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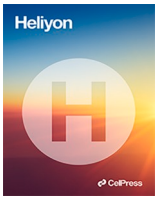

Research article

Sex- and age-based reference intervals for capillary complete blood count parameters among urban preschoolers in southeast China based on a large community population

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ABSTRACT

Background and aim: Pediatricians commonly use the complete blood count (CBC) of capillary blood to evaluate health status, guide diagnoses, and determine treatment strategies. This study aimed to establish sex- and age-specific reference intervals (RIs) for 23 capillary CBC parameters for urban preschoolers in Fuzhou, Southeast China.

Materials and methods: Capillary blood CBC data of 18,369 healthy preschoolers who underwent annual physical examinations at Fujian Maternity and Child Health Hospital between January 01, 2022, and November 31, 2023, were analyzed retrospectively. To fully validate the new RIs, the data of all apparently healthy children within the same age cohort at the same institution were comprehensively analyzed in December 2023. The new RIs were assessed by comparing them with the RIs currently used in laboratories and those obtained from different regions, sample types, or methodologies.

Results: Dynamic temporal changes that differ between males and females were observed in the blood system of 3-7-year-old children in this region. The new sex- and age-specific RIs for capillary CBC parameters were feasible to guide clinical decision-making in the local region.

Conclusions: Our findings demonstrated the importance of establishing sex- and age-specific RIs for each region and underscored the necessity of continuous adjustment of clinical Rls based on statistical rules and clinical responses.

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1. Introduction

Complete blood count (CBC) is a routine blood test conducted at specialized pediatric hospitals [1]. The erythrocyte, leukocyte, and platelet parameters obtained with the CBC provide significant clinical value in the diagnoses, treatment, and prognosis of anemia, infections, and hematological disorders, as well as in the evaluation of the health status of pediatric patients [2–4]. Venous blood collection in preschool-aged children (3–7 years) is often challenging due to factors such as non-compliance and resistance. Consequently, capillary blood sampling is preferred due to its minimally invasive nature, simplicity, convenience, and the requirement for smaller blood volumes [5]. Therefore, capillary blood samples are the primary source for CBC testing in preschoolers [6]. In China, the prevailing reference intervals (RIs) for capillary blood CBC among preschoolers in most regions primarily rely on the RIs for blood cell analysis in children (WS/T779-2021) issued by the Ministry of Health of the People's Republic of China in 2021 [7]. This provides standard reference values for preschool-aged children, which are distinct from those of other age groups but are not further subdivided by age. The ages spanning 3–7 years mark a pivotal phase of rapid physical development in children, which is accompanied by significant changes in their blood systems [8–10]. Furthermore, racial and environmental influences on physical growth and blood system development may vary [11]. Therefore, applying a single national RI for CBC parameters among children aged 3–7 years across diverse regions of China, each characterized by distinct racial and economic backgrounds, is inappropriate. Such an approach may impede effective diagnosis and treatment, potentially resulting in erroneous medical decisions and interventions [12]. Additionally, certain blood cell parameters in childhood exhibit sex disparities, although the findings in this regard are inconsistent [2,9,10,13]. The study will also seek to clarify which blood cell parameters of preschoolers in this region display sex differences.

Although the Clinical and Laboratory Standards Institute (CLSI) C28-A3 [14] recommends the"direct" approach as the standard method for defining RIs, this approach has limitations such as a long research cycle, high labor requirements, and significant capital investment. As such, the "indirect" approach, utilizing existing hospital big data, is increasingly popular in RI establishment, particularly for pediatric populations [15–17]. It is important to note that a portion of hospital data is derived from a "diseased" population that is difficult to distinguish using current statistical methods [18–20]. Therefore, to address the challenge of harmonization induced by this population during indirect RI establishment using existing hospital data, we capitalized on the annual physical examinations of more than half of Fuzhou's preschoolers by Fujian Maternity and Child Health Hospital.

2. Research participants and methods

2.1. Participants

This study was a retrospective analysis of the CBC data of healthy children obtained during physical examination. All participants were urban preschoolers who underwent physical examinations at Fujian Maternity and Child Health Hospital from January 01, 2022, to November 31, 2023. The inclusion criteria were as follows: (1) living in Fuzhou City for the past 2 years, (2) aged between 3 and 7 years (excluding 7-year-olds), and (3) having normal physical and psychological health. The exclusion criteria were as follows: (1) fever, acute infection, or medication in the past two weeks described by the guardian; (2) allergic diseases, autoimmune diseases, genetic diseases, or malignant tumors; (3) blood system diseases or abnormal function of the liver, kidney, heart, or spleen.

2.1.1. Capillary blood sample collection

According to the CLSI guidelines [21], capillary blood samples (200–250 μL) were collected from the tip inner side of the left middle or ring finger and placed in test tubes (0.5 mL) containing EDTA-K2 dry powder anticoagulant (Gongdong Medical Technology, China). To minimize the impact of interference factors such as dander or tissue mixing, tissue fluid exudation, and platelet pseudocoagulation, the finger was gently massaged to confirm the absence of cyanosis or cold, and the first drop of blood was discarded. Subsequently, the sample was gently mixed and allowed to stand at room temperature (20–26 °C) for 25 min before being tested within 1 h of collection.

2.1.2. Analysis and detection

The 23 CBC items from all samples were randomly tested using three different series of the Sysmex Fully Automatic Blood Analyzer (XS-500i, XS-800i, and XS-3000, Sysmex Company, Japan), which are routinely used for clinical analysis at the Clinical Laboratory of Fujian Maternity and Child Health Hospital. These items included eleven leukocyte-related parameters: white blood cell count (WBC), neutrophil count (NEUT), neutrophil percentage (NEUT%), lymphocyte count (LYM), lymphocyte percentage (LYM%), monocyte count (MONO), monocyte percentage (MONO%), eosinophil count (EO), eosinophil percentage (EO%), basophil count (BA), and basophil percentage (BA%); eight erythrocyte-related parameters: red blood cell count (RBC), hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), coefficient of variation of RBC distribution width (RDW-CV), and the standard deviation of RBC distribution width (RDW-SD); and four platelet-related parameters: platelet count (PLT), mean platelet volume (MPV), plateletcrit (PCT), and platelet large cell ratio (P-LCR).

Biannual precision calibration of all blood cell analyzers was performed by the manufacturer's engineers to guarantee the reliability of the test data outcomes for each device and the consistency of results across all instruments, according to the relevant provisions of the International Organization for Standardization (ISO) 15189. The coefficient of variation was maintained within the instrument's specified limits (Schedule 1). Additionally, all CBC items underwent a biannual interlaboratory quality evaluation organized by the Chinese National Center of Clinical Laboratories and Fujian Center for Clinical Laboratories. Furthermore, the daily analysis process for these instruments was closely monitored using three levels (high, medium, and low) of whole blood control

material (Bio-Rad, USA).

2.1.3. Statistical analysis and RIs determination

Participants were divided into four age groups for statistical analysis and determination of RIs. GraphPad Prism 9.5.0 software was used to conduct statistical analyses. Gaussian analysis was used for original or logarithmically converted data (BA and BA%, which exhibited highly skewed distribution and RIs that accommodate upper limits, so data transformation was not performed). Data conforming to Gaussian distribution were presented as the mean ± 2 standard deviations (SD), and group differences were analyzed using Student's t-test.

Data not conforming to Gaussian distribution were presented as medians, and group differences were analyzed using the Mann-

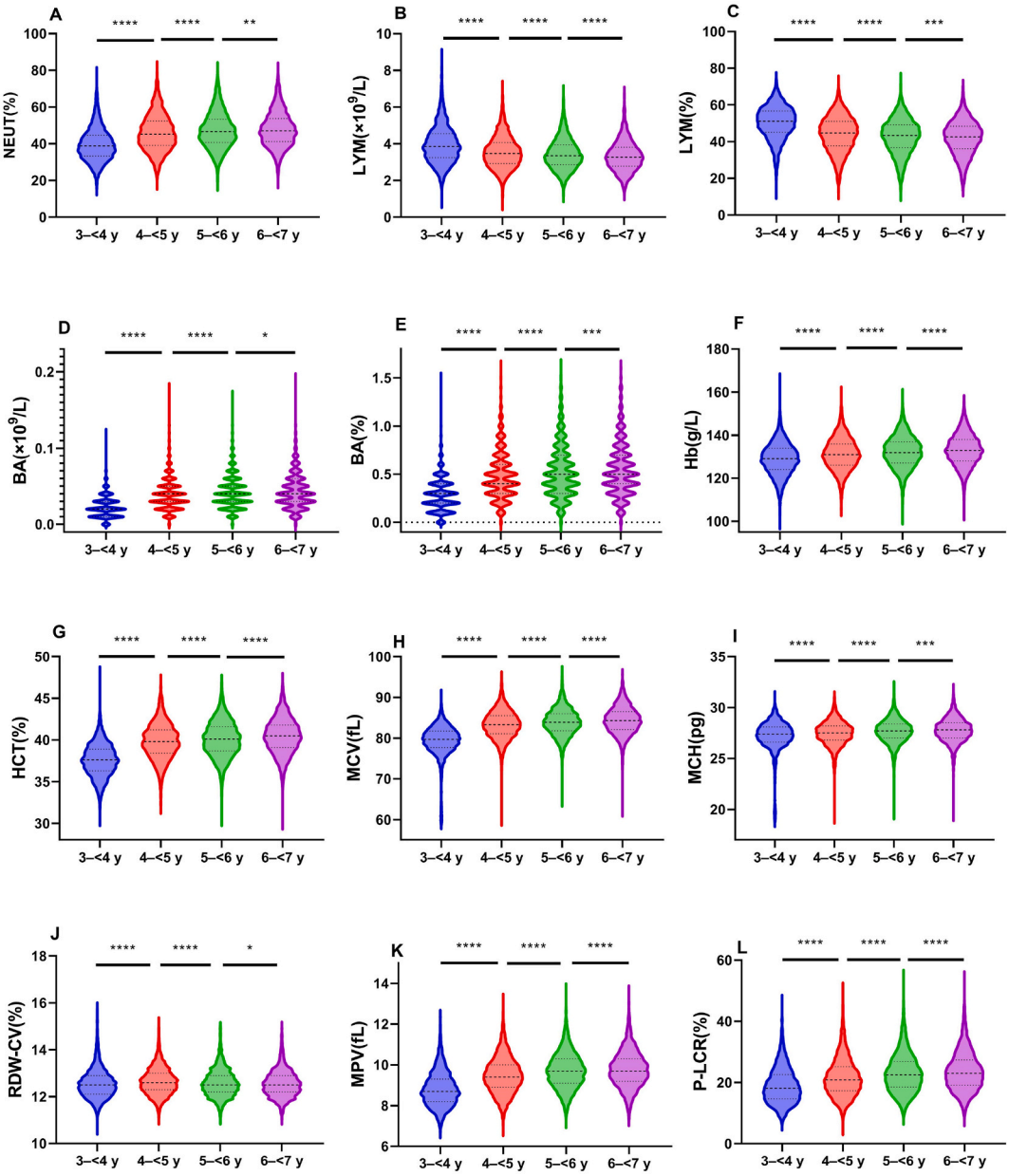

Fig. 1. Significant different parameters of CBC between adjacent age groups.A. NEUT%; **B.**LYM; **C**. LYM%; **D**. BA; **E**. BA%; **F**. Hb; **G**. HCT; **H**. MCV; **I**. MCH; **J**. RDW-CV; **K**. MPV; **L**. P-LCR. Data are presented as median (interquartile range); 3–<4y,n = 4037; 4-–<5y, n = 4677; 5–<6y, n = 5646; 6–<7y, n = 4009; *,P<0.05; **,P<0.01; ***,P<0.001; ****,P<0.0001.BA, basophil count; BA%,basophil percentage; CBC, complete blood count; Hb, hemoglobin; HCT, hematocrit; LYM, lymphocyte count; LYM%, lymphocyte percentage; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; MPV, mean platelet volume; NEUT%, neutrophil percentage; P-LCR, platelet large cell ratio; RDW-CV, coefficient of variation of RBC distribution width.

Whitney *U* test. Statistical significance was set at $P \leq 0.05$ for two-tailed analysis, except for BA and BA%, which employed single-tailed analysis. Age groups without statistical significance were combined, and the above steps were repeated until significant differences were observed between the two adjacent groups.

Following the CLSI C28-A3 guidelines [14], MedCalc20.100 software was used to eliminate outliers and establish RIs for all 23 parameters among the different age groups. Outliers were initially identified and removed using the D/R method [22], and the Tukey test [23] was repeatedly applied to further identify and remove outliers (if the original data were not Gaussian distributed, BOX-COX conversion was required first) [24] until all outliers were eliminated. To ensure the representativeness of new RIs, the elimination rate of all groups should be <10 % [9]. The method for establishing RIs involved calculating the 95%RI and 90 % confidence interval (CI) using a non-parametric method and then applying Lahti's method [25] to perform inter-group merging for subgroups where extreme values at both ends of the overall RI fell within 0.9–4.1 % (data that eliminated outliers). If no significant difference between the new group and adjacent subgroup was observed after merging, they were merged again until a significant difference was observed.

Similarly, the sex-specific RIs for all 23 parameters of the final age grouping were established using the same methods.

2.1.4. Scientific verification of the new RIs

In accordance with the outlined criteria in CLSI C28-A3 [14], all healthy children within the same age cohort who underwent routine physical examinations at Fujian Maternity and Child Health Hospital in December 2023 were enrolled as independent participants to validate the applicability of new RIs. Each verified participant conformed to the predefined inclusion and exclusion criteria. Ineligible data were identified and excluded according to the outlier identification methods used previously. If the number of cleaned data for any of the parameters was <60, new participants were recruited. The new RI covering more than 90 % of participants indicates that its clinical application was appropriate.

To further assess the necessity of establishing age and sex-specific RIs for capillary blood CBC in preschoolers within this region, we also compared the newly proposed RIs to the prevailing national RIs issued by the Ministry of Health of the People's Republic of China as well as those obtained from different regions, sample types, or methodology.

3. Results

3.1. General description

In total, 18,413 preschoolers aged 3–7 years were recruited. After excluding 44 participants due to fever (n = 13), allergy medication treatment (n = 25), and abnormal liver function (n = 6), the CBC data of 18,369 children from Fuzhou city were used to establish the RIs for 23 capillary blood CBC parameters for preschoolers in southern Chinese cities. Among these participants, 9793 were male; 8576 were female; 4037 were aged 3–4 years; 4677 were aged 4–5 years; 5646 were aged 5–6 years; and 4009 were aged 6–7 years (Schedule 2).

3.2. Establishment of new RIs

All parameters were preliminarily divided into four groups based on age ranges. The D'Agostino & Pearson test revealed that only data of two parameters, MONO and MONO%, followed a log-Gaussian distribution in all age groups. Analysis of differences between adjacent groups showed no significant differences in WBC, MONO, EO, EO%, RBC, and MCHC between the 4–5 and 5-6-year-old groups (P = 0.58, 0.33, 0.52, 0.53, 0.78, and 0.63, respectively). No significant differences in NEUT, PLT, and PCT were observed between the 5–6 and 6-7year-old groups (P = 0.82, 0.09, and 0.99, respectively; Fig. 1,Figure S1and Schedule 3). The groups without significant differences in the above parameters were preliminarily merged. After conducting a new inter-group difference analysis, no significant difference was found in PLT between the 4–5 and 5-7-year-olds (P = 0.14), necessitating the re-merging of these age groups (Schedule 4).

According to Dixon's rule and the Tukey test analysis, we identified and removed outliers, and the results showed that the elimination rate of outliers ranged from 0.13 to 5.59 % in all groups (Schedule 5), consistent with the suggestions of Zeljkovic et al. in establishing RIs (<10 %) [9]. However, considering the RI values for NEUT between the 4–5 and 5–7 years groups; LYM, Hb, and P-LCR between the 4–5 and 5–6 years groups; RDW-SD between the 5–6 and 6–7 years group; MCH between the 3–4, 4–5, and 5–6 years groups; and WBC, MONO, MONO%, and RBC among all age groups did not adhere to the grouping rules proposed by Lahti (Table 1); therefore, new group combinations were performed again. Similar actions were taken because of the same Rl values of BA and RDW-CV among the 4–5, 5–6, and 6-7-year-old groups, and BA%in both 5–6 and 6-7-year-old groups (Table 2). Subgroups were merged when the differences in the upper and lower limits were less than 2 % from the original limits. The RIs affected were NEUT%,LYM%, and MPV between 5 and 6 and 6–7years; EO%, Hb, and MCHC between 4-6 and 6–7 years; HCT among 4–5, 5–6, and 6–7 years(Schedule 6). As the value of RDW-SD was still not significantly different between the 4–5 and 5–7 years groups (P = 0.36), a new group combination was necessary (Schedule 7). At this point, a reasonable age grouping was established for all parameters (Schedule 8).

Consideringthe inconsistent conclusions regarding the influence of sex on CBC parameters in children [2,9,10,13], the current study aimed to establish a sex-based Rl for all CBC parameters. A comparison of sex differences in each parameter across all age groups revealed significant differences in WBC, LYM%, MONO, MONO%, EO, EO%, BA%, RBC, Hb, MCV, MCH, MCHC, RDW-CV, and P-LCR between the sexes in all age groups of this cohort (P < 0.05), while no significant differences in HCT, RDW-SD, and PLT were observed between sexes in any of the age groups (P > 0.05); the sex differences in other parameters varied across the age groups (Fig. 2, Fig. S2 and Schedule 8). According to the related description by Lahti et al. [25], new sex-specific RIs should be established for MONO in all

Table 1
Extreme value of each parameter among different groups of age and their overall Rl.

Parameters	Age	Left 0.9–4.1 %	Right 0.9–4.1 %	Overall RI
WBC ($\times 10^9$/L)	3–<4 y	4.77–5.34	11.45–12.87	5.13–12.54
	4–<6 y	4.75–5.38	12.02–13.51	
	6–<7 y	4.81–5.34	12.26–13.89	
NEUT ($\times 10^9$/L)	3–<4 y	1.48–1.69	5.62–7.11	1.77–7.75
	4–<5 y	1.53–1.90	7.12–8.61	
	5–<7 y	1.72–2.03	7.48–8.94	
NEUT (%)	3–<4 y	23.39–26.50	56.79–63.91	28.30–66.70
	4–<5 y	26.20–30.59	64.30–70.41	
	5–<6 y	29.10–32.30	65.85–71.86	
	6–<7 y	30.07–33.60	65.54–71.80	
LYM ($\times 10^9$/L)	3–<4 y	2.09–2.48	5.86–6.62	2.10–5.49
	4–<5 y	1.96–2.25	5.13–5.74	
	5–<6 y	1.90–2.20	5.00–5.57	
	6–<7 y	1.79–2.10	4.76–5.19	
LYM (%)	3–<4 y	26.71–33.67	64.20–68.09	24.10–62.30
	4–<5 y	20.20–26.44	59.56–64.20	
	5–<6 y	19.72–25.00	58.00–62.30	
	6–<7 y	19.20–24.90	56.54–61.20	
MONO ($\times 10^9$/L)	3–<4 y	0.24–0.28	0.74–0.86	0.27–0.84
	4–<6 y	0.24–0.29	0.81–0.94	
	6–<7 y	0.24–0.28	0.79–0.93	
MONO (%)	3–<4 y	3.50–3.90	9.00–10.20	3.80–9.50
	4–<5 y	3.58–4.10	9.10–10.60	
		3.50–4.00	9.00–10.30	
	5–<6 y			
	6–<7 y	3.50–3.90	8.90–10.10	
EO ($\times 10^9$/L)	3–<4 y	0.06–0.09	0.67–0.88	0.07–0.74
	4–<6 y	0.05–0.07	0.66–0.86	
	6–<7 y	0.04–0.07	0.71–0.87	
EO (%)	3–<4 y	0.90–1.20	8.10–9.38	0.90–8.50
	4–<6 y	0.60–0.90	7.80–9.10	
	6–<7 y	0.60–1.00	8.30–9.30	
BA ($\times 10^9$/L)	3–<4 y	/	0.05–0.06	0.00–0.07
	4–<5 y	/	0.07–0.08	
	5–<6 y	/	0.07–0.08	
	6–<7 y	/	0.08–0.08	
BA (%)	3–<4 y	/	0.60–0.70	0.00–0.90
	4–<5 y	/	0.90–1.00	
	5–<6 y	/	1.00–1.20	
	6–<7 y	/	1.00–1.10	
RBC ($\times 10^{12}$/L)	3–<4 y	4.13–4.25	5.26–5.42	4.22–5.37
	4–<6 y	4.14–4.29	5.31–5.48	
	6–<7 y	4.15–4.29	5.34–5.49	
Hb (g/L)	3–<4 y	112.00–116.00	141.00–145.00	118.00–145.00
	4–<5 y	115.00–119.00	144.00–148.00	
	5–<6 y	116.00–120.00	144.00–148.00	
	6–<7 y	119.00–122.00	145.00–149.00	
HCT (%)	3–<4 y	33.30–34.30	40.80–41.90	35.00–43.90
	4–<5 y	35.30–36.40	43.40–44.70	
	5–<6 y	35.50–36.70	43.64–44.90	
	6–<7 y	35.80–36.90	44.00–45.10	
MCV (fL)	3–<4 y	72.80–74.60	84.30–85.40	76.00–89.60
	4–<5 y	75.70–77.80	88.80–90.55	
	5–<6 y	77.10–78.60	89.30–91.00	
	6–<7 y	77.30–79.10	90.00–91.65	
MCH (pg)	3–<4 y	24.60–25.50	29.10–29.52	25.40–29.50
	4–<5 y	24.80–25.60	29.20–29.70	
	5–<6 y	25.00–25.80	29.40–29.90	
	6–<7 y	25.30–26.00	29.60–30.20	
MCHC (g/L)	3–<4 y	327.00–331.00	354.00–356.00	314.00–351.00
	4–<6 y	311.00–315.00	345.00–349.00	
	6–<7 y	311.00–315.00	343.00–347.00	
RDW–CV (%)	3–<4 y	11.40–11.70	13.72–14.40	11.70–13.80
	4–<5 y	11.60–11.80	13.70–14.10	
	5–<6 y	11.50–11.70	13.60–14.00	
	6–<7 y	11.50–11.70	13.60–14.00	
RDW–SD (fL)	3–<4 y	33.40–34.20	40.30–41.32	34.70–42.50
	4–<5 y	34.70–35.50	42.30–43.70	

(*continued on next page*)

Table 1 (*continued*)

Parameters	Age	Left 0.9–4.1 %	Right 0.9–4.1 %	Overall RI
	5–<6 y	34.60–35.50	42.10–43.45	
	6–<7 y	34.67–35.50	42.20–43.60	
PLT ($\times 10^9$/L)	3–<4 y	182.00–203.00	401.00–453.00	214.00–463.00
	4–<7 y	210.00–236.00	454.00–498.00	
MPV (fL)	3–<4 y	7.20–7.60	10.40–11.00	7.80–11.40
	4–<5 y	7.70–8.10	11.00–11.60	
	5–<6 y	7.90–8.30	11.30–11.80	
	6–<7 y	8.00–8.40	11.30–11.80	
PCT (%)	3–<4 y	0.17–0.19	0.34–0.38	0.20–0.44
	4–<5 y	0.20–0.22	0.42–0.46	
	5–<7 y	0.21–0.23	0.43–0.48	
P–LCR (%)	3–<4 y	8.72–10.70	30.10–35.10	11.70–36.00
	4–<5 y	10.88–12.80	33.56–38.10	
	5–<6 y	11.50–13.70	35.10–39.65	
	6–<7 y	12.30–14.40	35.80–41.13	

/: Lower limit value is not required.
BA, basophil count; BA%,basophil percentage; EO, eosinophil count; EO%, eosinophil percentage; Hb, hemoglobin; HCT, hematocrit; LYM, lymphocyte count; LYM%, lymphocyte percentage; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MONO, monocyte count; MONO%, monocyte percentage; MPV, mean platelet volume; NEUT, neutrophil count; NEUT%, neutrophil percentage; P-LCR, platelet large cell ratio; PCT, plateletcrit; PLT, platelet count; RBC, red blood cell count; RDW-CV, coefficient of variation of RBC distribution width; RDW-SD, standard deviation of RBC distribution width; WBC, white blood cell count.

age groups; EO in the 3–4 and 4-6-year-old groups; BA% in the 5-7-year-old group; MCV and RDW-CV in all age groups; MCH in the 6-7-year-old group; MCHC in the 3-4-year-old group and PCT in 5-7-year-old group (Table 3). As was done for age groups, sex subgroups were merged when the differences in upper and lower limits were less than 2 % from the original limits (Schedule 9).Therefore, we obtained 95%Rls and 90%Cls for age and sex for all capillary blood CBC parameters in children aged 3–7 years (Table 4).

3.3. Scientific verification of the new RIs

CBC data from 546 participants were independently collected for verification. Of these, 160 patients (male. 84; female. 76) were 3–4 years old, 127 (male. 62; female. 65) were aged 4–5 years, 131(male. 67; female. 64) were aged 5–6 years, and 128 (male. 66; female. 62) were aged 6–7 years. After excluding outliers, there were more than 60 Rl verification cases for all parameters. Moreover, the proportion of CBC values of the 23 parameters from participants among the scope of new RIs was 90.39–100 %, which fulfills the requirements of CLSI C28-A3 (Schedule 10) and indicates the clinical feasibility of the new RIs.

A further evaluation was conducted to determine the necessity of establishing sex- and age-based RIs for capillary blood CBC parameters in the specific geographical region, and we initially examined disparities between the new RIs and the existing national RIs (−100.00 % to +55.56 %) [7]. As depicted in Schedule 11, the RI ranges for most parameters for preschoolers from Fuzhou city were relatively narrow, and the blood cell system of 3-7-year-old children in this region displayed temporal dynamic changes that varied by sex. Subsequently, a comparison was conducted between venous and capillary CBC parameters in preschoolers in two Fujian coastal cities with similar racial and economic backgrounds [26]. The ranges of capillary blood RIs for most parameters were relatively wide and displayed one-sided offsets (Schedule 12). We also conducted inter-regional comparisons of capillary blood RIs in northern Chinese cities [6,13] and Serbia [9], which possess distinct racial and economic backgrounds, and found that although there was no unilateral migration, there were varying degrees of differences in the RIs of most parameters, particular in the leukocyte system. The differences were mild in the Beijing Capital Institute of Pediatrics (−37.94 % to +45.45 %) [6] (Schedule 13), followed by the Beijing multicenter study (−50.00 % to +45.45 %) [13] (Schedule 14), and greatest in Serbia (−92.63 % to +52.63 %) [9] (Schedule 15); however, these two research groups did not establish further RIs for different preschoolers of different ages in Beijing. Compared with the Beijing Capital Institute of Pediatrics, the normal RIs for NEUT, EO, EO%, MPV, and P-LCR in the 3–4 years agegroup; LYM, MCV, and MCH in the 6–7 years age group; NEUT%, LYM%, and PCT in the 5–7 years age group; Hb, HCT, and PLT in the 4–7 years age group were significantly different. Particularly, EO% in the 3–4 years age group had an upper limit difference of +45.45 % and a lower limit difference of +29.42 % (Schedule 13). Our capillary blood Rl was also compared with the RI of venous blood of Koreans [27] (Schedule 16), an Asian race, and Canadians [1] (Schedule 17), which is representative of North America, with a difference of −66.67 % to +63.64 % from Korea and −100.00 % to +100.00 % from Canada. These results indicate that establishing age and sex RIs for capillary blood CBC parameters in preschoolers for specific regions is crucial.

4. Discussion

To determine whether establishing age- and sex-specific RIs is necessary for capillary blood CBC parameters for preschoolers in specific regions is necessary, this study analyzed the CBC results of 18,369 preschoolers who underwent routine physical examinations in Fuzhou, China, and used the indirect method to establish the age and sex RIs for capillary blood CBC parameters of children aged 3–7 years in southern Chinese cities; the rationality and necessity of the new RIs were systematically evaluated.Consistent with most

Table 2
Rls of age preliminary established based on Lahti's method.

Parameters	Age	RI
WBC ($\times 10^9$/L)	3–<7 y	5.13–12.54
NEUT ($\times 10^9$/L)	3–<4 y	1.60–6.22
	4–<7 y	1.87–7.96
NEUT (%)	3–<4 y	25.20–59.13
	4–<5 y	28.74–66.60
	5–<6 y	31.00–68.40
	6–<7 y	32.40–68.10
LYM ($\times 10^9$/L)	3–<4 y	2.33–6.11
	4–<6 y	2.10–5.28
	6–<7 y	1.98–4.95
LYM (%)	3–<4 y	30.70–65.80
	4–<5 y	24.10–61.20
	5–<6 y	22.90–59.30
	6–<7 y	22.70–58.30
MONO ($\times 10^9$/L)	3–<7 y	0.27–0.84
MONO (%)	3–<7 y	3.80–9.50
EO ($\times 10^9$/L)	3–<4 y	0.08–0.74
	4–<6 y	0.06–0.73
	6–<7 y	0.06–0.77
EO(%)	3–<4 y	1.10–8.60
	4–<6 y	0.80–8.40
	6–<7 y	0.80–8.80
BA ($\times 10^9$/L)	3–<4 y	0.00–0.05
	4–<5 y	0.00–0.07
	5–<6 y	0.00–0.07
	6–<7 y	0.00–0.07
BA (%)	3–<4 y	0.00–0.60
	4–<5 y	0.00–0.90
	5–<6y	0.00–1.00
	6–<7 y	0.00–1.00
RBC ($\times 10^{12}$/L)	3–<7 y	4.22–5.37
Hb (g/L)	3–<4 y	115.00–142.00
	4–<6 y	118.00–146.00
	6–<7 y	121.00–147.00
HCT (%)	3–<4 y	33.90–41.30
	4–<5 y	35.93–43.90
	5–<6 y	36.30–44.10
	6–<7 y	36.50–44.40
MCV (fL)	3–<4 y	74.01–84.60
	4–<5 y	77.00–89.40
	5–<6 y	78.10–90.07
	6–<7 y	78.40–90.70
MCH (pg)	3–<6 y	25.30–29.50
	6–<7 y	25.70–29.80
MCHC (g/L)	3–<4 y	330.00–354.00
	4–<6 y	314.00–346.00
	6–<7 y	313.00–345.00
RDW–CV (%)	3–<4 y	11.60–14.00
	4–<5 y	11.70–13.80
	5–<6 y	11.70–13.80
	6–<7 y	11.70–13.80
RDW–SD (fL)	3–<4 y	33.90–40.70
	4–<5 y	35.20–42.90
	5–<7 y	35.10–42.70
PLT ($\times 10^9$/L)	3–<4 y	196.00–418.80
	4–<7 y	225.25–470.00
MPV (fL)	3–<4 y	7.40–10.60
	4–<5 y	7.90–11.30
	5–<6 y	8.10–11.50
	6–<7 y	8.20–11.50
PCT (%)	3–<4 y	0.18–0.36
	4–<5 y	0.21–0.44
	5–<7 y	0.22–0.45
P–LCR (%)	3–<4 y	9.70–31.94
	4–<6 y	12.44–36.30
	6–<7 y	13.53–37.60

BA, basophil count; BA%,basophil percentage; EO, eosinophil count; EO%, eosinophil percentage; Hb, hemoglobin; HCT, hematocrit; LYM, lymphocyte count; LYM%, lymphocyte percentage; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MONO, monocyte count; MONO%, monocyte percentage; MPV, mean platelet volume; NEUT, neutrophil count; NEUT%,

neutrophil percentage; P-LCR, platelet large cell ratio; PCT, plateletcrit; PLT, platelet count; RBC, red blood cell count; RDW-CV, coefficient of variation of RBC distribution width; RDW-SD, standard deviation of RBC distribution width; WBC, white blood cell count.

studies, the CBC parameters of preschoolers' capillary blood are significantly different from those of venous blood [28,29]. The normal ranges of CBC parameters for capillary blood in different regions are also significantly different [6,9,13]. More importantly, the results of this study showed that the blood cell system of preschoolers aged 3–7 years had temporal dynamic changes, and these dynamic changes had sex differences. These findings strongly suggest the necessity of establishing age and sex RIs for capillary blood CBC parameters in preschoolers in specific regions.

The majority of research on age categorization has primarily relied on the scatter plot distribution of artificial judgment. In this study, owing to the relatively small age range, utilizing a simple scatter plot was challenging. Moreover, the Z-score method recommended by Harris and Boyd was used only for the analysis of the two groups with Gaussian distribution of data [30,31]. However, most of the age group data analysis in this study did not display Gaussian distribution or conditions for application of the Z-score method. Significant differences were identified between the parameters in children of different groups, necessitating the division of data into more than two groups. Accordingly, the *t*-test and *U* test were used to analyze Gaussian and non-Gaussian distributed data, respectively, to examine differences between the age groups, and then according to the Lahti method recommended by the guidelines [25]. Subsequently, the internal independent sample verification results suggested that the new RIs established using the above method accurately reflected the reality of preschoolers in this specific region. Notably, in terms of software applications for pediatric Rl studies, some argued that Canadian Laboratory Initiative on Paediatric Reference Intervals (CALIPER) was better than MedCalc software on the aspect of both universality and accuracy [32–34]. However, due to copyright issues, and the acceptability of MedCalc software in the development of Rls [35], we used the MedCalc software in this study. The difference between these two kinds of software is worth further discussing.

Due to the interference of tissue fluid and anticoagulant form, the RIs of capillary blood CBC parameters were considerably different from those for venous blood [28,29].Compared with the venous blood RIs established in Xiamen, another city in Fujian Province with similar racial and economic backgrounds [26], we found that the upper and lower limits of most of the parameters based on capillary blood were relatively larger and exhibited the phenomenon of one-sided offsets. This suggests that it is necessary to establish independent RIs for capillary blood CBC parameters. It is well known that children between the ages of 3 and 7 years undergo rapid development of their immune and blood systems. In line with the consensus on physiological transformation of blood cells in the field of pediatrics, our study revealed noticeable fluctuations in capillary blood CBC parameters among preschoolers of different sexes and ages. Specifically, the leukocyte system of NEUT and NEUT% gradually increased with age, whereas LYM and LYM% gradually decreased with age. These variations may be attributable to the maturation of children's immune systems [8] and a physiological shift in the balance between lymphocytes and neutrophils [6,10]. Moreover, it may be attributed to the higher prevalence of asthma, allergic diseases, and parasitic infections among preschoolers [36–38], as well as disparities in immune defenses between males and females, which may be reflected in the lower serum levels of inflammatory cytokines of the same age in males [39]. In this study, EO and EO% were higher in the low age groups, and BA and BA% were higher in the high age groups, and significant differences were observed in these parameters between the sexes. Most parameters increased with age in the erythrocyte system. Increasing erythropoiesis between 3 and 7 years of age is synchronized with increased metabolism during rapid growth and development [1,2]. Interestingly, we observed a decline in MCHC with age, which warrants further investigation. The erythrocyte system is also affected by gonadal hormones [40], and our data support this notion. Similar to Lahti's research [25], this study only retained sex differences for MCV, MCH, MCHC, and RDW-CV in certain age groups. Several studies suggest that an increased level of thrombopoietin at birth is associated with a transient increase in the platelet count during early life, which subsequently decreases [1,26,41]. Notably, we found that the values for platelet-related parameters in children aged 3–7 years gradually increased with age. Whether this may be ascribed to the children's immune systems' resistance to pathogens and physiological anemia [42,43] remains to be ascertained. Previous studies yielded inconsistent results regarding differences in platelets between the sexes before 10 years old [13,44]. In this study, most platelet parameters exhibited no sex differences except PCT. Overall, our sex-different temporal dynamic changes data suggested that simple use of a single Rl of CBC in children between the ages of 3 and 7 years lacked rigor, and the establishment of continuous Rl was an important premise to ensure the accuracy of clinical diagnosis and treatment. It should be mentioned that overemphasizing differences may potentially lead to clinical confusion when interpreting patient results. To balance this, and we conservatively merged the subgroups of which total offset rates of the upper and lower limit in new RIs is less than2%, when compared with those of the original limits. Meanwhile, wewill further evaluate the clinical practicability of the merge after enough actual clinical consultation and review with medical colleagues. After all, it should not be ignored that the merging action would narrowly affect the range of new Rls narrowly. However, to our knowledge, there was not study on whether the narrow RI may result in false positives and false negatives.

To further evaluate the necessity to independently establish region-specific capillary blood CBC parameters for preschoolers, we conducted a horizontal comparison of the data of the same age group from regions with different ethnic compositions or economic backgrounds [1,6,7,9,10,13,26,27]. Consistent with most studies, the closer the economy and ethnicity, the smaller the differences found [11]. The ethnic composition of the Beijing area was similar to that of the participants in this study; however, owing to different economic levels and lifestyles in the two regions, significant differences in the normal value ranges of the three system-related parameters were observed, particularly in children aged 3–4 years, thereby highlighting the need to establish region-specific RIs for capillary blood CBC parameters in preschoolers.

There were some limitations in this study. Considering that retrospective big data was used in this study, we only excluded the children with symptoms of diseases, but not the minority without symptoms in the early stages of the disease. Another study is necessary to evaluate whether this set of children can affect the formulated outcome of the whole Rl. Meanwhile, the results of CBC test

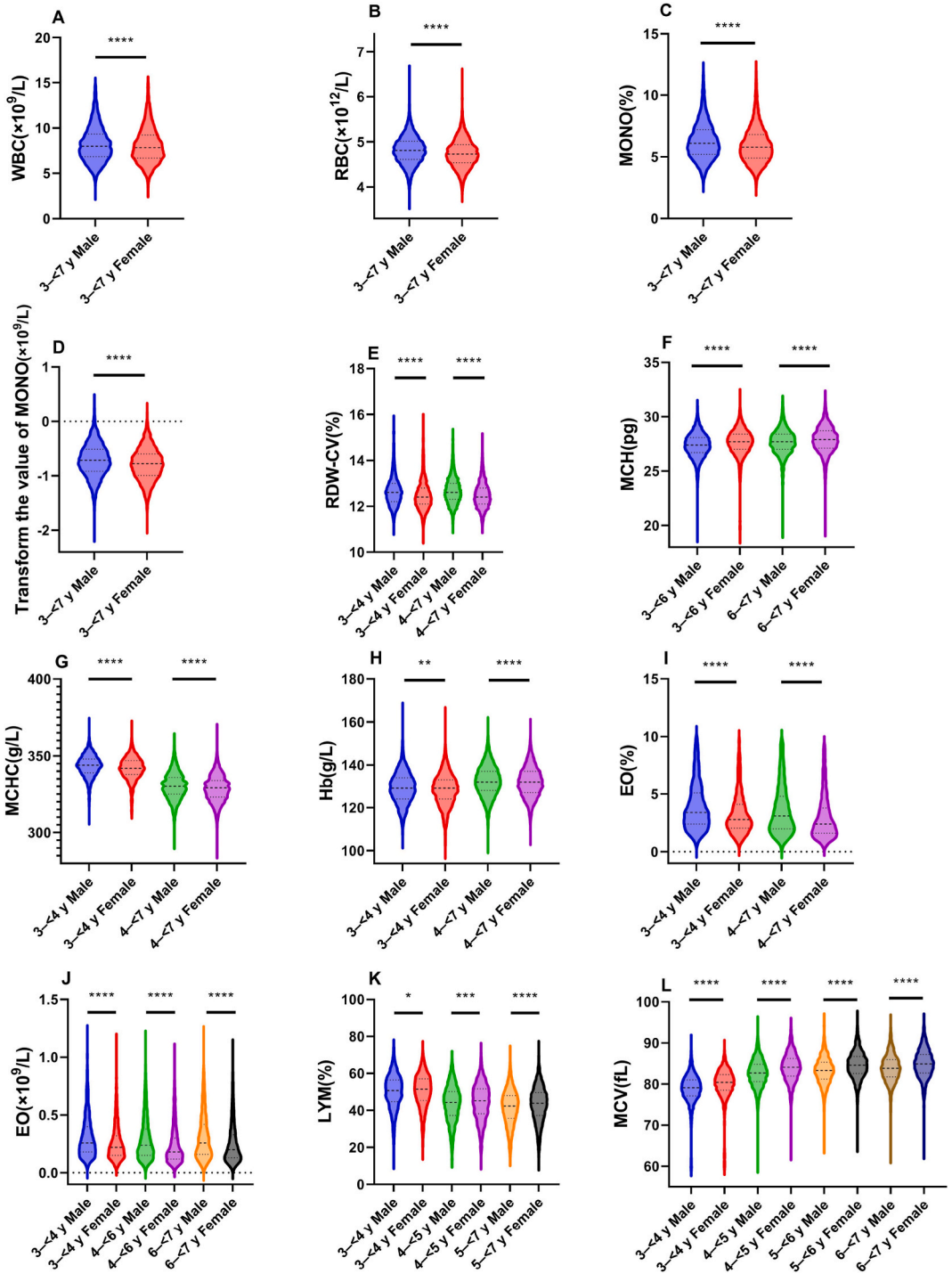

Fig. 2. Significant sex difference of CBC parameters between adjacent age groups. **A**.WBC;**B**.RBC; **C**. MONO%; **D**. MONO; **E**. RDW-CV; **F**. MCH; **G**. MCHC; **H**. Hb; **I**.EO%; J. EO; **K**. LYM%; **L**. MCV.Data are presented as median (interquartile range); 3–<4yMale, n = 2144; 3–<4yFemale, n = 1893; 4–<5yMale, n = 2527; 4–<5yFemale, n = 2150; 4–<6yMale, n = 5506; 4–<6yFemale, n = 4817; 4–<7yMale, n = 7649; 4–<7yFemale, n = 6683; 6–<7yMale, n = 2143; 6–<7yFemale, n = 1866; 3–<7yMale, n = 9793; 3–<7yFemale, n = 8576; *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001. CBC, complete blood count; EO, eosinophil count; EO%, eosinophil percentage; Hb, hemoglobin; LYM%, lymphocyte percentage; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MONO, monocyte count; MONO%, monocyte percentage; RBC, red blood cell count; RDW-CV, coefficient of variation of RBC distribution width; WBC, white blood cell count.

Table 3
Extreme values of sex subgroups across the age groups and their overall RI.

Parameters	Age	Male 0.9–4.1 %		Female 0.9–4.1 %		Overall RI
		Left	Right	Left	Right	
WBC ($\times 10^9$/L)	3–<7 y	4.83–5.41	12.04–13.67	4.74–5.30	11.92–13.44	5.13–12.54
NEUT ($\times 10^9$/L)	4–<7 y	1.69–2.04	7.46–8.95	1.65–1.93	7.22–8.77	1.87–7.96
NEUT (%)	5–<7 y	29.90–33.30	65.90–71.90	29.10–32.50	65.41–71.50	31.40–68.19
LYM ($\times 10^9$/L)	6–<7 y	1.80–2.09	4.71–5.18	1.77–2.10	4.79–5.21	1.98–4.95
LYM (%)	3–<4 y	26.52–33.30	64.07–67.98	26.30–33.74	64.26–68.10	30.70–65.80
	4–<5 y	20.47–26.10	59.16–63.53	20.00–26.90	60.10–65.61	24.10–61.20
	5–<7 y	19.29–24.60	56.40–60.70	19.60–25.39	58.30–62.54	22.80–58.90
MONO ($\times 10^9$/L)	3–<7 y	0.25–0.29	0.82–0.95	0.24–0.27	0.76–0.87	0.27–0.84
MONO (%)	3–<7 y	3.50–4.10	9.20–10.60	3.40–3.90	8.80–10.20	3.80–9.50
EO ($\times 10^9$/L)	3–<4 y	0.07–0.10	0.71–0.92	0.06–0.08	0.60–0.80	0.08–0.74
	4–<6 y	0.06–0.08	0.71–0.90	0.04–0.07	0.62–0.79	0.06–0.73
	6–<7 y	0.05–0.08	0.74–0.89	0.05–0.07	0.64–0.83	0.06–0.77
EO (%)	3–<4 y	1.00–1.37	8.40–9.58	0.89–1.20	7.50–9.00	1.10–8.60
	4–<7 y	0.70–1.00	8.30–9.35	0.60–0.90	7.30–8.90	0.80–8.50
BA ($\times 10^9$/L)	4–<7 y	/	0.07–0.08	/	0.07–0.08	0–0.07
BA (%)	3–<4 y	/	0.60–0.70	/	0.60–0.70	0–0.60
	4–<5 y	/	0.90–1.00	/	0.90–1.00	0–0.90
	5–<7 y	/	1.00–1.10	/	0.90–1.00	0–1.00
RBC ($\times 10^{12}$/L)	3–<7 y	4.15–4.31	5.34–5.50	4.12–4.25	5.27–5.44	4.22–5.37
Hb (g/L)	3–<4 y	114.00–117.00	141.00–145.00	112.00–115.10	140.00–144.00	115.00–142.00
	4–<7 y	117.00–121.00	145.00–148.00	116.00–120.00	144.70–149.00	119.00–146.00
MCV (fL)	3–<4 y	72.02–74.10	83.50–84.70	73.80–75.70	84.60–85.70	74.01–84.60
	4–<5 y	75.40–77.33	87.90–89.60	76.30–78.49	89.40–91.10	77.00–89.40
	5–<6 y	76.40–78.00	88.30–90.00	77.95–79.40	90.10–91.50	78.10–90.07
	6–<7 y	77.10–78.90	89.10–90.42	77.40–79.40	90.60–92.00	78.40–90.70
MCH (pg)	3–<6 y	24.80–25.50	29.10–29.60	24.90–25.80	29.40–29.80	25.30–29.50
	6–<7 y	25.20–25.90	29.40–29.80	25.40–26.04	29.70–30.30	25.70–29.80
MCHC (g/L)	3–<4 y	329.00–332.00	354.00–357.00	326.00–330.00	353.00–356.00	330.00–354.00
	4–<7 y	312.20–317.00	345.00–349.00	310.00–315.00	343.00–347.00	314.00–346.00
RDW–CV (%)	3–<4 y	11.60–11.80	13.70–14.11	11.40–11.60	13.60–14.20	11.60–14.00
	4–<7 y	11.60–11.80	13.70–14.10	11.50–11.70	13.50–14.00	11.70–13.80
MPV (fL)	5–<7 y	8.00–8.40	11.30–11.80	7.90–8.30	11.20–11.90	8.20–11.50
PCT (%)	5–<7 y	0.22–0.24	0.43–0.46	0.21–0.23	0.42–0.47	0.22–0.45
P–LCR (%)	3–<4 y	8.62–10.60	30.40–34.80	9.00–10.70	29.90–35.80	9.70–31.94
	4–<6 y	11.22–13.40	34.70–38.90	11.20–13.10	34.20–39.10	12.44–36.30
	6–<7 y	12.41–14.60	36.00–41.46	12.26–14.30	35.12–41.24	13.53–37.60

/: Lower limit value is not required.
BA, basophil count; BA%,basophil percentage; EO, eosinophil count; EO%, eosinophil percentage; Hb, hemoglobin; HCT, hematocrit; LYM, lymphocyte count; LYM%, lymphocyte percentage; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MONO, monocyte count; MONO%, monocyte percentage; MPV, mean platelet volume; NEUT, neutrophil count; NEUT%, neutrophil percentage; P-LCR, platelet large cell ratio; PCT, plateletcrit; PLT, platelet count; RBC, red blood cell count; RDW-CV, coefficient of variation of RBC distribution width; RDW-SD, standard deviation of RBC distribution width; WBC, white blood cell count.

was influenced by experimental platform (e.g. instrument, calibration, reagent lot variations). To eliminate this effect, biannual precision calibration was performed on all blood cell analyzers in our laboratory. All CBC items underwent a biannual interlaboratory quality evaluation and was closely monitored during daily analysis processusing three levels (high, medium, and low) of whole blood control material. However, due to lack of the detail of instrument, calibration, and reagent lot used by other labs, we do not have relevant discussions on these areas.

5. Conclusion

This study on comprehensive establishment of RIs for 23 capillary CBC parameters based on a larger population revealed distinct sex and age variations in the blood system among preschoolers within this developed region in Southeast China, demonstrated the importance of establishing sex- and age-specific RIs for each region, and underscored the necessity of continuous adjustment of clinical Rl basing on statistical rules and clinical response.

Ethics declarations

This study was reviewed and approved by the Ethics Committee of Fujian Maternity and Child Health Hospital(Approval No. 2023KY197), and informed consent was not required because this study was a retrospective analysis of the CBC data of healthy children obtained during the annual physical examination.

Table 4
95 % Rls and 90 % Cls for age and sex for all parameters.

Parameters	Age	RI	Lower 90 % CI	Upper 90 % CI
WBC ($\times 10^9$/L)	3–<7 y	5.13–12.54	5.09–5.16	12.47–12.60
NEUT ($\times 10^9$/L)	3–<4 y	1.60–6.22	1.58–1.62	6.01–6.39
	4–<7 y	1.87–7.96	1.85–1.88	7.87–8.05
NEUT (%)	3–<4 y	25.20–59.13	24.90–25.50	58.40–60.00
	4–<5 y	28.74–66.60	28.10–29.40	65.90–67.20
	5–<7 y	31.40–68.19	31.10–31.70	67.70–68.70
LYM ($\times 10^9$/L)	3–<4 y	2.33–6.11	2.28–2.36	6.04–6.21
	4–<6 y	2.10–5.28	2.08–2.13	5.23–5.32
	6–<7 y	1.98–4.95	1.95–2.03	4.89–5.01
LYM (%)	3–<4 y	30.70–65.80	29.80–31.60	65.40–66.20
	4–<5 y	24.10–61.20	23.50–24.90	60.80–61.60
	5–<7 y	22.80–58.90	22.50–23.20	58.50–59.20
MONO ($\times 10^9$/L)	3–<7 y	0.27–0.86^{M}	0.27–0.28	0.85–0.87
		0.26–0.80^{F}	0.26–0.26	0.79–0.81
MONO (%)	3–<7 y	3.80–9.50	3.80–3.80	9.40–9.60
EO ($\times 10^9$/L)	3–<4 y	0.09–0.78^{M}	0.09–0.10	0.76–0.83
		0.07–0.66^{F}	0.07–0.08	0.63–0.68
	4–<6 y	0.07–0.77^{M}	0.07–0.08	0.76–0.79
		0.06–0.67^{F}	0.06–0.06	0.65–0.69
	6–<7 y	0.06–0.77	0.06–0.06	0.75–0.79
EO (%)	3–<4 y	1.10–8.60	1.00–1.10	8.50–8.70
	4–<7 y	0.80–8.50	0.80–0.90	8.40–8.60
BA ($\times 10^9$/L)	3–<4 y	0.00–0.05	/	0.05–0.05
	4–<7 y	0.00–0.07	/	0.07–0.07
BA (%)	3–<4 y	0.00–0.60	/	0.50–0.60
	4–<5 y	0.00–0.90	/	0.90–0.90
	5–<7 y	0.00–1.00^{M}	/	1.00–1.00
		0.00–0.90^{F}	/	0.90–0.90
RBC ($\times 10^{12}$/L)	3–<7 y	4.22–5.37	4.22–4.23	5.36–5.38
Hb (g/L)	3–<4 y	115.00–142.00	114.00–115.00	142.00–143.00
	4–<7 y	119.00–146.00	118.00–119.00	146.00–146.00
HCT (%)	3–<4 y	33.90–41.30	33.80–34.00	41.10–41.40
	4–<7 y	36.20–44.20	36.10–36.30	44.10–44.20
MCV (fL)	3–<4 y	73.30–84.10^{M}	73.10–73.80	83.80–84.30
		74.80–85.10^{F}	74.50–75.20	84.90–85.30
	4–<5 y	76.70–88.57^{M}	76.40–77.00	88.40–88.90
		77.60–90.00^{F}	77.20–78.00	89.80–90.50
	5–<6 y	77.30–89.10^{M}	77.20–77.50	88.80–89.20
		78.93–90.60^{F}	78.70–79.10	90.40–90.80
	6–<7 y	78.23–89.67^{M}	78.00–78.60	89.40–89.90
		78.40–91.20^{F}	78.20–78.90	90.90–91.30
MCH (pg)	3–<6 y	25.30–29.50	25.30–25.40	29.40–29.50
	6–<7 y	25.70–29.60^{M}	25.60–25.80	29.50–29.60
		25.80–29.90^{F}	25.70–25.90	29.80–30.10
MCHC (g/L)	3–<4 y	331.00–355.00^{M}	330.00–331.00	355.00–356.00
		328.00–354.00^{F}	327.00–329.00	354.00–355.00
	4–<7 y	314.00–346.00	313.00–314.00	346.00–346.00
RDW–CV (%)	3–<4 y	11.70–13.90^{M}	11.60–11.70	13.80–13.90
		11.52–13.90^{F}	11.50–11.60	13.80–14.00
	4–<7 y	11.80–13.80^{M}	11.70–11.80	13.80–13.90
		11.60–13.70^{F}	11.60–11.60	13.60–13.70
RDW–SD (fL)	3–<4 y	33.90–40.70	33.80–34.00	40.60–40.80
	4–<7 y	35.20–42.70	35.10–35.20	42.60–42.80
PLT ($\times 10^9$/L)	3–<4 y	196.00–418.80	191.00–198.00	411.00–425.00
	4–<7 y	225.25–470.00	224.00–227.00	468.00–474.00
MPV (fL)	3–<4 y	7.40–10.60	7.40–7.50	10.50–10.70
	4–<5 y	7.90–11.30	7.90–8.00	11.20–11.30
	5–<7 y	8.20–11.50	8.20–8.20	11.50–11.50
PCT (%)	3–<4y	0.18–0.36	0.18–0.18	0.35–0.36
	4–<5 y	0.21–0.44	0.21–0.22	0.43–0.44
	5–<7 y	0.23–0.44^{M}	0.22–0.23	0.44–0.45
		0.22–0.44^{F}	0.22–0.23	0.44–0.45
P–LCR (%)	3–<4 y	9.70–31.94	9.60–10.00	31.40–32.40
	4–<6 y	12.44–36.30	12.30–12.60	35.90–36.60
	6–<7 y	13.53–37.60	13.20–13.90	37.10–38.20

/: Lower limit value is not required.
BA, basophil count; BA%,basophil percentage; EO, eosinophil count; EO%, eosinophil percentage; F, females; Hb, hemoglobin; HCT, hematocrit; LYM, lymphocyte count; LYM%, lymphocyte percentage; M, males; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MONO, monocyte count; MONO%, monocyte percentage; MPV, mean platelet volume; NEUT,

neutrophil count; NEUT%, neutrophil percentage; P-LCR, platelet large cell ratio; PCT, plateletcrit; PLT, platelet count; RBC, red blood cell count; RDW-CV, coefficient of variation of RBC distribution width; RDW-SD, standard deviation of RBC distribution width; WBC, white blood cell count.

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Data availability statement

The original data presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

CRediT authorship contribution statement

Xiaosong Lin: Writing – original draft, Software, Data curation. **Ruiqiong Lin:** Methodology, Data curation. **Huachuan Lin:** Investigation. **Boqiu Zhang:** Investigation, Formal analysis. **Feng Cheng:** Writing – review & editing. **Yueqing Su:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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