Comparison of neonatal reference intervals for 23 biochemical analytes in the cord blood-A single center study in South Korea

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Reference intervals for laboratory tests are important in the diagnosis and treatment of disease. However, due to difficulty in recruiting sufficient numbers of reference subjects, studies regarding reference intervals for biochemical analytes in neonates is lacking. The aim of this study was to compare and validate the reference intervals for 23 biochemical analytes in the cord blood of neonates. From August to December 2017, 79 consecutive neonates born at the Wonju Severance Christian Hospital (Wonju, Korea) with C-reactive protein concentration less than 0.05 mg/dL were included in this study. All of 23 biochemical analytes were measured by the cobas 8000 c702 (Roche Diagnostics, Switzerland). Mean ± 2 standard deviations (SD) were calculated if the values were normally distributed, and median and the range of 2.5–97.5 percentile were described when the values were not normally distributed. We compared the neonatal reference intervals for 23 biochemical analytes. Alkaline phosphatase and gamma glutamyl transferase showed significant differences according to sex, and direct bilirubin revealed significant differences depending on the delivery mode. These compared reference intervals of 23 biochemical analytes will be useful for clinical decision-making in the management of neonates.

Key words: biochemical, cord blood, neonates, reference interval.

Reference intervals are one of the most widely used clinical decision-making tools that help physicians differentiate between healthy and diseased populations.¹ Moreover, it has been emphasized that neonatal reference intervals play a significant role in the optimal management of the postnatal adaptation phase.² Current guidelines define a reference interval as the interval between two values within which 95% of the results from healthy individuals would fall; usually between the 2.5th and 97.5th percentiles of test results for a healthy population.³ The reference intervals of laboratory parameters vary according to the demographic characteristics such as ethnicity, sex, age, and the time of sample collection.⁴⁻⁷ Therefore, it is recommended that laboratories establish their own reference intervals from the local population or validate the use of those obtained from a different setting. However, it requires a lot of labor, time and cost for application in clinical conditions.⁸ Especially, it is more difficult in neonates due to the limitation of obtaining a sufficient number of reference individuals.⁹,¹⁰ For this reason, to date, only a few studies have been conducted on neonatal reference intervals, and there are no acceptable reference intervals for
many laboratory parameters in neonates. 
Thus, the aim of this study was to compare 
the reference intervals in neonates for 23 
biochemical analytes using the cord blood in 
our hospital.

Material and Methods

Study population

Twenty-eight preterm (26 to 31 weeks’ 
gestation: 3 neonates, 32 to 36 weeks’ 
gestation: 25 neonates) and 51 term (37 to 
42 weeks’ gestation) neonates born at Wonju 
Severance Christian Hospital between August 
and October 2017 were enrolled prospectively. 
The study protocol was approved by the 
Institutional Review Board of Wonju Severance 
Christian Hospital (approval no. CR317056). 
We obtained parental written informed 
consent prior to enrollment.

Sample collection and Laboratory procedure

Each cord blood sample (up to 10 mL) was 
collected in two serum separation tubes 
(Becton Dickinson, Franklin Lakes, New Jersey, 
USA) from the umbilical vein immediate 
after delivery by sterile puncture. The cord 
blood samples were immediately transported 
to the laboratory and centrifuged. Separated 
sera were transferred to cryovial tubes (SPL 
Life Sciences, Pocheon, Korea), and stored 
at -80°C until tested. Clinical data included 
delivery mode, spontaneous rupture of the 
membranes, gestational weeks, birth weight, 
and multiple pregnancies. Prior to analysis, all 
samples were thawed at room temperature, 
then analyzed with the cobas 8000 c702 
(Roche Diagnostics, Basel, Switzerland) 
according to the manufacturer’s instructions. 
The 23 biochemical analytes were as follows: 
total protein, albumin, blood urea nitrogen 
(BUN), creatinine, aspartate transaminase 
(AST), alanine transaminase (ALT), alkaline 
phosphatase (ALP), gamma-glutamyl 
transferase (GGT), creatine kinase, lactate 
dehydrogenase (LDH), total cholesterol, high 
density lipoprotein cholesterol (HDL-C), 
low density lipoprotein cholesterol (LDL-C), 
triglyceride, total bilirubin, direct bilirubin, 
calcium, inorganic phosphate, magnesium, 
iron, unsaturated iron binding capacity, uric 
acid, and glucose. C-reactive protein (CRP) 
was also tested with the cobas 8000 c702 to 
assess neonatal health status.

Statistical analysis

To determine the reference subjects, extreme 
observations were excluded. If the absolute 
difference between the largest observation 
and the second largest was equal to or 
greater than one-third of the range of all 
observations including the extreme values, 
the extreme values were regarded as outliers 
and were excluded. The same criterion was 
applied to the minimum observation. Then, 
the Kolmogorov–Smirnov test was used to 
confirm normality. Distribution of a variable 
was determined with normality when the p 
value of the Kolmogorov–Smirnov test was 
larger than 0.05. If the values were normally 
distributed, the parametric method (mean 
± 2SD) was used to compare the reference 
interval while the non-parametric method 
(median and the range of 2.5–97.5 percentile) 
was used when the values were not normally 
distributed.

The study population was divided into three 
subgroups, namely, delivery mode, sex, and 
gestational week of newborns. The mean of 
each subgroup was calculated and compared 
by an independent t-test when data showed 
normality in the distribution, while the 
Mann–Whitney U test was used when data 
were not normally distributed. A p value < 
0.05 was considered statistically significant. 
If the difference between the means of each 
subgroup exceeded 25% of the total range of 
all observations, then reference intervals were 
required for further evaluation or validation 
for each subgroup respectively. Statistical 
analyses were performed using MedCalc for 
Windows, version 14.8.1 (MedCalc Software, 
Ostend, Belgium) and IBM SPSS Statistics 
version 23 (IBM Corporation, Armonk, New 
York, USA).

Results

All of the 79 neonates had CRP concentrations 
less than 0.02 mg/dL except for 3 neonates (one 
term baby, 0.04 mg/dL, and two preterm babies, 
0.03 mg/dL). Table I shows the characteristics 
of two subgroups, vaginal delivery (n = 24)
Comparison of Neonatal Reference Intervals and Cesarean section (n = 55). Only the rupture of the amniotic membrane showed statistically significant higher proportions in the vaginal delivery group, whereas sex, birth weight, gestational age, and maternal age did not show any significant differences between the vaginal delivery and Cesarean section groups.

Total protein, albumin, BUN, total cholesterol, HDL-C, total bilirubin, direct bilirubin, iron, uric acid, and glucose showed normal distributions and were analyzed by the parametric statistical method. The other parameters showing non-normal distributions were analyzed by non-parametric statistical methods. Among the 23 biochemical analytes, ALP and GGT showed significant differences depending on sex, and direct bilirubin revealed significant differences depending on the delivery mode (Table II). However, the subgroup-specific reference intervals were not established because the differences were less than 25% of the total range of all observations.

Table III shows the proposed reference intervals for the 23 biochemical analytes in the cord blood of Korean neonates.

**Table I. The Demographic Characteristics of the Study Population According to Mode of Delivery.**

| Characteristics                        | Vaginal delivery (n = 24) | Cesarean section (n = 55) | P value |
|----------------------------------------|---------------------------|---------------------------|---------|
| Sex (male), n (%)                       | 11 (45.8)                 | 31 (57.1)                 | 0.536   |
| Birth weight (kg), mean ± SD           | 2.91 ± 0.5                | 2.76 ± 0.7                | 0.382   |
| Gestational age (weeks), mean ± SD     | 37.5 ± 2.6                | 36.3 ± 2.6                | 0.066   |
| Maternal age (years), mean ± SD        | 31.5 ± 6.3                | 34.0 ± 4.8                | 0.056   |
| Rupture of amniotic membrane, n (%)    | 22 (91.7)                 | 12 (21.8)                 | < 0.001 |

SD, standard deviation.

Discussion

Determining reference intervals for neonates, infants and children is a challenging assignment since the physiological characteristics are changing continuously as they grow.\(^{15}\) Especially in newborns, striking changes occur in the blood during the first few hours and days after birth.\(^{16}\) In addition, since most of the studies were conducted on hospitalized subjects rather than normal neonates,\(^{8}\) the evidence for determining reference intervals for neonates are scarce. Therefore, it is important to establish the reference intervals for normal neonates.

Given the substantial physiological changes in neonates, the time of blood sampling is crucial for determining the appropriate reference intervals. Therefore, a standardized method for blood sampling is required and immediate blood sampling from the umbilical cord at delivery provides uniform sampling conditions. In addition, this method allows avoidance of additional venipuncture and inclusion of healthy newborns as well as hospitalized neonates.

Compared with neonatal reference intervals for 21 biochemical parameters reported by Perkins et al.,\(^{17}\) there were no notable differences except for iron, but our analyzed ranges were slightly wider in some parameters. This might result from the different ethnicity and relatively small number of neonates in our study. For iron, analyzed range in our study was within neonatal reference interval, but the upper limit was lower than reference range. In this study, of the 79 neonates recruited, 28 (35.4) were preterm (gestational age less than 37 weeks). Previous studies reported that preterm birth is associated with body iron status.\(^{18}\) This is one of our limitation, so further evaluation with more neonates covering variable gestational ages are needed.

In comparison to the reference intervals for 1-year-old Korean children,\(^{19}\) the low values of total protein and albumin in the neonates were similar to the previous study, showing a gradual increase in total serum proteins and albumin with age.\(^{20}\) In contrast, GGT showed far higher levels in neonates than in 1-year-
Table II. Summary of Descriptive Statistics for 23 Biochemical Analytes in the Total Population and Subgroups According to Sex, Delivery Type, and Gestational Weeks in This Study.

| Analytes, unit | Total | Male | Female | K–S p value | Sex p value* |
|---------------|-------|------|--------|-------------|-------------|
| T-Pro†, g/dL  | 5.2 ± 0.6 | 5.2 ± 0.6 | 5.3 ± 0.7 | 0.189 | 0.511 |
| Alb†, g/dL | 3.3 ± 0.4 | 3.3 ± 0.4 | 3.3 ± 0.4 | 0.200 | 0.810 |
| BUN†, mg/dL | 9 ± 3 | 9 ± 2 | 8 ± 2 | 0.094 | 0.083 |
| Cr†, mg/dL | 0.6 | 0.6 | 0.6 | 0.037 | 0.133 |
| AST‡, U/L | 27.0 | 28.0 | 26.0 | < 0.001 | 0.838 |
| ALT‡, U/L | 7.0 | 6.0 | 8.0 | < 0.001 | 0.131 |
| ALP‡, U/L | 155.0 | 146.0 | 164.0 | 0.003 | 0.006 |
| GGT‡, U/L | 141.0 | 129.0 | 163.0 | < 0.001 | 0.037 |
| CK‡, U/L | 200.0 | 187.0 | 203.0 | < 0.001 | 0.260 |
| LDH‡, U/L | 342.0 | 325.5 | 356.0 | < 0.001 | 0.096 |
| T-Chol‡, g/dL | 54 ± 36 | 58 ± 35 | 48 ± 37 | 0.074 | 0.234 |
| HDL-C†, mg/dL | 34 ± 11 | 32 ± 11 | 36 ± 11 | 0.200 | 0.181 |
| LDL-C†, mg/dL | 25.0 | 25.0 | 26.0 | < 0.001 | 0.468 |
| TG†, mg/dL | 22.0 | 22.0 | 22.0 | < 0.001 | 0.644 |
| T-Bil†, mg/dL | 1.7 ± 0.4 | 1.7 ± 0.4 | 1.7 ± 0.4 | 0.200 | 0.872 |
| D-Bil‡, mg/dL | 0.5 ± 0.2 | 0.5 ± 0.2 | 0.5 ± 0.2 | 0.200 | 0.544 |
| Ca‡, mg/dL | 9.7 | 9.7 | 9.7 | < 0.001 | 0.926 |
| Pt‡, mg/dL | 5.7 | 5.7 | 5.8 | < 0.001 | 0.746 |
| Mg‡, mg/dL | 1.9 | 1.9 | 2.0 | < 0.001 | 0.362 |
| Fe†, μg/dL | 172 ± 48 | 177 ± 50 | 167 ± 45 | 0.200 | 0.359 |
| UIBC†, μg/dL | 55.0 | 47.0 | 59.0 | < 0.001 | 0.336 |
| UA†, mg/dL | 4.8 ± 1.4 | 5.0 ± 1.6 | 4.5 ± 1.1 | 0.200 | 0.069 |
| Glu†, mg/dL | 69 ± 23 | 67 ± 23 | 71 ± 23 | 0.184 | 0.469 |

K–S, Kolmogorov–Smirnov test; NSVD, normal spontaneous vaginal delivery; C/S, Cesarean section; T-Pro, total protein; Alb, albumin; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CK, creatine kinase; LDH, lactate dehydrogenase; T-Chol, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; T-Bil, total bilirubin; D-Bil, direct bilirubin; Ca, calcium; P, inorganic phosphate; Mg, magnesium; Fe, iron; UIBC, unsaturated iron binding capacity; UA, uric acid; Glu, glucose.

* A p value < 0.05 indicated a statistically significant difference between the two groups.
† Normally distributed data were expressed as mean ± 2SD and compared by an independent t-test.
‡ Variables with values not normally distributed were expressed as median and the range of 2.5–97.5 percentiles and compared by the Mann–Whitney U test.
Table II (Continue). Summary of Descriptive Statistics for 23 Biochemical Analytes in the Total Population and Subgroups According to Sex, Delivery Type, and Gestational Weeks in This Study.

| Analyte          | Unit | Total K–S | NSVD | C/S | p value* | Gestational week | Preterm | Term | p value* |
|------------------|------|-----------|------|-----|----------|------------------|---------|------|----------|
| K–S, Kolmogorov–Smirnov test; NSVD, normal spontaneous vaginal delivery; C/S, Cesarean section; T-Pro, total protein; Alb, albumin; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CK, creatine kinase; LDH, lactate dehydrogenase; T-Chol, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; T-Bil, total bilirubin; D-Bil, direct bilirubin; Ca, calcium; P, inorganic phosphate; Mg, magnesium; Fe, iron; UIBC, unsaturated iron binding capacity; UA, uric acid; Glu, glucose.

| Analyte          | Unit | Total K–S | NSVD | C/S | p value* | Gestational week | Preterm | Term | p value* |
|------------------|------|-----------|------|-----|----------|------------------|---------|------|----------|
| K–S, Kolmogorov–Smirnov test; NSVD, normal spontaneous vaginal delivery; C/S, Cesarean section; T-Pro, total protein; Alb, albumin; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CK, creatine kinase; LDH, lactate dehydrogenase; T-Chol, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; T-Bil, total bilirubin; D-Bil, direct bilirubin; Ca, calcium; P, inorganic phosphate; Mg, magnesium; Fe, iron; UIBC, unsaturated iron binding capacity; UA, uric acid; Glu, glucose.

* A p value < 0.05 indicated a statistically significant difference between the two groups.

†Normally distributed data were expressed as mean ± 2SD and compared by an independent t-test.

‡Variables with values not normally distributed were expressed as median and the range of 2.5–97.5 percentiles and compared by the Mann–Whitney U test.
The increased GGT levels, caused by enhanced transcriptional regulation of GGT genes in fetal liver, progressively decrease and maintain low levels for up to 18 years of age. GGT is a microsomal enzyme that catalyzes the hydrolysis of extracellular glutathione. Glutathione is essential for antioxidant defense in the lung and is found in epithelial lining fluid in 140-fold higher levels compared to in plasma, suggesting that GGT may be an indicator or predictor of diseases involving oxidative stress. Oxidative stress is unavoidable in preterm and even in full-term infants, as normal transition from the intrauterine to extrauterine environment involves an abrupt increase in oxygen. In this study, ALT showed the narrowest and lowest reference interval compared to AST, ALP, and GGT. This suggests that ALT is a useful screening test for neonatal liver disease. On the other hand, because the reference range of LDH in neonates was too wide and the upper limit level of the range was higher than 900 U/L in this study, clinicians need to be careful in interpreting the results.

**Table III. Proposed Reference Intervals for the 23 Biochemical Analytes in the Cord Blood of 79 Neonates.**

| Analytes, unit | Neonatal reference intervals | 1-year-old reference intervals |
|---------------|-----------------------------|-------------------------------|
| T-Pro, g/dL   | 4.0–6.4                     | 5.7–7.6                       |
| Alb, g/dL     | 2.5–4.1                     | 3.9–4.9                       |
| BUN, mg/dL    | 3–15                        | 5–19                          |
| Cr, mg/dL     | 0.2–0.9                     | 0.2–0.5                       |
| AST, U/L      | 16–73                       | 27–64                         |
| ALT, U/L      | 3–20                        | 11–45                         |
| ALP, U/L      | 91–269                      | 146–447                       |
| GGT, U/L      | 29–502                      | 4–16                          |
| CK, U/L       | 48–505                      | N/A                           |
| LDH, U/L      | 200–926                     | N/A                           |
| T-Chol, mg/dL | <126                        | 115–224                       |
| HDL-C, mg/dL  | 12–56                       | 26–71                         |
| LDL-C, mg/dL  | 4–59                        | 51–146                        |
| TG, mg/dL     | 10–79                       | 48–261                        |
| T-Bil, mg/dL  | 0.9–2.5                     | 0.2–0.9                       |
| D-Bil, mg/dL  | 0.1–0.9                     | N/A                           |
| Ca, mg/dL     | 4.8–11.2                    | 8.7–10.8                      |
| P, mg/dL      | 4.2–26.8                    | 4.4–6.6                       |
| Mg, mg/dL     | 1.6–3.6                     | N/A                           |
| Fe, μg/dL     | 76–268                      | N/A                           |
| UIBC, μg/dL   | 13–319                      | N/A                           |
| UA, mg/dL     | 2.0–7.6                     | 2.1–5.2                       |
| Glu, mg/dL    | 23–115                      | 68–121                        |

T-Pro, total protein; Alb, albumin; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CK, creatine kinase; NA, Not available; LDH, lactate dehydrogenase; T-Chol, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; T-Bil, total bilirubin; D-Bil, direct bilirubin; Ca, calcium; P, inorganic phosphate; Mg, magnesium; Fe, iron; UIBC, unsaturated iron binding capacity; UA, uric acid; Glu, glucose.
serum cholesterol and triglycerides at birth, which increase rapidly during the first week after birth.25,26 In addition, some parameters such as total bilirubin and phosphate showing increased and wider reference intervals in neonates may suggest variable organ development within a population or their immature homeostatic mechanisms.25

One of the limitations in our study is the fact that preterm neonates were comprised of a heterogeneous group ranging from extremely preterm (less than 28 gestational weeks) to moderate to late preterm (32 to 37 gestational weeks). The reference subjects used in the current study were considered to be in good health because all of their CRP concentrations were less than 0.05 mg/dL and all neonates were discharged without special problems. Nevertheless, it is difficult to demonstrate definitively that all newborns were truly free from underlying pathologies. The reference intervals could be affected if any of the included individuals were not truly disease-free and healthy. Therefore, our results should be confirmed by a large-scale, well-designed multi-center study. In addition, given the exclusion criteria considering the neonatal conditions after birth based on single tertiary center study, our study population may not represent the actual reference populations. In this study, we recruited only 79 neonates, which is less than the minimum number required of 120 according to CLSI guideline.3 So, we could not establish our own reference intervals for each analyte.

In conclusion, we compared the reference intervals for 23 biochemical tests in the cord blood of neonates in our hospital, and these data will be useful for clinical decision-making for the management of neonates.

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