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Reference ranges of presepsin (soluble CD14 subtype) in term and preterm neonates without infection, in relation to gestational and postnatal age, in the first 28 days of life

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ABSTRACT

Objective: To determine the reference ranges of presepsin in term and preterm neonates without infection, with respect to gestational and postnatal age, within the first 28 days of life.
Methods: A total of 144 neonates born at 24–42 weeks' gestation, including healthy term and preterm neonates without clinical signs or symptoms of infection, were included in this prospective observational study. Presepsin measurements included cord blood levels and serum levels on postnatal days 1, 3, 5, 7, 14, 21, and 28.
Results: The presepsin values corresponding to the 10th percentile ranged from 240.8 pg/mL (on day 1) to 129.9 pg/mL (on day 28), whereas those corresponding to the 90th percentile ranged from 725.8 pg/mL (on day 1) to 471.6 pg/mL (on day 28). Significantly higher presepsin levels were observed in cesarean deliveries than in spontaneous deliveries (p: 0.012 to < 0.001), in gestational ages ≤ 32 weeks than in gestational ages ≥37 weeks (p: < 0.05 to < 0.001), and in cases with a maternal history of chorioamnionitis than in those without (p: < 0.05 to < 0.001).
Conclusion: In conclusion, our findings revealed, for the first time, the reference ranges of presepsin in healthy term and preterm neonates without infection with respect to gestational and postnatal age, sex, and body weight. Presepsin levels within the first 28 days of life seem likely to be affected by the type of delivery, gestational and postnatal age, birth weight, and presence of respiratory distress syndrome or maternal chorioamnionitis.

1. Introduction

Early diagnosis of neonatal sepsis is crucial to reduce the high risk of mortality due to rapid progression to septic shock and multiple organ failure, and to prevent poor neurodevelopmental outcome in survivors [1–5].

However, alongside the subtle and nonspecific clinical signs of infection in neonates that make it difficult to distinguish them from manifestations of physiological and noninfectious processes [2,4–6], the gold standard blood culture test is also associated with low sensitivity, thus causing diagnostic delay [7–9].

C-reactive protein (CRP) and procalcitonin (PCT) have become the most widely used biochemical markers for neonatal sepsis [8–11]; however, both of them have drawbacks, such as later increase in blood levels and lack of specificity in discriminating between infections and noninfectious inflammatory conditions in CRP [11–16], and dependency on gestational age and postnatal age in PCT [8,14–17].

The soluble CD14 subtype (sCD14-ST; presepsin) has emerged as a novel marker with potential clinical utility in predicting the onset of systemic inflammation and sepsis, as it is correlated with phagocytic and lysosomal cleavage processes [18–20].

Presepsin is suggested to be a more specific and sensitive biomarker for sepsis, with an earlier increase in blood levels, than the well-known and widely used markers such as CRP and PCT in adult patients [20–26]. Although it has also been considered promising as an early diagnostic and prognostic marker in newborns with sepsis, studies in the pediatric population are scarce [27–31]. Moreover, reference ranges in healthy term and preterm neonates have been reported in only a few studies [9,19,32], despite their crucial role in making an accurate diagnosis [19,33].

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Although presepsin cutoff values for early and late sepsis have been reported in several studies, the presepsin levels in those studies referred to a single point measurement, either within the first 3 days or after 5 days of life. However, without knowing the daily physiological changes in presepsin levels, it seems challenging for a clinician to decide whether or not the measured presepsin level is abnormal in relation to the physiological changes on the day of the measurement.

Therefore, this study was designed to determine the reference ranges of presepsin in healthy term and preterm neonates without clinical signs or symptoms of infection, with respect to gestational and postnatal age within the first 28 days of postnatal life, as well as in relation to sex, birth weight, and antenatal/prenatal variables. Thereby, by providing data from a detailed analysis of presepsin levels, the current study aimed to offer guidance to clinicians in interpreting measured presepsin levels in relation to expected physiological levels on the day of measurement.

2. Materials and methods

2.1. Study population

A total of 144 neonates born at 24–42 weeks' gestation, including healthy term and preterm neonates without clinical signs or symptoms of infection admitted to the neonatal intensive care unit (NICU) with problems due to prematurity, were included in this prospective observational study conducted at a tertiary care center between April 2014 and January 2015. Newborns with infection, life-threatening congenital anomaly, or congenital anomalies requiring surgery (e.g., cardiopathy, hydrocephaly or meningomyelocele, severe obstetric trauma, or bleeding) were excluded from the study.

Written informed consent was obtained from the parent/legal guardian of each patient following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the institutional ethics committee (date of approval: January 20, 2014; protocol no. 13-12/4).

2.2. Study parameters

Data on the type of delivery, sex, gestation week, birth weight and height, maternal history of prolonged (> 18 h) rupture of membranes (PROM)/chorioamnionitis, gestational diabetes, respiratory distress syndrome (RDS), preeclampsia, intrauterine growth restriction, transient tachypnea, noninvasive ventilation support, invasive ventilation support, and surfactant administration were recorded. Clinical status was classified as mild (room air or oxygen treatment), moderate (noninvasive ventilation support), and severe (invasive ventilation support and/or positive inotropes) disease. Presepsin measurements were performed during the first 28 days of the postnatal period, including cord blood and serum level measurements on postnatal days 1, 3, 5, 7, 14, 21, and 28. In preterm neonates who developed clinical deterioration or mortality, presepsin values recorded during the latest measurements before the detection of clinical deterioration or mortality were included in the study. All measurements were performed by the same neonatology specialist immediately after the collection of blood samples, by using the PathFast™ (Mitsubishi Chemical, Japan) device in the study hospital laboratory. When blood samples were inappropriate (e.g., when there was difficulty in obtaining the sample), the collection was immediately repeated given the risk of inaccurately high presepsin levels. Conversely, blood samples were excluded from the analysis if they had an insufficient amount, had undergone hemolysis, or were not immediately analyzed after collection. Another blood sample for presepsin analysis was collected if the initial analysis revealed unexpectedly high presepsin levels with respect to clinical severity, whereas screening for sepsis was performed when the measurement remained inappropriately high after the second analysis. The presepsin data of patients diagnosed with sepsis were not included in the analysis, whereas data of patients without sepsis were included in the study regardless of the concordance between the measured presepsin levels and the clinical status of the patient.

Neonates with gestational ages of ≤32, 33–36, and ≥37 weeks were considered extremely to severely premature, moderately premature, and term neonates, respectively.

Presepsin levels were determined quantitatively (pg/mL) in 100 μL neonatal blood samples by using a commercially available rapid chemiluminescent enzyme immunoassay, as optimized in an automated immunoassay analyzer (PathFast).

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Independent-sample *t*-test and one-way analysis of variance were used to analyze parametric variables. Data were expressed as mean ± standard deviation (SD) or minimum–maximum and percent (%), as appropriate. Values of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Baseline characteristics, clinical status, and survival

Overall, the study population was composed of 76 (52.8%) boys and 68 (47.2%) girls who were born at mean ± SD 34.0 ± 4.0 weeks' gestation (33–36 weeks for 34.7%) and predominantly via a caesarean section (79.9%). The mean ± SD birth weight was 2295.4 ± 911.4 g (> 2500 g for 41.7%), whereas PROM or chorioamnionitis was evident in 10.4% and 6.3% of newborns, respectively. The clinical disease severity was mild in 61.8% of the study population, whereas the mortality rate was 8.3% in those admitted to the NICU (Table 1).

3.2. Presepsin levels in percentiles

The presepsin values corresponding to the 10th percentile ranged from 240.8 pg/mL (day 1) to 129.9 pg/mL (day 28) in the postnatal period. The presepsin values corresponding to the 50th percentile ranged from 422.0 pg/mL (day 1) to 243.0 pg/mL (day 28) in the postnatal period. The presepsin values corresponding to the 90th percentile ranged from 725.8 pg/mL (day 1) to 471.6 pg/mL (day 28) in the postnatal period (Table 2).

3.3. Presepsin levels at study visits in the overall study population

Overall, the mean presepsin level was 458.4 pg/mL in cord blood and ranged from 459.3 pg/mL on day 1 to 285.1 pg/mL on day 28, along with a significant decrease in cord blood levels on postnatal days 3, 5, 7, 14, 21, and 28 ($p < 0.001$ for each) (Table 3).

3.4. Presepsin levels according to demographic and clinical characteristics

No influence of sex on presepsin levels was noted in the cord blood analysis or during the 28-day follow-up period. Cesarean section was associated with significantly higher presepsin levels on postnatal day 3 ($p = 0.048$), day 5 ($p < 0.001$), and day 28 ($p = 0.013$) than spontaneous delivery (Table 4).

The presepsin levels in the postnatal period were significantly higher in newborns delivered at ≤32 weeks than in those delivered at ≥37 weeks (for the entire postnatal 28-day period) and 33–36 weeks (for days 14, 21, and 28) of gestation (p values ranged from < 0.05 to < 0.001). A birth weight of ≤1500 g was also associated with significantly higher presepsin levels than a birth weight of > 2500 g (for days 1, 5, 7, 14, and 21, p values ranged from < 0.05 to < 0.001) (Table 4).

Table 1
Baseline characteristics, clinical status and survival (n = 144) C/S: Cesarean delivery; PROM: prolonged rupture of membranes.

Gender, n(%)		
Boy		76(52.8)
Girl		68(47.2)
Gestation week		
Total, mean ± SD		34.0 ± 4.0
Category, n(%)	≤32 week (extreme-severe prematurity)	47(32.6)
	33–36 week (moderate prematurity)	50(34.7)
	≥37 week (term)	47(32.6)
Type of delivery, n(%)		
Spontaneous		29(20.1)
Cesarean		115(79.9)
Birth weight (g)		
Total, mean ± SD		2295.4 ± 911.4
Category, n(%)	≤1500	32(22.2)
	1501–2500	52(36.1)
	> 2500	60(41.7)
Apgar Scores		
1 min		8(3–10)
5 min		9(5–10)
PROM/chorioamnionitis, n(%)		
None		115(79.9)
PROM		15(10.4)
Chorioamnionitis		9(6.3)
PROM + Chorioamnionitis		5(3.5)
Gestational diabetes, n(%)		15(10.4)
Preeclampsia, n(%)		26(18.1)
Intrauterine growth restriction, n(%)		18(12.5)
Respiratory distress syndrome, n(%)		41(28.5)
Transient tachypnea, n(%)		18(12.5)
Noninvasive ventilation support, n(%)		52(36.1)
Invasive ventilation support, n(%)		31(21.5)
Surfactant administration, n(%)		21(14.6)
Clinical Status, n(%)		
Mild (room air or oxygen treatment)		89(61.8)
Moderate (noninvasive ventilation support)		28(19.4)
Severe (invasive ventilation support and/or positive inotropes)		27(18.8)
Survived, n(%)		132(91.7)
Expired n(%)		12(8.3)
Disseminated intravascular coagulation		3
Pulmonary hemorrhage		6
Intraventricular hemorrhage		2
Necrotizing enterocolitis perforation		1

C/S: Cesarean delivery; PROM: prolonged rupture of membranes.

A maternal history of chorioamnionitis was associated with significantly higher cord blood and postnatal presepsin levels than the absence of chorioamnionitis or PROM (p values ranged from < 0.05 to < 0.001) (Table 4).

The presence of RDS was associated with significantly higher cord blood and postnatal presepsin levels than the absence of RDS (p values ranged from 0.012 to < 0.001) (Table 4).

The day 1 presepsin levels were significantly higher in neonates with moderate to severe clinical disease status than in those with mild clinical status (p < 0.05 and p < 0.01, respectively). The presepsin levels remained higher in neonates with moderate clinical status than in those with mild clinical status until day 28 (p values ranged from < 0.05 to < 0.001) (Table 4).

4. Discussion

Our findings revealed, for the first time, the reference ranges of sCD14-ST (presepsin) in healthy term and preterm neonates with respect to gestational and postnatal age, sex, and birth weight. Analysis for the first 28 days of postnatal life revealed a gradual decline in mean (from 459.3 to 285.1 pg/mL), 10th percentile (from 240.8 to 129.9 pg/mL), and 90th percentile (from 725.8 to 471.6 pg/mL) presepsin levels from day 1 to day 28. The presepsin values significantly differed with respect to gestational age, birth weight, and type of delivery, as well as in relation to fetal RDS, history of maternal chorioamnionitis, and clinical status.

Pugni et al. [9], in their study on the reference ranges of presepsin in healthy term (n = 200) and preterm (n = 484) neonates without clinical signs of infection, reported mean ± SD presepsin values of 649 ± 257 pg/mL in term neonates and 720 ± 329 pg/mL in preterm neonates based on measurements performed at 3.6 days (SD 0.6) and 3.9 days (SD 0.8) of age, respectively [9]. The authors also reported the presepsin levels for the 10th, 25th, 50th, 75th, and 90th percentiles as 371, 466, 604, 791, and 1000 pg/mL in term neonates and as 390, 503, 620, 864, and 1160 pg/mL in preterm neonates [9]. In addition, no correlation was noted between presepsin levels and postnatal age, and no significant difference in presepsin levels was observed between spontaneous delivery and caesarean section, between female and male sex, different gestational ages, and birth weight groups [9].

When compared with the presepsin levels at 3.6 and 3.9 days of age reported in term and preterm neonates by Pugni et al. [9], our findings revealed lower average presepsin levels in term, moderately preterm, and severely preterm neonates on day 3 (295.5, 319.0, and 377.5 pg/mL, respectively) and day 5 (295.5, 319.0, and 377.5 pg/mL, respectively). In addition, the day 3 and day 5 presepsin values corresponding to the 10th percentile (180.1, 178.2, and 247.7 for day 3; 180.0, 172.5, and 240.7 for day 5, respectively) and the 90th percentile (545.0, 643.8, and 735.9 for day 3; 621.0, 744.0, and 698.8 for day 5) were also lower than those reported by Pugni et al. [9] in both term and preterm neonates. Moreover, our findings revealed significantly higher presepsin levels in cesarean cases than in spontaneous delivery cases, in neonates born at ≤32 weeks' gestation than in those born at ≥37 weeks' gestation, and in the ≤1500 g birth weight group than in the > 2500 g birth weight group for the entire 28-day postnatal period.

The average first-week levels of presepsin in term healthy newborns were reported to be 508 ± 165 pg/mL by Ozdemir et al. [30] and 508.33 ± 165.46 pg/mL by Mussap et al. [29]. Casani et al. [32] reported presepsin levels of 953 pg/mL (interquartile range: 661–1114 pg/mL) in cord blood and 741 pg/mL (interquartile range: 490–937 pg/mL) on day 3 of life in term or near-term neonates. In premature neonates, presepsin levels were reported to be 643.1 ± 303.8 ng/L at postnatal age of 25–160 h and 453 ng/L (ranged 223.4–599.7 ng/L) by Mussap et al. [19,29], to be 562 pg/mL (337–726 pg/mL) at postnatal age of 4–60 days by Poggi et al. [27], and to be 530 pg/mL (363–580 pg/mL) at postnatal age 4–30 days by Topcuoglu et al. [28].

Hence, the presepsin values in our study cohort of healthy term and preterm neonates without clinical signs and symptoms of infection seem to be lower than those reported in the above series of term/near-term neonates. This discrepancy may be associated with potential differences in clinical status in relation to gestational age between the study populations or the different methods of blood sample collection (i.e., performing repeat collection or not for inappropriately collected samples with a risk of false results, such as those in which difficulty in obtaining blood was encountered) and methods of analysis of blood samples (immediate analysis or storing samples until a later analysis) among the different studies.

Previous studies revealed no significant difference in presepsin levels between gestational ages of ≥32 and < 32 weeks [9] and between ≥30 and < 30 weeks [19] among preterm neonates, and between gestational ages of 37–38 and 39–41 weeks in term neonates [9].

The results of these two reports indicated the need to adopt unique reference ranges for term and preterm neonates, regardless of the gestational age [9,19]. The preliminary reference range for the whole-blood sCD14-ST (presepsin) level in preterm newborns was reported to be 254.9–1144 ng/L [19].

However, in our series, neonates with extreme to severe prematurity (gestational age ≤32 weeks) had significantly higher presepsin levels than term neonates (gestational age ≥37 weeks) on the entire first-28-day analysis. Further, their presepsin levels were higher than those of

Table 2
Presepsin levels in percentiles in the overall study population.

	Presepsin levels (pg/mL)							
	Cord blood	Day 1	Day 3	Day 5	Day 7	Day 14	Day 21	Day 28
Percentiles-Overall	144	135	123	115	109	104	95	92
10	257.0	240.8	199.4	187.0	180.0	157.5	144.6	129.9
50	433.0	422.0	341.0	337.0	347.0	295.0	256.0	243.0
90	654.5	725.8	649.2	675.0	723.0	655.5	625.6	471.6
Boys, n	76	71	64	61	58	55	52	49
10	253.2	245.6	177.0	187.4	193.5	158.0	145.9	114.0
50	425.5	387.0	344.0	333.0	369.0	261.0	274.5	235.0
90	667.5	714.6	691.0	660.2	738.3	583.4	687.7	581.0
Girls, n	68	64	59	54	51	49	43	43
10	258.5	222.0	202.0	181.0	171.6	141.0	125.6	162.0
50	441.0	485.5	333.0	343.0	330.0	302.0	253.0	245.0
90	659.6	779.0	633.0	711.0	687.8	700.0	497.2	436.8
≤32 weeks gestation	47	42	36	32	31	29	25	22
10	286.2	256.3	247.7	240.7	246.8	247.0	196.4	160.8
50	437.0	494.5	377.5	404.5	382.0	431.0	399.0	376.0
90	624.6	748.1	735.9	698.8	809.6	778.0	747.4	702.7
33–36 weeks gestation	50	48	45	44	43	42	38	38
10	254.1	220.9	178.2	172.5	180.8	136.9	133.8	131.6
50	406.5	406.0	319.0	348.5	358.0	262.5	246.5	211.0
90	867.3	805.8	643.8	744.0	732.0	691.3	363.2	428.4
≥37 weeks gestation	47	45	42	39	35	33	32	32
10	248.2	223.6	180.1	180.0	155.8	126.2	109.8	109.8
50	442.0	386.0	295.5	255.0	256.0	225.0	226.0	224.0
90	621.0	579.4	545.0	621.0	447.4	541.8	623.8	418.0

Table 3
Presepsin levels at study visits in the overall study population.

	N	Presepsin levels (pg/mL)		
		Mean ± SD	Median (min–max)	p value[1]
Cord blood	144	458.4 ± 191.2	433.0(141.0–1461.0)	–
Day 1	135	459.3 ± 190.7	422.0(147.0–1052.0)	0.732
Day 3	123	382.1 ± 175.2	341.0(99.2–1024.0)	< **0.001**
Day 5	115	385.3 ± 193.6	337.0(133.0–947.0)	< **0.001**
Day 7	109	386.1 ± 195.8	347.0(101.0–947.0)	**0.001**
Day 14	104	345.0 ± 185.2	295.0(116.0–806.0)	< **0.001**
Day 21	95	307.4 ± 175.6	256.0(83.6–787.0)	< **0.001**
Day 28	92	285.1 ± 155.7	243.0(89.4–873.0)	< **0.001**

Friedman test: $p < 0.001$; [1]compared to cord blood values (Wilcoxon test).

neonates with moderate prematurity (gestational age 33–36 weeks) at days 14, 21, and 28. Therefore, we conclude that one reference presepsin value cannot be applied to preterm neonates with different gestational ages. There was also an association of both postnatal age and gestational age with presepsin levels in healthy neonates, and a likelihood of a stronger impact of the severity of prematurity after 2 weeks of postnatal life.

Although presepsin levels were previously reported to be independent of postnatal age [9,27,28], our findings revealed a tendency for higher day 1 vs. cord blood levels as followed by a gradual decrease and correlation of presepsin levels from day 1 to day 28 in all subgroups.

In fact, activation of the innate immune system after birth, driven by the transition from a normally sterile intrauterine environment to the antigenically rich external world, has been considered to be associated with identification of higher presepsin levels in healthy babies than in healthy adults [9]. Thus, a more remarkable increase in presepsin levels on day 1 than the cord blood levels in preterm neonates and in those with low birth weight may indicate a more aggressive activation of the innate immune system in these neonates under the risk of abrupt changes in homeostasis [19]. This seems also notable, given that presepsin has emerged as a potential biomarker and an accurate marker for the diagnosis of early and late neonatal sepsis [9,19,27–31,34], with a level of 800.5 pg/mL established as a cutoff value with 67% sensitivity and 100% specificity [28].

Although a history of maternal diabetes or preeclampsia had no significant impact on neonatal presepsin levels in our study population, RDS and a history of chorioamnionitis were associated with higher presepsin levels. In addition, clinical disease severity in terms of use of ventilation support and/or positive inotropes also had a significant impact on presepsin levels. Our findings emphasize the likelihood of certain antenatal/prenatal variables to affect presepsin levels in neonates without infection. Therefore, consideration of these factors when interpreting findings of high presepsin levels is important.

Although presepsin is considered a more effective biomarker than CRP and PCT, as it is not affected by postnatal age and noninfectious conditions [9,27,28], our findings seem to indicate the possibility that certain variables commonly affecting CRP and PCT values also affect presepsin levels, at least in terms of gestational age and postnatal age and certain antenatal variables such as chorioamnionitis and RDS.

Nonetheless, it should be noted that in a meta-analysis of 11 studies in 783 neonates, the diagnostic odds ratio of the prediction of neonatal sepsis by presepsin was concluded to be 170.28 (95% confidence interval 51.13–567.11), indicating more sensitivity of presepsin than CRP (area under the curve [AUC]: 0.9748 vs. 0.8580) and PCT (AUC: 0.9596 vs. 0.7831) in detecting neonatal sepsis [35].

Our study is important in that it evaluated consecutively analyzed presepsin levels with respect to perinatal characteristics and birth weight, gestational age, and postnatal age. To our knowledge, this is the first study to evaluate the percentiles of normal reference values. However, certain limitations of this study should be considered. First, it would be preferable to include more neonates with gestational age < 28 weeks and birth weight < 1000 g in each group. Moreover, the long-term follow-up of these neonates was occasionally interrupted by bleeding, sepsis, or death. Furthermore, the impact of other factors, such as renal insufficiency, small-scale bleeding, asphyxia, and viral infections, on presepsin levels remains unclear. It has been observed that errors in blood sampling might lead to higher measurements of presepsin levels. In this study, all blood samples were immediately analyzed after being taken, and, in the case of any suspicious result, the process was repeated by taking a new blood sample.

Table 4
Presepsin levels according to demographic and clinical characteristics.

	Cord blood (n = 144)		Presepsin levels (pg/mL), postnatal follow-up period					
			Day 1(n = 135)		Day 3 (n = 123)		Day 5 (n = 115)	
	n	median (min–max)	n	median (min–max)	n	median (min–max)	n	median (min–max)
Gender								
Male	76	425.5(141.0–1461.0)	71	387.0(159.0–984.0)	64	344.0(99.2–1024.0)	61	333.0(150.0–947.0)
Female	68	441.0(198.0–1089.0)	64	485.5(147.0–1052.0)	59	333.0(154.0–795.0)	54	343.0(133.0–876.0)
p value[1]		0.489		0.348		0.643		0.980
Delivery type								
NSVD	29	452.0(165.0–748.0)	28	388.5(147.0–785.0)	24	287.0(166.0–620.0)	21	221.0(151.0–538.0)
C/S	115	427.0(141.0–1461.0)	107	450.0(159.0–1052.0)	99	348.0(99.2–1024.0)	94	363.0(133.0–947.0)
p value[1]		0.893		0.149		**0.048**		**< 0.001**
Gestation age								
≥37 week	47	442.0(165.0–872.0)	45	386.0(147.0–640.0)[aa]	42	295.5(148.0–788.0)[a]	39	255.0(151.0–863.0)[aa]
33–36 week	50	406.5(198.0–1089.0)	48	406.0(181.0–1046.0)	45	319.0(99.2–795.0)	44	348.5(133.0–876.0)
≤32 week	47	437.0(141.0–1461.0)	42	494.5(219.0–1052.0)	36	377.5(154.0–1024.0)	32	404.5(228.0–947.0)
p value[2]		0.823		**0.037**		**0.027**		**0.001**
Birth weight								
≤1500 g	32	489.0(141.0–787.0)	28	554.5(219.0–1052.0)	23	362.0(154.0–729.0)	20	384.5(228.0–947.0)
1501–2500 g	52	394.5(198.0–1461.0)	49	422.0(181.0–1046.0)	47	365.0(99.2–1024.0)	45	402.0(133.0–923.0)
> 2500 g	60	433.0(165.0–872.0)	58	382.0(147.0–785.0)[cc]	53	302.0(124.0–788.0)	50	251.0(151.0–863.0)[c]
p value[2]		0.170		**0.002**		**0.037**		**0.001**
PROM-CAM								
None	115	416.0(141.0–874.0)[ee]	107	390.0(147.0–984.0)[e]	98	320.5(99.2–925.0)[ee]	92	331.0(133.0–923.0)[e]
PROM	15	447.0(238.0–588.0)[ee]	14	495.0(233.0–785.0)	13	382.0(233.0–752.0)	12	336.5(170.0–947.0)
CAM	14	622.0(338.0–1461.0)	14	728.0(219.0–1052.0)	12	504.0(284.0–1024.0)	11	482.0(228.0–876.0)
p value[2]		**< 0.001**		**0.003**		**0.001**		**0.064**
Preeclampsia								
Absent	118	428.0(165.0–1461.0)	112	417.0(147.0–1052.0)	103	329.0(99.2–1024.0)	97	326.0(133.0–947.0)
Present	26	469.0(141.0–874.0)	23	492.0(159.0–813.0)	20	387.5(213.0–925.0)	18	406.0(187.0–923.0)
p value[1]		0.959		0.516		0.134		**0.045**
GDM								
Absent	129	427.0(141.0–1461.0)	122	417.0(147.0–1052.0)	110	331.0(99.2–1024.0)	105	333.0(133.0–923.0)
Present	15	452.0(217.0–650.0)	13	487.0(256.0–600.0)	13	378.0(192.0–729.0)	10	428.5(170.0–947.0)
p value[1]		0.756		0.958		0.166		0.234
RDS								
Absent	103	415.0(165.0–874.0)	99	386.0(147.0–845.0)	92	323.0(99.2–925.0)	87	295.0(133.0–923.0)
Present	41	469.0(141.0–1461.0)	36	589.5(219.0–1052.0)	31	375.0(154.0–1024.0)	28	459.5(228.0–947.0)
p value[1]		**0.021**		**< 0.001**		**0.005**		**< 0.001**
Clinical status								
Mild	89	416.0(165.0–874.0)	85	386.0(147.0–845.0)	79	303.0(99.2–925.0)	74	263.5(133.0–923.0)
Moderate	28	426.5(141.0–1461.0)	27	487.0(181.0–1046.0)[f]	27	461.0(270.0–1024.0)[ff]	27	464.0(295.0–876.0)[fff]
Severe	27	452.0(214.0–787.0)	23	538.0(219.0–1052.0)[ff]	17	344.0(154.0–729.0)	14	318.5(228.0–947.0)[g]
p value[2]		0.115		**0.007**		**0.001**		**< 0.001**

	Presepsin levels (pg/mL), postnatal follow-up period							
	Day 7 (n = 109)		Day 14 (n = 104)		Day 21 (n = 95)		Day 28 (n = 92)	
	n	median (min–max)	n	median (min–max)	n	median (min–max)	n	median (min–max)
Gender								
Male	58	369.0(101.0–933.0)	55	261.0(116.0–806.0)	52	274.5(83.6–787.0)	49	235.0(89.4–873.0)
Female	51	330.0(121.0–947.0)	49	302.0(116.0–799.0)	43	253.0(90.4–772.0)	43	245.0(99.6–660.0)

(*continued on next page*)

Table 4 (*continued*)

	Presepsin levels (pg/mL), postnatal follow-up period							
	Day 7 (n = 109)		Day 14 (n = 104)		Day 21 (n = 95)		Day 28 (n = 92)	
	n	median (min–max)	n	median (min–max)	n	median (min–max)	n	median (min–max)
p value[1]		0.107		0.261		0.640		0.772
Delivery type								
NSVD	18	334.5(142.0–543.0)	17	227.0(137.0–569.0)	17	192.0(95.5–326.0)	17	204.0(94.3–328.0)
C/S	91	353.0(101.0–947.0)	87	302.0(116.0–806.0)	78	270.5(83.6–787.0)	75	252.0(89.4–873.0)
p value[1]		0.178		0.161		0.016		**0.013**
Gestation age								
≥37 week	35	256.0(101.0–575.0)^{aaa,b}	33	225.0(116.0–806.0)^{aa}	32	226.0(83.6–772.0)^{aa}	32	224.0(89.4–802.0)^{aa}
33–36 week	43	358.0(121.0–947.0)	42	262.5(116.0–778.0)^{a}	38	246.5(101.0–457.0)^{aaa}	38	211.0(99.6–581.0)^{a}
≤32 week	31	382.0(209.0–933.0)	29	431.0(171.0–799.0)	25	399.0(159.0–787.0)	22	376.0(127.0–873.0)
p value[2]		**0.001**		< **0.001**		< **0.001**		**0.013**
Birth weight								
≤1500 g	20	370.0(209.0–883.0)	18	436.5(171.0–799.0)	16	457.5(234.0–787.0)	14	399.0(179.0–873.0)
1501–2500 g	44	389.5(126.0–947.0)^{c}	43	333.0(116.0–705.0)	37	273.0(101.0–772.0)	36	251.0(127.0–566.0)
> 2500 g	45	268.0(101.0–683.0)^{ccc}	43	207.0(116.0–806.0)^{ccc,d}	42	212.5(83.6–772.0)^{cccc,dd}	42	224.0(89.4–802.0)
p value[2]		< **0.001**		< **0.001**		< **0.001**		**0.028**
PROM-CAM								
None	86	334.5(101.0–947.0)^{ee}	83	271.0(116.0–806.0)^{ee}	78	241.0(83.6–772.0)	77	220.0(89.4–802.0)^{eee}
PROM	12	374.0(215.0–741.0)	10	303.5(173.0–594.0)	8	487.0(148.0–772.0)	8	319.5(103.0–721.0)
CAM	11	564.0(285.0–883.0)	11	437.0(261.0–799.0)	9	330.0(234.0–787.0)	7	466.0(305.0–873.0)
p value[2]		**0.003**		**0.011**		**0.008**		**0.001**
Preeclampsia								
Absent	91	340.0(101.0–883.0)	87	293.0(116.0–806.0)	80	250.5(90.4–787.0)	78	228.0(89.4–873.0)
Present	18	402.0(126.0–947.0)	17	398.0(116.0–799.0)	15	307.0(83.6–772.0)	14	281.5(179.0–426.0)
p value[1]		0.120		0.084		0.180		0.223
GDM								
Absent	101	340.0(121.0–947.0)	98	298.5(116.0–806.0)	90	254.5(83.6–787.0)	87	243.0(89.4–873.0)
Present	8	381.5(101.0–741.0)	6	283.0(207.0–778.0)	5	268.0(148.0–772.0)	5	200.0(180.0–588.0)
p value[1]		0.489		0.707		0.671		0.938
RDS								
Absent	81	329.0(101.0–947.0)	78	246.0(116.0–806.0)	73	237.0(83.6–772.0)	73	228.0(89.4–802.0)
Present	28	404.0(209.0–883.0)	26	460.0(127.0–799.0)	22	335.0(114.0–787.0)	19	305.0(179.0–873.0)
p value[1]		**0.001**		< **0.001**		**0.003**		**0.012**
Clinical status								
Mild	69	280.0(101.0–933.0)	66	237.5(116.0–806.0)	63	237.0(83.6–772.0)	63	243.0(89.4–802.0)
Moderate	26	480.0(209.0–947.0)^{fff}	26	398.0(127.0–779.0)^{f}	23	320.0(114.0–787.0)^{ff}	21	235.0(150.0–873.0)
Severe	14	339.0(274.0–741.0)	12	376.5(155.0–778.0)	9	575.0(234.0–690.0)	8	413.0(179.0–660.0)
p value[2]		< **0.001**		**0.005**		**0.003**		0.145

CAM: chorioamnionitis; GDM: Gestational diabetes mellitus; PROM: prolonged rupture of membranes; RDS: respiratory distress syndrome. $^{a}p < 0.05$, $^{aa}p < 0.01$ and $^{aaa}p < 0.001$ compared to ≤ 32 week; $^{b}p < 0.001$ compared to 33–36 week; $^{c}p < 0.05$, $^{cc}p < 0.01$ and $^{ccc}p < 0.01$ compared to ≤ 1500 g, $^{d}p < 0.05$ and $^{dd}p < 0.01$ compared to 1501–2500 g; $^{e}p < 0.05$, $^{ee}p < 0.01$ and $^{eee}p < 0.01$ compared to chorioamnionitis group, $^{f} < 0.05$, $^{ff}p < 0.01$ and $^{fff}p < 0.001$ compared to mild status, $^{g}p < 0.05$ compared to moderate status.
[1]Mann-Whitney *U* test, [2]Kruskal Wallis test.

5. Conclusion

In conclusion, our findings revealed, for the first time, the reference ranges of presepsin in healthy term and preterm neonates without infection with respect to gestational and postnatal age as well as body weight. Given that presepsin levels within the first 28 days of life were likely to be affected by the type of delivery, gestational and postnatal age, birth weight, and the presence of RDS or a history of maternal chorioamnionitis, we recommend the identification and interpretation of unique reference ranges of presepsin in term and preterm neonates with consideration of these factors. Further investigations in larger series of neonates in different clinical situations may confirm our results and also help clinicians in discriminating infectious from other non-infectious acute problems of neonates.

Disclosure of interest

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