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Research Article

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Laboratory Practice of Reference Intervals Modification for Children's Blood Cell Analysis in China

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Abstract

Background: *The unreliability of reference intervals (RIs) for children's blood cell analysis has led to an unnecessary effort in interpreting results. The Standard published in 2021 is expected to solve this problem in China but should be clinically evaluated before its application. In this study, we aim to analyse the advantages and disadvantages of the new reference intervals (RIs) and realize the optimization based on clinical communication with pediatricians.*

Methods: *Compared with the laboratory's original reference intervals (RIs), the RIs' numerical trends were mapped and analysed, and the data of the past seven years were retrospectively re-interpreted. Pediatricians were then consulted to discuss the data analyses.*

Results: *Basically, the new reference intervals (RIs) characterized with more detailed age stratification and two specimen types. The numerical range of some parameters was wider while some were unilaterally shifted. Retrospective analysis showed that the revised reference intervals (RIs) could correct previously abnormal results to the normal range in a large proportion. The recovery ratio of three lineage cells was white blood cells > red blood cells > platelets, and the ratio sorted by age is 28 days~1-year-old > 1~13years old > 13~18 years old. The leukocyte recovery ratio of 28 days~1-year was the largest, approximately 55% to 83%. Pediatricians recognized the value of the new reference intervals (RIs). The only exception is that the platelets' reference intervals (RIs) were too broad, recommending maintaining the original RI. The missing 0~28-day's reference intervals (RIs) were recommended to be supplemented with other reference books.*

Conclusions: *The new reference intervals (RIs) were optimized and, combined with clinical feedback, produced new reference intervals (RIs) derived from accumulated experience, evolving a better set of RIs.*

Keywords: Children, Blood Cell Analysis, Reference Intervals, Modification, Practice

Introduction

Complete blood count (CBC) is the most routinely used laboratory test in clinical practice, supporting an accurate and up-to-date reflection of the dynamic physiological changes in the body [1]. Children's blood cell analysis associated with growth and development plays a vital role in the diagnosis, curative effect observation, and prognosis judgment and health assessment of pediatric clinical diseases. However, critical gaps continue to exist in pediatric haematology reference intervals (RIs) due to the difficulty in collecting reference individuals and apparent differences in age and gender. In China, it has been nine years since the Health Industry Standard of Reference Intervals of Children Blood Cell Analysis (WS/T 779-2021) (Standard for short as below) was issued, later than the Reference Intervals of Adult (WST 405-2012) [2,3]. The Standard was released on April 19, 2021, and hopefully adopted on October 1, 2021. Considering the reference intervals (RIs) from the Standard were established based on multi-centre and large-sample epidemiological research, which took a considerable cost and quite challenging implementation, it was more realistic and reliable for clinical laboratories to use the RIs than self-built ones [4-6].

Before releasing the Children's Standard, pediatricians expressed their concerns. As no reliable RIs were available, unnecessary complex interpretation of abnormal results needed, with some patients receiving unnecessary drug treatment and intervention. Modifying the intervals according to the newly released Standards is expected to solve this problem. However, the Standards also recommend that laboratories evaluate the interval before the application, primarily consulting clinicians. Therefore, compared with the intervals initially used in the laboratory, the variation trends and characteristics of the reference intervals (RIs) were analysed and data from the past seven years re-evaluated. On this basis, clinical communication with paediatricians is undertaken to evaluate the value and inadequacy of the new reference intervals (RIs), leading to optimized reference intervals (RIs) based on clinical recommendations.

Material

Description of Specimen

In this retrospective study, the children's CBC report in the Laboratory Information System (LIS) database of the First Affiliated Hospital of Fourth Military Medical University screened from January 2015 to December 2021. Over the past seven years, sample requests came from the following departments: paediatrics (32.1%), emergency department (6.3%), haematology (3.8%), internal medicine (24.6%), surgery (21.8%), and other (11.2%). Among the abnormal blood results, 53.0% of children diagnosed with leukocyte-related diseases, such as infection, inflammation, and leukaemia. 2.1% diagnosed with red blood cell (RBC)-related diseases, such as anaemia and polycythaemia, and 1.1% diagnosed with platelet-related diseases. All data were anonymous, and the local Institutional Review Board approved the study.

Description of Reference Intervals (RIs)

The study initially used some RIs from the Chinese National Guide to Clinical Laboratory Procedures (third Edition) after consultation with paediatricians on October 30, 2014 [7]. The reference intervals (RIs) defined age stratification approximately for four levels; 0~28 days old, 28 days~1-year-old, 1~14 years old and 14~18 years old. Since the last age level of 14~18 years old is impinging on adulthood, the reference intervals (RIs) have adopted values from the Adult Standard [3]. The other three age groups provided incomplete data for the 18 parameters of blood cell analysis, with missing RIs borrowed from the closest age-stratified reference intervals (RIs) Table 1. The main subject of the modified reference intervals (RIs) for modification intended to use the latest published Standard Table 2 [2].

Table 1: The Reference Intervals initially used for Children's CBC in our Laboratory

No.	Parameter	Unit	0~28ds	28ds~1y	1y~14ys	14~18ys[a]	
						Male	Female
1	WBC#	$\times10^9$/L	20	11 ~ 12	8 ~ 10	3.5 ~ 9.5	
2	Neut#	$\times10^9$/L	→[b]	→	→	1.8 ~ 6.3	
3	Lymph#	$\times10^9$/L	→	→	→	1.1 ~ 3.2	
4	Mono#	$\times10^9$/L	→	→	→	0.1 ~ 0.6	
5	Eos#	$\times10^9$/L	→	→	→	0.02 ~ 0.52	
6	Baso#	$\times10^9$/L	→	→	→	0 ~ 0.06	
7	Neut%	%	31 ~ 40		50 ~ 70	40 ~ 75	
8	Lymph%	%	40 ~ 60		20 ~ 40	20 ~ 50	
9	Mono%	%	12 (2 ~ 7ds)	1 ~ 8		3 ~ 10	
10	Eos%	%	→	→	5 ~ 50	0.4 ~ 8	
11	Baso%	%	→	→	0 ~ 7	0 ~ 1	
12	RBC	$\times10^{12}$/L	5.2 ~ 6.4	4.0 ~ 4.3	4.0 ~ 4.5	4.3 ~ 5.8	3.8 ~ 5.1
13	Hb	g/L	180 ~ 190	110 ~ 120	120 ~ 140	130 ~ 175	115 ~ 150
14	Hct	%	→			40 ~ 50	35 ~ 45
15	MCV	fl	→			82 ~ 100	
16	MCH	pg	→			27 ~ 34	
17	MCHC	g/L	→			326 ~ 354	
18	PLT	$\times10^9$/L	100 ~ 300			125 ~ 350	

a: This age group actually uses the RIs for adults

b: Arrows indicate that this age group borrows the RIs from the next age group

Table 2: After Communication with the Paediatrics, the Final Reference Intervals confirmed for Children's Blood Cell Analysis

No.	Parameter	Unit	RIs		
			Age groups	venous blood	capillary blood
1	WBC	$\times 10^9$/L	0~28 ds	15 ~ 20[a]	
			28 ds ~ <6 ms	4.3 ~ 14.2	5.6 ~ 14.5
			6 ms ~ <1 y	4.8 ~ 14.6	5.0 ~ 14.2
			1 y ~ <2 ys	5.1 ~ 14.1	5.5 ~ 13.6
			2 ~ <6 ys	4.4 ~ 11.9	4.9 ~ 12.7
			6 ~ <13 ys	4.3 ~ 11.3	4.6 ~ 11.9
			13 ~ 18 ys	4.1 ~ 11.0	4.6 ~ 11.3
2	Neut#	$\times 10^9$/L	0 d ~ <6 ms	0.6 ~ 7.5b	0.6 ~ 7.1[b]
			6 ms ~ <1 y	0.8 ~ 6.4	0.8 ~ 6.1
			1 y ~ <2 ys	0.8 ~ 5.8	0.9 ~ 5.5
			2 ys ~ <6 ys	1.2 ~ 7.0	1.3 ~ 6.7
			6 ~ <13 ys	1.6 ~ 7.8	1.7 ~ 7.4
			13 ~ 18 ys	1.8 ~ 8.3	1.9 ~ 7.9
3	Lymph#	$\times 10^9$/L	0 d ~ <6 ms	2.4 ~ 9.5[b]	3.2 ~ 10.7[b]
			6 ms ~ <1 y	2.5 ~ 9.0	2.8 ~ 10.0
			1 y ~ <2 ys	2.4 ~ 8.7	2.7 ~ 9.1
			2 ~ <6 ys	1.8 ~ 6.3	2.0 ~ 6.5
			6 ~ <13 ys	1.5 ~ 4.6	1.7 ~ 4.7
			13 ~ 18 ys	1.2 ~ 3.8	1.5 ~ 4.2
4	Mono#	$\times 10^9$/L	0 d ~ <6 ms	0.15 ~ 1.56[b]	0.25 ~ 1.89[b]
			6 ms ~ <1 y	0.17 ~ 1.06	0.15 ~ 1.24
			1 y ~ <2 ys	0.18 ~ 1.13	0.20 ~ 1.14
			2 ~ <6 ys	0.12 ~ 0.93	0.16 ~ 0.92
			6 ~ <13 ys	0.13 ~ 0.76	0.15 ~ 0.86
			13 ~ 18 ys	0.14 ~ 0.74	0.15 ~ 0.89
5	Eos#	$\times 10^9$/L	0 d~ <1 y	0.07 ~ 1.02[b]	0.06 ~ 1.22[b]
			1y ~ 18 ys	0.00 ~ 0.68	0.04 ~ 0.74
6	Baso#	$\times 10^9$/L	0 d ~ <2 ys	0.00 ~ 0.10[b]	0.00 ~ 0.14[b]
			2 ~ 18 ys	0.00 ~ 0.07	0.00 ~ 0.10
7	Neut%	%	0~28 ds	31 ~ 40[c]	
			28 ds ~ <6 ms	7 ~ 56	7 ~ 51
			6 ms ~ <1 y	9 ~ 57	9 ~ 53
			1 y ~ <2 ys	13 ~ 55	13 ~ 54
			2 ~ <6 ys	22 ~ 65	23 ~ 64
			6 ~ <13 ys	31 ~ 70	32 ~ 71
			13 ~ 18 ys	37 ~ 77	33 ~ 74
8	Lymph%	%	0~28 ds	40 ~ 60[c]	
			28 ds ~ <6 ms	26 ~ 83	34 ~ 81
			6 ms ~ <1 y	31 ~ 81	37 ~ 82
			1 y ~ <2 ys	33 ~ 77	35 ~ 76

			2 ~ <6 ys	23 ~ 69	26 ~ 67
			6 ~ <13 ys	23 ~ 59	22 ~ 57
			13 ~ 18 ys	17 ~ 54	20 ~ 54
9	Mono%	%	0~7 ds	12[cd]	
			7~28 ds	1 ~ 8[c]	
			28 ds ~ <6 ms	3 ~ 16	3 ~ 18
			6 ms ~ <2 ys	2 ~ 13	2 ~ 14
			2 ~ 18 ys	2 ~ 11	
10	Eos%	%	0~28 ds	0.5 ~ 5	
			28 ds ~ <1 y	1 ~ 10	0.8 ~ 11
			1 y ~ 18 ys	0 ~ 9	0.5 ~ 9
11	Baso%	%	0~28 ds	0 ~ 0.75[c]	
			28 ds ~ 18 ys	0 ~ 1[c]	
12	RBC	$\times 10^{12}$/L	0~28 ds	5.2 ~ 6.4[c]	
			28 ds ~ <6 ms	3.3 ~ 5.2	3.5 ~ 5.6
			6 ms ~ <6 ys	4.0 ~ 5.5	4.1 ~ 5.5
			6 ~ <13 ys	4.2 ~ 5.7	4.3 ~ 5.7
			13 ~ 18 ys	4.5 ~ 5.9 (m)	4.5 ~ 6.2 (m)
				4.1 ~ 5.3 (f)	4.1 ~ 5.7 (f)
13	Hb	g/L	0~28 ds	180 ~ 190[c]	
			28 ds ~ <6 ms	97 ~ 183	99 ~ 196
			6 ms ~ <1 y	97 ~ 141	103 ~ 138
			1 y ~ <2 ys	107 ~ 141	104 ~ 143
			2 ~ <6 ys	112 ~ 149	115 ~ 150
			6 ~ <13 ys	118 ~ 156	121 ~ 158
			13 ~ 18 ys	129 ~ 172 (m)	131 ~ 179 (m)
				114 ~ 154 (f)	114 ~ 159 (f)
14	Hct	%	0~1 d	48 ~ 69[ce]	
			2 d	48 ~ 75[c]	
			3 d	44 ~ 72[c]	
			3 ~28 ds	28 ~ 42[c]	
			28 ds ~ <6 ms	28 ~ 52	29 ~ 57
			6 ms ~ <1 y	30 ~ 41	32 ~ 45
			1 y ~ <2 ys	32 ~ 42	32 ~ 43
			2 ~ <6 ys	34 ~ 43	35 ~ 45
			6 ~ <13 ys	36 ~ 46	37 ~ 47
			13 ~ 18 ys	39 ~ 51 (m)	39 ~ 53 (m)
				36 ~ 47 (f)	35 ~ 48 (f)
15	MCV	fl	0 d ~ <6 ms	73 ~ 104[b]	73 ~ 105[b]
			6 ms ~ <2 ys	72 ~ 86	71 ~ 86
			2 ~ <6 ys	76 ~ 88	
			6 ~ <13 ys	77 ~ 92	
			13 ~ 18 ys	80 ~ 100	80 ~ 98

16	MCH	pg	0 d ~ <6 ms	24 ~ 37[b]	
			6 ms ~ <6 ys	24 ~ 30	
			6 ~ 18 ys	25 ~ 34	26 ~ 34
17	MCHC	g/L	0d ~ <6 ms	309 ~ 363[b]	305 ~ 361[b]
			6 ms ~ 18 ys	310 ~ 355	309 ~ 359
18	PLT	$\times 10^9$/L	0 d ~ 18ys	100 ~ 300[f]	

a: Diagnostics, 9th Edition;
b: The RIs were borrowed from the closest age group 28 ds ~ <1 y, so the age groups were merged into 0 d ~ <1 y;
c: Paediatrics, 9th Edition;
d: The number of days here was relaxed from 2~7 to 0~7.
e: The number of days here was relaxed from 1 day to 0~1 day.
f: The PLT RIs here were not modified and still used the intervals from National Guide To Clinical Laboratory Procedures (3rd Edition).

Methods

The reference intervals (RIs) for laboratory test refers to the value distributed between the upper and the lower bound value usually derived from the 95% confidence interval for results from healthy individuals. Line segments were used to map the numeric range difference before and after the modifications, presenting reference intervals (RIs) in the same coordinate system for different age groups. In addition to age stratification, the RIs from the new Standard also consider specimen types, for example, venous and peripheral blood.

Furthermore, data of 18 children's blood cell analysis parameters in the past seven years were retrieved from Laboratory Information System (LIS). Python used to re-interpret the results using the reference intervals (RIs) from the new Standard. The typical result ratios of each parameter calculated separately according to the initially used and planned modified RIs. The recovery percentage (%) generated by the difference between the two ratios above. Excel was used for data presentation and graphing of each recovery percentage.

Results

Summary of Characteristics of the New Reference Intervals

More Detailed Age Stratification

Compared with the RIs before modification, the age stratification of the new reference intervals (RIs) is more detailed. Nine out of 18 parameters, including WBC, neutrophils (Neut#, Neut%), lymphocytes (Lymph#, Lymph%), monocytes (Mono#), Hb, HCT and platelets (PLT), had six age groups with the 28th day, the sixth month, the first, second, sixth, 13th and 18th year as the cut-off points respectively (missing 0~28 days of neonates) Figure 1A. Platelet (PLT) used twelve instead of 13-years-old as a cut-off point. The other parameters had less than six age groups because the adjacent age groups merged due to the similar boundaries for the RIs Figures 1B and Figure 1C.

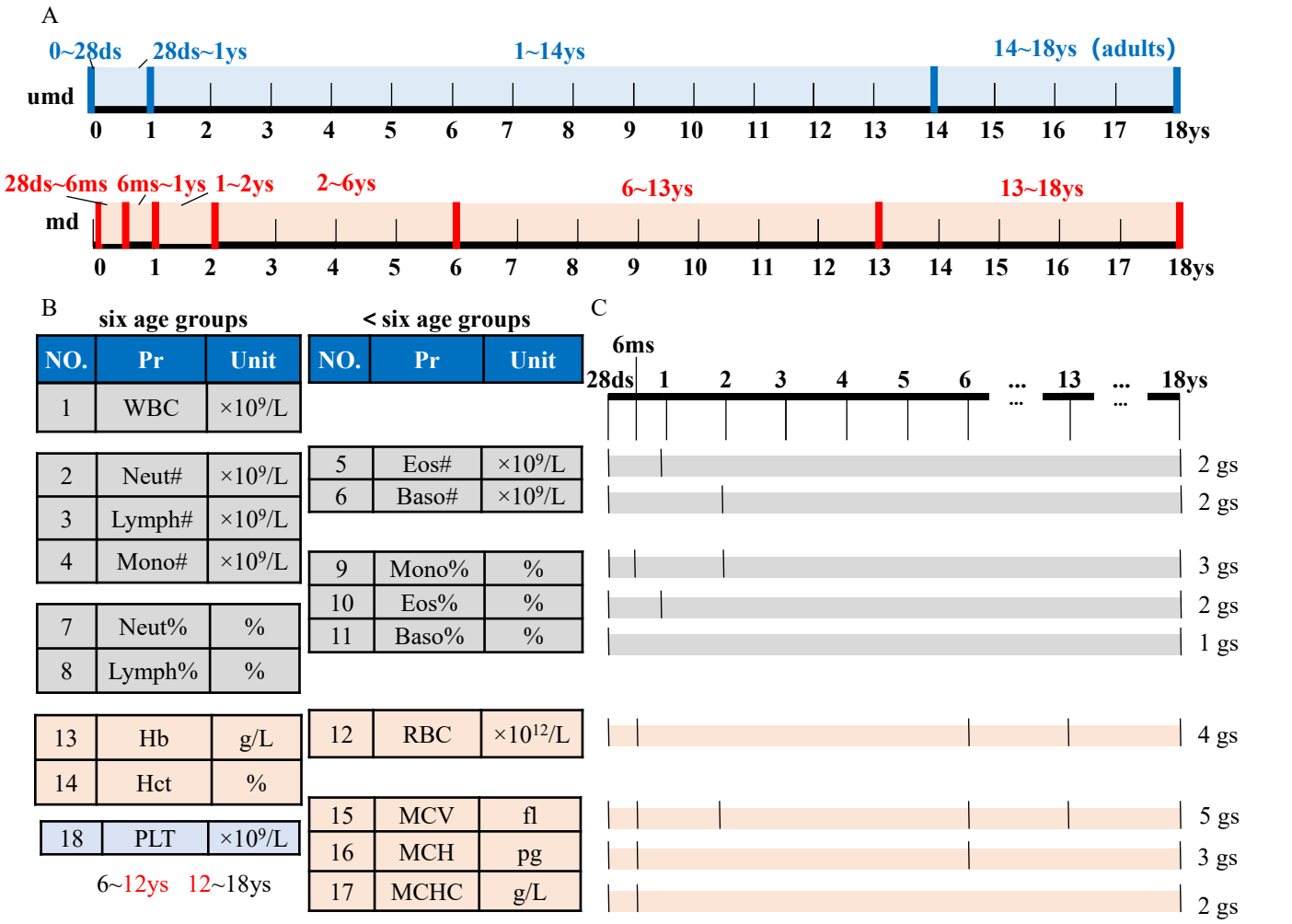


Figure 1: Age stratification of RIs for CBC parameters. (A), Age-stratified comparison of modified(red) and unmodified(blue) RIs. (B), Parametres of six age groups were shown in the right column and the parametres < six groups were shown in the left column. White blood cells, red blood cells and platelets were showed in grey, red and blue background respectively. (C), Age stratification of the parametres < 6 gs represented by line segments corresponding to the left column of B. Abbreviations: unmodified, umd; modified, md; ds, days; ms, months; ys, years; gs, groups.

Wider Numerical Range

The more detailed new reference intervals (RIs) mapped to the original intervals within four age groups (excluding 0~28 days). For the same age groups, the length of the line segment represents the width for different reference intervals (RIs) numerical ranges. First, in the leukocyte-related parameters, the interval range for WBC, Neut%, Lymph% includes the original reference intervals (RIs) in the 28 days ~ 1-year-old group. In the 1~13 years old group, the entire reference intervals (RIs) ranges for Neut% and Lymph% expands to the right (both of the upper and lower bound increased) and left (both of the upper and lower bound decreased). However, the known crossover of Neut% and Lymph% of 4~6 years old children are not reflected, which was covered in the 1~13 years old age group [8]. The original reference intervals (RIs) for Eos% are too broad, with the upper bound 50% higher and decreasing by approximately 11% after the correction. Second, the RBC parameters' upper bound for Hb and Hct shows a marked difference at the six-month-old cut-off, which is significantly lower in the second half-year than in the first half-year. Hb decreased from 180~190g/L to about 140g/L, and Hct decreased from 52~57% to 41~45%. Additionally, RBC, Hb, and Hct differentiated between males and females in the 13~ 18-age group, and the range values were broader for venous blood than for peripheral blood. Third, the interval Platelet (PLT) ranges are wider and shifted to the right, with the lower bound increasing and the upper bound increasing more significantly. Particularly in the 28 days~1-year-old and 1~13 years old age groups, the upper bound is as high as 600~650×10⁹/L and 450~520×10⁹/L, much higher than the previous 100~300×10⁹/L Figure 2.

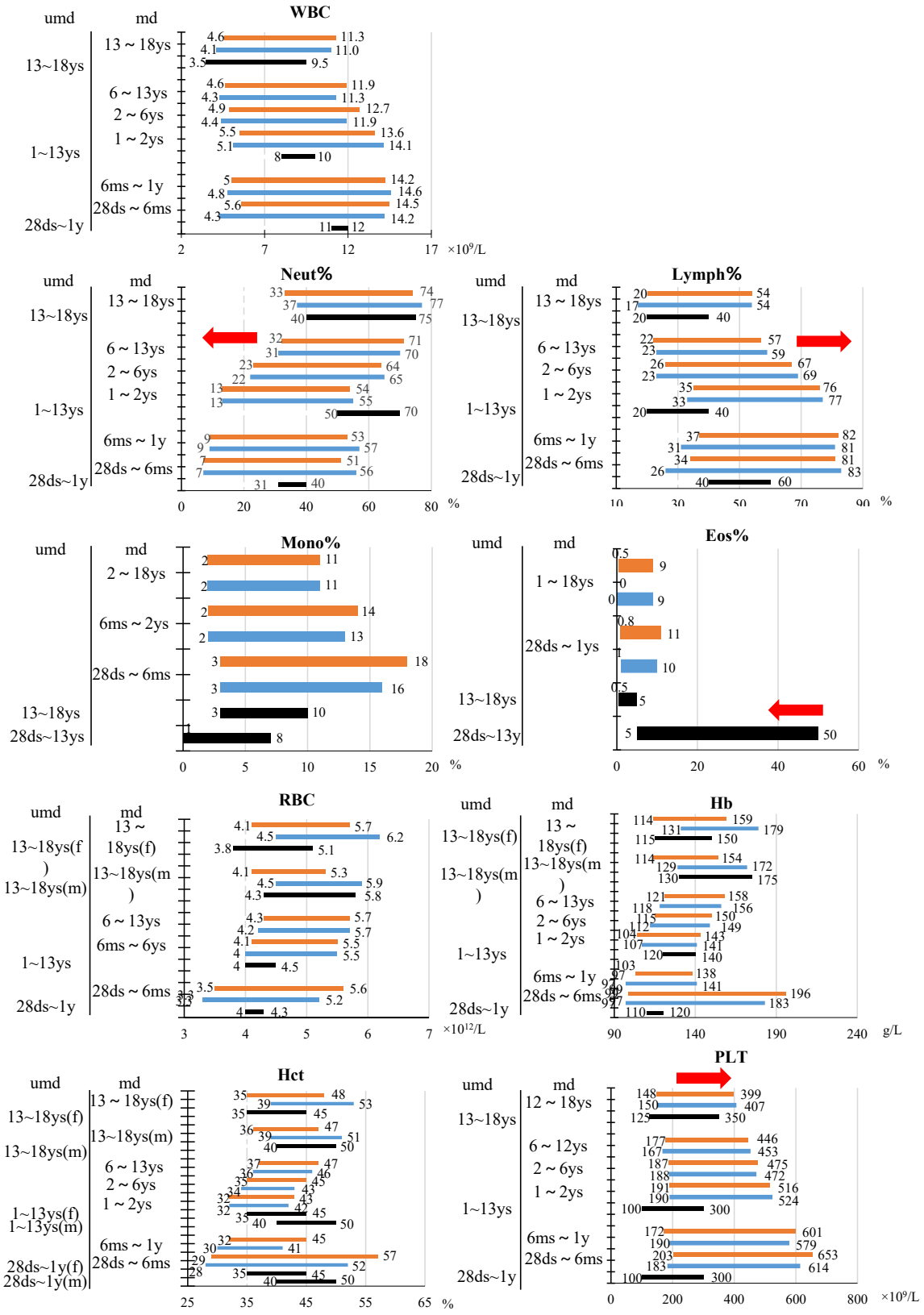


Figure 2: Reference Intervals numerical range of some key CBC parameters. Line segment colour of modified Reference Intervals was shown in blue (venous blood) and orange (capillary blood), compared with the unmodified Reference Intervals in black. The red arrows highlighted the overall shifting trend of Neut%, Lymph%, Eos% and Platelet (PLT)

Retrospective Analysis Based on Modified Reference Intervals Characterization

The Laboratory Information System derived children's complete blood count data for the past seven years (2015-2021) were re-analysed using the newly derived RIs. The results showed that the number of specimens increased with age in the six groups and more significantly over two years old Figure 3A. Few new-borns from 0 to 28 days have blood cell analysis, with approximately 200 patients in seven years Figure 3B. As expected, paediatrics performed the most children's CBC, accounting for about 1/3, followed by extra cardiac, skin, and emergency departments, with orthopaedic departments accounting for more than 5% Figure 3C. In the distribution of paediatrics diseases, the diagnoses where leukocyte parameters play an essential role account for approximately 53%, searched by keywords such as "inflammation", "infection", and "leukaemia". RBC-related diseases (searched with "Anaemia" and "polycythaemia") and PLT related diseases (searched with "platelets") accounted for about 2.1% and 1.1%, respectively Figure 3D.

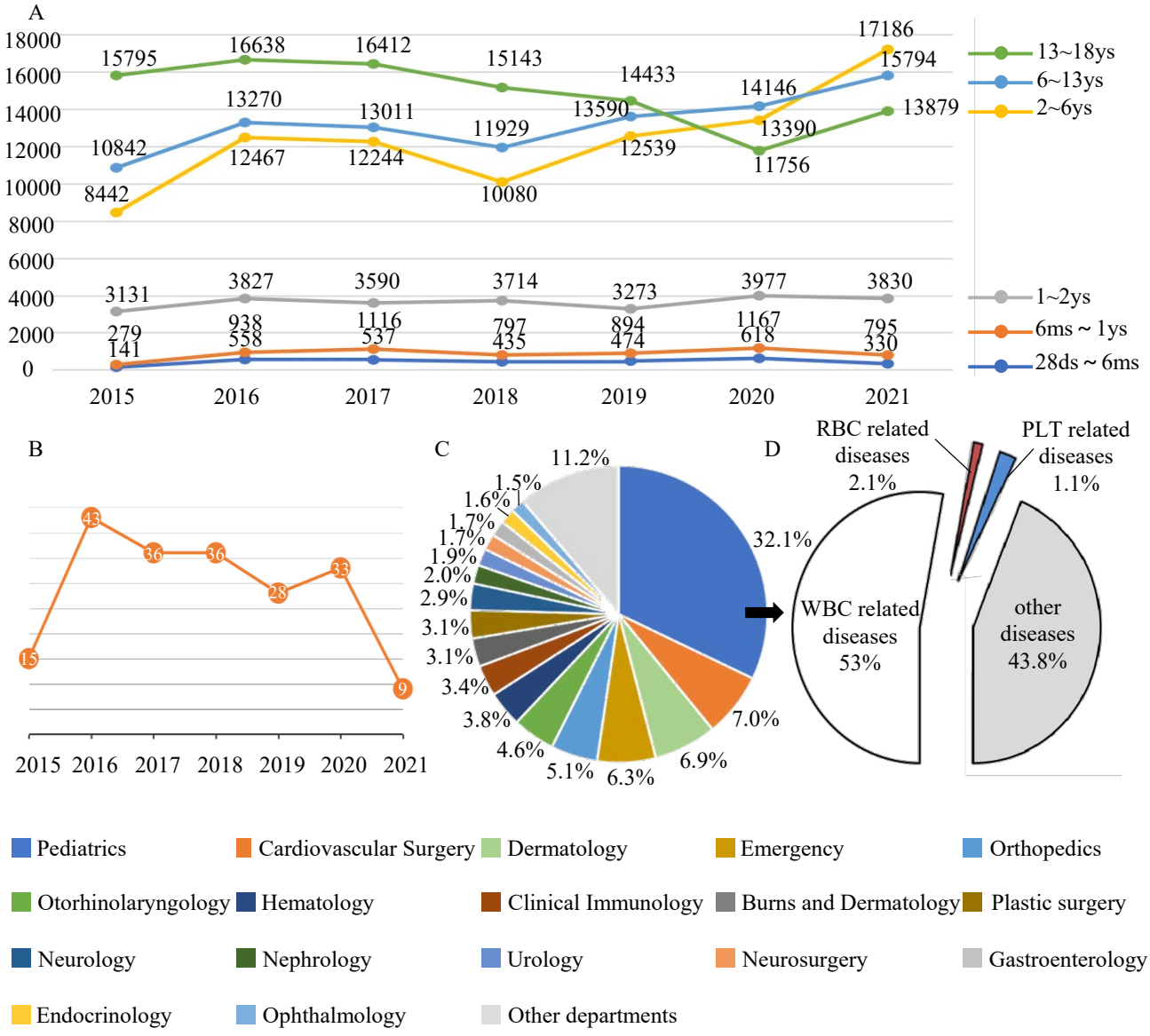
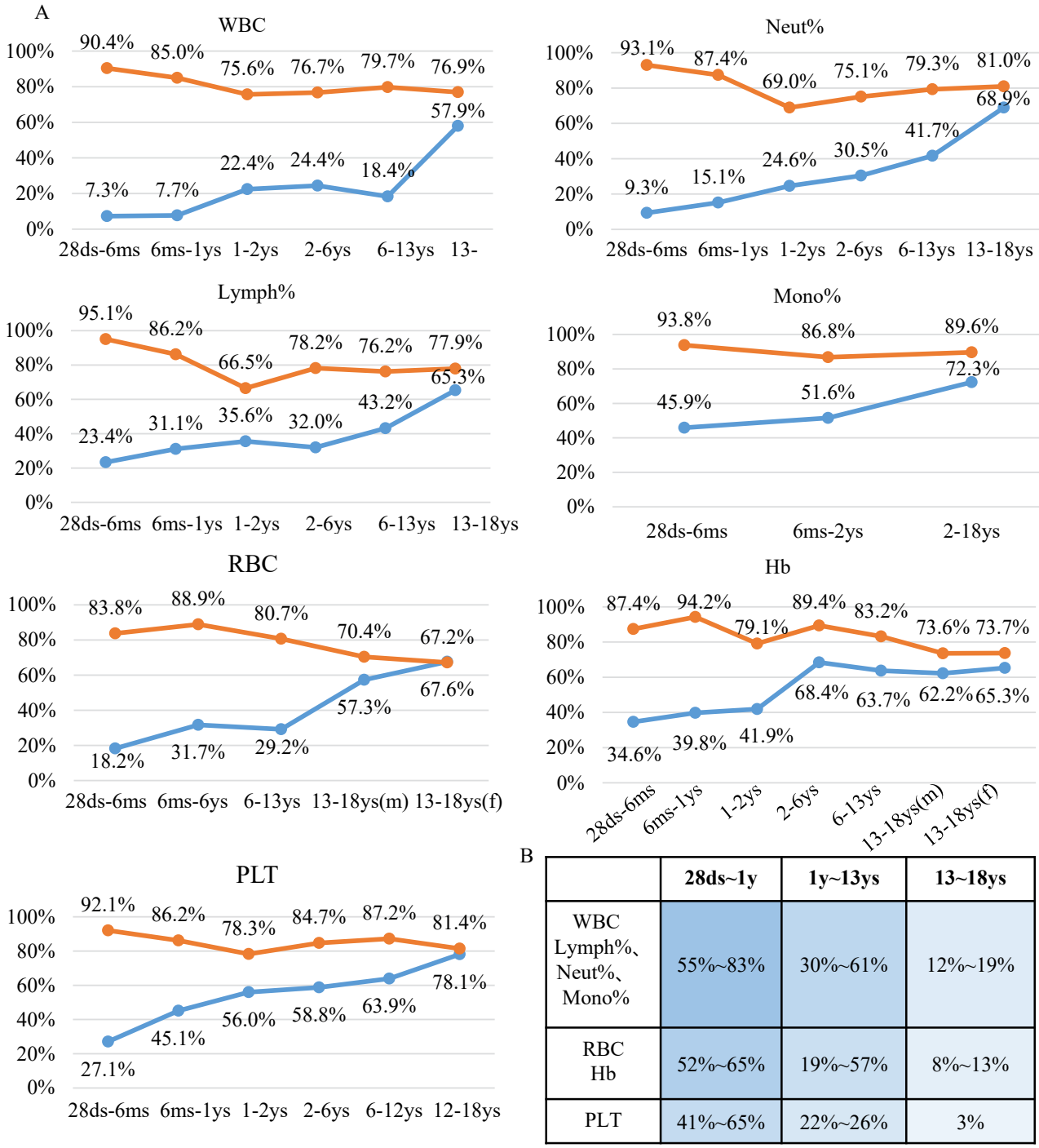


Figure 3: Characterization of Retrospective Analysis of Children Complete Blood Count from 2015 to 2021. A: Complete Blood Count Specimen Number for six age groups of 28 days~18 years. B: Complete Blood Count Specimen Number for New-Borns of 0~28 days C: Complete Blood Count Order Proportion of Different Departments D: Distribution of Paediatric Diseases related with Complete Blood Count

Recovery Percentage of Each Parameter

Using the original and the new reference intervals (RIs) to analyse the data for 317,407 samples over the past seven years, the RIs from the Standard corrected the abnormal results to normal in notably large proportions Figure 4A. The recovery ratio of trilineage cell parameters was leukocyte > erythrocyte > PLT. The recovery ratio stratified as age was 28 days ~1 year > 1~13 years old > 13~18 years old. The leukocyte recovery ratio of 28 days~1 year was the largest, approximately 55% to 83% Figure 4B. Therefore, if the reference intervals (RIs) were modified according to the Standards, a significant load of abnormal report interpretation can be avoided, which significantly meets clinical expectations.



B

	28ds~1y	1y~13ys	13~18ys
WBC Lymph%、Neut%、Mono%	55%~83%	30%~61%	12%~19%
RBC Hb	52%~65%	19%~57%	8%~13%
PLT	41%~65%	22%~26%	3%

Figure 4: Recovery percentage of Complete Blood Count parameters. A: For each parameter, the normal result ratios of six age groups were shown in blue by initially used Reference Intervals and in red by the Reference Intervals form the Standard. B: Recovery percentage of trilineage cells was stratified by correction degree indicated by colour shading

Discussion with Paediatrics and Feedback

The data analysis was followed up with communication with clinical paediatricians. After understanding the characteristics of the new reference intervals (RIs), Pediatricians recognized their value but anticipated several issues that needed to be resolved.

The First considering is whether the new reference intervals (RIs) are worth being adopted and needed to be verified. According to the requirements of the Standard, if new reference intervals (RIs) were to be adopted, a small sample size (20 reference individuals) could be used for verification, or it could be implemented with clinical agreements. Clinicians are particularly concerned about whether other similar hospitals, especially the leading children's specialty hospitals, have already adopted and verified the latest reference intervals (RIs). After contacting the laboratory departments of some major hospitals, the progress of adopting the latest RI values is inconsistent. Some laboratories that participated in establishing the Standard, such as West China Second Hospital of Sichuan University and Xian Children's Hospital, have adopted it without verification. Other hospitals, such as Shaanxi Provincial People's Hospital, Shandong Provincial Hospital Affiliated with Shandong First Medical University and the First Hospital of Jilin University, are still in the preparatory stage, seeking clinical opinions or undergoing verification. In Peking Union Medical College Hospital, the First and the Second Affiliated Hospital of Xian Jiao tong University, some pediatricians did not approve of the Standard and have not adopted it. After considering the different approaches of national counterparts, the pediatrician in our hospital decided to adopt the new reference intervals (RIs) after the following problems were overcome, and verification was unnecessary.

Secondly, the reference intervals (RIs) for new-borns from 0~28 days were not provided in the Standard, mainly because the data for very young reference individuals was challenging to collect. However, considering Laboratory Information System must cover all age stages and start from 0 days, the reference intervals (RIs) for this age group could be supplemented by referring to the authoritative textbook of Paediatrics (9th Edition) [8,9]. As the neonatal WBC in this reference is a single point value of 20×10^9/L, it does not meet the interval requirements. The $15\sim20\times10^9$/L in the textbook of Diagnostics (9th Edition) was used instead [10]. The reference intervals (RIs) not provided by these two authoritative references were derived from the next age group of 28 days to 1 year old. Consequently, the two adjacent age groups were merged into 0 days to 1 year old. Undoubtedly, such a strategy is not perfect. For example, previous studies have confirmed that RDW RIs for neonates are higher than for older children and adults, which could not be embedded within the latest RI values for the 0 days to 1-year-old age group [11].

Besides, the minimum unit of age stratification in the new reference intervals (RIs) is days, so it is necessary to know whether Laboratory Information System (LIS) could effectively extract patients' age information according to days and map it to the six age groups. Previously, the Hospital Information System (HIS) collected outpatients' age information through registered identity documents (ID) and converted the age less than 1-year-old to 0-year-old. Consequently, the ages for new-borns cannot be effectively grouped into 0~28 days, 28 days~6 months, and 6 months~1 year. After consulting with the Information Department, they guaranteed that age data for patients under 1-year-old would not be converted in advance by HIS, but communicated to laboratory information system in days. Additionally, the blood collection centre ensured that the blood specimen types of children noted as venous or peripheral blood.

Moreover, Pediatricians believe that the RI values for Platelet data are too wide in the Standard and may easily lead to missed diagnoses of thrombocytosis caused by myeloproliferative or acute infectious diseases. According to the over-wide reference intervals (RIs), typical results still required unnecessary interpretation work for patients and were equally detrimental to clinical diagnoses. Although data showed that a considerable proportion of children younger than six months had PLT at high levels, paediatricians still recommended keeping the original range of $(100\sim300)\times10^9$/L for all 0~18 years old [12].

Finally, the reference intervals (RIs) of the Standard were supplemented and optimized using clinical suggestions and revised with clinical approval. The modified reference intervals (RIs) are summarized in Table 2.

Abbreviations

CBC: Complete Blood Count
RIs: Reference Intervals
WBC: White Blood Cell (count)
Neut: Neutrophils
Lymph: Lymphocyte
Mono: Monocyte
Eos: Eosinophil
Baso: Basophils
RBC: Red Blood Cell (count)
Hb: Hemoglobin
Hct: Red Blood Cell Specific Volume
MCV: Mean Corpusular Volume
MCH: Mean Corpsular Hemoglobin
MCHC: Mean Corpuscular Hemoglobin Concentration
PLT: Platelet
LIS: Laboratory Information System
HIS: Hospital Information System
ID: Identity Document
RDW: Red Blood Cell Distribution Width

Conclusions

In China and worldwide, establishing pediatric reference intervals (RIs) for blood cell analysis is generally challenging due to the dynamic changes caused by physiological development and the ethical and practical difficulties of sample collection [13,14]. The long-term absence of nationally developed and harmonized reference intervals (RIs) limits their use when guiding clinical deci-

sion-making. The reference intervals (RIs) for pediatric complete blood count (CBC) values in China represent a critical gap [15]. Clinical laboratories have always expected to work with standardized and unified RIs, and the current study is a large-scale, multi-centre general screening approach in China. Twenty-two children's and comprehensive hospitals from 22 provinces (autonomous regions and municipalities) covering seven regions of East, North, Northeast, Northwest, South, Southwest, and Central China participated in the RIs development and validation. Finally, 6571 venous and 4995 peripheral blood samples selected for RIs verification. Through data analysis and communication with clinical departments, evolving the RI values based on the Standard will make blood cell analysis enable less challenging diagnoses of children's diseases and improve the quality of clinical services.

During the modification process, some problems require further investigation. First, consider that a medical laboratory modifies the reference intervals (RIs) following the Standard, it is then better for all sibling hospitals of the same system (such as several affiliated hospitals of a particular university) to co-operatively adopt the changes. Otherwise, data interpretation will be confusing and incongruent. Second, even when RIs based on national multi-centre participation and large sample sizes (as in this study), they are still imperfect, requiring further revision and optimization based on clinical suggestions. However, it is essential to note that clinical recommendations are somewhat subjective. Therefore, after using the revised reference intervals (RIs), laboratories and clinicians must review experiences and clinical issues, optimizing the reference intervals (RIs) step-wise and ensuring constant evolution. After all, factors such as possible heterogeneity of the reference population and statistical approaches will affect the reference intervals (RIs) accuracy during development [16,17].

Acknowledgments

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Ethics Statement

The local Institutional Review Board approved the study. The data are anonymous, and the requirement for informed consent was therefore waived.

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