Available online at www.SciMedJournal.org

SciMedicine Journal

(ISSN: 2704-9833)

Vol. 5, No. 3, September, 2023

Age- and Sex-Related Reference Intervals of Prothrombin Time and Activated Partial Thromboplastin Time

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Received 21 March 2023; Revised 17 August 2023; Accepted 23 August 2023; Published 01 September 2023

Abstract

Background: Due to the differences in reference intervals (RIs) for clinical parameters between geographical regions, each laboratory needs to establish its own RIs to aid in effective clinical diagnosis and management. This study developed age- and sex-specific RIs for prothrombin time (PT) and activated partial thromboplastin time (aPTT) among apparently healthy adults in Tamale, Ghana. *Methods:* This cross-sectional study recruited 206 apparently healthy individuals, aged 18-46 and residing in Tamale, Northern Region of Ghana. The PT and aPTT were determined using the HumaClot Duo Plus semi-automated coagulation analyzer. The data were analyzed using SPSS version 26. The RIs for PT and aPTT were established at 2.5th-97.5th percentiles. *Results:* The RIs for PT and aPTT were 10.2-13.37 seconds and 20.41–35.28 seconds, respectively. Females had relatively wider PT RI values than their male counterparts [(9.91–13.39) vs. (10.10–13.37) seconds]. Conversely, males showed relatively wider RIs for aPTT as compared to the female population [(19.86–35.47) vs. (21.40–35.20) seconds]. Adults between the ages of 31-46 years had the widest PT RIs (10.10–13.55) seconds, while the 18-20 years age group had the lowest range (10.10–12.85) seconds. For aPTT, individuals aged 18 -20 years had relatively wider RIs of 19.50–35.25 seconds than the rest of the age groups. A weak positive correlation was observed between PT and age (r =0.166, p=0.017), while aPTT showed a weak inverse correlation with age (r= -0.203, p=0.003). *Conclusion*: Relatively wider RIs for PT (10.02–13.37 seconds) and aPTT (20.41–35.28 seconds) were found among the population in Northern Ghana. PT correlated positively with age, while aPTT inversely correlated with age. Females had relatively wider PT-RI values than their male counterparts. Conversely, males showed relatively wider RIs for aPTT than the female group.

Keywords: Adult; aPTT; Coagulation; Prothrombin Time; Reference Interval.

1. Introduction

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are useful screening tests for coagulation disorders. PT measures the time in seconds for an individual's plasma to clot following the addition of calcium (Ca^{2+})

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http://dx.doi.org/10.28991/SciMedJ-2023-05-03-01

as a cofactor and a thromboplastin (an activator), and this assesses the integrity of the extrinsic as well as the common pathways of coagulation. This test is often prolonged in subjects with deficiencies of the factors or specific inhibitors of the proteins involved in both the extrinsic and the common pathways [1]. The integrity of the intrinsic and final common pathways in the coagulation system is checked by the aPTT test. This aPTT denotes the time in seconds for a person's plasma to clot after Ca^{2+} and the substrate, phospholipid, are added. Deficiencies or inhibitors of coagulation factors involved in both the intrinsic and common pathways often prolong aPTT [2].

Reference intervals (RIs) in the clinical laboratory serve an important function in the diagnosis and management of diseases and to monitor therapeutic responses to treatment [3]. The Clinical and Laboratory Standards Institute (CLSI) recommends each laboratory establish its own reference intervals for different analytes because of the differences in behavioral, physical, geographic, gender, age, and genetic variations among various populations [4]. However, most African countries still rely on values generated from Caucasian populations [5], which can lead to wrong therapeutic decisions.

Several reference range studies involving haematological parameters have been undertaken in recent years, following the guidelines outlined by CLSI [6–10]. Among healthy volunteers in China, the RIs for PT and aPTT were 8.4–10.2 s and 26.8–42.3 s, respectively [11]. RIs for TT was 10.8–12.8 s and aPTT was 27.9–42.7 s in a study by Kim et al. [12] that recruited individuals between 25 to 67 years of age. Among children aged 1 to 12 years in China, PT and aPTT RIs were reported to be 10.60–13.10 s and 27.87–40.80 s, respectively [13]. In Cameroun, Ngounou et al. [14] observed that within the adult population, PT and aPTT RIs were 10.2-15.2 s and 22.2-40.5 s, respectively. Among African blood donors in Nairobi, Kenya, Abdillah (2018) [15] reported RIs for PT and aPTT as 10.50–13.30 and 24.13–35.10 seconds, respectively. Another similar study in the Middle Belt of Ghana, Kumasi, concluded that the RI for PT was 11.4–15.9 seconds and the aPTT was 26.3–44.1 seconds [16]. Interestingly, these RIs are different from values established by the International Standard Laboratory (ISL) among the Caucasian population, where the RIs for PT and aPTT were 11.0–14.0 s and 20.0–35.0 s, respectively. The variations in the RIs from populations of different geographical areas signify the need to establish area-specific RIs for PT and aPTT to positively influence effective diagnosis and treatment.

Despite earlier studies reporting disparities in PT and aPTT RIs owing to various factors such as geographic area, gender, and age [6–8, 11, 12–14, 16–19], there is paucity of data on RIs for PT and aPTT in Ghana. Although PT and aPTT remain the most commonly used assays to evaluate coagulation profiles in health and disease in Ghana, healthcare facilities in the country rely on RIs developed for Caucasian populations, which could result in incorrect diagnoses and treatments due to differences among various populations [16]. The study by Ofosu et al. (2018) [16] remains the only recently known study in Ghana to determine PT and aPTT reference intervals among healthy individuals, but their study was conducted in the middle belt of the country and could not account for the geographic variations of inhabitants in the northern part of Ghana. Moreover, their study only considered age-specific PT and aPTT RIs but could not consider sex.

To the best of our knowledge, no known study has been conducted in the Northern Region of Ghana to establish the RIs for coagulation parameters. Hence, this study determined the RIs for PT and aPTT among the northern population in Ghana. This will provide essential information on PT and aPTT for effective diagnosis and management of coagulation disorders, prevent misdiagnosis, and avoid incorrect therapy.

2. Material and Methods

2.1. Study Design/Study Site

This cross-sectional study was conducted from April to October 2022 at the Tamale Teaching Hospital (TTH) in the Northern Region of Ghana. Tamale Teaching Hospital is located in the Tamale Metropolis and serves as a tertiary-level referral facility for the five Northern Regions: Savannah, Northern, North-East, Upper West, and Upper East. Tamale, the capital of the Northern Region, has a population of approximately 371,351, with the majority being farmers. The capital city is located at a longitude of 0.8235°W and a latitude of 9.3930°N, with the digital address of the hospital being NT-0101-5777. The hospital currently has a bed capacity of four hundred and eighty-four and provides services to over a hundred thousand patients every year [17].

2.2. Study Population and Sample Size

The study involved 206 apparently healthy individuals who visited the blood bank of TTH as voluntary or family replacement blood donors. All subjects were between the ages of 18 and 46 years and were not on any medication. The minimum number of participants required for establishing references is 120, as recommended by the Clinical and Laboratory Standards Institute [4]. However, this study employed 206 participants: 125 males and 81 females.

2.3. Inclusion/Exclusion Criteria

Apparently healthy blood donors between the ages of 18 and 46 were recruited for the study. Participants with a history of diabetes mellitus, liver disease, hypertension or other cardiovascular issues, tuberculosis, acute inflammatory

diseases, and risk factors like pregnancy, intense exercise, alcohol use, smoking, and those on medications including heparin, warfarin, aspirin, or similar drugs and oral contraceptive medications were excluded from the study.

2.4. Sample Collection and Processing

Five (5) mL of blood was aseptically taken from each participant, dispensed into 3.2% tri-sodium citrate-containing tubes, and inverted gently about 5–6 times to ensure adequate mixing of blood with the anticoagulant. The sample was immediately centrifuged at 4000 rpm for 15 minutes to obtain platelet-poor plasma (PPP) for the coagulation assays.

2.5. Measurement of PT and aPTT

Within four hours of sample collection, PT and aPTT were performed with the HumaClot Duo Plus semi-automated coagulation analyzer (Humaclot Duo Plus, Germany), according to the specifications and clinical laboratory operating procedure recommended by the manufacturer. PT was measured by pipetting 50 µL of platelet-poor plasma sample/control without air bubbles into a cuvette preheated to 37 °C in the measurement channel and covered with a light-tight cap. After sample incubation, 100 µL of the pre-warmed PT reagent was added vertically and carefully, without air bubbles, through the light-tight cap. Formed clots were automatically detected by the analyzer. Also, aPTT was measured by pipetting 50 µL of the aPTT reagent and 50 µL of the platelet-poor plasma into the pre-warmed cuvette. After that, the measuring channel was filled with the cuvette containing the mixture, which was then covered with the light-protection lid. After 5 minutes incubation of the mixture, 50 µL of calcium chloride ($CaCl_2$) was pipetted without air bubbles and vertically introduced to the mixture. The analyzer automatically detects the clot that has formed. All laboratory investigations were performed at the Haematology department of TTH. The protocols for the ELISA were adopted from the Appiah et al. (2022) study [17]. The overview of the study design is illustrated in Figure 1.

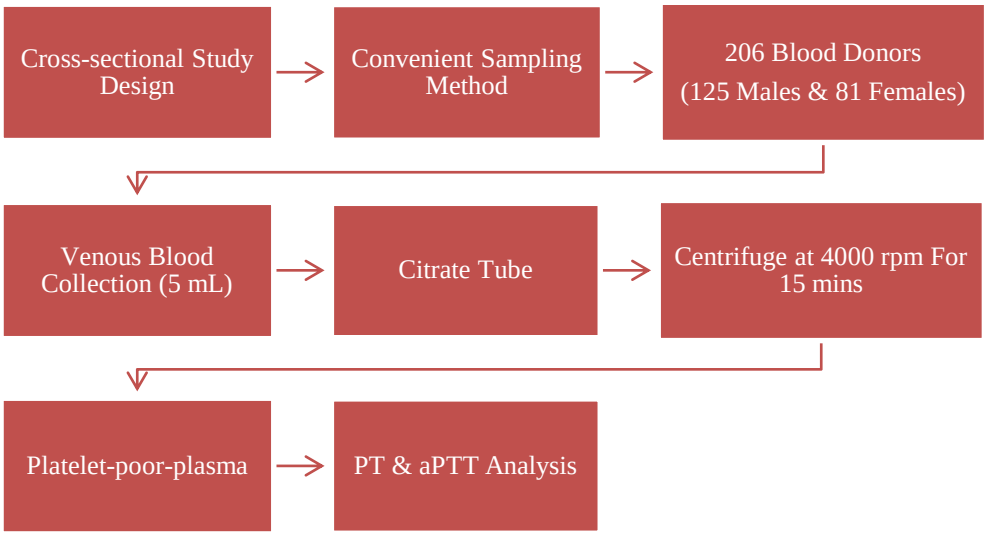


Figure 1. Overview of the study design

2.6. Data Analysis

Data generated were analyzed with IBM Statistical Package for the Social Sciences (SPSS) software, version 26.0 (IBM Corp., Armonk, NY, USA). Normality was tested with one-sample Kolmogorov-Smirnov tests and Shapiro-Wilk tests. The data were presented as medians (interquartile ranges). The reference intervals were established at 2.5th and 97.5th percentiles based on the CLSI guideline [4]. The Mann-Whitney U test was used to compare PT and aPTT values between males and females. Comparisons of PT and aPTT within the different age groups were done using the Kruskal-Wallis test, followed by the Bonferroni multiple comparison tests. To assess the relationship between age and the coagulation tests (PT and aPTT), the Spearman correlation test was performed. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Sociodemographic Characteristics of the Study Subjects

Table 1 shows the demographic characteristics of the study participants. Of the 206 healthy individuals who participated in the study, the majority were males (125/60.7%) and between the ages of 21-30 years (121/58.7%). The median age of the study participants was 24.22 (20.0–25.0) years (Table 1).

Table 1. Socio-Demographic Characteristics of the Study Population

Variables	Frequency (N)	Percentage (%)
Age (Years)	24.22 (20.00 - 25.00)	
18 – 20	59	28.6
21 – 30	121	58.7
31 – 46	26	12.6
Sex		
Male	125	60.7
Female	81	39.3

Categorical data are presented in frequencies with corresponding percentages in parentheses. Age is presented in median (25^{th}-75^{th} percentiles).

3.2. Reference Intervals for PT and aPTT among the Study Participants

The median PT and aPTT were 11.25 (10.70–12.03) and 29.40 (25.90–32.30) seconds, respectively. The minimum and maximum interval ranges for PT and aPTT were 9.90–13.80 seconds and 18.70–36.10 seconds, respectively. The RIs for PT and aPTT were established at the 2.5^{th} and 97.5^{th} percentiles, respectively. The RIs for PT and aPTT in this study were 10.02–13.37 s and 20.41–35.28 s, respectively (Table 2).

Table 2. Reference Intervals for PT and aPTT among the Study Participants

Variables	Median (IQR)	Reference Intervals (2.5^{th}-97.5^{th})		Interval Ranges	
		2.5^{th} (CI = 95.0%)	97.5^{th} (CI = 95.0%)	Minimum Value	Maximum Value
PT	11.25 (10.70 – 12.03)	10.02	13.37	9.90	13.80
aPTT	29.40 (25.90 – 32.30)	20.41	35.28	18.70	36.10

PT= Prothrombin time, aPTT= activated Partial Thromboplastin Time, CI= Confidence interval, QR= interquartile ranges. PT and APTT were presented as medians (25^{th}-75^{th} percentiles).

3.3. Comparison of PT and aPTT RIs from the Present Study to Other Studies

The RI for PT in this study is significantly shorter than the manufacturer-provided intervals, while that for aPTT was longer. The RI for PT in the present study is consistent with the studies by Abdillah (2018) [15] in Kenya and Kim et al. [12], but aPTT appeared wider compared to the Kenyan study. Also, the RIs of PT and aPTT in this study are wider than the RIs determined by the ISL among the Caucasian population. Again, the RIs for PT and aPTT from this study are significantly shorter than the RIs in the Middle Belt of Ghana (KATH, Kumasi) [16] (Table 3).

Table 3. Comparison of PT and aPTT RIs from the Present Study to Other Studies

Parameters	Reference Intervals of PT and aPTT from different sources							
	Present Study (Tamale, Ghana)	China [11]	Kim et al. [12]	Cameroun [14]	Nairobi, Kenya [15]	KATH, Kumasi, Ghana [16]	ISL (among Caucasian population)	Fortress Diagnostics (Manufacturer)
PT (sec)	10.02-13.37	8.4-10.2	10.8-12.8	10.2-15.2	10.50-13.30	11.4-15.9	11.0-14.0	13.0-15.0
aPTT (sec)	29.40 (25.90–32.30)	26.8-42.3	27.9-42.7	22.2-40.5	24.13-35.10	26.3-44.1	20.0-35.0	19.0-31.0

PT= Prothrombin Time; aPTT= activated Partial Thromboplastin Time; sec= Seconds; KATH= Komfo Anokye Teaching Hospital; ISL= International Standard Laboratory.

3.4. PT and aPTT of the Study Participants Stratified by Age and Sex

The median PT for males and females was 11.50 (10.70–12.10) seconds and 11.00 (10.60–11.70) seconds, respectively. The PT RIs were relatively higher among males compared to females (10.10–13.37 vs. 9.91–13.39) seconds, p=0.028. However, females showed relatively higher median (IQR) and RI for aPTT as compared to their male counterparts [Median (IQR): 29.60 (26.95–32.35), RI: (21.40–35.20) vs. Median (IQR): 29.10 (25.15–32.05), RI: (19.86–35.47), respectively], even though this was not significant (p=0.293). With regards to age, PT did not differ within the age periods (p=0.320), but aPTT among the participants within 18–20 years significantly differed from those above 30 years (p=0.007) (Table 4).

Table 4. PT and aPTT of the Study Participants Stratified by Age and Sex

Variables	Coagulation Parameters			
	PT		APTT	
	Median (IQR)	RI: 2.5th – 97.5th Percentiles	Median (IQR)	RI: 2.5th – 97.5th Percentiles
Sex				
Male	11.50 (10.70 – 12.10)	10.10 – 13.37	29.10 (25.15 – 32.05)	19.86 – 35.47
Female	11.00 (10.60 – 11.70)	9.91 – 13.39	29.60 (26.95 – 32.35)	21.40 – 35.20
P-Value		0.028*		0.293
Age (Years)				
18 – 20 **(a)**	11.10 (10.50 – 12.00)	10.10 – 12.85	30.65 (28.80 – 32.40)	19.50 – 35.25
21 – 30 **(b)**	11.30 (10.70 – 11.95)	10.00 – 13.40	29.00 (25.70 – 32.40)	21.41 – 35.50
31 – 46 **(c)**	11.65 (10.80 – 12.63)	10.10 – 13.55	26.45 (24.73 – 29.98)	20.20 –34.53
P-Value		0.320		0.007*
Significant Pairs				a & c

PT= Prothrombin time, aPTT= activated Partial Thromboplastin Time, CI= Confidence interval, QR= Interquartile ranges, RI= Reference interval. The Mann-Whitney U test was used to compare PT and aPTT between males and females. Bonferroni multiple comparison tests were performed after the Kruskal-Wallis test to determine the significant differences between variables by age groups. A P < 0.05 was considered statistically significant.

3.5. Correlation between Age and the Coagulation Parameters among the Study Participants

The current study revealed a significant negative correlation between age and aPTT (r= -0.212, *p=0.002*), but no correlation was found between age, and PT and aPTT respectively (Figure 2).

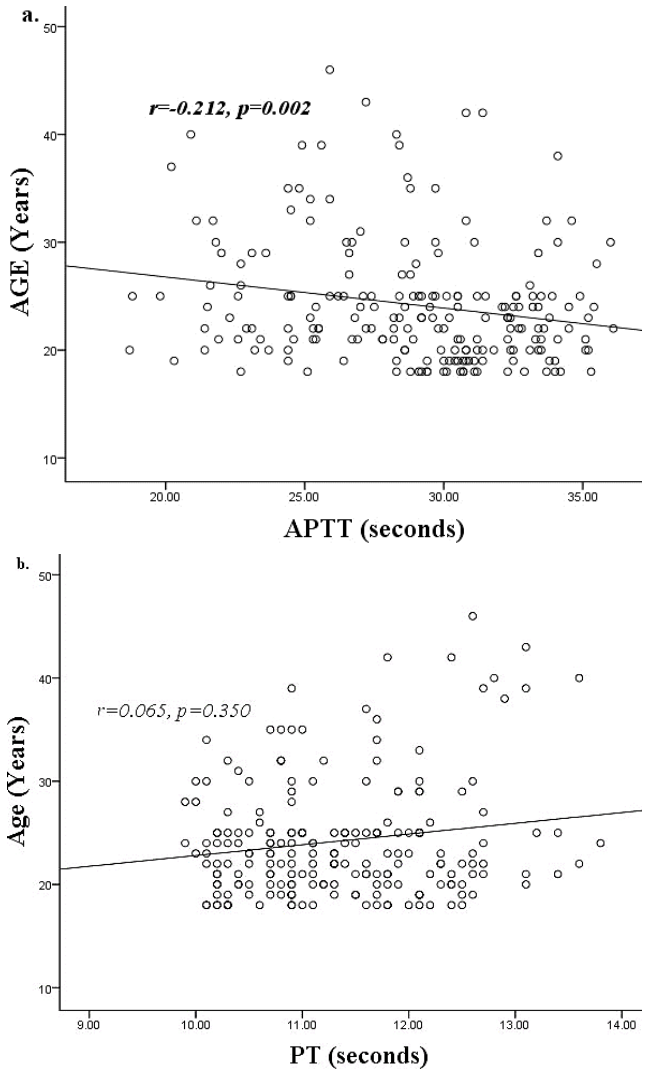
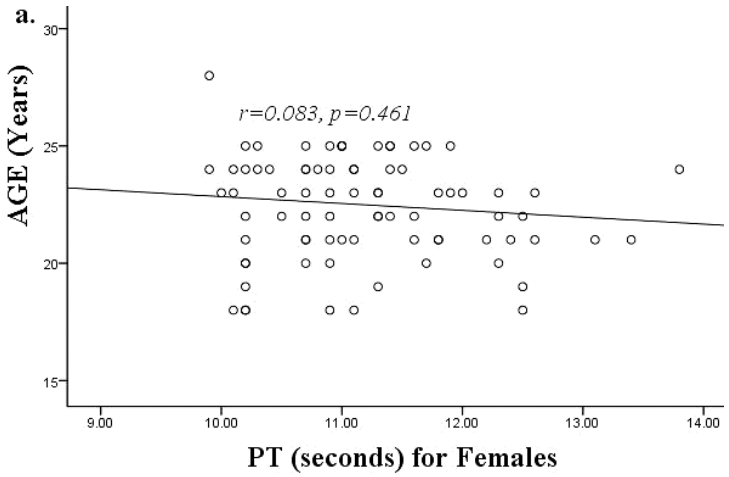
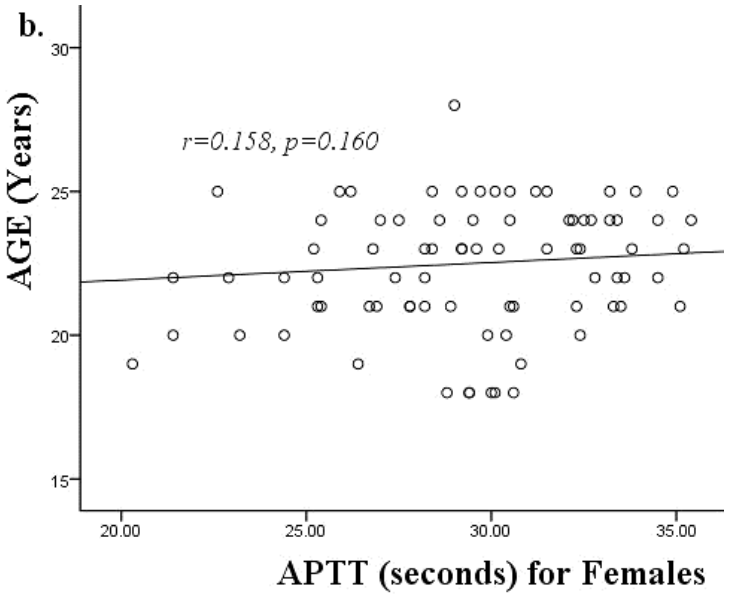


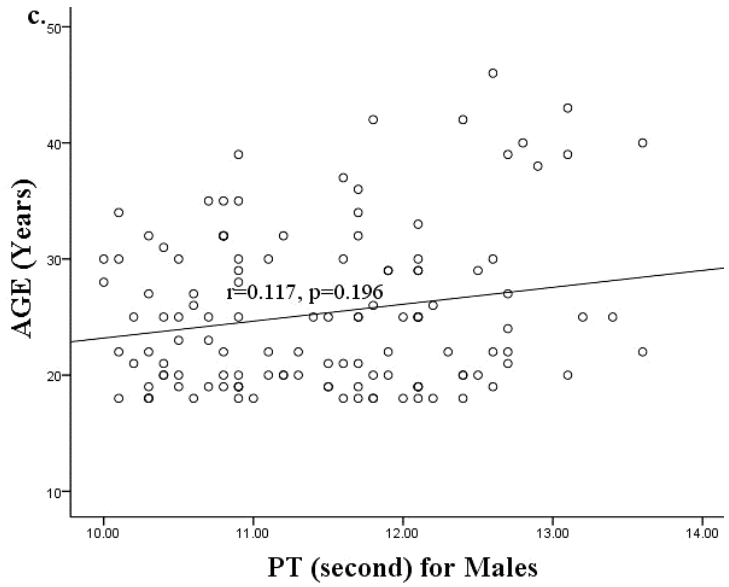
Figure 2. Correlation between Age, and (a) aPTT and (b) PT among the Study Participants. r=*Correlation coefficient, PT=Prothrombin Time, aPTT=activated Partial Thromboplastin Time, p= p-value. The correlation was assessed by Spearman's correlation test and p<0.05 was considered statistically significant.*

3.6. Correlation between Sex-Specific PT and APTT, and Age

After stratifying by sex, female PT and aPTT did not indicate any significant association with age [PT: (r= -0.083, *p*=0.461) and aPTT: (r= 0.158, *p*=0.160)] as shown in Figures 3a and 3b, respectively. Male PT did not show any significant association with age (r: 0.117, *p*=0.196) as seen in Figure 3c, but an inversely significant association was observed between male aPTT and Figure 3d (r= - 0.308**,** *p*<0.001).







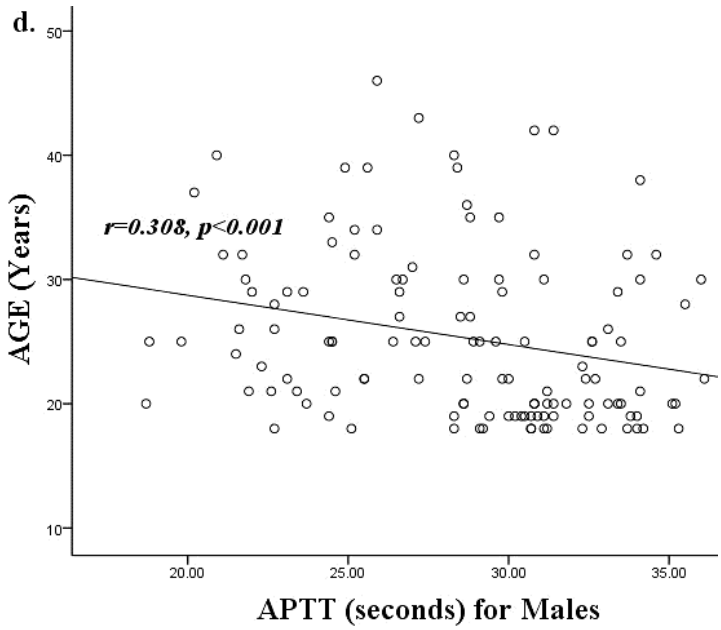


Figure 3. Correlation between Sex-Specific PT and APTT, and Age. *r=Correlation coefficient, PT= Prothrombin Time, aPTT=activated Partial Thromboplastin Time, p= p-value. The correlation was assessed by Spearman's correlation test and p<0.05 was considered statistically significant***.**

4. Discussion

Due to the variations in the normal physiology of individuals with different geographical locations, lifestyles, physical characteristics, and genetics, the use of pre-established reference intervals from other countries for making clinical decisions is inappropriate and can lead to misdiagnosis and mismanagement. TTH and other health facilities in Africa use RIs for haematological parameters established among Caucasians. This study established age- and sex-specific RIs of PT and aPTT among healthy individuals in northern Ghana.

The reference intervals for PT and aPTT were 10.02–13.37 and 20.41–35.28 seconds, respectively. The RI for PT established in this study was significantly shorter than the manufacturer-provided intervals, while that for aPTT was longer. The RI for PT in the present study is consistent with previous studies by Abdillah (2018) [15] and Kim et al. (2021) [12], where reference intervals for PT established among black African blood donors in Nairobi, Kenya, were 10.50–13.30 seconds. The aPTT reference intervals established for this study, however, were significantly wider compared to the Kenyan study. Again, the RIs of PT and aPTT established in this study are wider than the RIs determined by the ISL among a Caucasian population, which is currently being used by the Tamale Teaching Hospital in the northern region of Ghana. The differences in the findings could be attributed to geographic location discrepancies [6–10].

Findings from the current study contrast a similar study conducted in Kumasi, Ghana, by Ofosu et al. (2018) [16]. The RIs for PT and aPTT found in this study were significantly shorter than the RIs established for PT and APTT in the Middle Belt (Kumasi) of Ghana [16]. An earlier study by Valeri et al. (1995) [20] to assess the effect of local skin temperature ranging from +20 °C to +38 °C on bleeding time found that a 15% reduction in the serum thromboxane B_2 concentration was linked to each 1 °C decline in temperature, causing longer clotting times at lower temperatures than higher temperatures. This disparity, therefore, could be caused by the effects of higher temperatures in Tamale on the clotting times, as RIs for clinical parameters may be affected by geographical variations. It is thus essential to establish RIs for various clinical parameters in various geographical areas to aid in the proper diagnosis and management of clinical conditions.

Females had relatively wider PT reference interval values than their male counterparts [F: (9.91–13.39) vs. M: (10.10–13.37) seconds]. Conversely, males showed relatively wider reference intervals for aPTT as compared to the female population [M: (19.86–35.47) vs. F: (21.40–35.20)]. This could be the result of the oestrogenic effects in females, as sex hormones are related to hypercoagulability [21]. Additionally, bleeding, particularly menorrhagia in females, which is one of the reactive causes of thrombocytosis, could be blamed for the shorter PT and aPTT reference intervals reported in this study.

Again, participants in the 18–20 age group had a relatively wider aPTT result than those in the 21–30 and 31–46 age groups. The fact that increased levels of coagulation factors are related to aging could be a feasible explanation for this finding [22]. Another plausible explanation for this could be the fact that prolonged aPTT is associated with young age due to the combination of several slightly lowered clotting factors [23–25]. PT showed no significant difference between the age categories. This study contradicts the findings of Ofosu et al. (2018) [16], who recorded higher PT and APTT among age groups of 21–30 years compared to 18–20 years and 31–48 years.

The current study revealed a significant negative correlation between age and aPTT, but no correlation was found between age and PT. This finding is similar to a previous study by Kurachi & Kurachi (2000) [26] that reported an increase in coagulation factors with an increase in age with subsequent prolongation of PT. The inverse correlation between age and aPTT could be linked to the combination of several slightly lowered clotting factors associated with aging [23, 25].

After stratifying by sex, female PT and aPTT did not indicate any significant association with age. Also, male PT did not also show any significant association with age, but an inversely significant association was observed between male aPTT and age). The statistically insignificant link between sex and PT contradicts the findings of previous studies by Abdillah (2018) [15] and Ofosu et al. (2018) [16], where the PT showed a significant inverse association among males and a direct association among females.

The study was limited by our inability to determine the effects of temperature on PT and aPTT. Also, the RIs for PT and aPTT established in this study are limited to only adults from 18 to 46 years and may not be inferred in children and the elderly.

5. Conclusion

The reference intervals for PT and aPTT established at Tamale Teaching Hospital in the northern part of Ghana were 10.02–13.37 and 20.41–35.28 seconds, respectively. Relatively wider RIs for PT and aPTT were found among the population in northern Ghana. PT correlated positively with age, while aPTT showed an inverse correlation with age. The median PT among the male participants was significantly higher than that of the females. It is expedient to establish reference ranges for PT and aPTT for each laboratory owing to the variations in geographical characteristics, lifestyle, and genetic variability.

6. Declarations

6.1. Author Contributions

Conceptualization, S.K.A., C.N., C.S.L., E.O.-Y., K.M., S.B.B., and G.A.; methodology, C.N., S.K.A., K.M., C.A.D., S.D., C.S.L., and S.B.B.; formal analysis, C.N., K.M., S.K.A., V.K., D.S., and F.O-B.; investigation, S.K.A., C.N., C.S.L., E.O-Y., V.K., and G.A.; data curation, C.S.L., E.O-Y., V.K., and S.D.; writing—original draft preparation, S.K.A., C.N., K.M., C.S.L., E.O-Y., F.O-B., D.S., C.A.D., and S.D.; writing—review and editing, S.K.A., C.N., K.M., F.O-B., D.S., C.A.D., S.B.B., V.K., G.A., E.O-Y., and S.D. All authors have read and agreed to the published version of the manuscript.

6.2. Data Availability Statement

Data presented in this study are available on request from the corresponding author.

6.3. Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

6.4. Acknowledgements

Authors appreciate the efforts of the staff of Tamale Teaching Hospital Haematology Laboratory, and the Department of Biomedical Laboratory Sciences, School of Allied Health Sciences, University for Development Studies, Tamale, Ghana. We are also grateful to all the subjects who willingly participated in the study.

6.5. Institutional Review Board Statement/Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval for the study was obtained from the Research and Ethics Committee of the University for Development Studies, Tamale, Ghana (UDS/RB/033/22). Permission was sought from the management of Tamale Teaching Hospital. Written or oral informed consent was taken from the study participants.

6.6. Informed Consent Statement

Written or oral informed consent was taken from the study participants.

6.7. Declaration of Competing Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies have been completely observed by the authors.

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