	0.76 (0.69 to 0.83)	7.236*	3.3	99.5	55.8	83.5
pCO ₂ (mmHg)	Arterial	0.70 (0.61 to 0.78)	68.6*	2.4	99.5	63.5	73.7
	Venous	0.73 (0.66 to 0.80)	45.8*	2.1	99.6	71.1	65.6
pO ₂ (mmHg)	Arterial	0.68 (0.60 to 0.76)	10.3*	2.8	99.4	53.9	81.1
	Venous	0.64 (0.56 to 0.72)	24.9*	1.6	99.4	67.3	58.6
Lactate (mmol/L)	Arterial	0.73 (0.65 to 0.82)	6.5*	3.2	99.5	61.5	81.0
	Venous	0.68 (0.59 to 0.77)	5.5*	4.1	99.4	48.1	88.6
Base deficit (mmol/L)	Arterial	0.74 (0.66 to 0.82)	12	14.6	99.2	16.7	99.1
			8.1*	4.3	99.5	47.9	89.9
	Venous	0.69 (0.60 to 0.77)	12	40.0	99.1	3.9	99.9
			6*	3.5	99.4	47.1	87.1
HCO ₃ ⁻ (mmol/L)	Arterial	0.69 (0.61 to 0.77)	23*	2.1	99.5	58.3	73.9

* optimal cutoff value calculated by maximizing the Youden index