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SHORT REPORT

What is the origin of the normal ranges of blood cell counts? An evolutionary perspective

Manon Zala[1] | Vincent Alcazer[1,2] | Laetitia Largeaud[1] | Pierre Sujobert[1,3]

[1]Centre International de Recherche en Infectiologie (CIRI, INSERM U1111, CNRS UMR 5308, École Normale supérieure de Lyon), Lymphoma ImmunoBiology team, Faculté de Médecine Lyon sud, Université Claude Bernard Lyon 1, Lyon, France

[2]Hospices Civils de Lyon, Hôpital Lyon Sud, Service d'hématologie clinique, Pierre Bénite, France

[3]Hospices Civils de Lyon, Hôpital Lyon Sud, Service d'hématologie biologique, Pierre Bénite, France

Correspondence
Pr. Pierre Sujobert, Service d'hématologie biologique, Hôpital Lyon Sud, 165 chemin du Grand Revoyet. 69310 Pierre Bénite, France.
Email: pierre.sujobert@chu-lyon.fr

Abstract

Background: The normal values of the complete blood count are part of the foundational medical knowledge that is seldom questioned due to their well-established nature. These normal values are critical for optimal physiological function while minimizing the harmful consequences of an excessive number of blood cells. Thus, they represent an evolutionary trade-off likely shaped by natural selection if they significantly influence individual fitness and exhibit heritability.

Methods: On the basis of the analysis of normal blood count values of 94 mammalian species, we discovered that certain parameters are strongly associated with diet, habitat, and lifespan.

Results: Carnivorous mammals had higher hemoglobin levels than vegetarians, and aquatic mammals displayed red blood cell parameters probably selected to enhance for the diving capacities. Body weight influenced platelet counts and innate immune cells, with lighter animals having higher platelet counts and larger animals showing elevated monocytes and neutrophils.

Conclusions: By treating the history of life as an experiment, we have discerned some evolutionary constraints likely contributing to the selection for optimal trade-offs in blood cell count.

KEYWORDS
blood cell count, evolutionary constraint

1 | INTRODUCTION

Maintaining a normal blood cell count is critical for optimal physiological function while minimizing the harmful consequences of an excessive number of blood cells. For instance, the quantity of erythrocytes should be sufficient for effective oxygen transportation, yet not excessive to avoid increased blood viscosity [1]. Likewise, the optimal level of platelets strikes a balance between reducing the risk of bleeding and thrombosis. Additionally, while a sufficient number of leukocytes is necessary for robust immune defense against pathogens, excessive counts can lead to tissue damage and autoimmune or autoinflammatory reactions. In essence, the normal values of blood cell count represent an evolutionary trade-off, likely shaped by natural selection if they significantly influence individual fitness and exhibit heritability [2]. We hypothesized that a comparative analysis of blood cell counts across large datasets of mammal species could elucidate the evolutionary constraints that have determined these normal values.

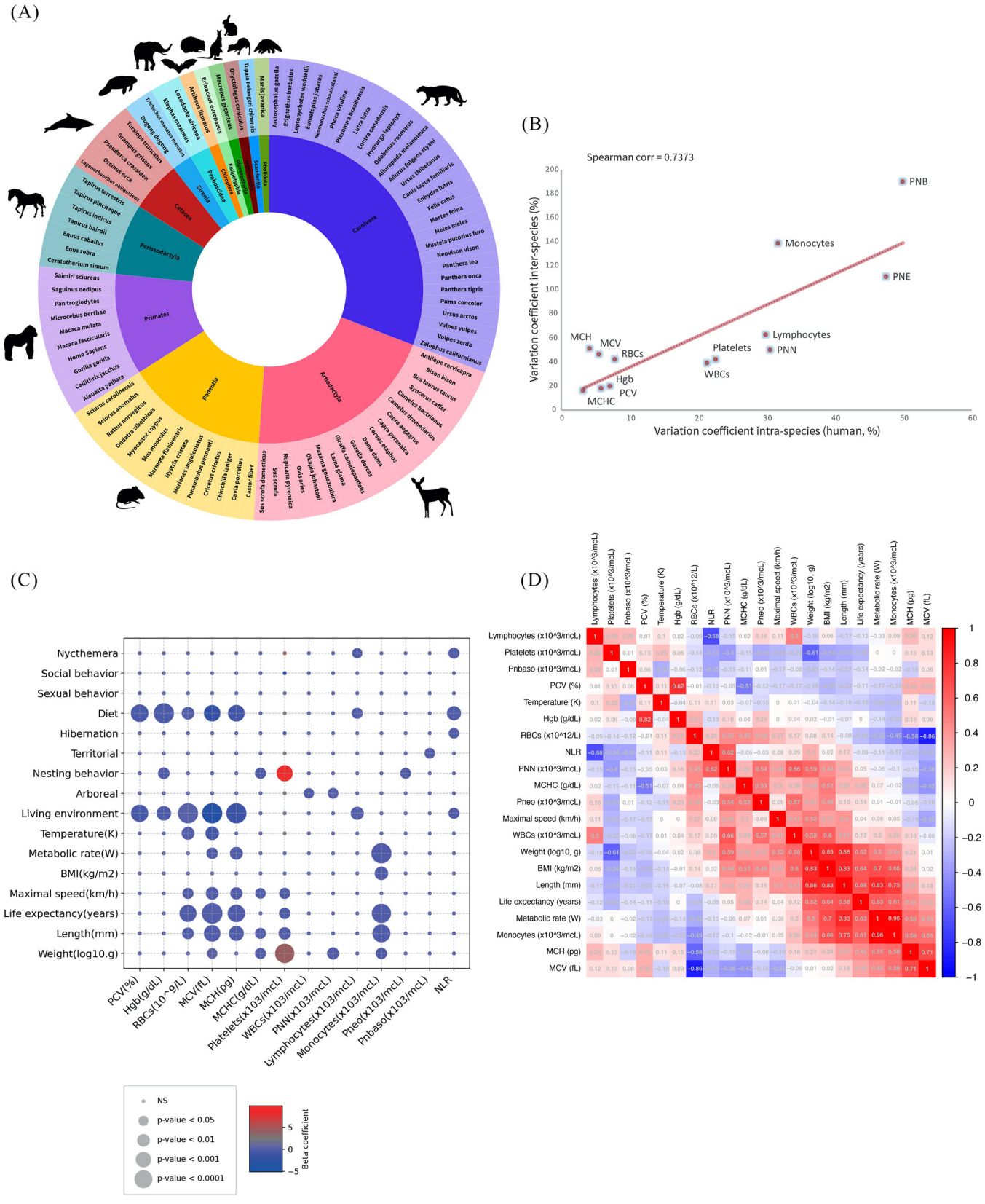

FIGURE 1 (A) Distribution of species included in the study across their respective order. Animal silhouettes used to visually represent mammalian orders were downloaded from PhyloPic (http://www.phylopic.org). (B) Inter- and intra- (human) species variation coefficient of blood count parameters. (C) Univariate analysis of the impact of lifestyle on blood cell count parameters (simple linear regression model with beta coefficients normalized using Z-score method). For each categorical variable (living environment, arboreal, nesting behavior, territoriality, hibernation, diet, sexual behavior, social behavior, and nocturnal/diurnal lifestyle), the corresponding reference categories in the univariate model

2 | MATERIAL AND METHODS

We conducted a thorough literature search to compile the values of blood cell counts from 94 mammalian species representing between 0.1% and 66.7% of the total number of species of their respective orders (Figure 1A, Figure S1A, Table S1). We focused on mammals, excluding data from fishes, birds, and reptiles, because identifying cell types in these classes is more challenging, and the reliability of automated blood cell count methods is less established, which could compromise the accuracy of comparisons [3, 4]. Normal blood cell counts were derived from datasets comprising between 4 to more than 1000 adult individuals, using the mean between males and females when gender specificities were described in a given species. The data encompassed animals from captive ($n = 2141$ animals from 46 species), wild ($n = 4061$ animals from 30 species) or both ($n = 93$ animals from 2 species) settings. For 17 species, the setting was not specified (Table S1). Additionally, we collected various phenotypic characteristics of the species, including weight, length, life expectancy, maximum speed, body mass index, metabolic rate, temperature, and hibernation patterns. We also gathered information on their habitat (aquatic vs. terrestrial, arboreal, nesting behavior), and lifestyle factors (diet, sexual and social behavior, territorial behavior, and nocturnal/diurnal lifestyle) [5, 6]. The proportion of missing data was below 10% for most parameters, except for platelets, maximal speed, temperature and metabolic rate (21%, 17%, 46%, and 67% respectively) (Figure S1B).

3 | RESULTS AND DISCUSSION

Firstly, we observed that interspecies variations were limited for some parameters, such as mean corpuscular hemoglobin concentration (MCHC), hemoglobin level (Hgb), and packed cell volume (PCV), with a variation coefficient below 20%. However, variations were more pronounced for eosinophils (PNE), monocytes, and basophils (PNB), with a variation coefficient above 100%. Interestingly, the interspecies coefficient of variation was highly correlated with the intraspecies coefficient of variation in humans (non-parametric Spearman coefficient $\rho = 0.7373$ ($p = 0.0053$), Pearson coefficient $r = 0.8219$, ($p = 0.0006$)) (Figure 1B). This correlation likely reflects the influence of fixed physicochemical constraints, such as the solubilization coefficient of hemoglobin, which determine the range of variability of blood cell parameters in a comparable manner across diverse biological levels.

Subsequently, we studied the influence of species phenotypic characteristics on each blood cell count parameter. We first explored the data by univariate analysis using Mann–Whitney test to assess the significance of observed differences (Figure 1C–E, Table S2). Given the strong association existing between specific phenotypic traits, we also applied multivariate analysis to assess their independent contributions. This analysis included phenotypic traits that showed high correlation with any blood cell count parameter in the univariate analysis (p-value < 0.001) (Figures S1C,S1D, Table S3). We observed well-established correlations such as between body weight and both life expectancy and metabolic rate [7], and also discovered phenotypic traits associated with normal blood cell counts.

Parameters with higher intra- and interspecies variation coefficients appeared to be less strongly associated with phenotypic traits than those with lower variability (such as red blood cell parameters—RBC, MCV, and MCH), with the exception of platelet and monocyte counts (see below). Regarding red blood cells parameters, diet and living environment had a strong impact that was still significant in multivariate analysis for packed cell volume (PCV), the size of red blood cells (mean corpuscular volume—MCV), and their hemoglobin content (mean corpuscular hemoglobin—MCH) (Figure 1E and Figure S1C,S1D). Carnivorous mammals exhibited higher hemoglobin levels (16.5 vs. 13.5 g/dL, $p < 0.00001$) with larger MCV (90 vs. 60.7 fL, p = 0,004) and higher hemoglobin content (MCH, 31.1 vs. 20 pg, $p = 0.0006$) but a lower red blood cell count (RBC, 6.04 vs. 8.20 $\times 10^{12}$/L, $p = 0.011$) compared to vegetarian ones (Figure 2A). Habitat was also strongly correlated with red blood cells parameters: aquatic or semi-aquatic mammals displayed higher hemoglobin level (15.9 vs. 14 g/dL, $p = 0.001$), achieved with a lower number of red blood cells (RBC, 4.8 vs. 8.2 10^{12}/L, $p < 0.0001$) of nearly twice the size of terrestrial mammals (MCV, 105.1 vs. 56.4 fL, $p < 0.0001$). Accordingly, aquatic mammals had higher mean corpuscular hemoglobin (MCH,35.9 vs. 19.7 pg, $p < 0.0001$) (Figure 2B). These variations might be partly due to a phylogenetic effect [8], because most of the aquatic species belong to the same order (cetacean). However, we also observed increased MCV in semiaquatic species belonging to the carnivora order (102.3 vs. 54 fL, $p = 0.00001$) and a trend in the rodentia order (89.6 vs. 67.1 fL, p = 0.078, unpaired t-test) (Figure S2A). We posit that these variations might enhance the breath-hold diving capacities of aquatic species. Noteworthy, such variations have not been documented among individuals within the human species, where the best described variation associated with breath-hold diving capacities is a polymorphism of PDE10A linked to increased spleen size in indigenous Bajau people [9]. Red cell parameters were also correlated with life expectancy: animals with shorter lifespan had lower MCH and MCV and higher RBC (linear regression,

were as follow: aquatic, non-arboreal, non-nesting, non-territorial, non-hibernating, carnivorous, non-polygynous, non-solitary, and diurnal behavior. The following criteria were grouped as follows for analysis: living environment: terrestrial versus aquatic and semi-aquatic; diet: carnivorous versus vegetarian. (D) Correlation matrix for continuous phenotypic variables and blood cell count parameters. The colors represent the degree of pairwise correlation. (E) Forest plot showing the estimated beta coefficients and 95% confidence intervals between lifestyle independent variables and blood cell parameters from univariate linear regression analysis (p-value < 0.001). BMI: body mass index; PCV: packed cell volume; Hgb: hemoglobin; RBCs: red blood cells; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; WBCs: white blood cells; PNN: polynuclear neutrophils; PNE: polynuclear eosinophils; PNB: polynuclear basophils and NLR: neutrophil-to-lymphocyte ratio.

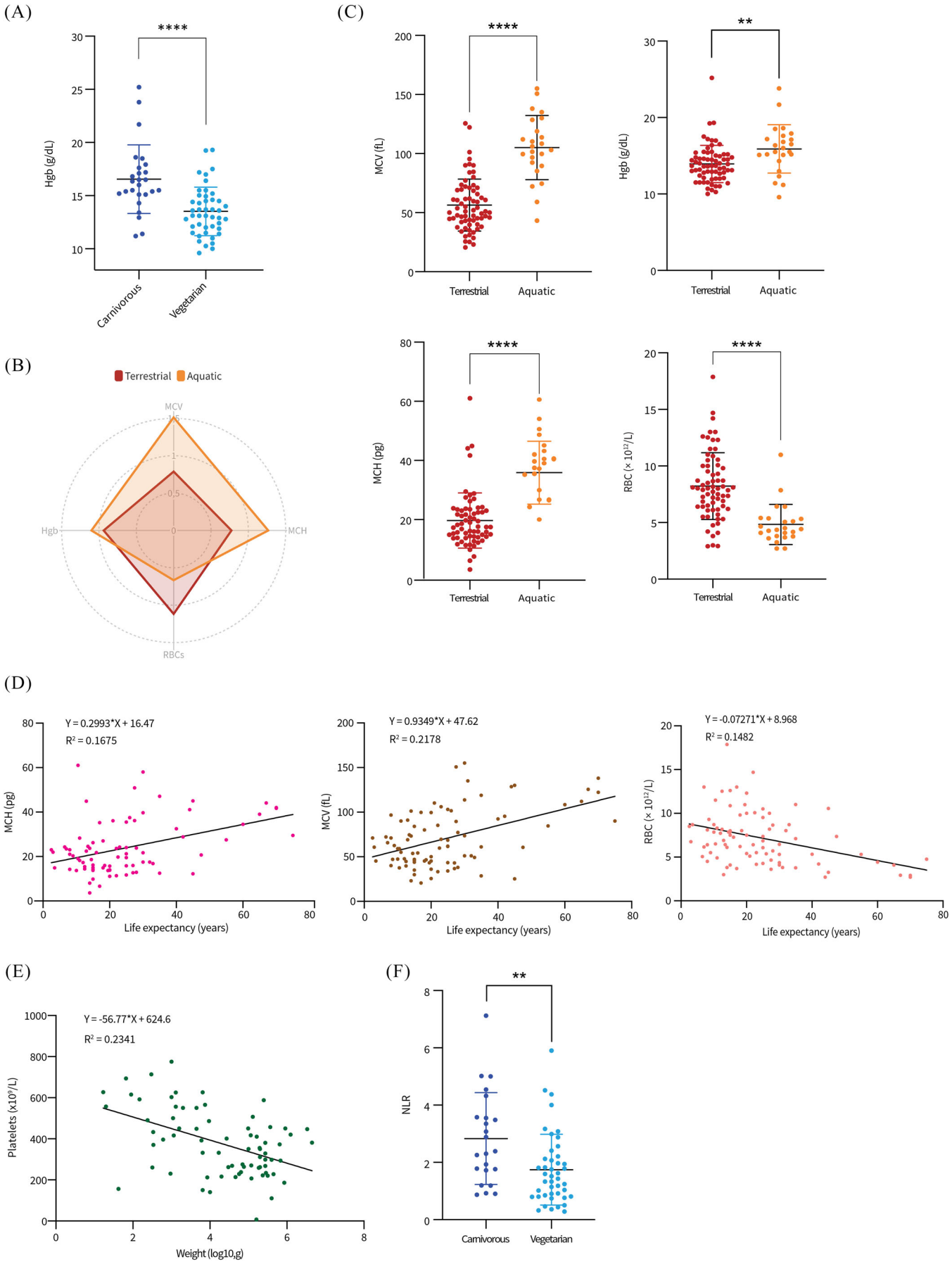
(A)
****
Hgb (g/dL)
Carnivorous
Vegetarian
(B)
Terrestrial
Aquatic
MCV
Hgb
MCH
RBCs
(C)
****
MCV (fL)
Terrestrial
Aquatic
**
Hgb (g/dL)
****
MCH (pg)
****
RBC (× 10^12/L)
(D)
Y = 0.2993*X + 16.47
R² = 0.1675
MCH (pg)
Life expectancy (years)
Y = 0.9349*X + 47.62
R² = 0.2178
MCV (fL)
Y = -0.07271*X + 8.968
R² = 0.1482
RBC (× 10^12/L)
(E)
Y = -56.77*X + 624.6
R² = 0.2341
Platelets (x10^9/L)
Weight (log10,g)
(F)
**
NLR
Carnivorous
Vegetarian

FIGURE 2 (A) Variations in hemoglobin levels (Hgb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and red blood cells (RBC) according to diet. The *p*-values are derived from Mann–Whitney test. (B) Variation in hemoglobin levels (Hgb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and red blood cells (RBC) according to the living environment. The *p*-values are derived from Mann–Whitney test. (C) Parameters linearly correlated with animal life expectancy (simple linear regression test, *p*-value < 0.001). (D) Correlation of platelets count with animal weight (simple linear regression test, *p*-value < 0.0001). (E) Variations in platelets count according to the nesting behavior. The *p*-value is derived from Mann–Whitney test. (F) Variation of neutrophil-to-lymphocyte ratio according to diet. The *p*-values are derived from Mann-Whitney test.

R^2 = 0.17/0.22/0.15 respectively, $p < 0.001$), but these effects were not independent from the influence of diet and habitat (Figure 2C and Figure S1C,S1D).

Regarding the influence of body weight (Figure 2D), lighter animals exhibited a higher platelet count than heavier ones (R^2 = 0.23, $p < 0.0001$, simple linear regression), which aligns with the expectation considering the potential dramatic impact of bleeding in animals with smaller blood volume. Platelet count was also higher in nesting animals (463.6 vs. 332.5 × 10^9/L, $p = 0.0012$, Figure 2E). Conversely, univariate analysis revealed that larger animals exhibited elevated levels of cells associated with innate immunity, such as monocytes and neutrophils (R^2 = 0.06, *p*-value = 0.0234 and *p*-value = 0.0137, respectively). This observation could be linked to their role to ensure efficient defense against pathogens across a larger body surface area. Monocyte count was also positively associated with basal metabolic rate (R = 0.96, $p = 1.1 \times 10^{-12}$), an observation which aligns with the increasingly recognized interactions between innate immunity and metabolic diseases such as insulin resistance [10] or steatohepatitis [11].

Finally, the absolute blood cell count is also influenced by the core architecture of hematopoietic differentiation, which is directed toward either the myeloid or lymphoid lineage. Consequently, we investigated whether evolutionary constraints might have shaped the neutrophil-to-lymphocyte ratio (NLR), which is associated with all-cause mortality in humans [12]. This ratio was significantly higher in carnivorous mammals than vegetarians (2.8 vs. 1.7, *p*-value = 0.0026, Mann–Whitney test) (Figure 2F), which can be explained by a direct effect of alimentation, as vegan diet has been shown to decrease neutrophil count [13].

4 | CONCLUSIONS

This study provides an examination of the factors influencing normal blood cell counts across the mammalian species. Of note, physiological variations of blood cell count and variations due to sampling conditions, might have biased the estimation of normal values of animals. However, given the low magnitude of physiological variations as compared to what we observed across species [14], this bias is probably limited. By treating the history of life as an experiment, we have discerned some evolutionary constraints likely contributing to selection for optimal trade-offs in blood cell count. An interesting extension of this work would be a comparative analysis of the genomic variations among species that are related to blood cell count parameters, as a way to identify genes involved in their regulation.

AUTHOR CONTRIBUTIONS

Pierre Sujobert conceptualized the study. Manon Zala, Vincent Alcazer, Laetitia Largeaud, and Pierre Sujobert performed the investigations, designed the methodology and wrote the original draft.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

All the data are publicly available.

ETHICS STATEMENT

The authors have nothing to report.

ORCID

Pierre Sujobert https://orcid.org/0000-0002-9108-1162

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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