Reference values of clinical pathology parameters in cynomolgus monkeys (*Macaca fascicularis*) used in preclinical studies

Hyun-Kyu Park[1], Jae-Woo Cho[1], Byoung-Seok Lee[1], Heejin Park[1], Ji-Seok Han[1], Mi-Jin Yang[2], Wan-Jung Im[1], Do-Yong Park[1], Woo-Jin Kim[1], Su-Cheol Han[3], Yong-Bum Kim[1],*

[1]Pathology Research Center, Korea Institute of Toxicology (KIT), 141 Gajeongro, Yuseong-Gu, Daejeon, Korea
[2]Pathology Research Center, Korea Institute of Toxicology (KIT), 30 Baekhak 1-gil, Jeongeup, Jeonbuk, Korea
[3]General Toxicology Research Center, Korea Institute of Toxicology (KIT), 30 Baekhak 1-gil, Jeongeup, Jeonbuk, Korea

Nonhuman primates are increasingly used in biomedical research since they are highly homologous to humans compared to other rodent animals. However, there is limited reliable reference data of the clinical pathology parameters in cynomolgus monkeys, and in particular, only some coagulation and urinalysis parameters have been reported. Here, we reported the reference data of clinical chemical, hematological, blood coagulation, and urinalysis parameters in cynomolgus monkeys. The role of sex differences was analyzed and several parameters (including hematocrit, hemoglobin, red blood cell, blood urea nitrogen, total bilirubin, alkaline phosphatase, creatinine kinase, gamma-glutamyl tranferase, and lactate dehydrogenase) significantly differed between male and female subjects. In addition, compared to previous study results, lactate dehydrogenase, creatinine kinase, and aspartate aminotransferase showed significant variation. Inter-study differences could be affected by several factors, including age, sex, geographic origin, presence/absence of anesthetics, fasting state, and the analytical methods used. Therefore, it is important to deliberate with the overall reference indices. In conclusion, the current study provides a comprehensive and updated reference data of the clinical pathology parameters in cynomolgus monkeys and provides improved assessment criteria for evaluating preclinical studies or biomedical research.

Keywords: Cynomolgus monkey, clinical chemistry, hematology, blood coagulation, urinalysis

Cynomolgus monkeys (*Macaca fascicularis*) are one of the most widely employed nonhuman primate species in drug development, toxicology, and biomedical research. Cynomolgus monkeys appear to originate from tropical insular Southeast Asia and are commonly observed near seashore, swamps, and river banks [1]. The typical life span of a cynomolgus monkey ranges from 25-30 years and males and females attain sexual maturity at six and four years of age, respectively [2]. Cynomolgus monkeys are anatomically and physiologically homologous to humans compared to other animal models (e.g., rats, dogs). Furthermore, they share many other characteristics with humans. They are omnivorous, reflecting the diverse

habitats they live in and they are susceptible to age-related pathologies commonly observed in humans. Because of the increased use of cynomolgus monkey in nonclinical studies, it is necessary to establish the clinical pathology parameters in this monkey species to monitor their health and pathological status.

Clinical pathology testing including clinical chemistry, hematology, blood coagulation, and urinalysis is a standard element of nonclinical toxicology studies. These test results provide information regarding organ systems, metabolic function, and pathophysiologic response. Reference values are important in clinical and preclinical studies to evaluates health condition indices and improve

*Corresponding author: Yong-Bum Kim, Pathology Research Center, Korea Institute of Toxicology (KIT), 141 Gajeongro, Yuseong-Gu, Daejeon, 305-343, Korea
Tel: +82-42-610-8072; Fax: +82-42-610-8171; E-mail: ybkim@kitox.re.kr

the accuracy of drug safety studies. In addition, these indices are valuable for assessing possible effects in early investigational or discovery-type studies that lack control animals or baseline data [3]. In order to build an integrated, high-quality foundation for future cynomolgus monkey-based research, comprehensive and accurate reference values of clinical pathology parameters are required. The values obtained in this study will be used as baseline data for clinical chemistry, hematologic, blood coagulation, and urinalysis parameters in healthy cynomolgus monkeys.

Materials and Methods

Animals and ethical statement

Pretest results of clinical pathology parameters were examined in 18 preclinical toxicology studies carried out at Korea Institute of Toxicology (KIT) between 2011 and 2014. The study population comprised 113 cynomolgus monkeys (76 males and 37 females; age: 24-60 months; body weights: 2-4 kg) obtained from NafoVanny (Tam Phuoc Hamlet, Bien Hoa City, Dong Nai Province, Vietnam). All imported monkeys were quarantined at the nonhuman primate facility at Korea Institute of Toxicology (KIT) for at least 30 days. Throughout the study, the animal room environment was controlled (temperature maintained at 20-29ºC, humidity of 40-70%, approximately 12-hour light/12-hour dark cycle (08:00 to 20:00) with 150-300 lux, ventilation 10-20 times/hour, and negative pressure), and monkeys were housed individually in a stainless-steel cage (543W × 715L × 818H mm). The groups received filtered, ultraviolet light-irradiated municipal

Table 1. Parameters and analytical methods

Item	Parameter	Unit	Method
Hematology			
WBC	Total leukocyte count	$\times 10^3/\mu L$	Laser optical with cytochemical reaction
RBC	Total red blood cell count	$\times 10^6/\mu L$	Laser optical flow cytometry
HGB	Hemoglobin	g/dL	Cyanmethemoglobin spectrophotometry
HCT	Hematocrit	%	(MCVxRBC)/1000
MCV	Mean Corpuscular Volume	fL	Laser optical flow cytometry
MCH	Mean Corpuscular Hemoglobin	pg	(Hgb/RBCx100)
MCHC	Mean Corpuscular Hemoglobin Concentration	g/dL	(HGB/(RBCxMCV))x1000
PLT	Platelet count	$\times 10^3/\mu L$	Laser optical flow cytometry
RETA	Reticulocyte Count (absolute)	$\times 10^9/\mu L$	Laser optical with cytochemical reaction
NEUA	Neutrophil (absolute)	$\times 10^3/\mu L$	Perox optical with cytochemical reaction
LYMA	Lymphocyte (absolute)	$\times 10^3/\mu L$	Perox optical with cytochemical reaction
MONA	Monocyte (absolute)	$\times 10^3/\mu L$	Perox optical with cytochemical reaction
EOSA	Eosinophil (absolute)	$\times 10^3/\mu L$	Perox optical with cytochemical reaction
BASA	Basophil (absolute)	$\times 10^3/\mu L$	Laser optical with cytochemical reaction
LUCA	Large Unstained Cells (absolute)	$\times 10^3/\mu L$	Perox optical with cytochemical reaction
RDW	Red Cell Distribution Width	%	Calculated from the RBC volume SD and the MCV
RET	Reticulocyte Count %	%	Laser optical with cytochemical reaction
NEU	Neutrophil (%)	%	Perox optical with cytochemical reaction
LYM	Lymphocyte (%)	%	Perox optical with cytochemical reaction
MON	Monocyte (%)	%	Perox optical with cytochemical reaction
EOS	Eosinophil (%)	%	Perox optical with cytochemical reaction
BAS	Basophil (%)	%	Laser optical with cytochemical reaction
LUC	Large Unstained Cells (%)	%	Perox optical with cytochemical reaction
MPV	Mean Platelet Volume	fL	Mean of platelet volume histogram
Urinalysis			
U-K	Urine Potassium	mmol/L	Ion selective electrode (indirect)
U-Cl	Urine Chloride	mmol/L	Ion selective electrode (indirect)
U-Na	Urine Sodium	mmol/L	Ion selective electrode (indirect)
UTP	Urine Protein	mg/dL	Pyrogallol red
UGLU	Urine Glucose	mg/dL	Hexokinase-UV
UCRE	Urine Creatinine	mg/dL	Jaffe-kinetic
UALB	Urine albumin	mg/dL	Bromo cresol green method
P/C	Urine Protein Creatinine ratio	ratio	Calculated with UTP, UCRE

Table 1. Parameters and analytical methods (Continued)

Item	Parameter	Unit	Method
Chemistry			
GLU	Glucose	mg/dL	HK-G6PD-UV method
BUN	Blood urea nitrogen	mg/dL	Urease-GLDH (NH₃ free)
CREA	Creatinine	mg/dL	Jaffe-Kinetic method
TP	Total protein	g/dL	Biuret
ALB	Albumin	g/dL	Bromo cresol green method
A/G	Albumin globulin ratio	ratio	Calculated with TP, ALB
TCHO	Total cholesterol	mg/dL	Enzymeatic (COD-POD) method
TG	Triglyceride	mg/dL	Lipase, GK, GPO, POD without Glycerol blank
PL	Phospholipid	mg/dL	Enzymatic method
AST	Aspartate aminotransferase	IU/L	JSCC, UV-Rate
ALT	Alanine aminotransferase	IU/L	GSCC (DGKC), Karman, JSCC
TBIL	Total bilirubin	mg/dL	Oxidation method
ALP	Alkaline phosphatase	IU/L	p-NPP-DEA method
CK	Creatine phosphokinase	IU/L	UV-Rate
Ca	Calcium	mg/dL	OCPC colorimetry
IP	Inorganic phosphorus	mg/dL	Enzymatic method
Na	Sodium	mmol/L	Ion selective electrode, indirect
K	Potassium	mmol/L	Ion selective electrode, indirect
Cl	Chloride	mmol/L	Ion selective electrode, indirect
GGT	Gamma glutamyl transferase	IU/L	JSCC/IFCC substrate method
CRP	C-reactive protein	mg/L	Lattex agglutinine
LDH	Lactate dehydrogenase	IU/L	UV-Rate
HDL	High density lipoprotein	mg/dL	Direct method
LDL	Low density lipoprotein	mg/dL	Direct method
GLO	Globulin	g/dL	Calculated with TP, ALB
C3	Complement C3	mg/dL	Immunoturbidimetric
Coagulation			
PT	Prothrombin time	sec	Nephelometric analysis
APTT	Activated partial thromboplastin time	sec	Nephelometric analysis
FIB	Fibrinogen	mg/dL	Nephelometric analysis

tap water *ad libitum* and were fed approximately 60 g of food (Certified Primate Diet #5048, PMI nutrition International, Inc.) twice daily. The animals were managed at KIT, an accredited animal facility, complying with the AAALAC International Animal Care Policies. The Animal Care and Use Committee of the KIT reviewed and approved all the study protocols.

Hematology, clinical chemistry, and coagulation analysis

The parameters' abbreviations, units, and analysis methods are presented in Table 1. All animals were fasted overnight and blood samples were collected from the cephalic vein of non-anesthetized monkey for analysis of hematologic, coagulation, and serum chemistry parameters; if blood cannot be obtained from the cephalic vein, the saphenous or femoral vein was used.

Blood samples were collected in tubes containing K2-EDTA for hematologic analysis. Hematological parameters were analyzed using an Advia 2120i hematology analyzer (Siemens, USA).

For serum chemistry analysis, blood samples were collected in tubes and placed at room temperature for at least 90 min prior to centrifugation (approximately 3000 rpm, 10 minutes, at room temperature). Serum chemistry parameters were measured using a Toshiba 200FR NEO chemistry analyzer (Toshiba Co., Japan).

In addition, blood samples were collected in tubes containing 3.2% sodium citrate and plasma samples were obtained after centrifugation (approximately 3000 rpm, 10 minutes, at room temperature) and analyzed for prothrombin (PT), activated partial thromboplastin time (APTT), and fibrinogen (FIB) using an ACL 9000 coagulation analyzer (Instrumental Laboratory, Italy).

Table 2. Reference values of hematologic and urinalysis parameters for male cynomolgus monkeys

Tests	Item	Unit	N	Mean	SD	MIN	MAX
Hematology (Male)	WBC	x10³/μL	76	11.42	3.61	4.48	21.76
	RBC	x10⁶/μL	76	5.89	0.34	5.08	6.75
	HGB	g/dL	76	13.9	0.9	11.3	16.7
	HCT	%	76	45.7	3.3	35.4	54.4
	MCV	fL	76	77.7	4.5	68.2	89.5
	MCH	pg	76	23.6	1.2	20.5	26.4
	MCHC	g/dL	76	30.4	1.3	27.2	33.5
	PLT	x10³/μL	76	438	92	275	742
	RETA	x10⁹/μL	76	73.5	29.8	25.5	210.2
	NEUA	x10³/μL	76	5.77	3.57	1.10	19.43
	LYMA	x10³/μL	76	5.19	2.08	1.87	11.44
	MONA	x10³/μL	76	0.30	0.14	0.12	0.82
	EOSA	x10³/μL	74	0.07	0.08	0.01	0.49
	BASA	x10³/μL	75	0.04	0.02	0.01	0.10
	LUCA	x10³/μL	76	0.06	0.03	0.02	0.18
	RDW	%	60	12.3	0.7	11.0	14.7
	RET	%	76	1.25	0.54	0.46	4.10
	NEU	%	76	48.4	16.4	8.3	89.3
	LYM	%	76	47.5	15.6	9.8	86.9
	MON	%	71	2.7	1.1	0.5	5.9
	EOS	%	75	0.6	0.6	0.1	3.4
	BAS	%	76	0.3	0.2	0.1	0.8
	LUC	%	76	0.6	0.3	0.1	1.8
	MPV	fL	31	9.3	1.2	7.0	11.2
Urinalysis (Male)	VOL	ml	69	43.6	40.9	3.5	165.0
	SG		67	1.02	0.00	1.01	1.03
	pH		71	8	1	5	9
	U-K	mmol/L	61	62.47	35.15	9.95	152.93
	U-Cl	mmol/L	61	48	27	11	125
	U-Na	mmol/L	61	43	22	6	110
	UTP	mg/dL	21	2.24	2.11	0.16	7.88
	UGLU	mg/dL	4	2.7	0.9	1.6	3.6
	UCRE	mg/dL	56	61.24	38.45	6.28	193.18
	UALB	mg/dL	10	0.843	0.618	0.179	2.200
	P/C	ratio	21	0.037	0.037	0.003	0.160

Urinalysis

Animals were fasted overnight prior to urine collection. Urine samples were collected with a clean cage pan on wet ice (first void in the morning of each collection day), and the total fresh urine volume (VOL) was recorded. Urine samples were collected in a urine specimen container and kept cool with wet ice before analysis. Urinalysis was performed using a COBAS U 411 urine analyzer (Roche, Germany) and Combur 10 TM urine stick (Roche, Germany) to determine the following parameters: color, specific gravity (SG), pH, urine total protein (UTP), urine glucose (UGLU), urine creatinine (UCRE), urine albumin (UALB), and urine protein to creatinine ratio (P/C). Urine potassium (U-K), urine chlorine (U-Cl), and urine sodium (U-Na) were measured using a Toshiba 200FR NEO chemistry analyzer (Toshiba Co., Japan).

Statistical analysis

Unpaired t-test was applied to detect significant differences between male and female subjects (Tables 2 to 5). The significance level was set to 0.05 (*), 0.01 (**), 0.001 (***), and 0.0001 (****). All data processing, data management, and statistical analysis were performed using Prism 6 for Windows (Version 6.0 5 (trial), GraphPad Software Inc.).

Results and Discussion

In this study, hematological and biochemical analyses

Table 3. Reference values of clinical chemistry and coagulation test parameters for male cynomolgus monkeys

Tests	Item	Unit	N	Mean	SD	MIN	MAX
Clinical Chemistry (Male)	GLU	mg/dL	72	76.1	27.5	29.4	146.5
	BUN	mg/dL	72	25.5	4.6	17.2	36.8
	CREA	mg/dL	72	0.94	0.14	0.70	1.37
	TP	g/dL	76	8.23	0.58	7.20	9.83
	ALB	g/dL	76	4.55	0.23	4.11	5.05
	A/G	ratio	72	1.25	0.13	0.84	1.57
	TCHO	mg/dL	76	150	29	97	255
	TG	mg/dL	72	37.9	17.4	6.2	98.2
	PL	mg/dL	32	227	33	164	303
	AST	IU/L	76	61.4	21.8	30.4	134.6
	ALT	IU/L	76	51.8	24.0	19.7	176.8
	TBIL	mg/dL	76	0.269	0.110	0.144	0.655
	ALP	IU/L	76	1283.7	389.5	562.0	2633.2
	CK	IU/L	56	604	498	91	1869
	Ca	mg/dL	72	10.63	0.50	9.19	11.96
	IP	mg/dL	72	6.28	1.41	3.17	10.54
	Na	mmol/L	72	151	4	142	160
	K	mmol/L	72	5.21	0.81	3.94	7.93
	Cl	mmol/L	72	106	3	100	113
	GGT	IU/L	65	76.32	19.41	35.58	136.45
	CRP	mg/L	51	1.49	1.33	0.13	6.81
	LDH	IU/L	49	1463	544	750	3858
	HDL	mg/dL	21	79.3	18.5	49.9	116.7
	LDL	mg/dL	21	55.8	12.8	35.1	87.8
	GLO	g/dL	56	3.65	0.47	2.97	5.34
	C3	mg/dL	49	126.8	22.8	78.1	188.6
Coagulation Test (Male)	PT	sec	70	9.8	0.6	8.3	11.3
	APTT	sec	70	19.1	2.0	15.7	28.0
	FIB	mg/dl	50	245	58	155	463

of 113 cynomolgus monkeys (76 males and 37 females) were performed in order to establish baseline reference indices for the macaque species. Also, limited data is available on coagulation and urinalysis parameters with some updated data on clinical chemistry parameters (e.g., PL, LDL, HDL, CRP, and C3) in cynomolgus monkeys. These reference indices are essential in evaluating preclinical findings and selecting healthy subjects.

Although there are a few published studies reporting hematological and biochemical values in cynomolgus monkeys, these values may be influenced by various factors. Previous studies that have established reference values in cynomolgus monkeys with similar ages [1,4,5] are compared to the current study to identify inter-study variability.

First, in the case of hematologic parameters, there were marked similarities between our study and previous study results (Tables 2 and 4). This indicates that the hematology data of cynomolgus monkeys are consistent and are not affected by environmental variables; hence,

these data could be used to interpret the health of the monkey regardless of the region.

Second, regarding clinical chemistry parameters, the values of aspartate transaminase (AST), alanine transaminase (ALT), LDH, CK, TCHO, CREA, and ALP observed in the present study were higher than those reported by Tadashi *et al.* (2005) [4]; further, LDH, CK, and AST values were higher than those reported by Schuurman and Smith (2005) [5] (Tables 3 and 5). Intra- and inter-study difference in nonhuman primates were known to more variable compare to rodent species. The variables that may account for inter-study variations in cynomolgus monkey include age, sex, geographic origin, presence/absence of anesthetics, fasting, and gravity [6-11]. In addition, analytical instruments, reagents, and methods are variables that could influence the values obtained for a particular parameter, particularly in serum chemistry analysis. These factors are considered by comparing our data to those of previous studies (analytical methods are shown in Table 1). The analytical instrument and

Table 4. Reference values of hematologic and urinalysis parameters for female cynomolgus monkeys

Tests	Item	Unit	N	Mean	SD	MIN	MAX
Hematology (Female)	WBC	x10³/μL	37	11.51	4.75	5.58	26.60
	RBC	x10⁶/μL	37	5.58	0.38	4.97	6.45
	HGB	g/dL	37	13.5	0.6	12.0	14.7
	HCT	%	37	44.3	2.8	39.8	51.3
	MCV	fL	37	79.6	3.9	72.1	87.2
	MCH*	pg	37	24.2	1.0	22.2	26.8
	MCHC	g/dL	37	30.4	1.1	28.3	32.6
	PLT	x10³/μL	37	459.1	82.5	332	673
	RETA	x10⁹/μL	37	79.8	24.3	39.7	131.1
	NEUA	x10³/μL	37	6.43	4.11	2.00	19.63
	LYMA	x10³/μL	37	4.91	2.05	2.50	11.75
	MONA	x10³/μL	37	0.28	0.12	0.09	0.56
	EOSA	x10³/μL	36	0.07	0.06	0.01	0.29
	BASA	x10³/μL	37	0.04	0.04	0.01	0.24
	LUCA	x10³/μL	37	0.07	0.05	0.01	0.22
	RDW	%	17	12.0	0.7	10.8	13.4
	RET	%	37	1.44	0.46	0.70	2.41
	NEU	%	37	50.7	14.6	25.2	86.7
	LYM	%	37	45.2	14.0	11.0	70.8
	MON	%	32	2.5	0.8	1.1	4.9
	EOS	%	36	0.7	0.6	0.1	2.7
	BAS	%	37	0.3	0.2	0.1	0.9
	LUC	%	37	0.6	0.3	0.1	1.3
	MPV	fL	7	8.7	0.4	8.3	9.4
Urinalysis (Female)	VOL	mL	35	83	78	8	340
	SG		36	1.017	0.004	1.010	1.025
	pH		36	8	1	7	9
	U-K	mmol/L	26	55.02	26.44	12.27	104.49
	U-Cl	mmol/L	26	47	22	13	95
	U-Na	mmol/L	26	42	22	7	87
	UTP	mg/dL	5	1.85	2.00	0.08	4.65
	UGLU	mg/dL	4	1.9	0.7	1.1	2.6
	UCRE	mg/dL	21	59.44	32.02	6.50	148.19
	UALB	mg/dL	10	1.052	0.724	0.311	2.561
	P/C	ratio	5	0.022	0.019	0.001	0.050

methods (ALT, ALP, LDH, CREA, and Ca) employed by Tadashi *et al.* (2005) [4] were different to those employed in our study. Physiologic variance of the indices also affected inter-study variation. ALP is present in biliary and canalicular membranes, the kidney, intestine, and bone and age-related changes in osseous ALP were observed, reflecting bone growth in juvenile periods [12,13]. LDH and CK were affected by skeletal muscle mass and there were many false positives for myotoxicity because of background injury associated with handling or restraint, especially with nonhuman primates since there were struggles, trauma, fever, and muscle puncture during sampling procedures [14]. Therefore, when applying these parameters, age, sex, body weight, and analytical methods should be

considered to evaluate the data accurately.

Third, in the coagulation study, mean PT and APTT values in male and female monkeys were 9.76 s and 9.75 s and 19.06 s and 19.33 s, respectively. No significant differences in PT and APTT were observed between male and female juvenile cynomolgus monkeys (Tables 3 and 5). Our study showed a similar result as previous research. However, it appears that there are significant differences in PT and APTT values between juvenile cynomolgus and rhesus monkeys; hence, the type of subspecies monkey should be considered [15]. Last, regarding the urinalysis parameters, values for urine SG, pH, U-K, U-Cl, and U-Na were similar between male and female monkeys (Tables 2 and 4). There is limited urinalysis data from previous study of cynomolgus

Table 5. Reference values of clinical chemistry and coagulation test parameters for female cynomolgus monkeys

Tests	Item	Unit	N	Mean	SD	MIN	MAX
Clinical Chemistry (Female)	GLU	mg/dL	37	72.9	34.8	31.3	184.2
	BUN	mg/dL	37	22.6	3.8	15.5	32.2
	CREA	mg/dL	37	0.90	0.12	0.69	1.20
	TP	g/dL	37	8.18	0.50	7.30	9.39
	ALB	g/dL	37	4.47	0.26	3.79	4.95
	A/G	ratio	37	1.21	0.14	0.93	1.50
	TCHO	mg/dL	37	137	36	60	226
	TG	mg/dL	37	30.8	16.1	7.7	83.7
	PL	mg/dL	20	204	39	126	277
	AST	IU/L	36	62.7	39.1	22.7	243.4
	ALT	IU/L	37	60.0	45.0	2.2	283.7
	TBIL	mg/dL	37	0.213	0.071	0.067	0.415
	ALP	IU/L	37	1059.4	324.9	563.5	2256.8
	CK	IU/L	33	344	225	113	1054
	Ca	mg/dL	37	10.52	0.44	9.77	11.55
	IP	mg/dL	37	6.20	1.19	3.27	8.70
	Na	mmol/L	37	150	4	145	165
	K	mmol/L	37	5.29	0.69	4.17	7.28
	Cl	mmol/L	37	107	3	102	113
	GGT	IU/L	37	64.68	16.59	35.64	106.73
	CRP	mg/L	17	1.32	0.90	0.22	4.36
	LDH	IU/L	17	1082	305	682	1683
	GLO	g/dL	17	3.65	0.44	2.93	4.63
	C3	mg/dL	15	109.8	21.4	73.4	135.9
Coagulation Test (Female)	PT	sec	37	9.7	0.5	8.8	11.3
	APTT	sec	37	19.3	2.0	16.6	24.1
	FIB	mg/dl	17	261	56	191	386

monkeys; the urinalysis data obtained from the present study will be valuable for future study of cynomolgus monkeys.

In the current study, sex-related differences were apparent in several hematological and biochemical parameters (Table 6). Red blood cell indices (RBC, HGB, and HCT) are important diagnostic parameters for anemia and internal hemorrhage. Consistent with previous data [1], our findings demonstrated that female monkeys have lower RBC, HGB, and HCT values than male monkeys. This tendency observed in red blood cell parameters was also observed in Sprague-Dawley rats and could be associated to the differential oxygen demand in relation to age and sex [16]. The clinical chemistry data showed that the most remarkable differences were observed in BUN, TBIL, ALP, CK, GGT, and LDH values (male vs. female, $P<0.01$). These indices showed sex-related difference attributed to the variation between male and female subjects in protein catabolism, food intake (BUN), mass of skeletal muscle (CK and LDH), specificity of tissue distribution (ALP), increased microsomal enzyme production, poor health

condition (GGT) [3], and different rates of bilirubin metabolism (TBIL).

In conclusion, there are significant similarities between studies in several parameters values including most blood indices; however, some parameters (e.g., LDH, ALP, and CK) displayed large inter-study variability. This study provides valuable supplementation to the less extensively studied clinical chemistry (e.g., PL, LDL, HDL, CRP, and C3), coagulation (FIB), and urinalysis parameters. Our results will thus provide supplemental information on reference data of clinical pathological parameters in cynomolgus monkeys.

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Table 6. Reference values of statistically significant sex differences

Tests	Item	Sex	Mean	SD	MIN	MAX
Hematology	RBC****	Male	5.89	0.34	5.08	6.75
		Female	5.58	0.38	4.97	6.45
	HGB*	Male	13.9	0.9	11.3	16.7
		Female	13.5	0.6	12.0	14.7
	HCT*	Male	45.7	3.3	35.4	54.4
		Female	44.3	2.8	39.8	51.3
	MCV*	Male	77.7	4.5	68.2	89.5
		Female	79.6	3.9	72.1	87.2
	MCH*	Male	23.6	1.2	20.5	26.4
		Female	24.2	1.0	22.2	26.8
Clinical Chemistry	BUN**	Male	25.5	4.6	17.2	36.8
		Female	22.6	3.8	15.5	32.2
	TCHO*	Male	150	29	97	255
		Female	137	36	60	226
	TG*	Male	37.9	17.4	6.2	98.2
		Female	30.8	16.1	7.7	83.7
	PL*	Male	227	33	164	303
		Female	204	39	126	277
	TBIL**	Male	0.269	0.110	0.144	0.655
		Female	0.213	0.071	0.067	0.415
	ALP**	Male	1283.7	389.5	562.0	2633.2
		Female	1059.4	324.9	563.5	2256.8
	CK**	Male	604	498	91	1869
		Female	344	225	113	1054
	GGT**	Male	76.32	19.41	35.58	136.45
		Female	64.68	16.59	35.64	106.73
	LDH**	Male	1463	544	750	3858
		Female	1082	305	682	1683

Unpaired t-test was applied to detect significant differences between male and female subjects. The significance level was set to 0.05 (*), 0.01 (**), 0.001(***), and 0.0001(****).

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