Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Original Research

Comprehensive hematological reference intervals in a healthy adult male population

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Received January 08, 2020; **Accepted** May 5, 2020; **Published** May 15, 2020

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Doi: http://dx.doi.org/10.14715/cmb/2020.66.2.16

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Abstract: Reference intervals (RIs) are important tools for improving medical decision-making. Hematology reference values can be influenced by important covariates such as genetic and environmental factors, rendering it essential to define RIs for specific populations. Therefore, we aimed to establish accurate and robust RIs for hematological markers in a healthy adult male Iranian population. This cross-sectional study was conducted in a population of 723 males aged 20-60 years old. Hematological parameters were routinely measured using a Sysmex auto analyser system (KX-21 N). The quality of assays was monitored using commercial quality control samples**.** The nonparametric rank method, as recommended by the Clinical and Laboratory Standards Institute (CLSI) guidelines, was used to calculate the 2.5th and 97.5th percentiles as the lower and upper reference limits, respectively. Of the 12 hematological parameters assessed, only mean platelet volume (MPV) demonstrated significant age-specific differences, requiring two partitions from 20 to 35 years (8.7-12.2 fL) and 35 to 65 years (8.5-11.5 fL). The remaining hematological parameters (e.g. leukocyte, erythrocyte, and platelet parameters) could be defined by one age range. This study established RIs for 12 routinely used hematological parameters in a healthy male population living in the northeastern region of Iran. Established RIs differed from those previously reported by other cohorts, highlighting the importance of population-specific RIs.

Key words: Reference interval; Hematological parameters**;** CLSI guidelines.

Introduction

Reference intervals (RIs) for laboratory tests are important tools to more accurately evaluate disease, improve medical decision-making (1, 2) and interpret laboratory and clinical findings. Laboratory findings, including hematological parameters, require accurate and robust RIs for clinical test interpretation (3). RIs are typically established by assessing a large population of healthy individuals with similar characteristics (e.g. age, sex, ethnicity) (4). They are commonly defined as the central 95% of test results with lower and upper limits corresponding to the 2.5th and 97.5th percentiles, respectively (3). Accurate and population-specific RIs can lead to better treatment for patients as well as serve as an important tool for disease diagnosis and monitoring (5, 6).

Abnormal levels of several hematological parameters are good indicators of a wide array of clinical disorders. Several studies have reported a high white blood cell (WBC) count as a marker of inflammation (7). It has also been associated with insulin resistance (7), rheumatoid arthritis, inflammatory bowel disease (IBD), and acute coronary syndrome (8). In addition to their important roles in the clinical diagnosis of bleeding disorders and infectious diseases, hematological parameters have also been associated with other metabolic and neurological disorders. In the case of platelet (PLT) count, there is a known relationship between higher PLT counts and cardiovascular outcomes (9). Platelet distri-

bution width (PDW) has also recently been the center of research regarding cardiovascular diseases (10). In addition, mean platelet volume (MPV) has been shown to correlate with a high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level in diseases such as ankylosing spondylitis (11). Studies have also reported that varying levels of hemoglobin (HGB) are associated with a higher risk of Parkinson's Disease and cyanotic nephropathy (12). Finally, red blood cell distribution width (RDW) may be a potential risk indicator of Sjögren's syndrome (11), lung carcinoma (13) and a sign for iron deficiency (14). Thus, hematological parameters have various clinical indications, assisting clinical decision-making in various areas.

Hematological parameters and their associated RIs can be influenced by many factors, including age, sex, ethnicity, and environment. The differential RIs established by cohorts globally make it essential to define RIs for a specific population. Accordingly, the Clinical and Laboratory Standards Institute (CLSI) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC C28-A3) have provided guidelines designed for defining, verifying, and establishing RIs in a systemic manner (15-17). In many countries, such as Iran, the results of laboratory tests for hematological parameters are usually compared with RIs obtained from European or American populations (18, 19). Given the differences between populations such as genetic variation, nutritional status, altitude, lifestyle and alcohol consumption, RIs for this population are urgently needed (4, 20).To address this gap and ensure reliable hematological RIs, we aimed to establish RIs for 12 key hematological parameters in a healthy Iranian adult population.

Materials and Methods

Study population

This study was conducted in a population of 723 males aged 20-60 years old. These subjects were employees of Shahid Hasheminejad Gas Processing Company (S.G.P.C), Sarakhs, Iran. Sarakhs, a small town with a population of about 90000, is located in northeastern Iran. In this study, subjects with poorly controlled diabetes, severe hypotension, and overt signs/symptoms of CVD, hematology disorders, endocrine abnormalities and participants with hs-CRP ≥10 mg/L, with any weight control measures, iron supplementation and consumption of drugs related to metabolic, CVD and hematology disorders were excluded. Additionally, individuals who had a blood transfusion, phlebotomy and/or surgery in the 6 past months were also excluded. This study was approved by the Human Research Ethics Committee of Mashhad University of Medical Sciences (MUMS) and written informed consent was obtained from all participants.

Participant acquisition and sample analysis

All participants completed a questionnaire that collected demographic information and health history**.** Participants were instructed to fast for 12 hours before collection. After venipuncture, blood samples were centrifuged at 5000g for 15 minutes at 4°C. Hematological parameters were measured using the Sysmex auto analyser system (KX-21 N). The quality of assays was monitored using commercial control samples. Intra- and inter-assay coefficient of variation (CV) was 2% for WBC, RBC and MPV, 1% for HGB, HCT, MCV, MCH, MCHC, and RDW, and 4% for PLT and PDW.

Statistical analysis

The nonparametric rank method was used to calculate the 2.5th and 97.5th percentiles and associated 90% confidence intervals for each age partition. This method was used by the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) and recommended by the Clinical and Laboratory Standards Institute (CLSI) guideline version EP28-A3 (21). Significant age- and sex-specific partitions were determined by the Harris and Boyd method (22) and (23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(24)(23)(23)(23)(23) outliers were excluded using the Tukey method.

Results

Calculated hematological reference intervals (RIs) are provided in Table 1. Age-specific scatterplots of the reference value distributions for all 12 hematological parameters are shown in Figures 1-3. Regarding established RIs (Table 1), no age partitions were required except for MPV. Generally, reference values for WBC,

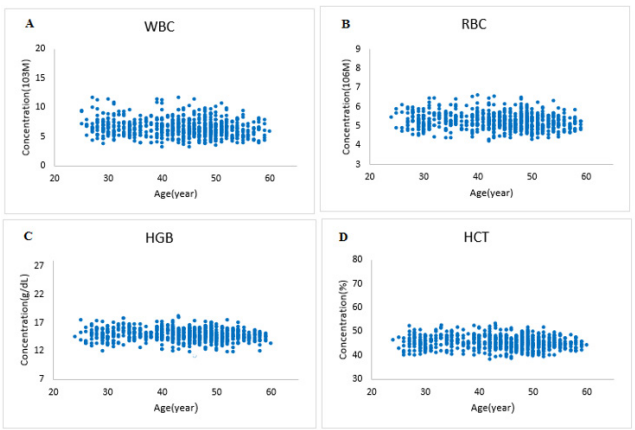

Figure 1. Scatterplot distributions for White Blood Cell (A), Red Blood Cell (B), Hemoglobin (C) and Hematocrit (D).

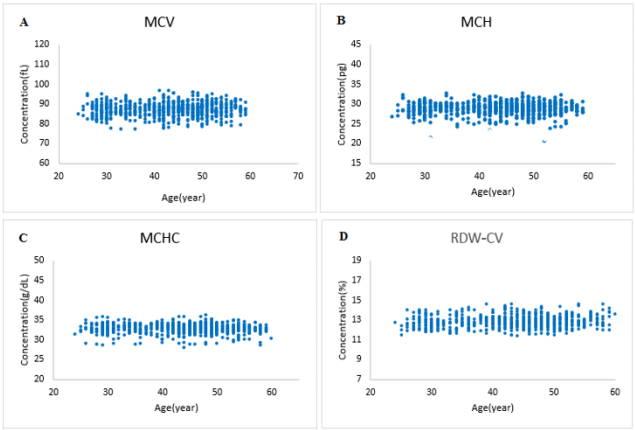

Figure 2. Scatterplot distributions for Mean Corpuscular Volume cells (A), Mean Corpuscular Hemoglobin (B), Mean Corpuscular Hemoglobin Concentration (C) and Red Cell Distribution Width (D).

Table 1. Reference Intervals for various blood cells.

Variable	Age (year)	Male				
		Sample size	Lower limit	Upper limit	Lower confidence	Upper confidence
WBC (10^3/M)	20-60	692	4.1	10.2	(1.9-4.3)	(9.5-10.7)
RBC (10^6/M)	20-60	680	4.6	6.1	(4.5-4.6)	(6.0-6.1)
HGB (g/dL)	20-60	674	13.2	16.8	(13.1-13.3)	(16.6-16.9)
HCT (%)	20-60	697	40.2	50.9	(40.0-40.6)	(50.2-51.3)
MCV (fL)	20-60	657	79.5	92.8	(78.5-80.4)	(92.5-93.0)
MCH (pg)	20-60	656	25.0	31.0	(24.7-25.7)	(30.8-31.2)
MCHC (g/dL)	20-60	679	29.3	34.4	(28.6-29.5)	(34.4-34.5)
PLT (10^3/µL)	20-60	693	139	319	(134-146)	(311-329)
RDW (%)	20-60	613	12.0	14.2	(11.9-12.0)	(14.1-14.4)
PDW (fL)	20-60	666	10	17.6	(9.8-10.2)	(17.2-18.3)
P_LCR (%)	20-60	664	14.9	41.2	(14.0-15.4)	(40.0-43.0)
MPV (fL)	20-35	142	8.7	12.2	(8.4-8.7)	(11.9-12.5)
	35-60	506	8.5	11.5	(8.4-8.8)	(11.4-11.6)

WBC; white blood cells, RBC; red blood cells, HGB; hemoglobin, HCT; hematocrit, MCV; Mean Corpuscular Volume cells, MCH; Mean Corpuscular Hemoglobin, MCHC; Mean Corpuscular Hemoglobin Concentration, PLT; platelet, RDW; Red Cell Distribution Width, PDW; Platelet Distribution Width, P- LCR; Platelet Larger Cell Ratio, MPV; Mean Platelet Volume.

RBC, HGB, and HCT remained relatively stable throughout the age range (Fig. 1). Established RIs for MPV were separated into two partitions at 35 years of age with a significant decrease in concentrations observed in the older age range (20 to 35 years: 8.7 to 12.2 fL, 35 to 60 years: 8.5 to 11.5 fL) (Fig. 3). Finally, established RIs for other hematology parameters including RBC indices (MCV, MCH, MCHC, and RDW) and platelet indices (PDW-P-LCR and PLT) could be represented by one age range (Fig. 2 & 3).

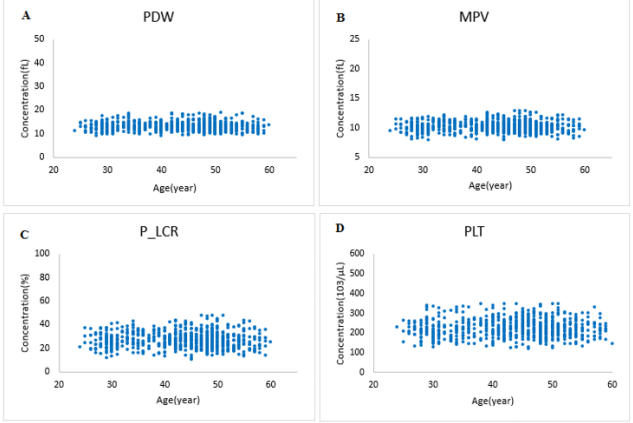

Figure 3. Scatterplot distributions for Platelet Distribution Width (A), Mean Platelet Volume (B), Platelet Larger Cell Ratio (C), and Platelet (D).

Discussion

Clinical laboratory test interpretation and thus diagnostic rigor are heavily dependent on the availability of appropriate and accurate RIs. This is particularly important for hematology parameters given their routine use in patient disease diagnosis and management (24, 25). RIs can be influenced by various parameters including age, genetics, diet, ethnicity, gender and geographical location, requiring the establishment of accurate and robust RIs for specific populations (26). To our knowledge, this is the first study to establish RIs for RBC indices (e.g. RBC count, HGB, HCT, MCV, MCH, MCHC and RDW), platelet indices (e.g. PLT, PDW, P_LCR and MPV) and WBC count in healthy adult males in the northeastern population of Iran.

In the present study, established RIs demonstrated some differences to those previously published in the literature. Some factors that could have contributed to these discrepancies include 1) inter-laboratory sample processing procedure and analytical platform variation, 2) exclusion criteria for study cohort, 3) definition of RI (i.e. central 90% or 95%) and 4) nutritional status and genetic factors (22, 27).

We compared our findings with similar studies conducted in various parts of the world, including Iran, Africa, and Canada. A summary of this comparison is presented in Table 2. For RBC indices, the established RI for RBC count showed a similar range in comparison to another population of Iranians aged 19-64 (18). Other studies also demonstrated similar results (28, 29), while most western-based studies showed an increased upper limit (30, 31). Such differences could be attributed to the environment and testing conditions (30). According to the Canadian study conducted by Adeli and colleagues (30) to determine RI for males and females aged 13-79, RI of HGB for males aligned most closely with our results. However, other studies did report slightly higher upper reference limits (18, 24) compared to our results. In conjunction with the factors described above, differential reference limits could be the result of preanalytical factors, including repeated phlebotomy which can lead to decreased HGB concentrations (24). Concerning HCT, the RI established in our study was most consistent with that reported by Adeli et al (30). Some slight differences were observed in HCT reference limits reported by other studies. Specifically, the reported RI for HCT in our study was slightly wider in comparison to that of Miri-Dashe and colleagues (32). The lower limit of HCT established in several studies was also lower when compared to our results (24, 28, 29). All studies demonstrated no statistically significant age-specific differences, confirming our findings

Table 2: Published studies on hematological reference intervals in various populations.

	Our study	(Rasouli, Pourmokhtar et al. 2017)(18)	(Karita, Ketter et al. 2009)(24)	(Adeli, Raizman et al. 2015)(30)	(Miri-Dashe, Osawe et al. 2014)(32)	(M Pekelharing, Hauss et al. 2010)(26)	(Hong, Min et al. 2015)(34)	(Maluf, Barreto et al. 2015)(36)	(Kratz, Ferraro et al. 2004)(31)	(Eller, Eller et al. 2008)(28)	(A, Parameaswari et al. 2012)(29)
Study population	Males/ aged 20-86	Males and females/ aged 19-64	Males and females/ aged 18–60	Males and females/ aged 3-79	Males and females/ aged 18-65	Males and females/ aged 16-63	Males and females/ aged 20-79	Males and females/ aged	Males and females/ aged	Males and females/ aged 18-56	Males and females/ aged 18-70
Guideline/ Percentile	CLSI/ 2.5 - 97.5	CLSI C28-A2/ 2.5 - 97.5	CLSI C28-A2/ 2.5 - 97.5	CLSI C28-A3/ 2.5 – 97.5	- 2.5 - 95	- 2.5 - 97.5	IFCC & CLSI C28-A3/ 2.5 - 97.5	CLSI C28-A3/ 2.5 - 97.5	-	CLSI C28-A2/ 2.5 - 97.5	IFCC & CLSI C28-A3/ 2.5 - 97.5
WBC 10^3/M	4.1-10.2	4.4-10.7	3.1-9.1	4.4-12.9	4.3-4.6	3.9-10.9	-	-	4.5-11.0	2.8-8.2	4.6-13.5
RBC 10^6/M	4.6-6.1	4.7-6.6	4.0-6.4	4.2-5.5	5.1-5.3	4.4-5.6	-	-	4.5-5.9	3.8-6.1	4.0-6.0
HGB g/dL	13.2-16.8	13.4-18.4	12.2-17.7	13.6-16.9	14.0-14.4	13.5-16.9	-	-	13.5-17.5	11.6-17.1	11.1-17.4
HCT %	40.2-51	39.9-55.5	35-50.8	40-50	43.5-45	40-49.4	-	-	41-53	34-50	33-50
MCV fL	79.5-93	77.5-96.5	68-98	77.2-89.5	84.3-86.6	81.8-95.5	-	-	80-100	71-97	73.3-91.7
MCH pg	25-31	24.9-31.4	-	27.6-33.3	27.2-28.1	27-32.3	-	-	26-34	23-33.8	24-33.4
MCHC g/dL	29.3-34.4	30.2-35.7	-	32.4-34.9	31.9-32.4	32.4-35	-	-	31-37	32.4-35.3	32.1-36.9
PLT 10^3/µL	139-319	131.8-351.8	126-438	187.4-444.6	206.8-226.8	166-308	111-305	-	150-350	106-362	148.3-404
RDW %	12-14.2	-	-	11.4-13.5	-	12-13.6	-	-	11.5-14.5	10.9-16.8	12.2-15.4
PDW fL	10-17.6	-	-	-	-	10.1-16.1	9.2-18.4	12-12.4	-	-	9-16.6
P_LCR %	14.9-41.2	-	-	-	-	18.5-42.3	18.6-50.6	26.4-27.8	-	-	-
MPV fL	8.7-12.2 8.5-11.5	-	-	6.4-9.5	-	9.3-12.1	9.2-13.2	10.2-10.4	- -	6.8-10.2	7.9-13.7

(30). MCV results in the present study were relatively consistent with other cohorts, demonstrating a slight increase throughout the adult age range. However, established lower and upper limits differed slightly in comparison to previous reports. Specifically, our study showed an increased lower limit in comparison to both the previous Iranian (18) and Canadian (30) studies and was more similar to those established by Kratz and colleagues (33). In the case of MCH and MCHC, our study depicted similar results when compared to other cohorts with slight variation observed (25, 26, 28-30, 34). Furthermore, while our investigations demonstrated a similar RI for RDW in comparison to other studies, some published reports established a wider range (18, 29, 30).

For platelet parameters, only MPV required age partitioning. As expected, the lower and upper limit established for PLT varied in comparison to previous reports (24, 29, 30). In comparison to the Canadian study (30), our platelet range was much narrower with a decreased lower limit. Genetic factors are known to influence platelet counts at a population level and likely contribute to these observed differences (33). In the case of MPV, some studies conducted in a population of males and females aged 20-79 established a higher range (34), others established a lower range (30), and some established a wider range (29). Considering PDW, the established lower limit in our cohort was in line with another study conducted in a population of males and females aged 16-63 (26). Other studies have reported slightly decreased lower limits (29, 34), while our study reported a higher upper limit in comparison to most studies included in Table 2. Fewer studies have established a RI for P_LCR. In our investigation, P_LCR lower and upper limits were decreased in comparison to other studies (35).

Regarding WBC count, our results were in accordance with some studies, including an Iranian and US-based study, demonstrating relatively constant levels throughout the adult age range (18, 31). It is important to note that some studies showed slightly different upper and lower reference limits for WBC (24, 30). This can be explained by analytical differences in study methodology and/or population cohort differences.

It is important to note the limitations of the current study. Firstly, our cohort did not include the female population of Sarakhs, eliminating the possibility of assessing sex-specific differences. Additionally, our study cohort is comprised of individuals from the same organization that is likely of similar socioeconomic status and thus not an ideal representation of the total population. Our study was also limited to individuals aged 20 to 60 years and thus pediatric and geriatric populations were not examined. Finally, differential WBC counts and percentages were not assessed.

The results reported in this study partially correlated with RIs established in other studies (Table 2). In fact, WBC, HGB and HCT ranges were consistent with reports from western countries, while RBC, MCH and MCHC, were more consistent with previous reports from the Iranian population. Established RIs for PLT, PDW and P_LCR were not well correlated when compared to other studies. As shown in Table 2, it is important to consider age, ethnicity and environmental context when defining RIs, underscoring the importance of population-specific RIs. RIs adjusted to a population's characteristics will likely lead to a more accurate test result in interpretation and thus improved diagnosis and patient management.

Acknowledgements
We would like to thank the National Institutes for Medical Research Development (NIMAD) of Tehran and Mashhad University of Medical Sciences Research Council for their financial supports.

Grant
The research reported in this publication was supported by Mashhad University of Medical Sciences, Mashhad, Iran and Elite Researcher Grant Committee under award number [982928] from the National Institutes for Medical Research Development (NIMAD), Tehran, Iran

Conflict of interest
The authors have no conflict of interest to disclose

Ethical approval
This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Mums), Mashhad, Iran.

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