Journal of the American Association for Laboratory Animal Science
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Vol 61, No 1
January 2022
Pages 21–30

Biochemical and Hematologic Reference Intervals for Anesthetized, Female, Juvenile Yorkshire Swine

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Swine are widely used in biomedical research, translational research, xenotransplantation, and agriculture. For these uses, physiologic reference intervals are extremely important for assessing the health status of the swine and diagnosing disease. However, few biochemical and hematologic reference intervals that comply with guidelines from the Clinical and Laboratory Standards Institute and the American Society for Veterinary Clinical Pathology are available for swine. These guidelines state that reference intervals should be determined by using 120 subjects or more. The aim of this study was to generate hematologic and biochemical reference intervals for female, juvenile Yorkshire swine (*Sus scrofa domesticus*) and to compare these values with those for humans and baboons (*Papio hamadryas*). Blood samples were collected from the femoral artery or vein of female, juvenile Yorkshire swine, and standard hematologic and biochemical parameters were analyzed in multiple studies. Hematologic and biochemical reference intervals were calculated for arterial blood samples from Yorkshire swine (*n* = 121 to 124); human and baboon reference intervals were obtained from the literature. Arterial reference intervals for Yorkshire swine differed significantly from those for humans and baboons in all commonly measured parameters except platelet count, which did not differ significantly from the human value, and glucose, which was not significantly different from the baboon value. These data provide valuable information for investigators using female, juvenile Yorkshire swine for biomedical research, as disease models, and in xenotransplantation studies as well as useful physiologic information for veterinarians and livestock producers. Our findings highlight the need for caution when comparing data and study outcomes between species.

Abbreviations: ASVCP, American Society for Veterinary Clinical Pathology; CLSI, Clinical and Laboratory Standards Institute

DOI: 10.30802/AALAS-JAALAS-21-000014

Swine are one of the most commonly used species for surgical training, biomedical studies and translational research.[34] These uses include a wide range of disease models and applications, including xenotransplantation,[28,35] medical device translation,[19] infectious disease models,[30] and cardiovascular disease models.[2] This popularity is largely due to their similarities to humans with regard to their size, body and organ weight, blood volume,[38] capacity for clinical monitoring,[39] lifespan, physiology, metabolism and biochemistry[2,38] response to pathogens,[30] and gastrointestinal disturbances.[7] Indeed, for medical device translation, the FDA requires that technologies must be evaluated in one large animal, for which swine are recommended.[44] In addition, porcine xenografts are already used clinically in humans for specific indications, including porcine heart valves and acellular matrices.[5] Recent advances in genomic editing of pigs establishes the possibility to better replicate human diseases or generate organs for xenotransplantation with reduced rejection rates.[26,41] In particular, female, juvenile, Yorkshire swine are one of the most commonly used sex, age range, and breed for all of the types of biomedical research just listed.[20,24,30,33,36,39,43]

In all these applications, monitoring the health status of animals and identifying abnormalities is critical to disease diagnosis.[6,10] Reference intervals of clinical laboratory results form the basis of diagnostic interpretation and are the most widely used decision-making tool.[4,15,22,32] In addition, accessibility to clinical data is extremely important for the refinement of animal studies.[37]

The National Committee for Clinical Laboratory Standards, Clinical and Laboratory Standards Institute (CLSI), and the American Society for Veterinary Clinical Pathology (ASVCP) recommend nonparametric reference intervals consisting of at least 120 values from separate individuals.[1,12,15,17] However, few laboratories can define their own reference intervals for a range of reasons including the time, cost, and capacity to do so.[22] At present, little information is available on hematologic and biochemical reference values for Yorkshire swine (*Sus scrofa domesticus*). Existing studies report reference values that were based on sample sizes too small for accurate designation of reference intervals,[9,23,37,40] used swine that belonged to specifically defined groups (for example, pathogen free[7,27]), used animals that originated from multiple farms,[3,23] or used animals that were from specific populations (for example, midgestation sows.[3]

Received: 8 Feb 2021. Revisions requested: 19 Mar 2021. Accepted: 5 Aug 2021.
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The goal of the present study was to compile and report reference intervals that were generated according to CLSI and ASVCP guidelines for arterial hematology and blood chemistry for Yorkshire swine (*Sus scrofa domesticus*) and to compare these swine values with published reference intervals for baboons (*Papio hamadryas*) and humans. These *Sus scrofa domesticus* reference intervals and comparisons will provide researchers and veterinarians with information that should be helpful for interpretation of clinical laboratory parameters and research refinement in future studies.

Materials and Methods

Animal husbandry and procedure. This study was conducted at an AAALAC-accredited and USDA-registered facility in accordance with NIH guidelines. Samples were collected from animals as part of various studies from 2012 to 2018 for which experimental protocol approval was obtained from the IACUC (protocol numbers 12-06-2202, 13-07-2453, 14-03-2519/17-03-3400, and 15-11-3100/18-10-3802) and the Animal Care and Use Review Office of the US Army Medical Research and Materiel Command Office of the Department of Defense. The quality assurance program of the facility included triennial AAALAC inspections, annual USDA inspections and semiannual IACUC inspections. Samples were collected from 150 healthy, female, anesthetized, conventional (single herd), juvenile Yorkshire swine (*Sus scrofa domesticus*; age, 3 to 4 mo; weight, 42.7 kg ± 5.9) purchased from a USDA-licensed vendor in Massachusetts (details available upon request from the corresponding author). The herd had a comprehensive vaccination and parasite control program and was validated brucellosis-free and certified pseudorabies-free through quarterly blood testing by the Massachusetts state veterinarian. Swine were housed individually in adjacent pens (20.7 ft^2; temperature set point, 72 ± 2 °F, which was centrally monitored and alarm-controlled) and acclimated for 72 h (minimum) with a 12:12-h light:dark cycle (0700 to 1900). Animals were fed Laboratory Mini-Pig Grower Diet 5081 (Purina LabDiet, St. Louis, MO) based on animal weight and required caloric intake. Food was withheld for 12 h prior to the study, and water was freely accessible throughout studies.

Swine were premedicated, anesthetized and ventilated according to previously described procedures.[39] Briefly, swine were anesthetized via intramuscular injections of atropine (0.04 mg/kg), tiletamine–zolazepam (4.4 mg/kg), and xyalzine (2.2 mg/kg); randomized pairs of animals were anesthetized, and individual animals were staggered by approximately 2 h. Anesthesia was maintained by endotracheal tube (8 to 9 mm) delivery of isoflurane (1.5% to 3.0%) and oxygen (1.4 to 2.0 l/min) by using a positive-pressure ventilator. Swine were placed in the supine position and had a 20-gauge intravenous cannula placed in the left or right marginal ear vein for the administration of sterile saline (0.9% NaCl), which was given continuously at a rate of 100 to 400 mL/h during anesthesia, and other drugs and fluids that were provided as indicated for specific protocol procedures. A 12-French Foley catheter was placed for urinary drainage (SurgiVet, Smiths Medical, Dublin, OH). Ventilator settings were determined on an individual basis, depending on animal size. Animals on mechanical ventilation were given a tidal volume of 10 mL/kg and a set respiratory rate, which were adjusted to maintain peak airway pressure between 12 to 18 mm Hg. Throughout the anesthetic procedure, manual breaths were given at intervals to allow lung expansion to prevent any lung collapse. End tidal CO_2 was continuously monitored, and ventilation settings were adjusted to maintain $ETCO_2$ at 30 to 40 mm Hg. In addition, blood gas values (obtained as described later) were used to ensure that ventilation settings provided adequate support. At the conclusion of the study, swine were heparinized (300 U/kg) and then received atropine (0.04 mg/kg), tiletamine–zolazepam (4.4 mg/kg) and xyalzine (2.2 mg/kg), prior to an intravascular lethal dose of Fatal Plus (Vortech Pharmaceuticals, MI).

Blood sampling and processing. The femoral artery (n = 128) or femoral vein (n = 22) was cannulated by using a 6- to 9-French percutaneous sheath catheter (Arrow, Teleflex, NC). Samples for blood gas, biochemistry, and hematology analysis were obtained prior to subsequent research procedures as stipulated in each approved protocol. Blood was sampled preferentially from the artery first, but if the venous line was placed first, a blood sample was taken from that vessel prior to placement and blood sampling from the arterial line. Blood was split into individual vacuum phlebotomy tubes immediately after being drawn and was analyzed within 1 h of collection (stored at room temperature) as follows: CBC analysis of K_2-EDTA-treated whole blood was performed by using a fully automated VetScan HM5 (Abaxis Veterinary Diagnostics, Union City, CA); blood gas analysis was performed by using heparinized whole blood on an automated Stat Profile pHOx Analyzer (Nova Biomedical, Waltham, MA); blood chemistry was performed by using heparinized whole blood on an automated VetScan VS2 (Abaxis Veterinary Diagnostics, Union City, CA); coagulation analysis was performed on citrated whole blood by using an automated VetScan VSpro (Abaxis Veterinary Diagnostics) for partial thromboplastin time and activated partial thromboplastin time, and activated clotting time was measured from whole blood using an automated Hemochron Response (Accriva Diagnostics). All machines were automated, reducing human-induced variability and error and were used according to the manufacturer's instructions. This included monthly calibration and quality control procedures according to manufacturer's recommendations to ensure accuracy. Maintenance and service were likewise performed according to the manufacturer's instructions.

Statistical analysis. All data processing, data management, and statistical analysis for all plots and tables were performed by using R (3.6.0). All variables are continuous. The normality of the arterial and venous data was assessed by using graphical methods and the Shapiro–Wilk test for normality, considering 5% as the level of significance. According to ASVCP guidelines, the reference interval is defined as the 95% interval between the 2.5% and 97.5% points of the distribution.[1,12] Data were ordered, and the 2.5th and 97.5th percentiles of each analyte along with their respective 90% CI were identified to form the 95% reference interval. Outliers were detected and removed at the upper and lower extremities by using Tukey interquartile fences and the Boyd and Harris criteria (on an individual parameter basis, n=2-7/parameter) so that the width of the 90% CI of the 2.5th and 97.5th percentiles did not exceed 0.2 times the width of the reference interval.[14,16] After removal of outliers, the descriptive statistics mean, median, and measures of variability including ± 1 SD, first and third quartile, interquartile range, and minimum and maximum values for both arterial and venous analytes were calculated. Reference intervals of both the arterial analytes and the 90% CI of the 2.5th and 97.5th percentiles were identified nonparametrically as recommended by the ASVCP guidelines; CI of the mean were also calculated for the venous data.

Results were deemed as statistically significant when the null hypothesis could be rejected with greater than 95% confidence ($P < 0.05$). Statistically significant differences between the arterial and venous data were identified for each parameter by using

t test when both parameters had normal distribution or if not by using the Mann–Whitney *U* test. Comparisons between arterial swine results and human data and between arterial swine results and baboon data were performed by using single-sample *t* tests. Arterial analyte data were visualized by using combined raincloud plots (split-half violins and dot plots) with box plots, which provide an overview of the examined data. Interspecies comparisons were presented as point-range plots. Human (adult, gender not specified) and baboon (age, 11 mo to 11 y; male and female) data were obtained from the literature.[13,21]

Results

After stabilization of anesthesia, blood samples were collected from the femoral artery of 124 swine for analysis of 11 hematologic and 14 biochemical parameters. Mean values, 1 SD, median, interquartile ranges and 90% CI, and reference intervals were calculated when the number of animals was at least 120 after the removal of outliers for hematologic parameters (Table 1) and biochemical parameters (Table 2). Reference intervals were calculated according to CLSI and ASVCP guidelines. Raincloud plots including box plots show the number of samples for each parameter, the spread of the data, and descriptive statistics for hematology parameters (Figure 1) and biochemistry parameters (Figure 2).

Blood samples were also collected from the femoral veins of 21 pigs for comparison to arterial hematologic (Table 3) and biochemical values (Table 4). Statistical comparison of arterial and venous hematologic values showed that only the platelet count was significantly higher in venous samples ($359 \pm 87.85 \times 10^9$/L) than in arterial samples ($301.8 \pm 78.84 \times 10^9$/L; $P < 0.05$; Table 3). Phosphorous ($P < 0.05$), Na^+ ($P < 0.001$), total protein ($P < 0.001$), and globulin ($P < 0.05$) values were significantly higher in venous samples than in arterial samples, and K^+ was significantly ($P < 0.05$) lower in venous than arterial samples (Table 4).

Swine reference intervals were compared with published baboon (*Papio hamadryas*)[13] and human[21] reference intervals for hematologic (Table 5) and biochemical (Table 6) parameters. Point-range plots of reference interval comparisons between species are shown in Figure 3 for comparison. All swine hematologic reference intervals were significantly different from those for humans and baboon ($P < 0.01$) except for platelets, for which swine and human values were similar. All swine biochemical reference intervals were significantly different from those for both humans and baboon ($P < 0.001$) except for glucose, for which swine and baboons were similar.

Discussion

In this study, we generated reference intervals according to the CLIS and ASVCP guidelines for 11 hematologic and 14 biochemical parameters collected from the femoral arteries of anesthetized, juvenile, female Yorkshire swine (*Sus scrofa domesticus*). Reference intervals are important for the interpretation

Table 1. Descriptive statistics and reference intervals for arterial hematologic parameters of juvenile Yorkshire swine (*Sus scrofa domesticus*)

Analyte (unit)	*n*	Mean	1 SD	Median	Interquartile range	Minimum	Maximum	Lower limit of 90% CI	Upper limit of 90% CI	Reference interval
WBC ($\times 10^9$/L)	124	14.76	3.27	14.32	5.3	9.73	23.4	9.73–10.32	20.10–22.04	9.9–21.97
Lymphocytes ($\times 10^9$/L)	124	10.05	1.93	9.8	2.69	5.98	15.25	5.98–7.3	13.37–14.56	6.35–14.41
Monocytes ($\times 10^9$/L)	123	0.19	0.1	0.14	0.15	0.06	0.44	0.06–0.08	0.38–0.44	0.06–0.41
Neutrophils ($\times 10^9$/L)	121	4.35	1.78	4.05	2.43	1.43	9.21	1.43–2.19	7.72–9.06	1.96–8.81
Lymphocytes (%)	124	69.11	8.11	69.45	11.25	46.7	85.5	50–55.3	79.9–85.5	50.05–83.46
Monocytes (%)	122	1.26	0.59	1.1	0.9	0.5	3	0.5–0.6	2.3–3	0.50–3
Neutrophils (%)	124	29.56	7.94	29.05	11	12.6	51.7	12.6–19	42.3–49	15.78–48.95
RBC ($\times 10^{12}$/L)	122	6.1	0.55	6.08	0.73	4.67	7.24	4.59–5.05	7.01–7.24	4.80–7.11
Hgb (g/dL)	123	9.77	0.82	9.7	1.05	8	11.7	8–8.3	11.1–11.7	8.20–11.7
Hct (%)	124	32.46	3.01	32.47	4.06	24.92	39.84	24.92–27.01	36.25–38.79	25.38–38.77
Platelets ($\times 10^9$/L)	123	301.8	78.84	294	126	154	462	154–186	438–462	161.6–449

Table 2. Descriptive statistics and reference intervals for arterial biochemical parameters of juvenile Yorkshire swine (*Sus scrofa domesticus*)

Analyte (unit)	*n*	Mean	1 SD	Median	Interquartile range	Minimum	Maximum	Lower limit 90% CI	Upper limit 90% CI	Reference interval
Albumin (g/dL)	124	3.53	0.53	3.6	0.83	2	4.4	2.5–2.8	4.2–4.4	2.5–4.39
ALP (U/L)	122	85.77	20.33	82.5	26.5	55	137	55–58	121–137	56–133.7
ALT (U/L)	124	37.94	8.08	38	11.25	24	61	24–26	49–55	25–54.88
Amylase (U/L)	124	1831.73	558.57	1756.5	924	670	3066	670–980	2702–3066	739–2882
Total bilirubin (mg/dL)	124	0.33	0.07	0.3	0.1	0.2	0.5	0.2	0.4–0.5	0.2–0.5
BUN (mg/dL)	124	5.52	2	5	3	2	11	2–3	9–10	2–10.88
Ca^{2+} (mg/dL)	124	10.26	0.50	10.3	0.6	9.1	11.3	9.1–9.3	11–11.3	9.2–11.2
Phosphorus (mg/dL)	124	8.21	0.92	8.1	1.23	6.6	10.9	6.6–6.9	9.8–10.4	6.8–10.58
Creatinine (mg/dL)	124	1.34	0.24	1.3	0.3	0.8	2	0.8–1.0	1.8–2	0.9–1.89
Glucose (mg/dL)	124	100.35	25.35	98.5	30	48	181	48–61	147–159	52–153.88
Na^+ (mmol/L)	124	135.72	3	136	3	124	144	129–131	140–141	129–142.75
K^+ (mmol/L)	124	4.1	0.3	4.1	0.4	3.4	4.8	3.4–3.6	4.6–4.8	3.5–4.7
Total protein (g/dL)	124	6.28	0.53	6.3	0.8	4.9	7.8	4.9–5.3	7–7.2	5.1–7.19
Globulin (g/dL)	124	2.75	0.59	2.7	0.8	1.6	4.2	1.6–2.0	3.9–4.2	1.8–4.09

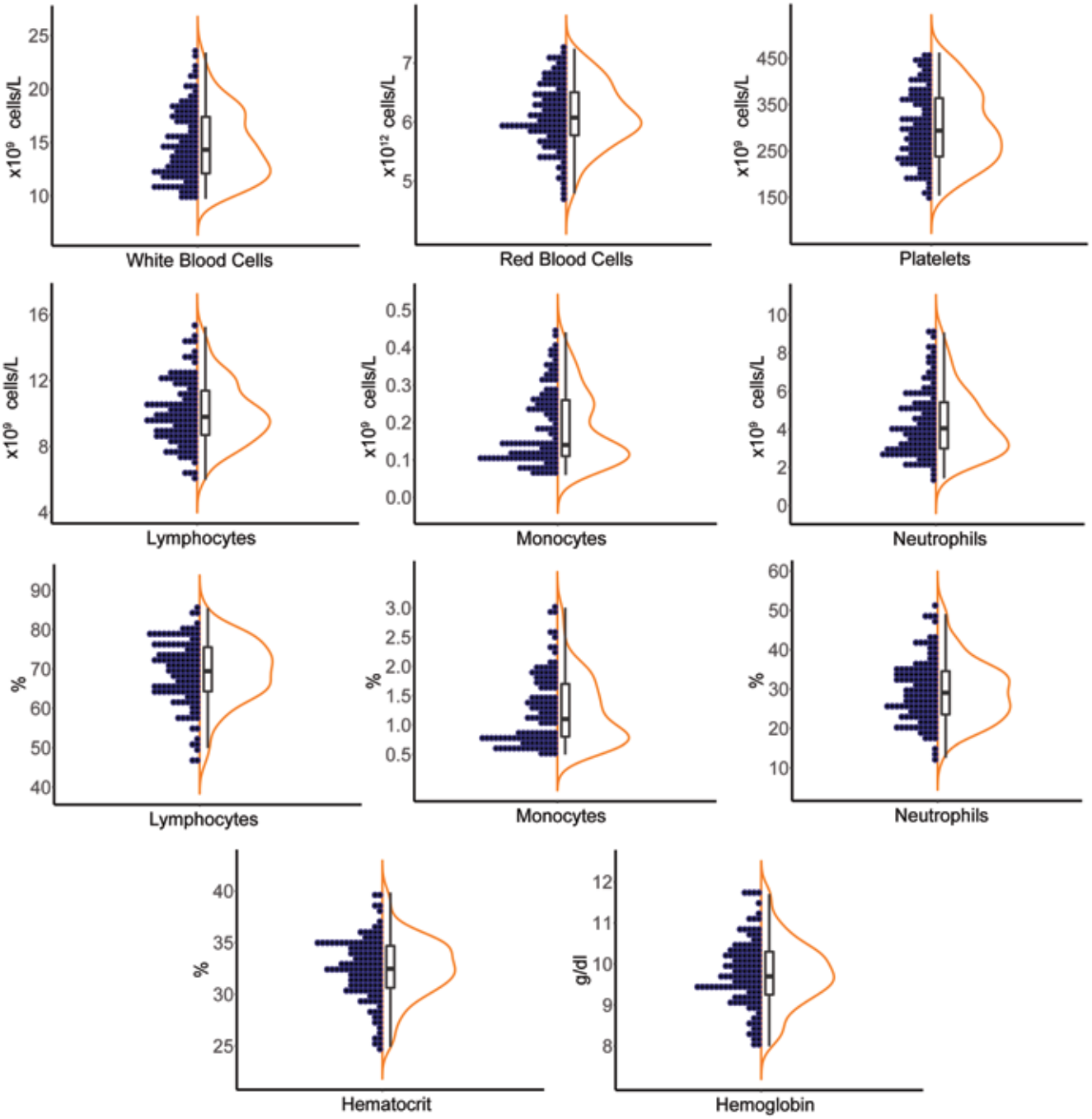

Figure 1. Raincloud and box plots of hematology markers enable simultaneous visualization of multiple statistics (n = 121–124). Raincloud plots display individual sample values plotted as individual blue dots in the rain plots and as density curves (orange lines), whereas box plots display the distribution and skewness of the data via descriptive statistics (including first quartile, median, and third quartile). Cell counts are expressed as cell number per liter for RBC, WBC, platelets, lymphocytes, monocytes, and neutrophils. Lymphocytes, monocytes, and neutrophils are also expressed as a percentage of total WBC. Hct is measured as a percentage of blood volume, and Hgb is in g/dL.

of clinical hematology and biochemistry results to accurately determine animal health. Existing reference intervals for Yorkshire swine are sparse, likely due to the cost, resources, and personnel capacity necessary to sample enough animals to generate reference intervals according to the CLIS and ASVCP guidelines. While these reference values cannot be used to replace the inclusion of appropriate control groups as part of a well-designed study, they can be used to evaluate the reliability of control results with expected ranges, thereby allowing faster identification of abnormal values and saving time, expense, and animal lives.

We compared samples from the femoral artery (n = 121 to 124) with a smaller number of samples collected from the femoral vein (n = 20 to 21) and found only platelet count was different between sites (significantly higher in venous samples). Although the number of animals in the venous group was too small to define reference intervals, this difference in platelet count agrees with previously findings of higher platelet counts in venous samples;[42] however, the opposite has also been reported.[8] In addition, several biochemical parameters were significantly different in arterial and venous samples. Phosphorus, Na^+, total protein, and globulin values were higher in our venous samples,

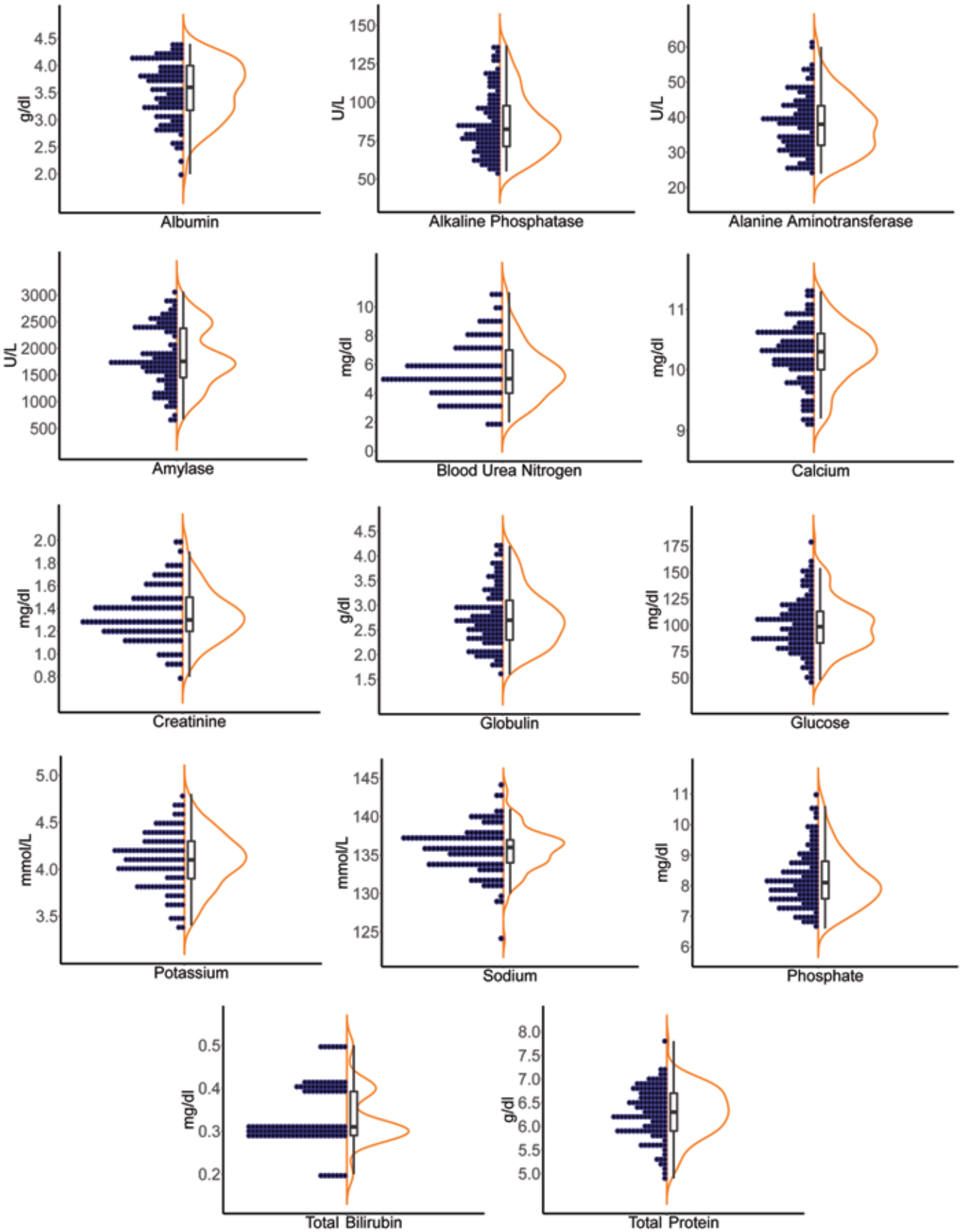

Figure 2. Raincloud and box plots of biochemical markers (n = 121–124). Albumin, globulin, and total protein are expressed in g/dL. ALP, ALT, and amylase are expressed as U/L. BUN, calcium, creatinine, glucose, potassium, sodium, phosphate, and total bilirubin are expressed as mg/dL.

Table 3. Descriptive statistics and reference intervals for venous hematologic parameters of juvenile Yorkshire swine (*Sus scrofa domesticus*) and statistical comparison with arterial parameters

Analyte (unit)	*n*	Mean	1 SD	Median	Interquartile range	Minimum	Maximum	95% CI of the mean	Test statistic (arterial compared with venous)	*P*
WBC ($\times 10^9$/L)	21	16.17	3.33	16.06	4.99	10.94	22.14	14.75–17.6	Mann–Whitney *U* test	ns
Lymphocytes ($\times 10^9$/L)	21	10.77	1.88	10.51	2.72	7.3	14.89	9.97–11.58	*t* test	ns
Monocytes ($\times 10^9$/L)	21	0.18	0.11	0.16	0.11	0.05	0.44	0.14–0.23	Mann–Whitney *U* test	ns
Neutrophils ($\times 10^9$/L)	21	5.22	2.74	4.09	3.43	1.62	12.68	4.05–6.39	Mann–Whitney *U* test	ns
Lymphocytes (%)	21	67.98	11.43	70.1	17.3	41.9	85.6	63.09–72.86	Mann–Whitney *U* test	ns
Monocytes (%)	21	1.1	0.53	0.9	0.8	0.5	2.3	0.87–1.33	Mann–Whitney *U* test	ns
Neutrophils (%)	21	31.15	10.98	29	16.4	13.9	57.3	26.46–35.85	*t* test	ns
RBC ($\times 10^{12}$/L)	21	6.38	0.93	6.23	0.67	4.38	8.54	5.98–6.78	*t* test	ns
Hgb (g/dL)	21	9.99	1.44	10	1.3	8.00	14	9.37–10.6	*t* test	ns
Hct (%)	21	34.47	4.78	34.55	3.29	25.25	47	32.42–36.51	*t* test	ns
Platelets ($\times 10^9$/L)	21	359	87.85	342	70	180	559	321.43–396.57	Mann–Whitney *U* test	<0.05

ns, nonsignificant

Table 4. Descriptive statistics and reference intervals for venous biochemical parameters of juvenile Yorkshire swine (*Sus scrofa domesticus*) and statistical comparison with arterial parameters

Analyte (unit)	*n*	Mean	1 SD	Median	Interquartile range	Minimum	Maximum	95% CI of the mean	Test statistic (arterial compared with venous)	*P*
Albumin (g/dL)	21	3.66	0.52	3.6	0.9	2.4	4.5	3.44–3.89	Mann–Whitney *U* test	ns
ALP(U/L)	21	85.24	39.44	69	32	40	224	68.37–102.11	Mann–Whitney *U* test	ns
ALT(U/L)	21	37.29	7.43	37	11	27	55	34.11–40.46	Mann–Whitney *U* test	ns
Amylase (U/L)	20	1650.25	422.73	1631.5	462.25	1040	2689	1464.98–1835.52	Mann–Whitney *U* test	ns
Total bilirubin (mg/dL)	21	0.35	0.07	0.3	0.1	0.2	0.5	0.32–0.38	Mann–Whitney *U* test	ns
BUN (mg/dL)	21	5.38	2.58	5	3	2	13	4.28–6.48	Mann–Whitney *U* test	ns
Ca^{2+} (mg/dL)	21	10.44	0.46	10.4	0.5	9.4	11.5	10.24–10.63	Mann–Whitney *U* test	ns
Phosphorus (mg/dL)	21	8.55	0.94	8.7	1	5.8	10	8.15–8.95	Mann–Whitney *U* test	<0.05
Creatinine (mg/dL)	21	1.28	0.29	1.3	0.2	0.6	1.8	1.15–1.4	Mann–Whitney *U* test	ns
Glucose (mg/dL)	21	91.76	27.03	89	27	51	168	80.20–103.32	*t* test	ns
Na^+ (mmol/L)	21	138.10	2.39	138	3	132	141	137.07–139.12	Mann–Whitney *U* test	<0.001
K^+(mmol/L)	21	3.95	0.32	3.9	0.4	3.6	4.7	3.81–4.08	Mann–Whitney *U* test	<0.05
Total protein (g/dL)	21	6.68	0.43	6.7	0.6	5.9	7.5	6.50–6.87	*t* test	<0.001
Globulin (g/dL)	21	3.02	0.45	3	0.4	1.8	3.9	2.83–3.22	Mann–Whitney *U* test	<0.05

Ns, nonsignificant

and K^+ was higher in the arterial samples. These differences could be due to the low number of animals that contributed venous samples or the difference in collection location (femoral artery or femoral vein) or differences in fluidic conditions during blood collection between the artery and vein.[8] The majority of studies report venous hematologic and biochemical data. One study reported hematologic and biochemical data from femoral artery blood samples of 5-d-old Italian Large white × Duroc × Landrace swine as compared with 30-d-old animals that had received an iron supplement on day 3 (n = 33 to 66).[37] The platelet count, percent monocytes, and ALP were higher and total protein measurements were lower than the corresponding reference interval ranges in our animals. These differences could be related to the difference in age or the iron supplementation. In comparison, venous blood from 1-mo-old female, Yorkshire swine (n = 35) had lymphocyte and RBC counts and Hct, albumin, and Na^+ values below our reference range and monocytes, Hgb, ALP, ALT, and total bilirubin values were higher than our reference interval range. However, these variations may result from differences in age or sampling location (i.e., the femoral vein in our animals as compared with the jugular vein of the 1-mo-old swine).[27]

Table 5. Comparison of hematologic reference intervals among juvenile Yorkshire swine (*Sus scrofa domesticus*), humans, and baboons (*Papio hamadryas*)

	Reference intervals			Comparisons of reference intervals (*P* value from single *t* test)	
Analyte (unit)	Swine	Human	Baboon	Swine arterial compared with human	Swine arterial compared with baboon
WBC ($\times 10^9$/L)	9.9–21.97	3.54–9.06	3.02–18.7	<0.001	<0.001
Lymphocytes ($\times 10^9$/L)	6.35–14.41	0.71–4.53	NA	<0.001	not available
Monocytes ($\times 10^9$/L)	0.06–0.41	0.14–0.72	NA	<0.001	not available
Neutrophils ($\times 10^9$/L)	1.96–8.81	1.42–6.34	NA	<0.01	not available
Lymphocytes (%)	50.05–83.46	20–50	NA	<0.001	not available
Monocytes (%)	0.50–3	4–8	NA	<0.001	not available
Neutrophils (%)	15.78–48.95	40–70	NA	<0.001	not available
RBC ($\times 10^{12}$/L)	4.80–7.11	4–5.20	4.21–5.96	<0.001	<0.001
Hgb (g/dL)	8.20–11.7	12–15.8	10.58–14.45	<0.001	<0.001
Hct (%)	25.3838.77	35.4–44.4	33–46	<0.001	<0.001
Platelets ($\times 10^9$/L)	161.6–449	165–415	232–666	nonsignificant	<0.001

Table 6. Comparison of biochemical reference intervals among juvenile Yorkshire swine (*Sus scrofa domesticus*), humans, and baboons (*Papio hamadryas*)

	Reference intervals			Comparisons of reference intervals (*P* value from single *t* test)	
Analyte (unit)	Swine	Human	Baboons	Swine arterial compared with human	Swine arterial compared with baboon
Albumin (g/dL)	2.5–4.39	3.5–5.5	3.16–5.01	<0.001	<0.001
ALP (U/L)	56–133.7	33–96	0–1399.80	<0.001	<0.001
ALT (U/L)	25–54.88	7–41	0–122.16	<0.001	<0.05
Amylase (U/L)	739–2882	4–400	not available	<0.001	not available
Total bilirubin(mg/dL)	0.2–0.5	0.3–1.3	0–0.24	<0.001	<0.001
BUN (mg/dL)	2.0–10.88	7–20	not available	<0.001	not available
Ca^{2+} (mg/dL)	9.2–11.2	8.7–10.2	8.3–10.7	<0.001	<0.001
Phosphorus (mg/dL)	6.8–10.58	8.1–14	not available	<0.001	not available
Creatinine (mg/dL)	0.9–1.89	0.5–0.9	0.39–1.1	<0.001	<0.001
Glucose (mg/dL)	52–153.88	65–95	36–167.2	<0.001	nonsignificant
Na^+ (mmol/L)	129–142.75	136–146	138.31–153.07	<0.001	<0.001
K^+ (mmol/L)	3.5–4.7	3.5–5	2.52–4.63	<0.001	<0.001
Total protein (g/dL)	5.1–7.19	6.7–8.6	5.9–8.4	<0.001	<0.001
Globulin (g/dL)	1.8–4.09	3.5–5.5	not available	<0.001	not available

Because female, juvenile, Yorkshire swine are some of the most commonly used animals for many major areas of biomedical research, surgical training, and xenotransplantation, we compared our swine reference intervals to those for baboons and humans.[11,18,25,29,31] The majority of the measured parameters differed significantly among these species. Although swine are similar to humans and baboons in numerous aspects, our study highlights that the use of Yorkshire swine as an animal model should be done with awareness of the differences in hematologic and biochemical parameters and that the model should be well suited to the study of interest.[40]

The data in the present study provide valuable reference material for comparison of Yorkshire swine with other swine breeds and other species for the evaluation of a wide range of parameters including organ function, metabolism, infection, and coagulation. These data could facilitate the use of swine in biomedical research, medical device and drug translational research, xenotransplantation, and agriculture.[19,30,34,35,41]

A number of limitations and other considerations apply to interpretation of the current data. Many factors can affect hematologic and biochemical parameters. For example, our animals were anesthetized and ventilated, and therefore arterial blood gas values were not reported. In addition, the animals were hydrated, which could have diluted kidney parameters such as BUN and creatinine. As previously mentioned, the number of animals sampled from the femoral vein was not adequate for calculating reference intervals and might have affected statistical comparison of arterial and venous parameters. Furthermore, the swine in this study were sexually immature juveniles (age, 3 to 4 mo; weight, 42.7 ± 5.9 kg). This information should be taken into consideration when comparing data with other swine breeds, especially minipigs, which reach sexual maturity at different ages.

Furthermore, our animals were conventional in regard to their health status; therefore, previous pathogen exposure was unknown. All animals lacked visible or clinical signs of infection or abnormalities but might have harbored subclinical disease or other abnormalities that could have affected WBC counts and other parameters. We likewise recognize limits due to the sex of the species used for comparison with human and baboon

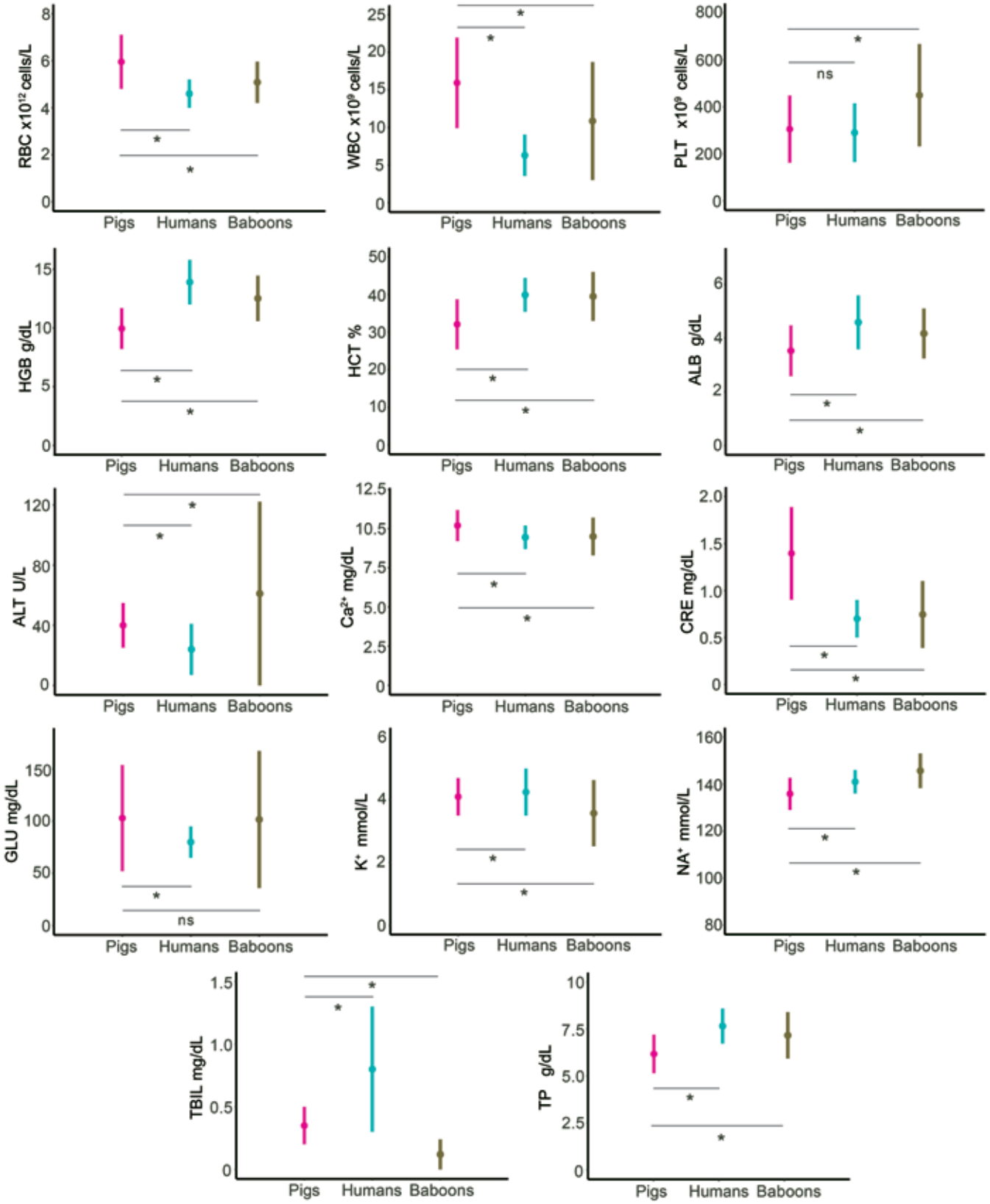

Figure 3. Point-range plots of reference intervals of *Sus scrofa domesticus* compared with those of baboons (*Papio hamadryas*) and humans for hematologic and biochemical parameters that showed significance.

reference intervals. The swine used in our study were all female, but we compared them with groups of humans and baboons of both sexes. In addition, the human and baboon data were not age- or sex-matched with the swine, and blood was analyzed by different laboratories using different analyzers. Therefore, these limitations should be taken into consideration when making any comparisons or attempting to draw any conclusion.

Acknowledgments

We acknowledge support for this work from the Defense Advanced Research Projects Agency (grants N66001-11-1-4180, HR0011-13-C-0025, and W911NF-16-C-0050), the Department of Defense (W81XWH-17-2-0028), and the Wyss Institute for Biologically Inspired Engineering at Harvard University.

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