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ORIGINAL ARTICLE

Umbilical cord blood lactate is associated with transient tachypnoea of the newborn in near-term and term neonates☆

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KEYWORDS
Lactate;
Neonatal intensive care unit;
Transient tachypnea of the newborn;
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Abstract
Introduction: Transient tachypnea of the newborn (TTN) is the main reason of admission to the neonatal intensive care unit (NICU). The aim of the study was to analyze the association of umbilical cord (UC) lactate with TTN.
Patients and methods: Retrospective observational study in a level III NICU including infants born alive at or after 34 weeks. We fitted a multivariate logistic regression model for TTN diagnosis, adjusted for confounders, and assessed its diagnostic performance by means of the area under the curve (AUC) and the sensitivity, specificity, and predictive values at the best cut-off point.
Results: A total of 2120 neonates (50.7% male) with a median age of 39.5 weeks (IQR, 38.6–40.5) were included between August 2022 and December 2023, of whom 101 (4.8%) were preterm. In the total sample, 120 infants (5.7%) developed TTN. We found that UC lactate was independently associated with TTN (adjusted OR, 1.365; 95% CI, 1.246–1.495), with an AUC of 0.61 (95% CI, 0.56–0.67). The best cut-off point was 5.9 mmol/L, with a sensitivity of 34.5% (95% CI, 26.0–43.0), a specificity of 84.9% (95% CI, 83.3–86.5), a negative predictive value of 95.6% (95% CI, 94.7–96.5), and a positive predictive value of 12.0% (95% CI, 8.6–15.4).
Conclusion: Umbilical cord blood lactate was independently associated with TTN in near-term and term neonates Although its diagnostic performance makes its use in isolation inapropriate for decision-making, it can be considered as an additional biomarker in the global evaluation of newborn infants in the delivery room.
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PALABRAS CLAVE
Lactato;
Unidad de cuidados intentivos neonatales;
Taquipnea transitoria del recién nacido;
Sangre de cordón umbilical

El ácido láctico en sangre de cordón es un factor asociado a taquipnea transitoria en neonatos a término y pretérminos tardíos

Resumen
Introducción: La taquipnea transitoria del recién nacido (TTRN) es la primera causa de ingreso en cuidados intensivos neonatales (UCIN). El objetivo del estudio fue analizar la asociación del lactato en sangre de cordón (SCU) con el diagnóstico de TTRN en neonatos a término y pretérmino tardíos.
Pacientes y método: Estudio observacional retrospectivo en una UCIN de nivel III de neonatos $\geq$ 34 semanas. Se realizó una regresión logística multivariante para diagnóstico de TTRN, ajustando por factores de confusión y se calculó su rendimiento diagnóstico mediante el cálculo del área bajo la curva (AUC) y la sensibilidad, especificidad y valores predictivos en el mejor punto de corte.
Resultados: Entre agosto de 2022 y diciembre de 2023 se incluyeron 2.120 neonatos (50,7% varones) con una mediana de edad gestacional de 39,5 semanas (RIC 38,6-40,3) y una tasa de prematuridad del 4,8%. De ellos, 120 (5,7%) fueron diagnosticados de TTRN. El lactato en SCU se asoció de forma independiente con TTRN (aOR 1,365 (IC95% 1,246−1,495)], con un AUC de 0,61 (IC95% 0,56-0,67). El mejor punto de corte fue 5,9 mmol/L, con una sensibilidad de 34,5% (IC95% 26,0-43,0), especificidad de 84,9% (IC95% 83,3-86,5), valor predictivo negativo 95,6% (94,7-96,5) y valor predictivo positivo 12,0% (8,6-15,4).
Conclusiones: El lactato en SCU es un factor asociado a TTRN en neonatos a término y pretérmino tardíos. Aunque su rendimiento diagnóstico hace que no deba utilizarse de forma aislada, puede considerarse como un biomarcador adicional en la valoración global de los recién nacidos en partorio.
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Introduction

Umbilical cord blood gas analysis is frequently used to assess the metabolic condition of the fetus immediately before birth and to identify perinatal asphyxia and severe acidosis. In fact, a cord blood pH below 7.00 is one of the criteria established by some guidelines to determine eligibility for therapeutic hypothermia,[1,2] so measurement of cord blood pH is universally recommended and is performed routinely in all deliveries.[3] However, there is no consensus regarding the cord blood pH cut-off associated to other outcomes, with proposed values ranging between 7.00 and 7.20, depending on the study.[4–6]

Point-of-care blood gas analyzers now provide not only the cord blood pH value, but also the lactate level in the sample. Lactate is an indirect marker of anaerobic metabolism, as it is one of the final metabolites in the process.[7] There is evidence from animal models of earlier and longer lactate elevation in cases of hypoxia.[8] In the case of neonates, cord blood lactate is associated with gestational age (GA),[9] and elevated levels are a risk factor for admission, need of resuscitation and lower Apgar scores.[5,10,11] It is also associated with increased mortality.[12] Finally, cord blood lactate has been found to be a stronger predictor than cord blood pH for the composite outcome of mechanical ventilation, hypoxic-ischemic encephalopathy and neonatal death.[13]

In late preterm and term neonates, transient tachypnea of the newborn (TTN) is the leading cause of respiratory distress, frequently requiring admission to the neonatal intensive care unit (NICU).[14,15] As for its pathophysiology, accumulation of fluid in the lung has been described[16] which was confirmed more recently with techniques like lung ultrasound and electric cardiometry.[17] In addition, recent studies have demonstrated that this accumulation is not only the result of delayed resorption of fluid at birth, but also of an abnormally high baseline volume.[18,19] Plasma lactate has been associated with poorer outcomes of TTN and proposed as a predictor of the need of respiratory support.[20] However, the evidence on the association between TTN and cord blood lactate levels is still limited.

Objective

The main objective of our study was to analyze the association between cord blood lactate and the diagnosis of TTN and to assess its diagnostic performance.

Sample and methods

Study design

We conducted a retrospective observational study in a level III NICU in a healthcare area with approximately 1700 births per year. In our hospital, umbilical cord blood gas analysis is performed routinely on all neonates. After birth, the midwife attending the delivery (or the obstetrician in the

case of instrumental delivery) clamps the umbilical cord at two points and collects a single sample of umbilical cord blood with a heparinized needle and syringe.[21] Arterial blood is usually collected, and the obtained specimen is analyzed immediately with the GEM 5000 system (Instrumentation Laboratory, Werfen, Germany). The study adhered to the umbilical cord management guidelines of the Spanish Society of Neonatology, which recommend delayed cord clamping (at least 1 min) for newborn infants who do not require resuscitation.[22] Information regarding the type of cord blood sample or the time to cord clamping is not documented routinely in the unit, so it was not possible to analyze these variables due to the retrospective design of the study.

We selected patients retrospectively, starting from December 31, 2023 and going back until we obtained the calculated necessary sample size. The data were retrieved from the electronic health records.

Study sample

The sample included all neonates born at or after 34 weeks of gestation with 5- and 10-minute Apgar scores greater than 0, identified through the birth registry of the hospital.

Variables

We collected data on several variables that could act as confounders.[23] These included GA, sex assigned at birth, and birth weight. We also analyzed obstetric variables, including the type of delivery (uncomplicated, instrumental or cesarean), cord blood pH values and cord blood lactate levels. Since the study was retrospective, we were unable to obtain data regarding the characteristics or duration of labor, as this information is not routinely documented in the health record.

The primary outcome was the diagnosis of TTN, defined as signs of respiratory distress (chest wall retractions, grunting, tachypnea, nasal flaring) requiring respiratory support with positive airway pressure for a minimum of 2 h and admission to the NICU. To be classified as TTN, the condition had to resolve spontaneously with no intervention beyond supportive care, and signs of air leak or symptoms suggestive of sepsis had to be absent.

Sample size

Based on the unit's data, the expected prevalence of TTN was 6.3%. We estimated that cord blood gas analysis data would be missing in 1% of the patients, based on a preliminary review of 100 health records. Assuming a cord blood lactate standard deviation of 1.98 mmol/L (for the mean in neonates born between 34 and 42 weeks of GA[9]), we calculated that we needed a sample of at least 2114 neonates to detect a minimum difference of 0.5 mmol/L with a 95% level of confidence and a power of 80%.

Statistical analysis

Quantitative data were summarized as mean and standard deviation or median and interquartile range, according to their distribution. Categorical data were summarized as percentages. To compare quantitative data, we used the Mann-Whitney *U* test if the data were not normally distributed and the Student *t* test for independent samples otherwise. For categorical variables, we used the χ^2 test or Fisher exact test. Statistical significance was defined as a *p* value of less than 0.05.

We performed multivariate logistic regression analysis to assess the association between cord blood lactate levels and the diagnosis of TTN, calculating adjusted odds ratios (aORs) and their 95% confidence intervals (CIs). We used a causal directed acyclic graph to select variables for inclusion in the model with the aim of performing the minimum necessary adjustment to obtain an unbiased estimate of the effect of cord blood lactate and avoiding overfitting and collider bias.[24] Finally, we assessed the diagnostic performance of cord blood pH and lactate through the calculation of the area under the curve (AUC), sensitivity, specificity, and predictive values at the cut-off point that maximized the Youden index.[25] The statistical analysis was performed with the software IBM SPSS Statistics, version 26.

Missing data

First, we analyzed missing cord blood pH and lactate data by means of the Little MCAR (Missing Completely At Random) test. The initial analyses were carried out using listwise deletion. Subsequently, we used multiple imputation (including the variables sex, GA, type of delivery and resuscitation in delivery room, with five imputations with the Markov Chain Monte Carlo method) to impute the missing cord blood pH and lactate values. Finally, we repeated the analyses to confirm the consistency of the results.

Ethical considerations

The study was approved by the local Ethics Committee (PI-24-124-H). Since it was a retrospective observational study, the committee approved the waiver of informed consent.

Results

Of the 2173 births between August 8, 2022, and December 31, 2023, 2120 (97.6%) were live births at or after 34 weeks of gestation (male infants, 50.7%). The median gestational age was 39.5 weeks (IQR, 38.6—40.5), and 101 infants (4.8%) were born preterm. Table 1 summarizes the characteristics of the sample. A total of 120 infants (5.7%) were classified as having TTN. The median cord blood lactate level in the total sample was 3.7 mmol/L (IQR, 2.6–5.0), and the median cord blood pH was 7.30 (IQR, 7.24–7.35). We were unable to retrieve cord blood pH values in 63 patients (3.0%) and cord blood lactate levels in 88 (4.2%). The Little MCAR test for the missing cord blood pH and lactate values was not significant (0.08).

Table 1 Description of the study sample.

Variable	Statistic
Gestational age in weeks (median, IQR)	39.5 (38.6—40.5)
Male sex (n, %)	1074 (50.7%)
Cesarean delivery (n, %)	517 (24.4%)
Birth weight in g (median, IQR)	3240 (2950–3555)
Gestational diabetes (n, %)	158 (7.5%)
Maternal asthma (n, %)	53 (2.5%)
Antenatal corticosteroids (n, %)	29 (1.4%)
Meconium-stained amniotic fluid (n, %)	345 (16.3%)
Resuscitation in delivery room (n, %)	168 (7.9%)
Admission to neonatal intensive care unit (n, %)	198 (9.3%)
Diagnosis (n, %)	
Healthy neonate	1922 (90.7%)
Transient tachypnea of the newborn	120 (5.7%)
Neonatal respiratory distress	2 (0.1%)
Hypoglycemia	7 (0.3%)
Hyperbilirubinemia	21 (1.0%)
Culture-negative sepsis	5 (0.2%)
Shock	2 (0.1%)
Confirmed sepsis	1 (0.0%)
Low birth weight	3 (0.1%)
Preterm birth	9 (0.4%)
Perinatal asphyxia	2 (0.1%)
Air leak	5 (0.2%)
Transient feeding intolerance	4 (0.2%)
Other	17 (0.8%)

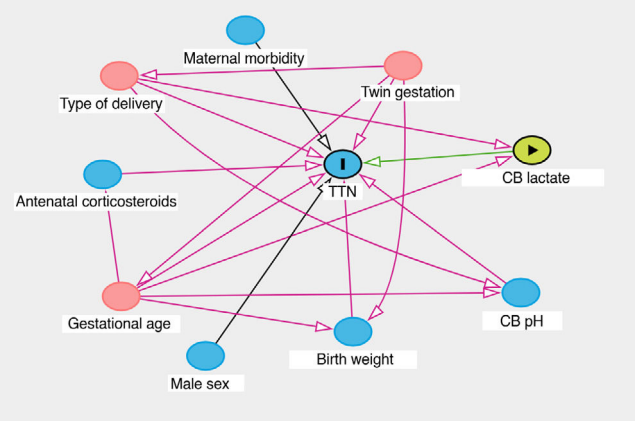

Figure 1 Causal directed acyclic graph used to select variables for inclusion in the multivariate model. CB, cord blood; TTN, transient tachypnea of the newborn.

Table 2 presents the results of the bivariate analysis based on the diagnosis of TTN, and Fig. 1 shows the causal directed acyclic graph used to select the minimal sufficient adjustment set, which in the end consisted of GA and the type of delivery. Other variables under consideration (such as birth weight or sex) turned out to be redundant or not strictly necessary. In the multicollinearity test, we found variance inflation factors of 1.04 for GA, 1.08 for type of delivery, 1.99 for cord blood lactate and 2.11 for cord blood pH. Although these values were tolerable, we fitted two separate multivariate models, one including cord blood lactate and the other cord blood pH, as they are interrelated markers of perinatal acid-base status. Fig. 2 shows the box plots for cord blood lactate levels (a) and cord blood pH (b) in the two groups.

In the multivariate model that included cord blood lactate, the variables significantly associated with diagnosis of TTN were GA (aOR, 0.66; 95% CI, 0.59—0.75; $P < .001$), type of delivery (instrumental vs uncomplicated: aOR, 1.91 [95% CI, 1.14–3.21; $P = 0.015$]; cesarean vs uncomplicated: aOR, 2.78 [95% CI, 1.74–4.36; $P < .001$]) and cord blood lactate (aOR: 1.37; 95% CI, 1.25–1.50; $P < .001$).

In the second model that included the cord blood pH, the same variables were significantly associated with TTN: GA (aOR, 0.66; 95% CI, 0.59—0.75; $P < .001$), type of delivery (instrumental vs uncomplicated: aOR, 2.14 [95% CI, 1.28–3.56; $P = .004$]; cesarean vs uncomplicated: aOR, 2.08 [95% CI, 1.34–3.24; $P < .001$]), and cord blood pH (aOR, 0.000; 95% CI, 0.000—0.004; $P < .001$).

The AUC was similar for both markers: 0.61 for cord blood lactate (95% CI, 0.56—0.67; $P < .001$) and 0.64 for cord blood pH (95% CI, 0.59—0.70; $P < .001$). Table 3 shows the results of the analysis of the diagnostic performance of the two markers. The multiple imputed values yielded similar results in all the analyses, demonstrating the consistency of the findings.

Discussion

In the sample of late preterm and term neonates under study, cord blood lactate was a factor associated with TTN.

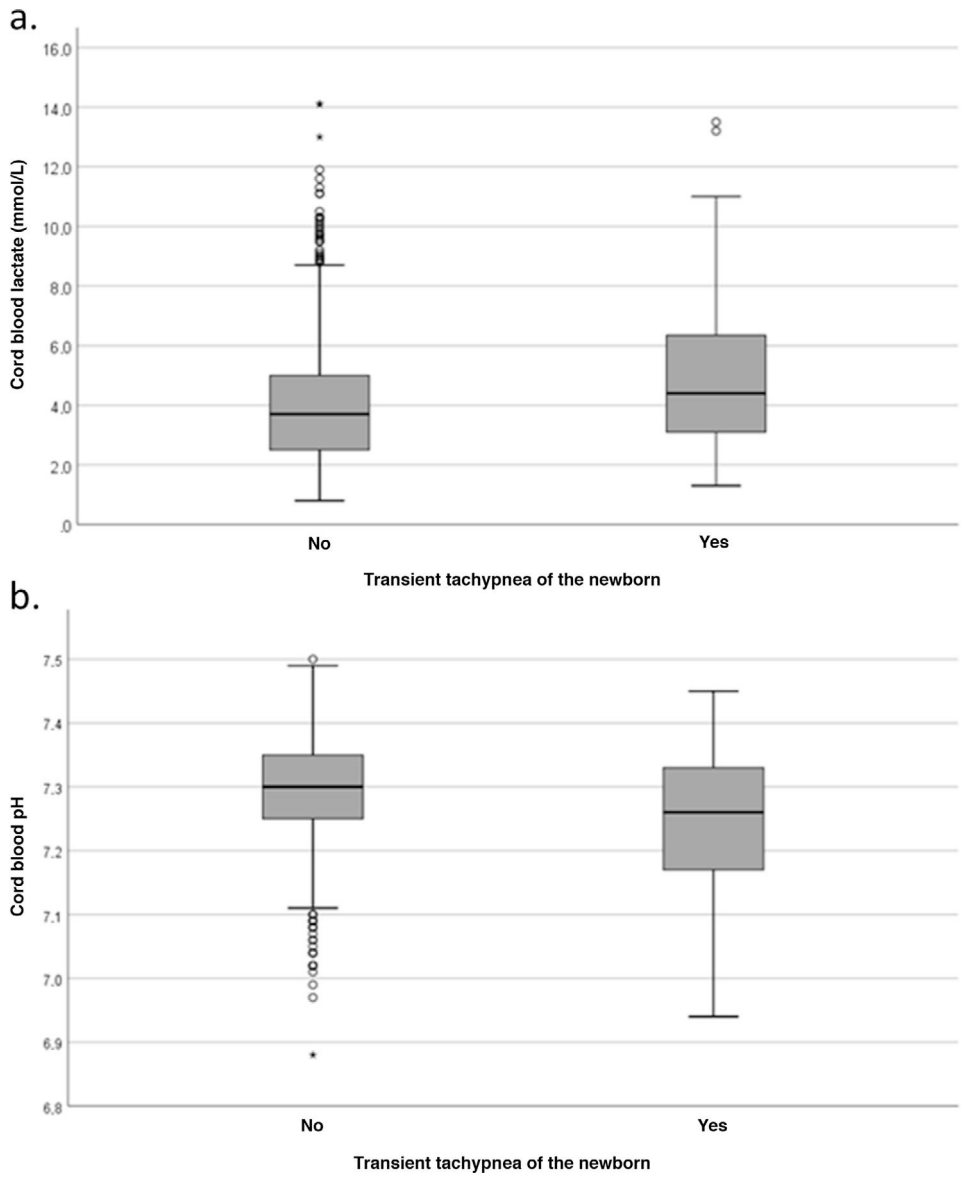

Figure 2 Box plots showing the values of cord blood lactate (a) and cord blood pH (b) according to the diagnosis of transient tachypnea of the newborn.

Although its AUC showed that it has a modest discriminative power, the multivariate regression analysis confirmed the presence of a significant positive association with TTN and suggested that, while it would not be appropriate to use it as a diagnostic marker in isolation, it could be included as an additional marker in the evaluation of the newborn infants in the delivery room.

Cord blood pH has been previously described as a predictor of neonatal admission and outcomes, although its optimal cut-off point remains unclear.[6] Cord blood lactate, which has not been investigated as extensively, performed better than pH for prediction of adverse outcomes in a previous study.[13] In our sample, both markers were associated with TTN and their AUCs showed a similar diagnostic performance. When we assessed the specificity and sensitivity of cord blood pH and lactate levels, we found that they were complementary from a clinical viewpoint. Cord blood lactate stood out for its high specificity (84.9%), while cord blood pH displayed a higher sensitivity (75.8%). These findings suggest that these two markers offer complementary information on the metabolic status of the neonate.

However, leaving aside the individual predictive ability of cord blood pH and lactate (which proved modest in this study), lactate can be valuable as an additional risk marker. While pH has historically been the standard biomarker, lactate offers a linear and direct interpretation for pediatricians: a 36.5% increase in the risk of TTN for every 1 mmol/L increase in lactate. Since pH is measured on a logarithmic scale, the interpretation of its OR is less intuitive, as minimal numerical variations result in significant clinical changes. These findings do not justify a change or substitution in conventional blood gas analysis, but rather support the role of cord blood lactate as an additional parameter to consider in the comprehensive evaluation of the neonate in the

Table 2 Bivariate analysis of transient tachypnea of the newborn.

Variable	No TTN (n = 2000)	TTN (n = 120)	*P*
Gestational age (median, IQR)	39.6 (38.6—40.5)	39.2 (37.2—40.4)	<.001
Male sex (n, %)	991 (49.6%)	83 (69.2%)	<.001
Weight in g (median, IQR)	3245 (2955—3555)	3218 (2840—3513)	.105
Antenatal corticosteroids (n, %)	18 (0.9%)	11 (9.2%)	<.001
Maternal obesity (n, %)	36 (1.8%)	7 (5.8%)	.002
Maternal asthma (n, %)	51 (2.6%)	2 (1.7%)	.766
Maternal diabetes (n, %)	149 (7.5%)	9 (7.5%)	.984
Risk of infection *(n, %)*	352 (17.6%)	25 (20.8%)	.368
Type of delivery (n, %)			
Normal	1 236 (61.8%)	50 (41.7%)	<.001
Instrumental	291 (14.6%)	26 (21.7%)	
Cesarean	473 (23.7%)	44 (36.7%)	
Meconium-stained amniotic fluid (n, %)	322 (16.1%)	23 (19.2%)	.377
Resuscitation in delivery room (n, %)	127 (6.4%)	41 (34.2%)	<.001
1-minute Apgar (mean, SD)	8.8 (0.8)	7.7 (1.7)	<.001
5-minute Apgar (mean, SD)	9.9 (0.4)	9.2 (0.9)	<.001
Cord blood pH (median, IQR)	7.3 (7.3–7.4)	7.3 (7.2–7.3)	<.001
Cord blood lactate (median, IQR)	3.7 (2.5—5.0)	4.4 (3.1—6.4)	<.001

Abbreviation: TTN, transient tachypnea of the newborn.

Table 3 Diagnostic validity parameters for the prediction of transient tachypnea of the newborn.

Marker	Cut-off	Sensitivity	Specificity	PPV	NPV
Cord blood lactate	5.9 mmol/L	34.5% (26.0—43.0)	84.9% (83.3—86.5)	12.0% (8.6—15.4%)	95.6% (94.7—96.5%)
Cord blood pH	7.25	75.8% (68.1—83.5)	48.3% (46.1—50.5)	8.1% (6.5—9.7%)	97.1% (96.1—98.1%)

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

delivery room, taking into account other factors, such as GA or the type of delivery, in its interpretation. In addition, the multifactorial nature of TTN and the diagnostic performance of cord blood lactate, based on the AUC, suggest that this marker should not be used in isolation to guide decision-making, but rather as an additional risk indicator.

In respect to lactate, it is one of the final products of anaerobic metabolism, a metabolic pathway that is less efficient energetically, as it generates 2 ATP molecules compared to the 30 or 36 molecules produced in the aerobic pathway.[7] In the uteroplacental circulation, the net movement of lactate is represented by the arterio-venous lactate gradient, and there is controversy whether this gradient is positive or negative.[26,27] Furthermore, a study on cord blood gas analysis at birth that included paired arterial and venous blood samples found that both positive and negative gradients are physiological.[28] We hypothesize that the potential association between TTN and cord blood lactate could involve changes in lung fluid clearance, which is mainly regulated by epithelial sodium channels, aquaporin channels and the Na^+-K^+-ATPase pump. The onset of labor gives rise to an increase in catecholamines that stimulate epithelial sodium channels and, therefore, the passive transport of sodium ions into the cell. The Na^+-K^+-ATPase contributes by actively transporting sodium ions to the interstitial space, promoting the passive movement of water into this space and, subsequently, to the pulmonary circulation and lymphatic vessels. The inhibition, lack of stimulation or impaired function of any of these mechanisms reduces fluid clearance.[29,30] Lactate, a marker of anaerobic metabolism, may reflect hypoxic conditions, which have been associated with the inhibition of epithelial sodium channels.[31,32] In addition, the lower ATP yield of anaerobic glycolysis could result in decreased Na^+-K^+-ATPase pump activity.

Another plausible explanation is that some of the patients with a diagnosis of TTN did not actually have this condition. Although we established a case definition of TTN in our study, it continues to be a clinical diagnosis subject to variability, and the data were collected retrospectively. It is also worth noting that, even today, TTN is still poorly understood in terms of both its pathophysiology and its diagnosis. It could be that some patients presented with tachypnea as the most prominent clinical sign, but that this was not a consequence of lung fluid accumulation, but rather a compensatory mechanism for regulating acid-base balance, so that the disturbance in homeostasis was due to a condition other than TTN.

There are several limitations to this study. First, due to its retrospective observational design, it was not possible to infer causality. Furthermore, data were not available for certain factors associated with TTN, among which the lack of information on the characteristics and duration of labor is particularly significant.[33] The high proportion of cesarean delivery in the study cohort may have affected patient outcomes, but since the type of delivery was included in the multivariate models, we do not believe that this com-

promises the results. On the other hand, it is known that delayed cord clamping affects cord blood lactate levels.[34,35] We were not able to obtain data on this factor, but the time window applied in our hospital, which adheres to the recommendations of the Spanish Society of Neonatology, would be short in any case, and changes in lactate during these short intervals are not large,[36] so we consider this a minor limitation. One of the most important limitations that we must highlight is the lack of data regarding the type of cord blood specimen (arterial or venous). Although the customary practice in our hospital is to obtain arterial blood samples, we cannot guarantee that this was the case in every patient. There is evidence that the difference in lactate values between arterial and venous cord blood may be negative, positive, or none, ranging between −1 and +1 mmol/L.[28] These differences in lactate and pH levels may have affected the internal validity of the study. However, given the range of the differences in values between the two types of sample and the fact that this limitation reflects everyday clinical practice, we believe that, although it must be taken into account, the study provides useful information for real-world clinical settings, regardless of the type of sample used. Finally, since TTN is a clinical diagnosis, some patients categorized as having TTN may have actually had a different condition.

As for the main strengths of our study, we ought to highlight that it analyzed a large, well-defined cohort of term and late preterm neonates, and that the design had adequate statistical power. Furthermore, the analysis of missing data revealed no significant biases, and we found substantial consistency in multiple imputations. Finally, we selected confounding variables using causal directed acyclic graph analysis to avoid overfitting, and assessed for collinearity appropriately.

In future research, it would be interesting to use animal models to examine the relationship between cord blood lactate levels and lung fluid volume, as well as the expression of mechanisms associated with fluid clearance, to thoroughly investigate the pathophysiological mechanism underlying the association identified in our study.

Conclusions

We found an association between cord blood lactate and TTN in late preterm and term neonates. Although the diagnostic performance of lactate does not suffice for its use in isolation, it can be considered as an additional biomarker to include in the evaluation of newborn infants in the delivery room.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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