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Reference intervals for platelet indices using Sysmex XT-1800i in Egyptian population

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Abstract

Background: Platelet indices have been receiving attention recently as clinically valuable biomarkers. However, these indices are influenced by many factors such as ethnicity origin, age, gender and the type of technology used in measurement. Hence, determination of method-specific reference interval with regards to age, gender and ethnic base has been recommended. This study aimed to define reference intervals for platelet count and indices for medical research and practice.

Method: Blood samples were collected from 380 healthy adult who underwent routine medical checkup. The study population consisted of 184 male and 196 female. Their ages ranged from 16 to 82 years with median age of 52 years. Samples were analyzed using Sysmex XT1800i. The platelet count and indices were recorded. The median values of each parameter were compared after stratifying the samples according to gender and then according to age. The reference intervals were presented as 2.5 and 97.5 percentile.

Results: There were significant gender based differences for platelet count and indices. Therefore, separate reference intervals for the two genders were defined. The reference intervals for each parameter were as follows: platelet count, 158.0 - 387.0 $\times 10^9$/L for females and 169.2 - 324.7 $\times 10^9$/L for males; platelets distribution width (PDW), 10.0 - 16.9 fL for females and 10.4 - 15.9 fL for males; mean platelets volume (MPV), 9.3 - 12.2 fL for females and 9.5 - 11.8 fL for males; platelets -large cell ratio (P-LCR), 20.0 - 42.3% for females and 21.6 - 39.0% for males; plateletcrit (PCT),0.18 - 0.41% for females and 0.18 - 0.34% for males. When we categorized the patients according to age we didn't find significant difference except for platelet count and PCT ($P < 0.001$). Weak, but significant correlations were found between age and each of platelet count and PCT. Negative significant correlations were observed between platelet count and each of PDW, MPV and P-LCR, while positive correlation was found between platelet count and PCT ($P<0.001$). The PDW was positively correlated with each of MPV and P-LCR.

Conclusion: The reference intervals obtained in this study differed from the previously established reference values. Gender differences that have been observed are worthwhile. Therefore, this study validate the principle that it is essential to determine local reference intervals, taking into consideration the gender differences, since it reflects the population for which the test will be applied for better clinical interpretation and proper intervention.

Keywords: Egyptian, mean platelet volume, platelet distribution width, platelets indices, reference interval, sysmex

Introduction

Since its first introduction in 1953, the automated cell counters provided rapid, accurate and precise complete blood count (CBC) results. Moreover, recent improvement of cell counters allowed determination of several parameters that hadn't been used before. Among these parameters are the platelet indices namely mean platelet volume (MPV), platelet distribution width (PDW), platelet large cell ratio (P-LCR) and plateletcrit (PCT). Such parameters are related to platelet activation [1, 2].

The MPV is a measurement of the average size of platelet in the peripheral blood. It is derived from the impedance platelet size distribution curve which is calculated from a log transformation of the platelet volume distribution curve, to yield a geometric mean for this parameter. The MPV is calculated by dividing the plateletcrit (PCT), by the number of platelets. On instruments that use light-scattering technology to count platelets, the MPV is obtained from the modal platelet size. While PDW is a reflection of platelet size heterogeneity and it is the width of the size distribution curve in femtolitre (fL) at the 20% level of the peak with a total curve height of 100% [3, 4]. Another parameter is P-LCR which indicates the number of circulating platelets falling above the 12 fL threshold divided by the total number of platelets [4]. The PCT is the percentage of the volume of blood occupied by platelets [5].

Although platelets indices are routinely provided by the automated counters, many laboratories don't display them as a part of the CBC report. Hence, they are not applied in clinical practice [6]. Platelet indices were evaluated in many studies and had been related to many hematological and non hematological diseases; additionally they were correlated with prognosis and even mortality rate in some pathologies [2, 7-9]. Since the value of these parameters is becoming increasingly important, establishment of reference interval is essential. It has been suggested that determination of local reference interval according to the type of technology used and the population on which the test will be applied is necessary [10]. According to the recommendations of the International Federation for Clinical Chemistry (IFCC) [11] and the Clinical and Laboratory Standards Institute (CLSI) [12] each laboratory has to establish its own reference interval. This study therefore aimed to determine the reference intervals for platelet indices using Sysmex XT1800i in healthy adult Egyptian population.

Materials and methods

The study was conducted according to the stipulations of the

local ethical committee. A total of 380 healthy individuals attending to Ain Shams University Hospitals for routine medical checkup were enrolled in this study. Fully informed consent was obtained from each participant. Individuals involved in the study had no relevant disease such as diabetes, arterial hypertension, cardiopathy, renal disease, or hepatic disease. The results for CBC, chemistry profile, and coagulation profile were within the reference intervals for all the participants in this study. Sample collection and test conduction were performed according to institutional standard operating procedures. Two mL of venous blood were aseptically collected into K3 EDTA (tripotassium ethylene diamine tetraacetate) vacutainer tubes. Samples were analyzed using automated blood cell counter (Sysmex XT-1800i, Kobe Japan) within 2 hours of collection. All the samples didn't show any flags. Procedures for quality control (both internal and external) were followed throughout the study to ensure good performance and the instrument was regularly calibrated by standardized calibrators. The median values of each parameter were compared after stratifying the samples according to gender and then according to age.

Statistical Analysis

All data was conducted using Statistical Package for Social Science (IBM SPSS) version 20 software. The qualitative data were presented as number and percentages while quantitative data with non-Gaussian distribution were presented as medians, interquartile ranges and percentiles. The comparison between two groups with qualitative data were done by using Chi-square test and/or Fisher exact test when the expected count in any cell found less than 5. The comparison between two independent groups with quantitative data and non-Gaussian distribution was done by using Mann-Whitney test. Spearman correlation coefficients were used to determine the inter-correlations between parameters. *P*-value was considered significant at the level of <0.05.

Results

This study recruited 380 healthy individual comprising 184 (48.8%) males and 196 (51.6%) females. Their ages ranged from 16 to 82 years with median age of 52 years. There were 104 (53.10%) females and 76 (41.30%) males younger than 52 years while 92 (46.90%) females and 108 (58.70%) males aged above 52 years. Significant difference was found regarding the age of females and males (*P*=0.022*)*.The distributions of platelet count and indices were found to be non-Gaussian; therefore the median rather than the mean was used. Also the reference intervals were defined as recommended by IFCC [11] as 95% confidence limits for values between the 2.5 and 97.5 percentiles. In Table 1, the medians, interquartile ranges and reference intervals of platelet count and indices of the study population are presented.

Table 1: Descriptive statistics for platelet count and indices of the study population (n=380)

	Median	Interquartile range	Reference Interval**
Platelet count ($\times10^9$/L)	246	211 – 303	158.0 - 385.0
PDW (fL)	12.9	11.5 – 14.4	10.0 –16.9
MPV (fL)	10.8	10 – 11.3	9.3 – 12.2
P-LCR (%)	30.8	25.3 – 35.6	20.0 – 42.3
PCT (%)	0.27	0.23 – 0.31	0.18 – 0.4

PDW: Platelet distribution width, MPV: Mean platelet volume, P-LCR: Platelet large cell ratio, PCT: plateletcrit.
**95% reference interval (2.5 percentile–97.5 percentile).

There were statistically significant difference upon comparing the median values of platelet count, PDW, MPV, P-LCR and PCT between males and females (*P*<0.05) where females presented higher values (Table 2, Figure 1). Table 3 shows reference intervals for platelet count and indices obtained in females and males separately. Significantly higher median platelet count and PCT were observed in the group aged below 52 years when compared with the group aged above 52 years (Figure 2), while no difference was found regarding the PDW, MPV and P-LCR (Table 4). Reference intervals for platelet count and indices according to age are presented in Table 5.

Table 2: Medians and interquartile ranges of platelet count and indices in females and males

	Females (n=196)	Males (n=184)	Mann-Whitney test	
	Median (IQR)	Median (IQR)	Z	P-value
Platelet count ($\times10^9$/L)	254 (221 – 318)	234 (198 – 273)	-4.456	<0.001*
PDW (fL)	13.2 (11.5 – 14.5)	12.6 (11.5 – 14.1)	-2.020	0.043*
MPV (fL)	10.9 (10.3 – 11.4)	10.6 (10 – 11.1)	-3.039	0.002*
P-LCR (%)	32.4 (25.6 – 36.2)	30 (25.3 – 34.2)	-2.782	0.005*
PCT (%)	0.28 (0.25 – 0.33)	0.26 (0.22 –0.28)	-5.606	<0.001*

IQR: Interquartile range, PDW: Platelet distribution width, MPV: Mean platelet volume, P-LCR: Platelet large cell ratio, PCT: plateletcrit.
*Statistical significance at *P*<0.05.

Table 3: Reference intervals of platelet count and indices in females and males

	Females (n=196)	Males (n=184)
	Reference Interval**	**Reference Interval****
Platelet count (×10^9/L)	158.0 - 387.0	169.2 - 324.7
PDW (fL)	10.0 - 16.9	10.4 - 15.9
MPV (fL)	9.3 - 12.2	9.5 - 11.8
P-LCR (%)	20.0 - 42.3	21.6 - 39.0
PCT (%)	0.18 - 0.41	0.18 - 0.34

PDW: Platelet distribution width, MPV: Mean platelet volume, P-LCR: Platelet large cell ratio, PCT: plateletcrit.
**95% reference interval (2.5 percentile–97.5 percentile).

Table 4: Medians and interquartile ranges of platelet count and indices in individuals aged below and above 52 years

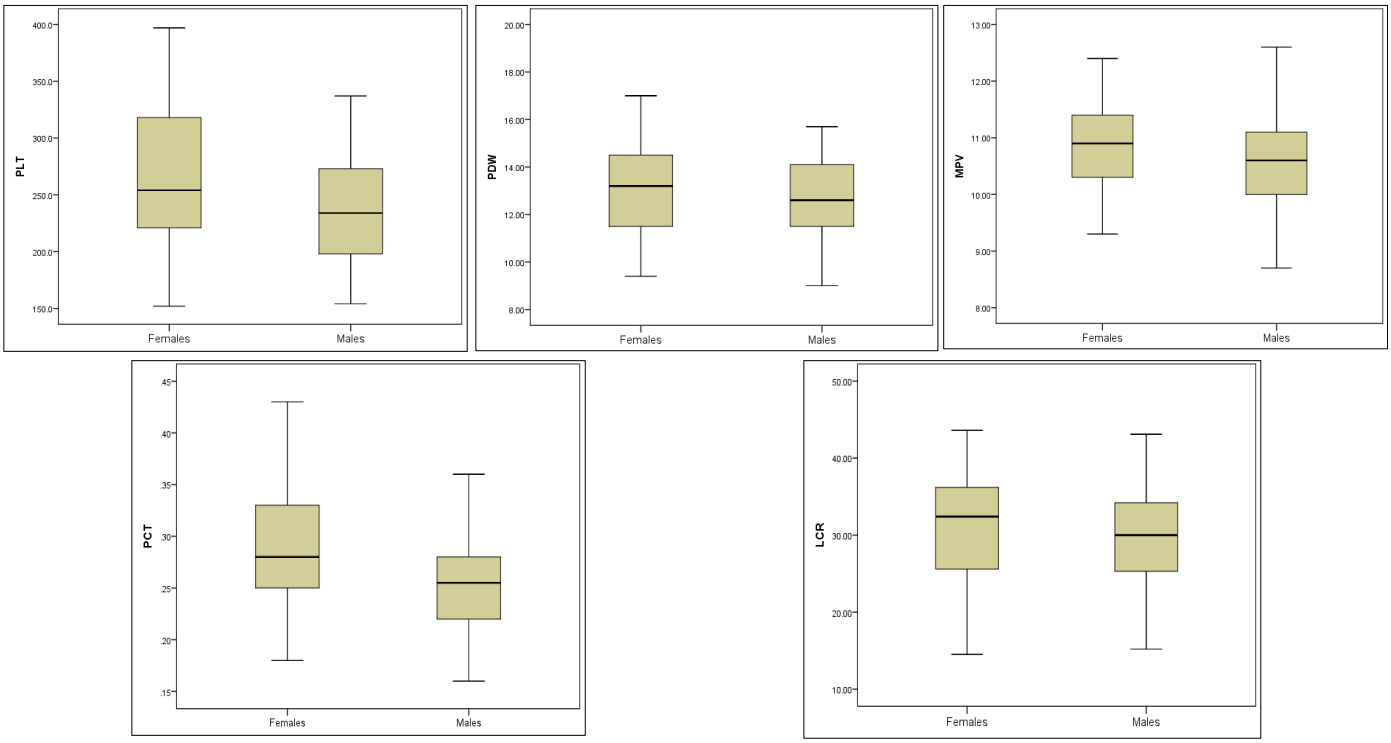
	Age < 52 yrs (n=180)	Age ≥ 52 yrs (n=200)	Mann-Whitney test	
	Median (IQR)	**Median (IQR)**	**Z**	**P-value**
Platelet count (×10^9/L)	254 (219 – 309)	237 (206 – 274)	-4.064	<0.001*
PDW (fL)	12.9 (11.3 – 14.2)	12.6 (12 – 14.4)	-0.105	0.917
MPV (fL)	10.9 (10 – 11.4)	10.7 (10.1 – 11.3)	-0.202	0.840
P-LCR (%)	32 (24.8 – 35.6)	30.55 (27.2 – 35.1)	-0.195	0.846
PCT (%)	0.28 (0.25 – 0.33)	0.25 (0.22 – 0.3)	-4.493	<0.001*

IQR: Interquartile range, PDW: Platelet distribution width, MPV: Mean platelet volume, P-LCR: Platelet large cell ratio, PCT: plateletcrit.
*Statistical significance at P<0.05.

Table 5: Reference intervals of platelet count and indices according to age

	Age < 52 yrs (n=180)	Age ≥ 52 yrs (n=200)
	Reference Interval**	**Reference Interval****
Platelet count (×10^9/L)	162.9 - 389.2	158.0 - 376.2
PDW (fL)	9.3 - 16.5	10.5 - 16.9
MPV (fL)	8.7 - 12.1	9.6 - 12.2
P-LCR (%)	15.02 - 40.4	22.5 - 42.3
PCT (%)	0.18 - 0.41	0.18 - 0.4

IQR: Interquartile range, PDW: Platelet distribution width, MPV: Mean platelet volume, P-LCR: Platelet large cell ratio, PCT: plateletcrit. *Statistical significance at P<0.05.
**95% reference interval (2.5 percentile–97.5 percentile).



PLT: Platelet count, PDW: Platelet distribution width, MPV: Mean platelet volume, P-LCR: Platelet large cell ratio, PCT: plateletcrit

Fig 1: Platelet count and indices in females and males.

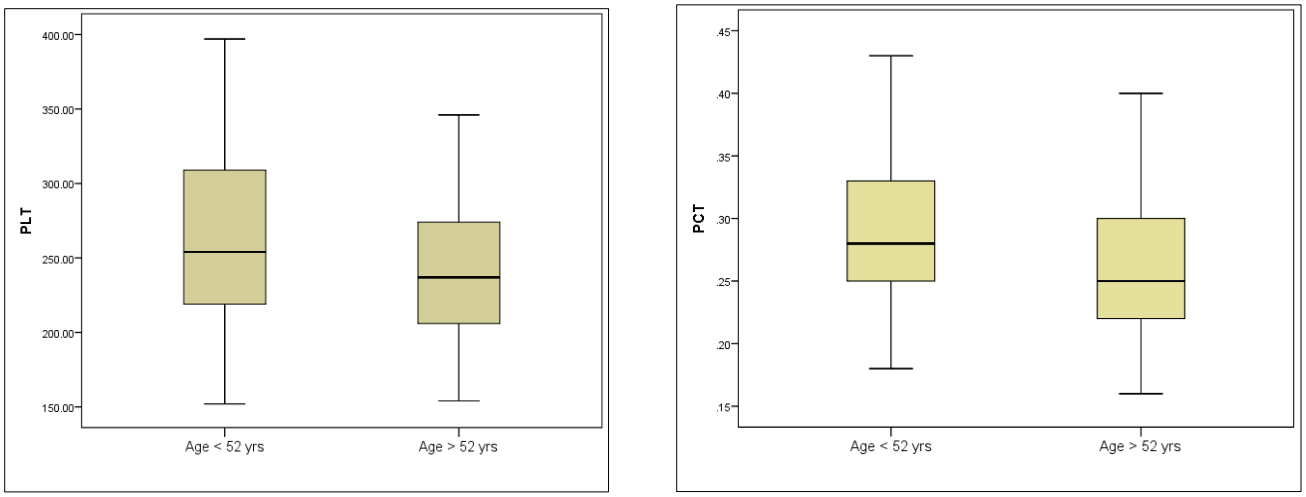
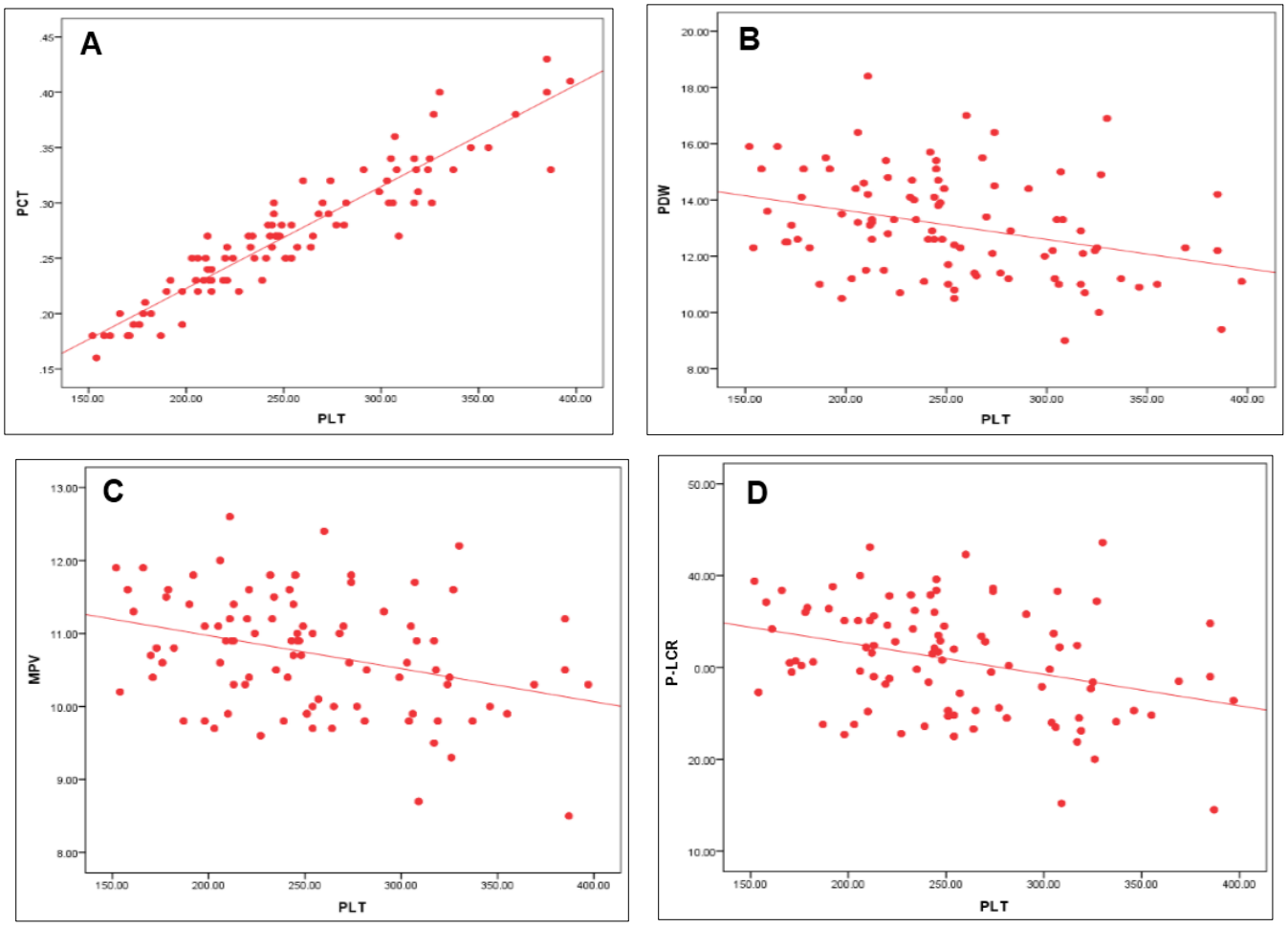


Fig 2: Platelet count (PLT) and plateletcrit (PCT) according to age below and above 52 years**.**

Platelet count showed positive correlation with PCT (r =0.934; *P*<0.001) (Figure 3A) and negative correlations with each of PDW (r = - 0.340; *P*<0.001) (Figure 3B), MPV (r = - 0.304; *P*<0.001) (Figure 3C) and P-LCR (r = - 0.314; *P*<0.001) (Figure 3D). Positive significant correlations were observed between PDW and each of MPV (r =0.945; *P*<0.001) (Figure 3E) and P-LCR (r =0.957; *P*<0.001) (Figure 3F). Also MPV showed positive correlation with P-LCR (r =0.990; *P*<0.001). A significant but weak negative correlations were observed between age and each of platelet count (r = - 0.262; *P*<0.001) and PCT (r = - 0.276; *P*<0.001).



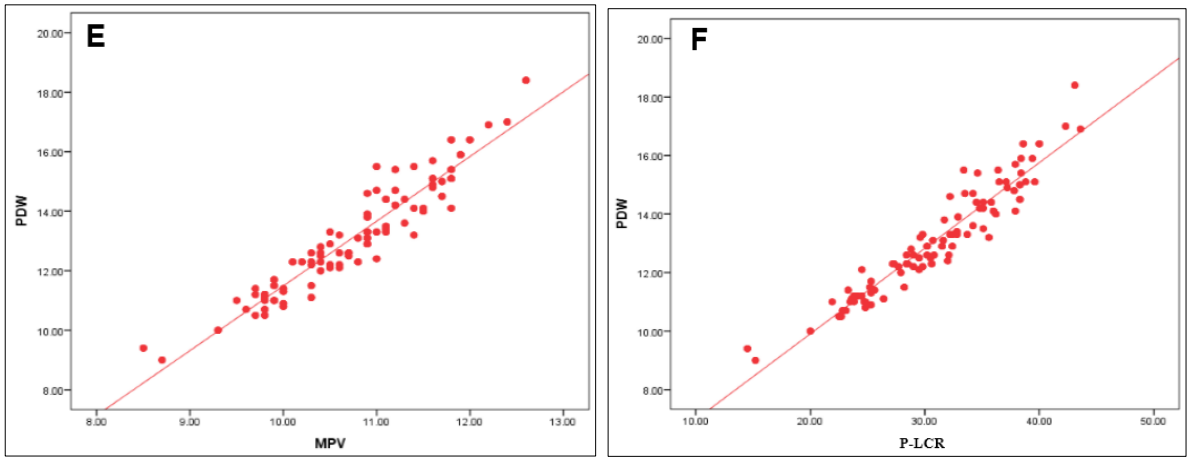


Fig 3: (A) Positive correlation between platelet count (PLT) and plateletcrit (PCT)
(B) Negative correlation between platelet count (PLT) and platelet distribution width (PDW)
(C) Negative correlation between platelet count (PLT) and mean platelet volume (MPV)
(D) Negative correlation between platelet count (PLT) and platelet large cell ratio (P-LCR)
(E) Positive correlation between Platelet distribution width (PDW) and mean platelet volume (MPV)
(F) Positive correlation between Platelet distribution width (PDW) and platelet large cell ratio (P-LCR)

Table 6 compares the reference intervals of the studied parameters with those of similar published studies. Some PDW results are expressed as percentage when measured by Technicon and Pentra in contrast to other instruments where PDW is expressed in fL. Therefore, PDW results obtained from Technicon and Pentra couldn't be compared with other instruments' measurements.

Table 6: Reference intervals of platelet count and indices in the present study compared to previous published studies

Author	Population	Sample size	Type of the instrument	Platelet count (×10^9/L)	PDW	MPV (fL)	P-LCR (%)	PCT (%)
Abass [13]	Sudanese	300	Sysmex KX -21	146– 378	8.3 - 15.9 fL	8.2-11.6	11.8 - 37.4	0.13 - 0.34
Adibi [14]	Iranian	19 993	Technicon H*2	145–356	40.2–57.4%	7.4–10.7		0.13–0.32
Alexander [15]	Nigerian	500	Sysmex KX 21N			9.7-11.5		
Botma [16]	South African	60	Sysmex XE-2010	178-429	9.3-16.0 fL	8.80-12.5		0.19-0.40
Farias [10]	Brazilian	231	Pentra 120 ABX		10.1-17.9%			
Hong [17]	Chinese	4642	Sysmex XE-2100	115–323	9.13–18.33%	9.27–13.22	18.50–50.72	14.05–35.95
Kim [18]	Korean	480	ADVIA 2120		39.3-64.7%	6.7-9.6		Female: 0.15-0.31 Male: 0.14-0.28
Maluf [19]	Brazilian	580	Sysmex XE-2100		9.6–15.3 fL	8.9–11.8	15.6–39.5%	
Sachdev [20]	Indian	945	Sysmex XE-2100	247-254	14.33-14.72fL	11.6-11.78	37.75-39.13	0.2853-0.2928
Subhashree [21]	Indian	500	Sysmex KX 21	148.53-406.42	8.90-16.4 fL	8.0-13.15		
The current study	Egyptian	380	Sysmex XT -1800i	158.0 - 385.0	10.0-16.9 fL	9.3-12.2	20.0- 42.3	0.18-0.4

4. Discussion

Recently many studies had been concerned with the clinical utility of platelet indices especially they are part of the readily available routine CBC and this will not add any additional cost for the patients; also they decrease the test burden on both the physicians and the patients. However, these indices are affected by several factors such as ethnic base differences, age, gender, pre-analytical influences (method of venipuncture, the degree of accuracy of filling and mixing the sampling tubes, temperature, delay time from sampling to analysis, and the type of the used anticoagulant) in addition to the measurement technique of the automated cell counter [17]. Therefore, specific reference intervals as regards ethnicity, age, gender and the used technologies should be defined to assess the use of platelet indices in clinical practice [10]. The objective of the current study was to determine reference intervals for platelet indices in healthy adult Egyptian population using Sysmex XT-1800i automated cell counter. In this study the methodological problems involved in acquiring the results of platelet indices had been taken into consideration, so the samples were collected, handled and analyzed uniformly and laboratory sources of variation were minimized.

In the present study, platelet counts were obtained using impedance methods. The reference interval for platelet count (158.0 - 385.0 ×10^9/L) did not show much differences from the reference interval that is in current use in our laboratory (150-410 ×10^9/L) [22]. Females had significantly higher median platelet count than males (P<0.001). This finding is in agreement with the previously published literature [13, 14, 16, 18, 21, 25]. Although the reason of this difference is controversial, it may be attributed to the hormone-based differences [23] or a compensatory mechanism associated with blood loss during menstruation [24]. Despite that there was no correlation between platelet count and thrombopoietin concentration in males and females in physiological conditions, thrombopoetin levels were found to be lower in females than males [25]. In our study, a weak but significant negative correlation was observed between platelet count and age (r = - 0.262). Similar finding

was observed in another study [14]. In contrast Bain [23] found no correlation between platelet count and age in both males and females.

The PDW is an indicator of platelet activation. It represents variability in platelets size (anisocytosis) and heterogeneity in platelet morphology. An increase in the PDW is caused by change of platelets shape from discoid to spherical with pseudopod formation [4]. Similar to other studies [14, 21, 26], we found a statistically significant gender based difference for PDW (P=0.043), in contrast, some researchers didn't find difference between males and females regarding PDW [10, 13, 16, 19]. In the current study, the reference intervals for PDW were 10.0 - 16.9 fL in females and 10.4 - 15.9 fL in males. Nearly similar results were found by Pekelharing *et al.* [26] on the Sysmex XE-5000 as the reference intervals were 9.9-15.4 fL in females and 10.1-16.1 fL in males. On the other hand, Sachdev *et al.* [20] found wider reference interval for PDW (8.3-25.0 fL) and this may be attributed to variances in the ethnicity origin of the study population.

Another marker of platelet activation is MPV. It increases as the platelet production by the bone marrow increases and larger platelets enter into the circulation. In the current study, no statistically significant difference was detected when we compared the median values of MPV according to age. However, we found that females had significantly higher median MPV values than males. This result is in accordance with Subhashree *et al.* [21] who reported that females had higher MPV than males. On the other hand, few researchers found that males had higher MPV than females [23, 25, 26] while other studies found no significant difference in MPV between males and females [1, 13, 16, 18, 27]. The MPV reference intervals of this study were 9.3 - 12.2 fL in females and 9.5 - 11.8 fL in males. Our reference intervals for MPV were close to those found by previous study done on Sysmex XE-2100 where the reference intervals of MPV were 9.2-12.9 fL in females and 9.4-12.2 fL in males [28]. In contrast to our findings another study found an increase in both the limits of MPV in both genders (females: 8.0-13.28 fL, males: 7.9-13.7 fL) and the authors of that study reflected this to the possibility of higher risk of cardiovascular diseases in their population [21].

Platelet larger cell ratio is an indicator of circulating larger platelets (> 12 fL), and it is presented as percentage. The P-LCR, when interpreted in association with the other platelet indices, assess in the differential diagnosis of the thrombocytosis-related disease [29]. Our study shows a significant difference between gender as regard the P-LCR, therefore separate reference intervals were calculated being 20.0 - 42.3% in females and 21.6 – 39.0% in males. Pekelharing *et al.* [26] determined reference ranges for P-LCR separately for females (17.5 – 42.3%) and males (18.5 – 42.3%) on the Sysmex XE-5000 and concluded that there was significant difference between males and females (P = 0.0004). However, there were also a few studies whose findings were different from those found in the present study [13, 17, 19, 20].

Plateletcrit is directly related to the platelet count and size [26, 30]. Although the median PCT for this study population was significantly higher in individuals younger than 52 years compared to those aged above 52 years, the reference intervals were almost the same for both groups. Moreover, the significant negative relationship between age and PCT was weak (r = -0.276). This finding was consistent with Adibi *et al.* [14] in a large sample size study (r = - 0.129). Giacomini *et al.* [30] found that PCT decreased in age group 1-10 years and 18-45 years but remained steady afterwards. However, Taylor *et al.* [31] observed that PCT increased only in girls in the peri-pubertal age and related this to the onset of menstruation. A previous study [18] noted that the median PCT was significantly higher in females than males, which is in keeping with the finding of the present study (P < 0.001). Our PCT reference intervals were 0.18 - 0.41% in females and 0.18 - 0.34% in males, which closely resemble that of Botma *et al.* [16] (females: 0.22-0.40%, males: 0.19 - 0.39%). Much lower results for PCT were obtained by Kim *et al.* [18] (using ADVIA 2120) than our findings (females: 0.15 - 0.31%, males: 0.14 - 0.28%). This difference could be due to different type of cell counters, type of reagents and also determination of the reference interval in population with different genetic base.

Combined use of platelet indices with platelet count gives better knowledge of platelet disorders [10]. In order to be interpreted carefully, we evaluated the correlation between platelet count and platelet indices and also the relationship between the platelet indices and each other in healthy individuals. We found significant negative correlation between platelet count and each of MPV, PDW, P-LCR (P < 0.001). The inverse relationship between platelet count and size in physiological conditions highlights the ability to preserve a stable platelet mass in order to maintain haemostasis [32]. Similar to our results, direct relationship was found between MPV and PDW in previous study [33]. Meanwhile, there are conflicting reports in the literature about the relationship between platelet volume and numbers, which suggests that they are affected by different mechanisms [34-36]. In cases of hyper-destructive thrombocytopenia, the megakaryocytes are stimulated in the bone marrow to produce larger platelets that are haemostatically more active resulting in higher MPV. However, platelets with a lower MPV are expected in cases of hypo-productive thrombocytopenia [5]. In agreement with a large previous study [37], P-LCR was positively correlated with MPV and PDW in the present study.

5. Conclusions

In the light of our findings, there were substantial differences between males and females for all platelet count and indices therefore, separate reference intervals were defined. The reference intervals of platelet indices in our population were found to be different from previously established reference values emphasizing that determination of own reference interval with orientation to gender is fundamental.

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