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ORIGINAL ARTICLE

Cord blood procalcitonin level and early-onset sepsis in extremely preterm infants

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Abstract

Early-onset neonatal sepsis (EOS) is observed in 1.7% of extremely preterm infants, with high morbidity and mortality rate. Cord blood procalcitonin (PCT) is a sensitive marker of EOS in full-term newborns, but it has been rarely studied in premature infants. The diagnostic value of cord blood PCT by immunofluorescence has been assessed as an early marker of EOS in a prospective cohort of extremely preterm infants, with a threshold at 0.5 μg/L. EOS was defined by a positive bacterial culture or by the association of postnatal biological/clinical signs of EOS and antibiotic treatment for more than 72 h. Correlation between PCT serum concentrations and postnatal morbidities was also analyzed. Among a total of 186 infants, 45 (24%) were classified as EOS. Blood PCT concentration was ≤ 0.5 μg/L in 114 infants, including 11 EOS (9.6%) and PCT was > 0.5 μg/L in 72 babies including 34 EOS (47.2%). PCT concentration > 0.5 μg/L was associated with higher risk of EOS (OR 2.18; CI95% 1.58–3.02; $p < 0.0001$). The receiver operating characteristic curve determined a cutoff of 0.7 μg/L as the best compromise, with an area under the curve of 0.75 (sensitivity 69%, specificity 70%). In multivariate analysis, clinical chorioamnionitis was associated with PCT concentration > 0.5 μg/L (OR 2.58; CI95% 1.35–4.94; $p = 0.004$). Cord blood PCT is a marker significantly associated with EOS in extremely preterm infants, but its sensitivity remains low. Its added value in combination with other early marker of EOS needs to be further investigated in this high-risk population.

Keywords Early-onset sepsis · Neonatology · Procalcitonin · Extremely preterm infants · Biological marker

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Abbreviations

BPD	Bronchopulmonary dysplasia
CRP	C reactive protein
CI95%	95% Confidence interval
EOS	Early-onset sepsis
IVH	Intra-ventricular hemorrhage
LOS	Late-onset sepsis
NEC	Necrotizing enterocolitis
OR	Odds ratio
PCT	Procalcitonin
ROC	Receiver operating characteristics

Introduction

Nearly 15 million infants are born prematurely every year and preterm birth is still the most common cause of neonatal mortality with ~ 1 million deaths/year. Even if the survival rate in this population is increasing, morbidity associated with preterm birth remains more or less unchanged. They are particularly

exposed to early-onset neonatal sepsis (EOS) [1], with an incidence around 1.7% among infants born before 28 weeks of gestation [2], resulting in an increased mortality risk up to 24% [3]. EOS is also associated with long-term complications, including bronchopulmonary dysplasia (BPD), severe brain injuries, and neurodevelopmental impairments [4].

EOS is defined by clinical and biological evidences of systemic infection occurring within the first 72 h of life [4]. The diagnosis can be challenging especially in preterm babies as the clinical signs are often poor and early biological markers are neither sensitive nor specific enough. Consequently, infants at risk of EOS are exposed to biological monitoring based on repeated blood tests to confirm the diagnosis or to assess the therapeutic efficacy [5, 6]. This approach has many disadvantages: multiple, invasive, painful, expensive exams, as well as unnecessary antibiotics treatments. Indeed, antibiotics are initiated in the majority of extremely preterm infants and are frequently continued despite sterile blood cultures [2]. In particular, prolonged and repeated antibiotic administrations lead to a dramatic increase in the emergence of antibiotic-resistant bacteria, an increased risk of late-onset sepsis (LOS), necrotizing enterocolitis (NEC), and long-term consequences such as autoimmune, allergic, or metabolic diseases [5].

Procalcitonin (PCT) is a biological marker of bacterial infection, and it appears to be more sensitive and specific than C reactive protein (CRP) in children [7, 8]. However, neonatal PCT blood concentrations physiologically increase within the first 48 postnatal hours, making its interpretation speculative as soon as 2 h following birth [7, 9]. Conversely, umbilical cord blood PCT concentration appears a specific marker of EOS in term newborns, and it has been recently considered in diagnostic algorithms in combination with perinatal risk factors and clinical evidence of EOS [8–11]. To date, no prospective study has specifically assessed cord blood PCT as early marker of EOS in extremely preterm infants.

The aim of this study was to assess whether umbilical blood cord PCT concentration could be an early marker of EOS in extremely preterm infants. Secondary objective was to investigate an association between PCT concentrations at birth with antenatal characteristics, clinical chorioamnionitis, postnatal morbidities, and neonatal mortality.

Patients and methods

We performed a monocentric observational prospective analysis of collected data from September 2008 to March 2017 at Robert Debré University Children's Hospital, Paris, France. Written informed consent was obtained from all parents of eligible infants. The local clinical research committee approved the study (No. 2017/368-2).

Inclusion criteria

All extremely preterm neonates born between $24^{0/7}$ weeks and $27^{6/7}$ weeks with cord blood PCT lab testing were included in the study.

PCT laboratory test

Blood samples were obtained from umbilical vein blood in standard vacuum blood collection tubes containing lithium heparin at delivery room. Two hundred microliters of plasma was used for immunofluorescence by technology assay with the KRYPTOR® automated analyzer (BRAHMS, Hennigsdorf, Germany).

Data collection

Data were recorded in a customized database at the time of newborn discharge. Maternal data included ethnic group, presence of diabetes, or high blood pressure. Perinatal data included tocolysis, antenatal antibiotics and glucocorticoids exposure, clinical chorioamnionitis defined by maternal fever and uterine contractions [12], prolonged membrane rupture (more than 24 h before birth), analgesia and mode of delivery, gestational age at birth, birthweight, multiple pregnancy, and APGAR score at 5 min of life.

Biological data included cord blood PCT at birth and CRP serum concentrations at birth and at 24 h of life (cutoff for elevated CRP was ≥ 10 mg/L), gastric fluid, blood and cerebrospinal fluid sampling.

The following postnatal complications of prematurity were collected: death, bronchopulmonary dysplasia (BPD) defined using a standardized oxygen-reduction test performed at 36 weeks of postmenstrual age [13], severe intraventricular hemorrhage (IVH) grade 3 or 4 according to Papile's classification [14], NEC ≥ 2a according to Bell's classification [15], surgery of patent ductus arteriosus, and LOS defined by the detection of a bacterial pathogen in the blood after 72 h of life requiring antibiotic treatment for more than 72 h [16].

EOS classification

Based on national French consensus guidelines, EOS was a posteriori defined by a positive culture of central (blood or cerebrospinal fluid) samples (definite EOS) or by the association of postnatal biological (leukopenia < 5000/mm^3 or hyperleukocytosis ≥ 21,000/mm^3, CRP > 10 mg/dL, PCT is excluded) and clinical signs of sepsis (as lethargy, hypothermia, poor feeding, respiratory and cardiac symptoms including apnea, grunting, cyanosis, desaturation, bradycardia, poor perfusion, and hypotension) or a microbiological identification of a pathogen in the gastric aspirate and antibiotic treatment for more than 72 h (probable EOS) [6]. Clinicians were

informed of PCT value, but it was not used as a criterion for diagnosis and therapeutic decision.

Taking into consideration the reported values in studies about cord blood PCT [8, 9] and accordingly to the laboratory threshold, we have chosen a cut off limit of 0.5 μg/L. Then, newborns were classified in one group with PCT value above 0.5μg/L and a second group with PCT value below or equal to 0.5μg/L.

Statistical analysis

A descriptive analysis on the baseline characteristics was firstly done presenting the results in a form of frequencies (percentages) or medians (interquartile range: 1st quartile–3rd quartile) for the qualitative and quantitative variables respectively.

We analyzed the PCT distribution among infected and non-infected newborns and compared the PCT median in these two groups using the Wilcoxon–Mann–Whitney statistical test. A receiver operating characteristic (ROC) curve using SAS software was calculated in order to obtain the best cutoff value for PCT measured in cord blood. The sensitivity, specificity, negative, and the positive predicting values were estimated in this analysis. Additionally, in order to assess the ability of PCT to predict the infection, we examined their statistical association performing a univariate analysis followed by a multivariate analysis applying a logistic regression model.

Furthermore, in order to evaluate the ability of PCT to predict the neonatal complications of prematurity, a logistic regression model was applied and analyzed in the entire study population performing a univariate analysis followed by a multivariate analysis. The aggregate risk was defined by the occurrence of at least one complication (i.e., severe IVH (grade 3 or 4), leukomalacia, NEC, surgery of ductus arteriosus, LOS, or death).

Finally, in order to describe more accurately all the factors that are increasing the PCT value, we performed a logistic regression model. The statistical tests were bilateral using a significance level of 5% (i.e., a statistically significant result is the one where the observed p value is less than 5%). All the statistical analyses were performed using the statistical software SAS 9.4, ©2002–2012 SAS Institute Inc., Cary, NC, USA, for Windows version 9.4.

Results

Description of the population

During the study period, 188 extremely preterm neonates were eligible. Two were excluded due to insufficient plasma quantity to measure PCT (Fig. 1). Baseline characteristics of patients are described in Table 1. Incidence of probable or certain EOS was 45/186 (24%) and 2/186 (1.08%), respectively. As shown in Fig. 1, 114 infants had PCT ≤ 0.5 μg/L, including 11 infected newborns (9.6%) and 72 had PCT > 0.5 μg/L, including 34 infected infants (47.2%).

Among infants with EOS, microbiological distribution was: 48.6% none identified, 8.1% *Escherichia coli*, 5.4% *Streptococcus agalactiae*, 5.4% *Candida albicans*, 13.5% other *Streptococcus*, 5.4% other Gram-negative bacilli, and 13.5% anaerobic bacteria.

Cord blood PCT and EOS

Distribution of PCT value among infected and non-infected patients is shown in Fig. 2. PCT median concentration was significantly higher in infected newborns compared to non-infected patients (0.9 μg/L vs 0.4 μg/L, $p < 0.0001$). PCT concentration > 0.5 μg/L was statistically associated with EOS in extremely premature with an odds ratio (OR) of 2.18 (95% confident interval (CI95%) 1.58–3.02; $p < 0.0001$).

To validate the chosen threshold at 0.5 μg/L, we realized a ROC curve. Considering the entire study population, analysis of the ROC curve (Fig. 3) determined a cutoff of 0.7 μg/L as the best compromise, with an area under the curve of 0.75, a sensitivity 68.9%, and a specificity 70.4%. At the cutoff of 0.7 μg/L, there were 40 false positives and 14 false negatives.

Comparison of PCT and CRP values to predict EOS

Among the 186 studied patients, 183 CRP values were available at birth, including 166 CRP < 10 mg/L (9%) and 17 ≥ 10 mg/L (9%). EOS were observed in 19% infants with CRP < 10 mg/L and 82% in infants with CRP ≥ 10 mg/L ($p < 0.0001$). CRP concentration was found ≥ 10 mg/L when PCT > 0.5 μg/L in 15/70 infants (21.4%) and in 2/113 (1.8%) infants with PCT ≤ 0.5 μg/L. In infants with CRP < 10 mg/L, PCT measurement was found > 0.5 μg/L in 21/31 infants with EOS (OR 6.52; CI95% 2.76–15.37; $p < 0.0001$).

Relationship between antenatal risk factors of EOS and PCT at birth

In bivariate analysis, clinical chorioamnionitis (OR 2.46; CI95% 1.30–4.66; $p = 0.006$), rupture of membranes > 24 h (OR 2.14; CI95% 1.14–4.01; $p = 0.02$), and vaginal delivery (OR 2.04; CI95% 1.04–3.97; $p = 0.04$) were significantly associated with PCT > 0.5 μg/L, after adjustment on gestational age. In multivariate analysis, only clinical chorioamnionitis remained significantly associated with PCT concentration (OR 2.58; CI95% 1.35–4.94; $p = 0.004$).

Association between neonatal morbidities and PCT at birth

The incidences of neonatal morbidities were reported according to PCT concentration groups in Table 2. The

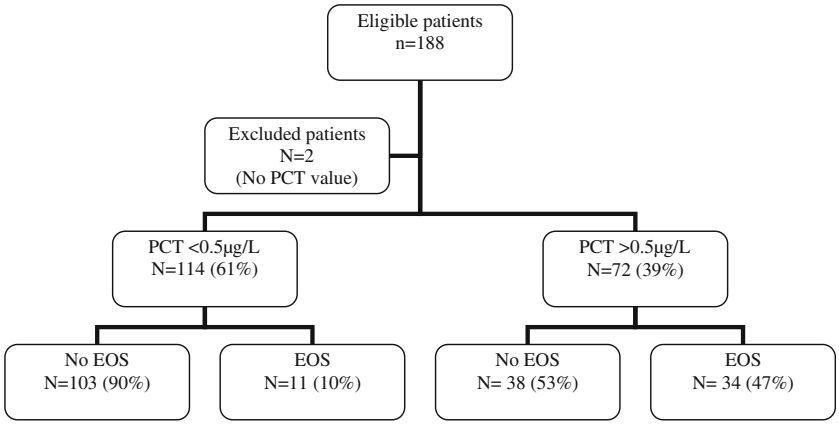

Fig. 1 Study flow diagram. PCT procalcitonin, EOS early-onset sepsis

PCT: procalcitonin; EOS: early onset sepsis

aggregate risk including severe IVH (grade 3 or 4), leukomalacia, NEC, surgery of ductus arteriosus, LOS, or death was not found statistically associated with PCT values (OR 0.90; CI95% 0.43–1.85; $p = 0.77$).

Discussion

This study analyzed PCT, as an early marker of EOS in the largest cohort of extremely preterm neonates reported to date

Table 1 Baseline characteristics of patients and their mothers according to the PCT values

Variable	Total *N* = 186	PCT ≤ 0.5 µg/L *N* = 114	PCT > 0.5 µg/L *N* = 72
Race or ethnic group of mother, *N* (%)			
Caucasian	47 (27)	34 (31)	13 (21)
African	94 (55)	52 (48)	42 (67)
Asian	9 (5)	6 (6)	3 (5)
Maternal diabetes during pregnancy, *N* (%)	10 (5)	6 (5)	4 (6)
Maternal high blood pressure, *N* (%)	20 (11)	15 (13)	5 (7)
Tocolysis, *N* (%)	116 (67)	73 (69)	43 (65)
Antenatal antibiotics exposure, *N* (%)	143 (78)	84 (74)	59 (83)
Antenatal glucocorticoids exposure, *N* (%)	160 (90)	103 (91)	57 (88)
Clinical chorioamnionitis, *N* (%)	63 (37)	30 (29)	33 (51)
Prolonged rupture of membranes > 24 h, *N* (%)	60 (33)	29 (26)	31 (45)
Epidural analgesia, *N* (%)	93 (55)	56 (53)	37 (60)
Vaginal delivery, *N* (%)	114 (62)	64 (57)	50 (71)
Birth weight (g)			
Median (IQR)	870 (750; 970)	870 (750; 960)	875 (758; 1018)
Min; max	565; 1440	565; 1310	580; 1440
Gestational age (weeks)			
Median (IQR)	26.0 (25.6; 27.0)	26.0 (25.6; 27.0)	26.3 (25.3; 27.0)
Min; max	24.0; 27.9	24.0; 27.9	24.0; 27.9
Multiple pregnancy, *N* (%)	59 (32)	41 (36)	18 (25)
Male sex, *N* (%)	101 (54)	63 (55)	38 (53)
APGAR at 5 min			
Median (IQR)	8 (6; 10)	8 (6; 10)	8 (6; 10)
Min; max	1; 10	1; 10	1; 10

PCT procalcitonin

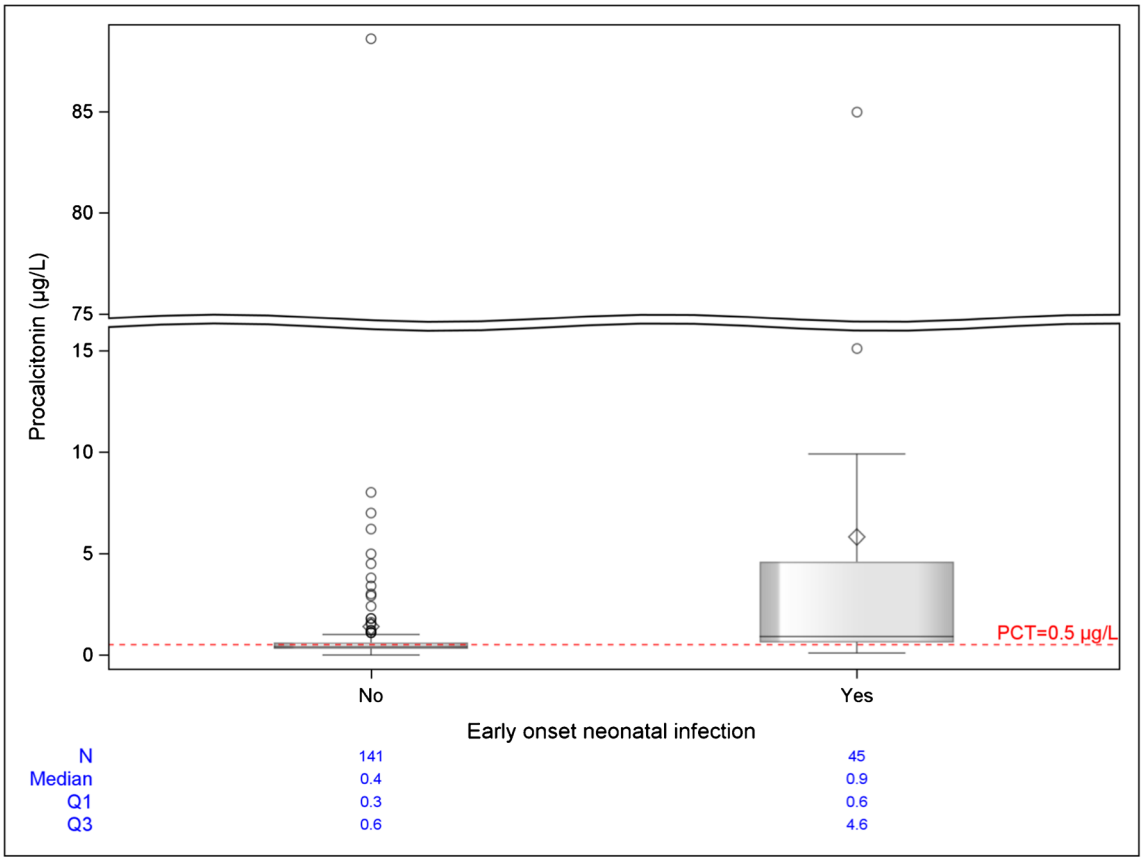

Fig. 2 Box and whisker plot showing PCT concentration according to the infectious status. PCT level is expressed in micrograms per liter. The box represents first and third quartiles, horizontal lines represent medians with the corresponding numerical value, and whiskers give 10/90 percentiles. Open circle represent outliers. The dotted line represents the cutoff 0.5 µg/L. Q1 1st quartile, Q3 3rd quartile, PCT procalcitonin

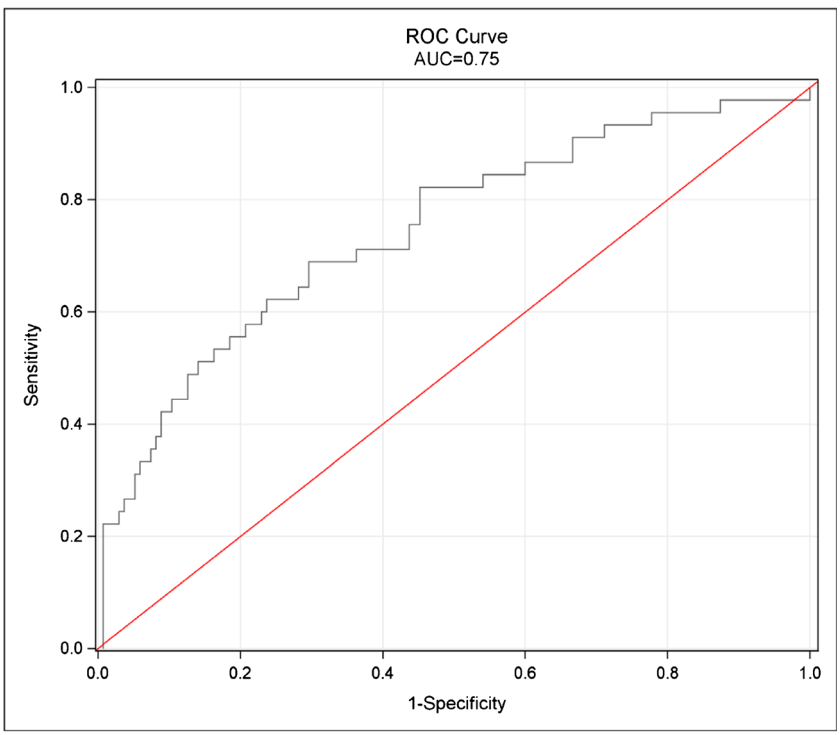

Fig. 3 Receiver operating characteristics (ROC) curves of procalcitonin value (PCT) on PCT logarithm

Table 2 Morbidity events according to procalcitonin value (PCT)

Variable	Total $N = 186$	PCT ≤ 0.5 μg/L $N = 114$	PCT > 0.5 μg/L $N = 72$
Bronchopulmonary dysplasia, *N* (%)	102 (55)	58 (51)	44 (61)
Severe intraventricular hemorrhage (grades 3 and 4), *N* (%)	38 (21)	26 (23)	12 (17)
Periventricular leukomalacia, *N* (%)	24 (13)	15 (13)	9 (13)
Necrotizing enterocolitis, *N* (%)	9 (5)	4 (4)	5 (7)
Surgery of ductus arteriosus, *N* (%)	21 (12)	15 (14)	6 (8)
Nosocomial sepsis, *N* (%)	107 (59)	64 (58)	43 (60)
Death, *N* (%)	29 (16)	19 (17)	10 (14)

[8, 17]. This study confirms that cord blood PCT level > 0.5 μg/L is associated with an increased risk of EOS in extremely preterm infants, notably when CRP concentration at birth was ≤ 10 mg/L.

We reported here a higher incidence of proven or highly suspected EOS ($n = 45/186$, 24%), compared to previous studies. Stoll et al. reported a rate of certain EOS of 10 to 96 per 1000 livebirths among < 1500 g birthweight neonates [3] and Puopolo et al. a rate of 1.7% in extremely preterm infants [2]. In our study, 2 EOS (1.1%) were confirmed by positive microbiological blood samples. Most of EOS was classified as probable using the 2002 national French guidelines criteria [6].

The PCT concentrations were found variable, although most of values ranged between 0 and 0.6 μg/L, as also previously reported [8]. The chosen threshold of cord blood PCT varies between studies, depending on the population studied and the evaluating criteria. Joram et al. published a first study in 2006, where the PCT cutoff of 0.5 μg/L was considered as the most sensitive and specific in late preterm and full term infants [9]. In a 2011 study conducted by the same group on a larger cohort with 38% of preterm and 72% of full term newborns, analysis of the ROC curve with a cut off of 0.6 μg/L was the best compromise between sensitivity and specificity, with an AUC of 0.96 (CI 95% 0.95–0.98) [8]. Taking into consideration the reported values in these studies and accordingly to the laboratory threshold, we have chosen a cutoff limit of 0.5 μg/L. Looking at the best cutoff in extremely preterm infants, the ROC curve showed here a PCT value at 0.7 μg/L, with a sensitivity and a specificity of 69% and 70%, respectively, both lower compared to those reported in infants with higher gestational age. Evaluating outliers may be especially important for the ROC model since difficult cases have the potential for being missed by a reader (e.g., a difficult positive case is rated as an unquestionably negative case) and can have a considerable influence on the estimated area under the ROC curve, especially if the study has a small set of cases. Therefore, 6 extreme values of PCT were removed from the analysis to minimize this bias. The threshold of 0.7 μg/L in extremely preterm infants should be confirmed in other longitudinal cohort studies. Cord blood PCT showed significantly higher sensitivity than CRP for EOS in extremely preterm infants, as also described in another study [9].

Chorioamnionitis is recognized as one of the main risk factors for EOS [6]. Not surprisingly, it was identified as a statistically associated with high cord blood level of PCT. Chorioamnionitis and elevated fetal and neonatal plasma cytokine levels were found associated with an increased risk for neonatal neurological and pulmonary morbidity [18]. Joram et al. speculated on the capacity of cord blood PCT to be an early prognostic marker of long-term consequences of fetal inflammatory response syndrome and neonatal inflammation early after birth [8]. In our study, all comorbidities related to perinatal inflammation or inducing postnatal systemic inflammation (BPD, IVH, periventricular leukomalacia, NEC, surgery of ductus arteriosus, or LOS) were found with similar incidences compared to the literature [1]. No change was detected according to the PCT concentrations split into two subgroups (≤ or > 0.5 μg/L at birth). Neonatal mortality was found also similar between the two groups. Lautridou et al. reported that cord blood PCT > 0.33 μg/L was associated with higher neonatal mortality (OR 8.3; CI97.5% 1.1–61.4), $p = 0.018$) and neurological adverse outcomes (OR 2; CI97.5% 0.6–6.2), $p = 0.15$) in a population of infants born before 33 weeks [19]. However, PCT has been tested only in 49% of the population study and mortality is significantly higher in infants with missing data (11 vs 5.4%, $p = 0.02$) [19].

We studied a large cohort of extremely low gestational age infants. Our findings suggest that cord blood PCT may be a helpful marker to guide best management of infants at risk of EOS. However, several limits must be discussed. Very few patients were diagnosed with certain EOS (only 2 infants, who had PCT > 0.5 μg/L, were diagnosed certainly infected) due to (i) difficulties of microbiological sampling in neonates which decrease their sensitivity and (ii) high-level antenatal antibiotic treatment (78%). Changes in practices during the 9-year recruiting period could mitigate some statistical associations. Moreover, the definition criteria used in the study were adapted by the previous French recommendations [6], which included gastric aspirate sampling at birth. This practice was widely debated in view of the limited impact on neonatal

sepsis identification [20]. The updated French recommendations [21] have finally eliminated gastric aspirate in the decisional criteria for neonatal EOS, but it persists in our analysis.

In conclusion, our study shows that elevated cord blood PCT is associated with higher incidence of EOS in extremely preterm neonates. The added value of this marker in the diagnostic algorithms for EOS to ensure an appropriate antibiotic treatment during the first days of life should be confirmed in other studies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The trial was approved by the Local Ethics Committee (Robert Debré Hospital No. 2017/368-2) and by the French data protection authority, the Commission Nationale de l'Informatique et des Libertés (CNIL).

Informed consent Written informed consent was obtained from all parents of eligible infants.

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