Age-dependent changes of total and differential white blood cell counts in children

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Abstract

Background: Total and differential white blood cell counts are important for the diagnostic evaluation of suspected diseases. To facilitate the interpretation of total and differential white blood cell counts in pediatric patients, the present study investigated age-dependent changes in total and differential white blood cell counts in healthy reference children.

Methods: Data were obtained from the Pediatric Reference Intervals in China study (PRINCE), which aims to establish and verify pediatric reference intervals for Chinese children based on a nationwide multicenter cross-sectional study from January 2017 to December 2018. Quantile curves were calculated using the generalized additive models for location, shape, and scale method. The 2.5th, 50th, and 97.5th quantile curves were calculated for both total and differential white blood counts. Percents of stacked area charts were used to demonstrate the proportions of differential white blood cells. All statistical analyses were performed using R software.

Results: Both 50th and 97.5th quantiles of total white blood cell count and monocyte count were highest at birth, then rapidly decreased in the first 6 months of life; relatively slow reduction continued until 2 years of age. The lymphocyte count was low during infancy and increased to its highest level at 6 months of age; it then exhibited moderate and continuous reduction until approximately 9 years of age. The pattern of neutrophil count changed with age in a manner opposite to that of lymphocyte count. Besides, there were two inter-sections of lymphocyte count and neutrophil count during infancy and at approximately 5 years of age, based on locally weighted regression (LOESS) analysis. There were no apparent age-related changes in eosinophil or basophil counts.

Conclusion: These data regarding age-related changes in total and differential white blood cell counts can be used to assess the health of pediatric patients and guide clinical decisions.

Keywords: Leukocyte count; Trends; Pediatrics; Development; Growth

Introduction

The complete blood count (CBC) is the most frequent laboratory test used in clinical practice. The use of the CBC has been promoted in the routine diagnostic investigation for persons who are sick, as well as in wellness screening programs.[1] Clinicians refer to white blood cell (WBC) count and differential WBCs (eg, monocyte count [MONO#], lymphocyte count [LYMPH#], neutrophil count [NEUT#], eosinophil count [EO#], and basophil count [BASO#]; all of these are generated by myeloid or lymphoid progenitors) for diagnosis or evaluation of disease because these cells play essential roles in immunity. For example, total WBC and percentages of differential WBCs are included in the diagnostic evaluation of suspected appendicitis or acute pancreatitis.[2,3] Also, new findings suggest that lymphocyte changes in patients with 2019 novel coronavirus (COVID-19) should be carefully monitored.[4]

However, physiological development is known to cause some degree of changes in laboratory test results, particularly during infancy and puberty. For example, serum alkaline phosphatase activity increases as a child

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reach puberty, reflecting rapid bone growth; it then declines as a child reaches adulthood.[5,6] Similarly, the total WBC and differential WBCs also change with increasing age. Therefore, interpretations of total WBC and differential WBCs should be performed in the context of age- and sex-dependent dynamics.[7] Without this context, unadjusted diagnostic evaluation based on laboratory tests may impact diagnostic efficiency, causing misdiagnosis or missed diagnosis.

To the best of our knowledge, age-dependent changes in WBCs in Chinese children have rarely been reported thus far. The present study investigated age-dependent changes in total and differential WBCs among healthy children aged 0 to 18 years, based on the Pediatric Reference Intervals in China study (PRINCE),[8] which aims to establish and verify pediatric reference intervals for Chinese children based on a nationwide multicenter cross-sectional study. Changes in the proportions of five differential WBCs and the neutrophil-to-lymphocyte ratio (NLR) were also assessed; these are expected to aid in applications of WBC data and the proportions of five differential WBCs in pediatric clinical practice.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki*. The PRINCE study protocol was approved by the Institutional Review Board of Beijing Children's Hospital (No. IEC-C-028-A10-V.05) and the current study protocol, which used PRINCE data was approved by the institutional review boards of the ten collaborating centers. Furthermore, informed consent was obtained from each participant's legally authorized representative (parent or guardian) if children were less than 8 years of age; assent was obtained from children at least 8 years of age, in addition to consent from their legally authorized representatives.

Data source

Data were obtained from the results of the PRINCE study. The eligibility criteria and other detailed information were previously published.[8] In brief, 15,150 healthy children aged 0 to 19 years were recruited from the northeast (Liaoning), north (Beijing and Hebei), northwest (Shaanxi), middle (Henan and Hubei), south (Guangdong), southwest (Chongqing and Sichuan), and east (Shanghai and Jiangsu) regions of China from January 2017 to December 2018. All participants were confirmed to be eligible based on a questionnaire screening and subsequent physical examination. Participants aged 0 to 18 years were included in this exploration of age-dependent changes in total and differential WBCs.

Laboratory examinations

All blood specimens were collected by trained pediatric nurses using a BD vacutainer and vacuum tube needles (Becton, Dickinson and Company, Dublin, Ireland). Assessments of all samples were completed within 6 months after collection; repeated freeze-thaw cycles were avoided during the examination process. The CBC was performed using an automated hematology analyzer, Sysmex XS (Sysmex Corporation, Kobe, Japan).

Data cleaning and management

Data cleaning was performed to detect missing values and outliers. Missing values were defined as the absence of information regarding age, sex, or CBC results. All test results that might be adversely affected by specimen quality (eg, hemolysis) were identified and excluded from statistical analysis. Outliers were tested using the Tukey method, in which outlying values were defined as less than (Q_1 – 1.5 × inter-quartile range) or more than (Q_3 – 1.5 × inter-quartile range), where Q_1 and Q_3 represented the 25th percentile and 75th percentile, respectively, and the inter-quartile range was denoted as Q_3–Q_1. When variables did not exhibit a Gaussian distribution, the Box-Cox method was used for transformation.[9]

Statistical analysis

All statistical analyses were performed using R software (version 3.5.1, https://www.r-project.org/). Percentiles were estimated using the generalized additive models for location, shape, and scale (GAMLSS) method, which was implemented in the GAMLSS package. The GAMLSS method is an extension of the Lambda-Median-Sigma method, which was introduced by Rigby and Stasinopoulos to address some of the limitations associated with generalized linear models and generalized additive models.[10,11] To more clearly represent the dynamic changes during the first 2 years of life, separate charts were constructed to depict the CBC results. Percent of stacked area charts were used to show the proportions of differential WBCs.

Results

The data cleaning procedure is shown in Figure 1. Some results of MONO# and EO# were reported as zero, we excluded them from this study thus, some results were

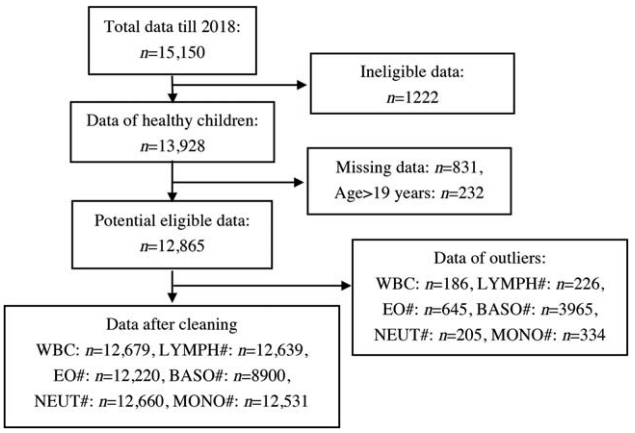

Figure 1: Data cleaning procedure. WBC: White blood cell count; LYMPH#: Lymphocyte count; EO#: Eosinophil count; BASO#: Basophil count; NEUT#: Neutrophil count; MONO#: Monocyte count.

Table 1: Total and differential white blood cell counts, stratified by sex, and age group.

Analytes	*n*	<6 months	6 months to <2 years	2 to <9 years	9 to <12 years	12–18 years
White blood cell count ($\times 10^9$/L)						
Males	6278	9.00 (7.64, 10.55)	8.55 (7.08, 9.69)	7.34 (6.30, 8.60)	7.00 (6.03, 8.09)	6.68 (5.81, 7.85)
Females	6401	8.83 (7.24, 10.80)	8.59 (7.28, 10.17)	7.24 (6.20, 8.55)	6.70 (5.81, 7.85)	6.91 (5.97, 8.20)
Lymphocyte count ($\times 10^9$/L)						
Males	6271	4.30 (3.02, 5.71)	5.08 (4.12, 6.34)	3.27 (2.70, 3.94)	2.79 (2.38, 3.29)	2.53 (2.10, 3.00)
Females	6368	4.65 (3.40, 6.07)	5.29 (4.22, 6.42)	3.22 (2.69, 3.94)	2.67 (2.29, 3.15)	2.34 (1.99, 2.78)
Neutrophil count ($\times 10^9$/L)						
Males	6263	2.63 (1.40, 5.58)	2.20 (1.64, 3.00)	3.20 (2.50, 4.14)	3.44 (2.73, 4.32)	3.49 (2.83, 4.39)
Females	6397	2.50 (1.51, 4.91)	2.30 (1.80, 3.07)	3.16 (2.46, 4.16)	3.36 (2.71, 4.28)	3.98 (3.15, 5.08)
Monocyte count ($\times 10^9$/L)						
Males	6205	0.69 (0.46, 1.04)	0.50 (0.40, 0.60)	0.40 (0.31, 0.50)	0.39 (0.30, 0.48)	0.38 (0.30, 0.47)
Females	6326	0.68 (0.44, 1.08)	0.50 (0.39, 0.62)	0.38 (0.30, 0.48)	0.35 (0.27, 0.44)	0.35 (0.29, 0.44)
Eosinophil count ($\times 10^9$/L)						
Males	6093	0.37 (0.26, 0.52)	0.27 (0.18, 0.40)	0.19 (0.10, 0.29)	0.14 (0.09, 0.24)	0.12 (0.08, 0.20)
Females	6107	0.39 (0.25, 0.53)	0.20 (0.14, 0.31)	0.15 (0.10, 0.23)	0.11 (0.08, 0.19)	0.10 (0.07, 0.16)
Basophil count ($\times 10^9$/L)						
Males	4530	0.02 (0.01, 0.03)	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.02 (0.02, 0.04)	0.02 (0.01, 0.03)
Females	4370	0.02 (0.01, 0.03)	0.02 (0.01, 0.04)	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)

Data are presented as *n* or median (inter-quartile range).

reported as zero after rounding. These records were excluded from this study. The medians and inter-quartile ranges of total and differential WBCs are shown in Table 1. The total WBC decreased with increasing age. Similar changes were observed in terms of MONO#, EO#, and BASO#. In terms of LYMPH#, the highest median was observed in the age group of 6 months to <2 years; LYMPH# subsequently decreased with increasing age. Changes in NEUT# with age were opposite to those of LYMPH#.

Continuous age-dependent changes in total and differential WBCs are shown in Figures 2 and 3. The 2.5th, 50th, and 97.5th quantile curves were calculated for both total and differential WBCs. Age-related changes in total and differential WBCs were as follows: (1) For both WBC [Figure 2A] and MONO# [Figure 3A], the 50th and 97.5th quantiles were highest at birth, then rapidly decreased in the first 6 months of life; relatively slow reduction continued until 2 years of age. As in other studies, males exhibited a slightly higher MONO#, compared with females; in contrast, females exhibited a slightly higher concentration than males for WBC during puberty.[7,12] (2) LYMPH# [Figure 2B] was low during infancy and increased to its highest level at 6 months of age; then, the 50th and 97.5th quantiles of LYMPH# exhibited moderate and continuous reduction until approximately 9 years of age. In addition, LYMPH# appeared slightly higher in males than in females during puberty. (3) In contrast to the changes in LYMPH#, NEUT# [Figure 2C] exhibited the highest level at birth, then exhibited rapid reduction until 6 months of age. Whereas WBC and MONO# exhibited continuous reduction, the 50th and 97.5th quantiles of NEUT# exhibited mild and continuous elevation with age. Besides, the NLR showed more rapid age-dependent changes during puberty; it increased nearly three-fold from 2 to 18 years of age [Figure 4]. Notably, both the NLR and NEUT# were higher in females than in males during puberty. (4) Both the 2.5th and 50th quantiles of EO# [Figure 3B] and BASO# [Figure 3C] did not exhibit age-related changes. However, the 97th quantiles of EO# and BASO# exhibited mild reduction throughout childhood.

The proportions of differential WBCs are shown in percent stacked area charts [Figure 5], which comprehensively depict the relative changes in differential WBCs during development from infancy to 18 years of age. Notably, there were two inter-sections of LYMPH# and NEUT# during infancy and at approximately 5 years of age [Figure 6], which indicated changes in these components of WBCs.

Discussion

As a routine laboratory test, total and differential WBCs are important assays for assessment of immune status in children; they are also vital in the diagnostic evaluation of suspected diseases, such as bacterial infections encountered in the emergency department.[3]

Pneumonia is a common illness that continues to cause high mortality among young children in developing countries.[13] Ongoing and prior epidemiological situations involving COVID-19, severe acute respiratory syndrome, and the 2009 pandemic influenza A (ie, H1N1) virus emphasize the roles of respiratory viruses in the onset of severe pneumonia. Several studies have indicated that the NLR, WBC, and NEUT# are important in the differential diagnosis of patients with viral and bacterial pneumonia, as well as prediction of complications in these patients[14,15]; for example, the NLR is higher in patients with bacterial pneumonia than in patients with viral pneumonia.[16] Early exclusion of bacterial pneumonia could reduce unnecessary antibiotic therapy, thereby reducing the potential for

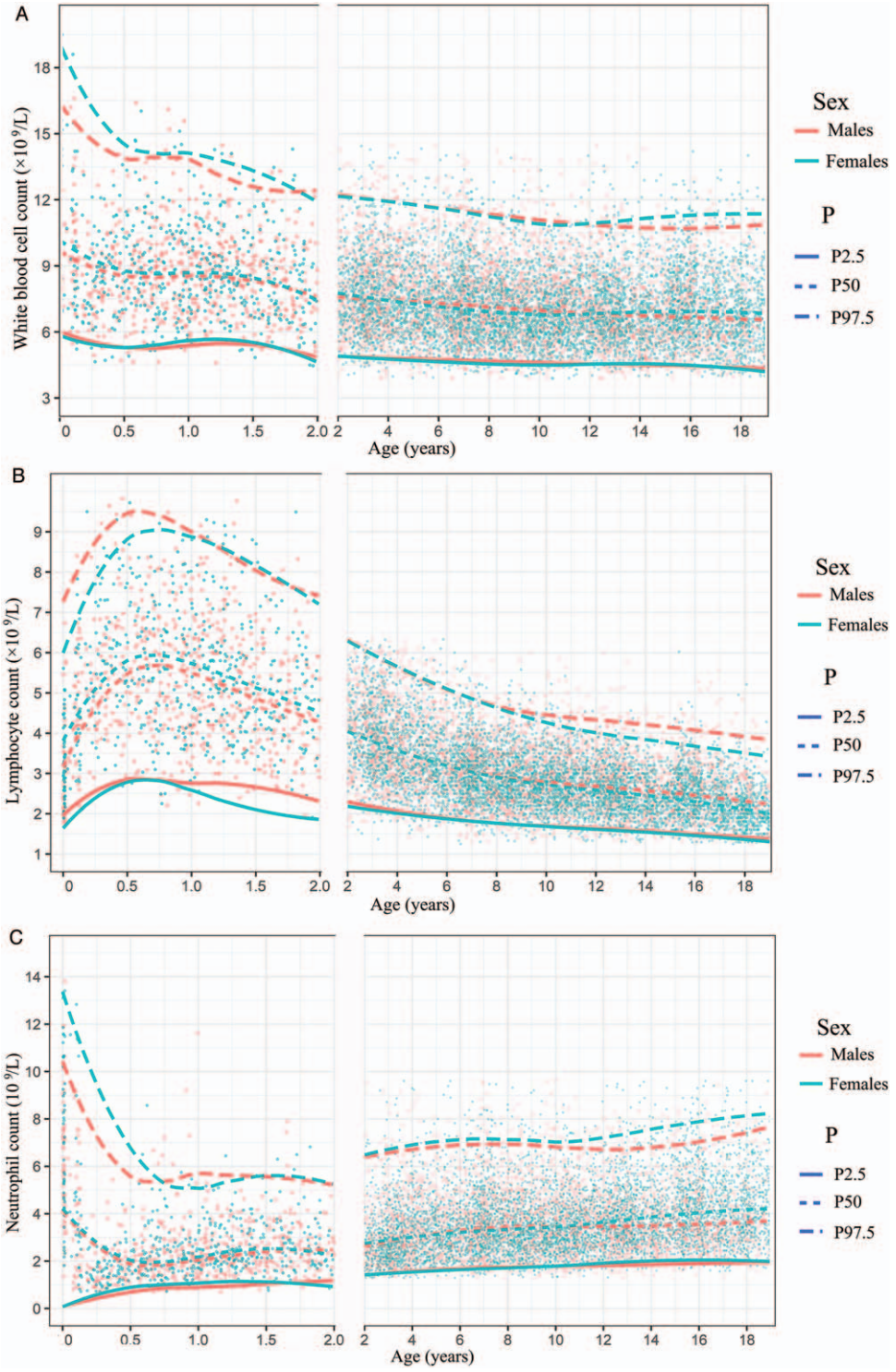

Figure 2: Age-dependent changes in white blood cell count (A), lymphocyte count (B), and neutrophil count (C).

antibiotic resistance.[16] Moreover, COVID-19 may cause a reduction of LYMPH#[17,18]; the NLR and NEUT# may be important clinical indicators for distinguishing COVID-19 and other viral infections during the early stages of the disease.[4]

The present study demonstrated dramatic changes in both total and differential WBCs throughout childhood, especially in the early stages of life, which was consistent with previous research.[7,12] Also, LYMPH# and NEUT# exhibited more obvious age-dependent changes during childhood, compared with EO#, BASO#, and MONO#. As shown in Figure 2B, LYMPH# exhibited its lowest level during infancy and increased to its highest level at 6 months of age, then exhibited moderate and continuous reduction until approximately 9 years of age; these patterns reflect the changes in children's exposure to foreign antigens with increasing age,[19] and are consistent

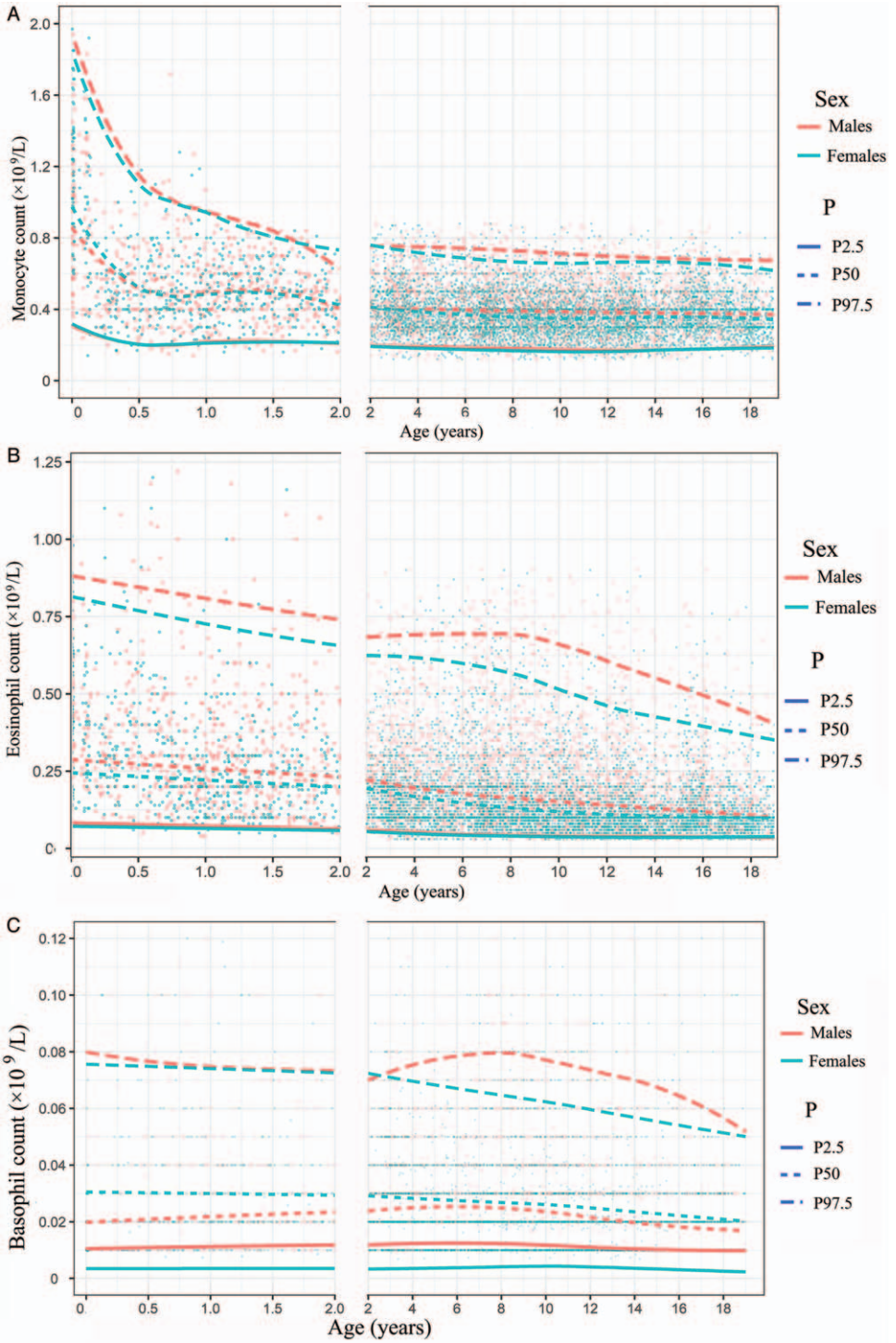

Figure 3: Age-dependent changes in monocyte count (A), eosinophil count (B), and basophil count (C).

with the overall timing of pediatric diseases. The pattern of NEUT# changes with age in a manner opposite to that of LYMPH#.

These observations support the notion that reference intervals or clinical decision limits for total and differential WBCs should be modified in accordance with the growth and development of children. Such changes can aid in efforts to reduce misdiagnosis and missed diagnosis in clinical practice. Notably, the diagnostic performance of WBCs in appendicitis showed considerable change with increasing age if the clinical decision limit was not adjusted for age.[20] Moreover, for new infectious diseases that can lead to major public health events, it is important to attain a timely and accurate understanding of clinical characteristics to ensure disease identification and control. In recent months, many studies have been published regarding COVID-19; however, most of these studies have not investigated age-dependent

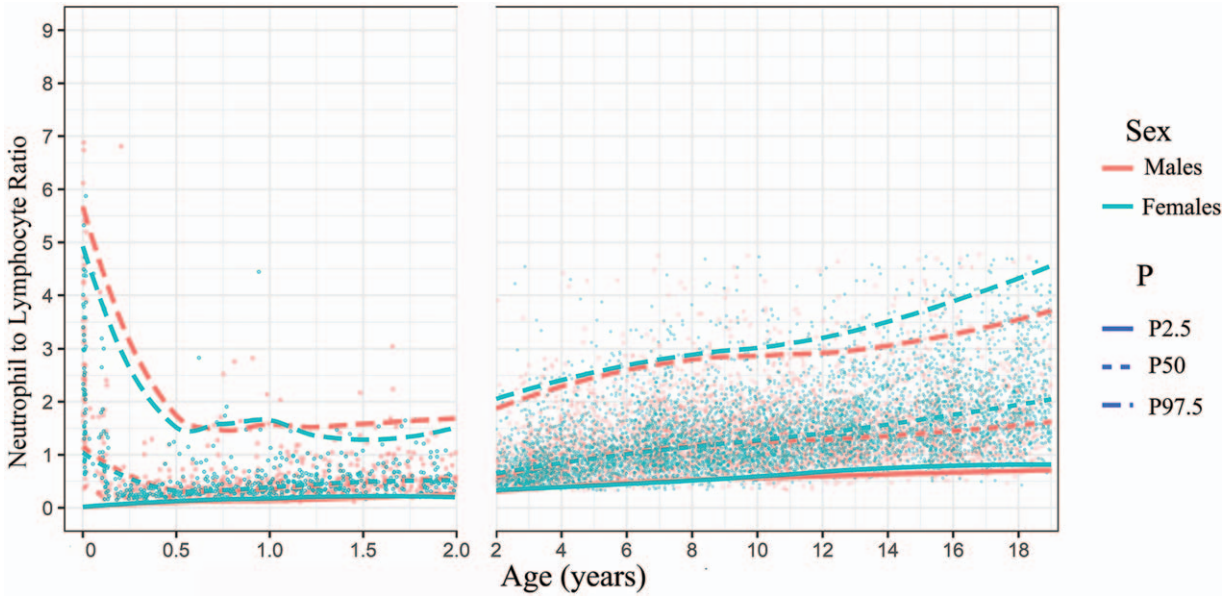

Figure 4: Age-dependent changes in neutrophil-to-lymphocyte ratio.

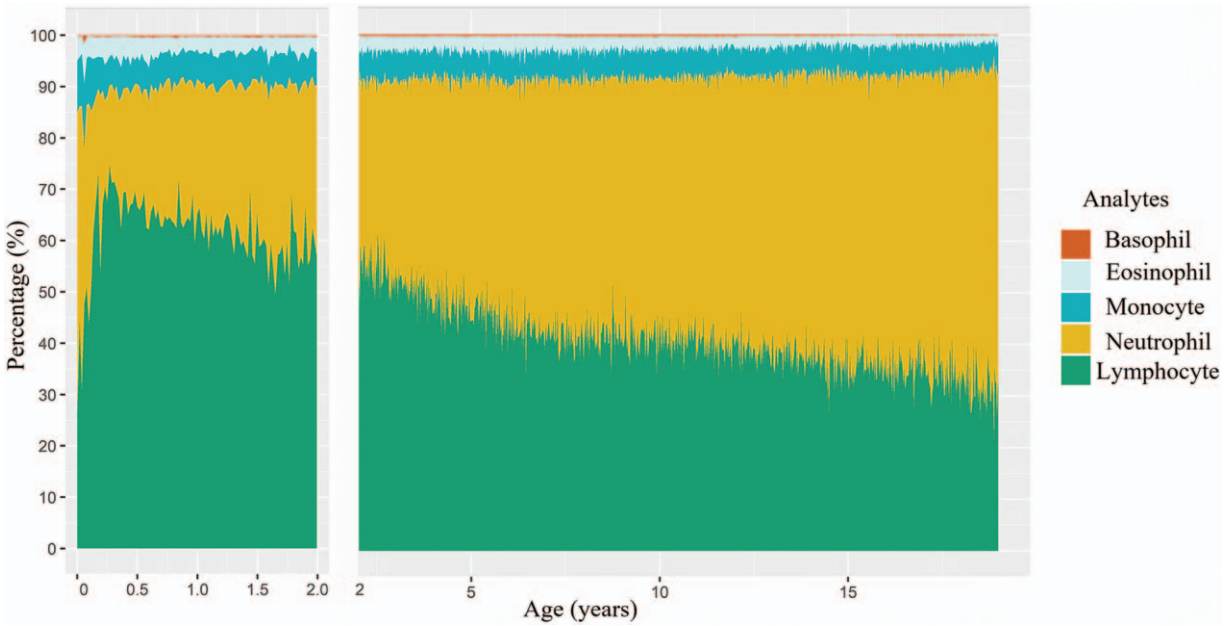

Figure 5: Proportions of differential white blood cell counts for children aged 0–18 years.

changes in LYMPH#, WBC, or NEUT# for children, which may reduce their usefulness in the treatment of COVID-19.[18,21]

Mild sex differences in NEUT#, LYMPH#, and EO# were observed during puberty. Several studies have shown that sex hormones serve as immunomodulators. In particular, estrogen can increase immunologic responses, while testosterone suppresses such responses; thus, sex-related differences may be observed in these laboratory indexes.[22] Accordingly, sex-related differences should be considered when using these analytes as diagnostic criteria for the disease. Although BASO# exhibited fewer age-dependent changes, any changes during bacterial infection may affect patient outcomes.

Although total and differential WBCs are the most frequent clinical laboratory tests in medical practice, some potential uses of these analyses in clinical practice have been ignored. Recent studies findings suggest that the role of neutrophils in cancer-related inflammation may require a careful reassessment of their infiltration, polarization, and prognostic significance in human cancer.[23] Furthermore, neutrophils are useful for immune monitoring and assessment of prognosis in patients with some tumors (eg, kidney cancer, lung cancer, and

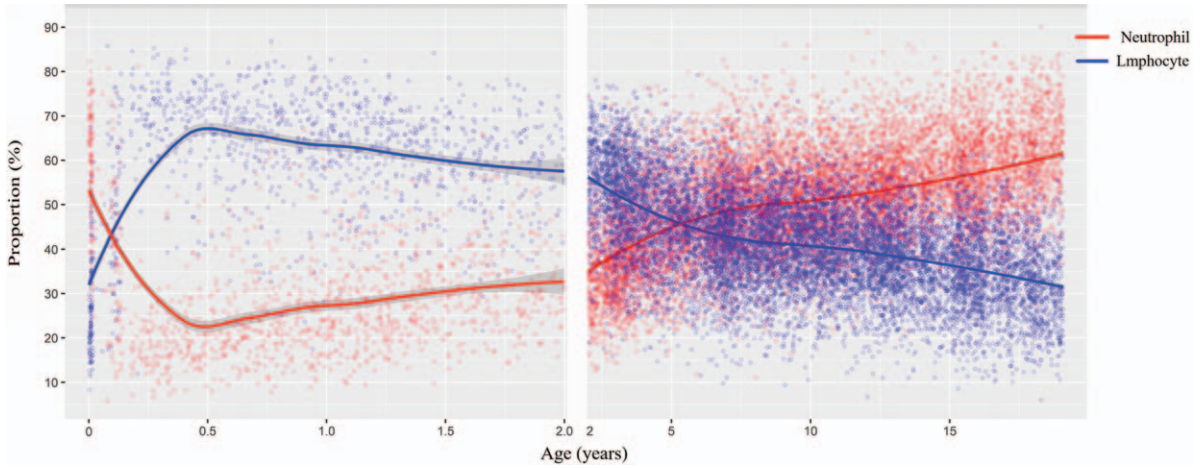

Figure 6: Age-dependent changes in lymphocyte and neutrophil proportions.

gastrointestinal stromal tumors).[3,23] In addition, the NLR can predict the severity of hypertriglyceridemia-induced acute pancreatitis, whereas the WBC is less predictive[2]; the NLR also can aid in the diagnosis of ankylosing spondylitis and prognostic assessment of cancers such as renal cell carcinoma.[24]

This study has some limitations. Most importantly, there was obvious edge-effect in the quantile curves calculated by the GAMLSS method, which may have been caused by the relatively small sample size, especially for children aged 0 to 2 years. It is difficult to recruit healthy infant volunteers worldwide; the difficulty of collecting blood from infants also limited the sample size of this study.

In summary, there is a need to understand the age-dependent changes in total and differential WBCs to ensure proper clinical decisions and avoid misdiagnosis or missed diagnosis of children. Our data demonstrated specific changes in total and differential WBCs with age, which can aid in the application of these analyses in clinical practice.

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Conflicts of interest

None.

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