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Symmetric Dimethylarginine (SDMA) as a Predictor of Anemia in Early Canine Kidney Dysfunction

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Abstract: Traditional markers such as creatinine and BUN have limited sensitivity for detecting early kidney dysfunction, whereas symmetric dimethylarginine (SDMA) offers a more reliable indication of reduced glomerular filtration rate. Chronic kidney disease (CKD) in dogs is often associated with anemia due to decreased erythropoietin production, but the relationship between SDMA levels and anemia severity remains unclear. This retrospective cross-sectional study analyzed canine patients presented to INI Veterinary Service, Surabaya, Indonesia, between January 2024 and August 2025, with available complete blood counts and renal function profiles including SDMA, creatinine, and hematocrit (HCT). Anemia severity was classified by HCT values, renal dysfunction was staged according to IRIS criteria, and statistical analyses included Chi-square testing, regression modeling, and ROC curve analysis. Among 157 dogs, anemia was present in 28.2% of cases and increased in prevalence and severity with advancing CKD stage. SDMA concentrations were significantly higher in dogs with severe anemia, yet regression analysis revealed that SDMA, creatinine, and age were not independent predictors of anemia severity. ROC analysis showed moderate discriminatory ability of SDMA (AUC 0.666), with high specificity (81.2%) but limited sensitivity (56.8%). In conclusion, anemia in dogs was more frequent and severe in advanced CKD, but SDMA was not an independent predictor after adjusting for creatinine and age. While ROC analysis suggests SDMA may serve as a supportive "rule-in" biomarker, it lacks sensitivity to function as a standalone diagnostic tool.

Keywords: *symmetric dimethylarginine; anemia; chronic kidney disease; creatinine; canine*

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1. Introduction

The kidney plays a central role in maintaining homeostasis by regulating fluid, electrolyte, acid-base, glucose, protein, lipid, and ion balances, as well as removing metabolic waste [1,2]. Serum creatinine and blood urea nitrogen (BUN) are traditional biomarkers widely used in clinical practice to assess kidney function. However, their sensitivity and specificity are limited, as they are influenced by multiple factors unrelated to kidney function, including age, sex, muscle mass, diet, and certain medications. Moreover, alterations in serum creatinine and BUN are subtle and may not be readily detectable during the early stages of kidney dysfunction [3,4].

Symmetric dimethylarginine (SDMA) is a methylated derivative of the amino acid arginine, produced during protein turnover and released into the bloodstream. It is primarily eliminated by the kidneys through glomerular filtration, with minimal influence from muscle mass, age, or sex. Because SDMA is almost exclusively excreted by the kidneys, its blood concentration rises as glomerular filtration rate (GFR) declines. SDMA increases in the blood with even mild reductions in GFR, often before serum creatinine rises [5,6]. In dogs, SDMA can detect as little as a 20–25% decrease in GFR, making it a highly sensitive early marker of kidney dysfunction [7].

The decline of kidney function and anemia are closely linked, especially in chronic kidney disease (CKD). The kidneys normally produce erythropoietin (EPO), a critical hormone that stimulates red blood cell production [8]. In CKD, however, damaged kidneys lose the ability to produce adequate EPO, resulting in normochromic-normocytic anemia that progressively worsens as kidney function declines [9,10]. Anemia is not only highly prevalent among CKD patients, but also contributes significantly to poorer prognosis and reduced quality of life. It is strongly linked to faster progression to end-stage renal disease, higher rates of cardiovascular events, and elevated all-cause mortality. Therefore, the early identification and management of anemia are essential for improving outcomes in CKD patients [11,12].

In this context, the detection of early or subclinical kidney dysfunction becomes particularly important, as it may enable the recognition of anemia before significant renal damage occurs. SDMA, as previously highlighted, is recognized as a more sensitive biomarker for detecting early kidney dysfunction compared to creatinine [13]. An elevation in SDMA despite normal creatinine values suggests the presence of early or subclinical renal impairment, which could represent a critical window for intervention. However, the association between SDMA-detected early dysfunction and the risk of developing anemia has not yet been clearly established, underscoring the need for further investigation. In response of the current research gap, this study seeks to characterize anemia patterns across early and advanced stages of renal dysfunction in canines by evaluating hematologic and kidney function biomarkers.

The early detection of anemia allows earlier intervention, which can improve patient outcomes and reduce complications. In cases of early or subclinical kidney dysfunction, supportive therapy may help prevent the development of anemia. Moreover, the use of SDMA for early anemia detection could refine CKD staging and patient monitoring. These insights highlight not only their significance in veterinary medicine but also potential parallels in human nephrology.

2. Materials and Methods

2.1 Study Design and Setting

A retrospective cross-sectional research design was used to determine the role of SDMA as a predictor of anemia in early canine kidney dysfunction. The population consisted of canine patients who were hospitalized or seen as outpatients at INI Veterinary Service, Surabaya, Indonesia, between January 2024 and August 2025, and in whom complete blood count (CBC) and renal function tests had been conducted.

2.2 Participants

The inclusion criteria were canine patients presented to INI Veterinary Service, Surabaya, Indonesia, between January 2024 and August 2025, who underwent blood work that included SDMA, HCT, and creatinine measurements obtained during the same clinical encounter. Only cases with complete data sets, measured on standardized analyzers (IDEXX Catalyst One and ProCyte One), were included. The exclusion criteria included: (1) poor sample quality or analyzer flags that could invalidate measurements (marked hemolysis, lipemia, or icterus); (2) evidence of acute kidney injury or clearly prerenal azotemia at the time of sampling (e.g., dehydration/hypovolemia, urinary obstruction), as defined in the medical record; (3) known non-renal causes of anemia (e.g., acute hemorrhage or recent surgery/trauma, gastrointestinal bleeding, hemolysis, hemoparasitosis such as *Babesia/Ehrlichia*, severe systemic infection/inflammation, or neoplasia affecting red cell mass); (4) prior blood transfusion within 30 days; or (5) recent therapy that directly alters erythropoiesis (erythropoiesis-stimulating agents, iron/B12/folate supplementation) within the preceding 14–30 days. The independent variable was the SDMA concentration, while the dependent variable was anemia severity, categorized into five levels (normal, mild, moderate, severe, very severe) according to HCT values. Potential confounding variables included patients' age, sex, breed or body size, hydration status, concurrent diseases, and medications that may influence kidney function or red blood cell levels.

2.3 Data Collection

2.3.1 Clinical Data

Demographic and clinical information recorded for each patient included name, sex, age, date of testing, and body weight. Laboratory data consisted of renal function markers (SDMA, creatinine, blood urea nitrogen, and phosphorus) and CBC parameters, including HCT.

2.3.2 Laboratory Assessment

The data were collected by the attending veterinarians responsible for each patient. Blood samples were obtained via venipuncture and placed in EDTA tubes for hematological analysis, while serum samples were processed for biochemical evaluation. Hematological parameters were measured using the IDEXX ProCyte One hematology analyzer, and biochemical markers, including creatinine and SDMA, were assessed using the IDEXX Catalyst One chemistry analyzer. All reference ranges applied were those validated for canine patients.

2.3.3 Early and Advanced Renal Dysfunction Grouping

Subjects were categorized into four groups according to SDMA and creatinine levels, in line with the 2023 IRIS CKD staging system. The normal group had SDMA levels of 0–14 μg/dL and creatinine levels of 0.5–1.4 mg/dL. The early renal dysfunction group (Stage 1) was defined by SDMA levels of 15–17 μg/dL with creatinine levels remaining at 0.5–1.4 mg/dL. Moderate renal dysfunction (Stage 2) included subjects with SDMA levels between 18–35 μg/dL and creatinine levels of 1.4–2.8 mg/dL. The advanced renal dysfunction group (Stages 3 and 4) was characterized by SDMA levels ≥36 μg/dL and creatinine levels ≥2.9 mg/dL [14].

2.3.4 Anemia Severity Grouping

The analysis categorized canine patients into groups based on the severity of anemia. Classification was determined using HCT values, with anemia defined as HCT <37%. Severity was further stratified into the following categories: mild anemia (HCT 30–36.9%), moderate anemia (HCT 20–29.9%), severe anemia (HCT 13–19.9%), and very severe anemia (HCT < 13%). Dogs with HCT ≥ 37% were classified as having no anemia [15].

2.4 Statistical Analysis

Data were analyzed using IBM SPSS Statistics (version 31, IBM Corp., Armonk, NY). Descriptive statistics were reported as mean ± standard deviation (SD) or median (interquartile range, IQR) for continuous variables, and frequency (percentage) for categorical variables. Comparisons of anemia severity (normal, mild, moderate, severe, very severe) across renal dysfunction stages (normal, early, moderate, advanced) were performed using the Chi-square test for trend. Differences in SDMA and hematocrit (HCT) levels across anemia severity groups were evaluated using one-way ANOVA or the Kruskal–Wallis test, depending on data distribution, followed by appropriate post hoc tests. Correlation between SDMA and HCT values was assessed using Pearson's or Spearman's correlation coefficients. To explore the relationship between SDMA and anemia severity, an ordinal logistic regression model was applied with anemia severity (five categories) as the dependent variable and SDMA as the independent predictor, adjusting for potential confounders such as age, sex, and creatinine. Receiver operating characteristic (ROC) curve analysis was additionally performed to assess the discriminatory performance of SDMA for detecting clinically relevant anemia (defined as HCT <37%). A two-sided p-value <0.05 was considered statistically significant.

2.5 Ethical Considerations

This study was based on a retrospective review of canine patient records. All blood samples were collected as part of routine clinical diagnostic procedures, and no additional samples were drawn for research purposes. Informed consent for blood collection and diagnostic testing had been obtained from the owners by the attending veterinarians at the time of clinical evaluation. Patient confidentiality was maintained throughout the study by anonymizing identifying information such as name and medical record number. Ethical approval for the use of clinical data was obtained from INI Veterinary Service, Surabaya, Indonesia, in accordance with guidelines for the ethical use of animals in research (Protocol No. IACUC-INIVET-2025-001).

3. Results

3.1 Study Population and Baseline Characteristics

A total of 173 blood test results were initially collected, but cases without creatinine values were excluded. After this adjustment, 157 canine patients were included in the analysis. Among them, 60.5% were female. The dogs had a mean age of 10 years (range: 1–17 years) and a mean body weight of 19.9 lbs (range: 2.4–79.4 lbs). The data were collected between January 2024 and August 2025. Detailed baseline characteristics are presented in **Appendix A**.

3.2 Frequencies of CKD Staging and Anemia

A total of 157 canine patients were included in the analysis. Most patients had normal hematocrit values (71.8%), while mild (13.4%), moderate (8.3%), severe (2.5%), and very severe (3.8%), where anemia was less common. This distribution of data indicates that anemia severity was toward the non-anemic group, with only a minority of patients experiencing anemia. Based on the IRIS classification, nearly half of the dogs (49.7%) were classified as having early CKD, 30.6% as moderate, 8.3% as advanced, and 11.5% showed normal renal function. Thus, the majority of cases are presented in the early to moderate stages of disease.

3.3 Relationship between CKD stage and Anemia Severity

Chi-square analysis **(Table 1)** indicated a significant association between CKD stage and anemia severity ($\chi^2 = 28.4$, df = 12, $p = 0.005$). However, more than 60% of the expected cell counts were <5, limiting the reliability of the result. Despite this limitation, descriptive trends were observed. Patients with advanced CKD showed the highest proportion of anemia (54%), compared to moderate CKD (42%), early CKD (17%), and those without CKD (22%). Mild to moderate anemia was most commonly found in patients with early and moderate CKD, while severe and very severe anemia was uncommon and appeared primarily in advanced CKD stages. Notably, a few individuals without CKD also presented with very severe anemia, indicating that anemia can develop from causes unrelated to CKD.

Table 1. Chi-square analysis on the relationship between CKD stage and anemia severity.

		Anemia Severity Classification					**Total**
		Mild	Moderate	Normal	Severe	Very Severe	
CKD IRIS[1] Classification	Normal	1	1	14	0	2	18
	Moderate	9	8	28	2	1	48
	Early	8	3	65	0	2	78
	Advanced	3	1	6	2	1	13
	Total	21	13	113	4	6	157

[1] Chronic Kidney Disease-International Renal Interest Society

3.4 SDMA levels across anemia categories

The Kruskal–Wallis test **(Fig. 1)** demonstrated significant differences in SDMA across anemia categories ($H = 18.3$, df = 4, $p = 0.001$). Post-hoc analysis revealed that only the severe anemia group differed significantly from the normal group after Bonferroni adjustment ($p = 0.031$). Descriptively, SDMA concentrations were lowest in the normal and very severe anemia groups, intermediate in mild and moderate anemia, and highest in severe anemia. The severe anemia category also showed the widest variability, with several markedly elevated values (>70 µg/dl), suggesting heterogeneity of renal dysfunction within this group. Interestingly, patients with very severe anemia demonstrated relatively low and clustered SDMA values, which may reflect small sample size or anemia from non-renal etiologies. Outliers were also noted in the normal group, indicating that elevated SDMA can occur even in the absence of anemia. Overall, these findings suggest that SDMA elevations become most apparent in association with severe anemia, whereas mild to moderate anemia may not consistently reflect underlying renal impairment.

3.5 Ordinal Logistic Regression on Predictors for Anemia Severity and CKD Staging

Ordinal logistic regression using anemia severity as the dependent variable showed that SDMA ($p = 0.477$), creatinine ($p = 0.871$), and age ($p = 0.120$) were not significant predictors. The model did not significantly improve fit compared with the intercept-only model ($\chi^2 = 3.88$, $p = 0.275$), indicating that anemia severity was not explained by these variables. In contrast, ordinal regression with CKD stage as the outcome demonstrated a significant overall model fit ($\chi^2 = 38.9$, $p < 0.001$; Nagelkerke $R^2 = 0.245$), with creatinine emerging as a significant predictor ($B = -0.837$, $p = 0.010$). SDMA and age were not significant. Goodness-of-fit statistics (Pearson $\chi^2 = 341.3$, $p = 0.999$) indicated adequate model fit. These findings suggest that while creatinine is strongly associated with CKD stage, neither creatinine, SDMA, nor age predicted anemia severity, underscoring the importance of direct hematologic assessment in CKD patients.

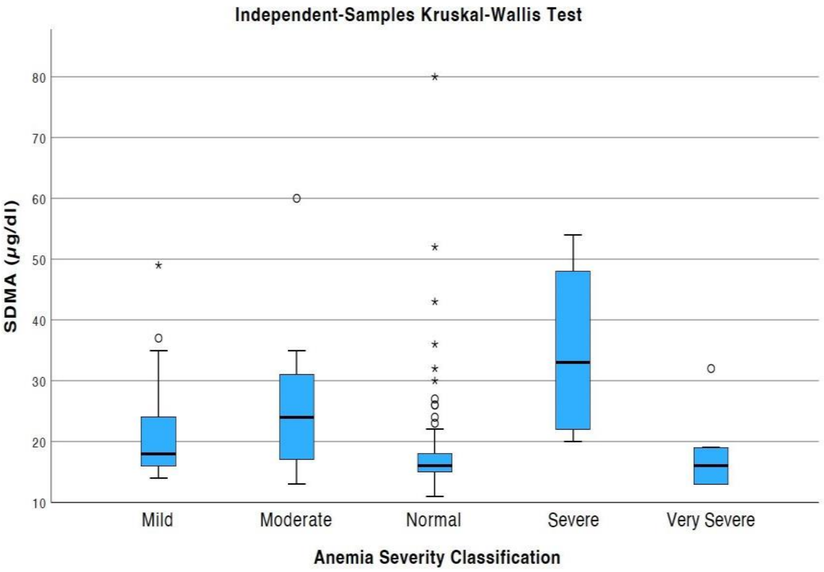

Figure 1. Kruskal–Wallis test on SDMA levels across anemia severity categories. The blue boxes represent the interquartile range (IQR), with the horizontal line inside each box indicating the median SDMA concentration. The whiskers extend to the minimum and maximum values within 1.5 × IQR, while circles and asterisks denote outliers and extreme values, respectively.

3.6 ROC Curve Analysis

ROC analysis for detection of clinically relevant anemia (≥ mild) showed that SDMA had moderate discriminatory ability (AUC = 0.666, 95% CI 0.560–0.773, p = 0.002), whereas creatinine demonstrated poor and insignificant performance (AUC = 0.592, p = 0.118) **(Fig. 2)**. The optimal SDMA cutoff of 18.5 µg/dL provided 56.8% sensitivity and 81.2% specificity, yielding a Youden index of 0.381. In contrast, the optimal creatinine cutoff of 1.35 mg/dL resulted in lower sensitivity (45.5%) but similar specificity (87.5%), with a Youden index of 0.330 **(Table 2).** These findings indicate that SDMA is more reliable than creatinine for identifying anemia associated with renal dysfunction, particularly due to its higher discriminatory ability and good specificity. However, the modest sensitivity of SDMA suggests that normal or near-normal values do not exclude the presence of anemia, underscoring the need for SDMA to be interpreted alongside other clinical and laboratory parameters.

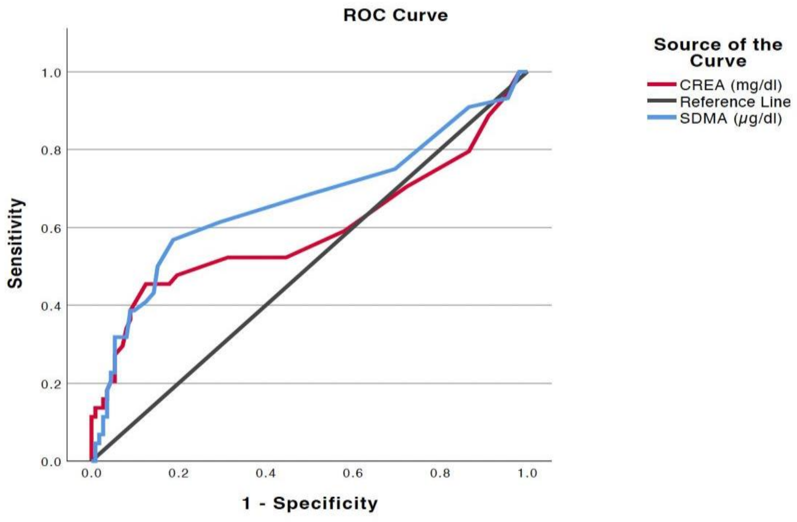

Figure 2. Receiver operating characteristic (ROC) curve with binormal smoothing for the detection of clinically relevant anemia. The light blue line represents the creatinine, the cyan line represents SDMA, and the diagonal magenta line represents the reference line for a non-discriminatory test.

Table 2. The optimal cutoff, sensitivity, 1-specificity, and Youden index of SDMA and creatinine in detecting clinically significant anemia.

	Parameter			
Biomarkers	Optimal Cutoff	Sensitivity	1-Specificity	Youden Index
SDMA	18.50	0.568	0.188	0.381
Creatinine	1.350	0.455	0.125	0.330

4. Discussion

The results of this study indicate that anemia becomes more prevalent and severe with advancing CKD stage, consistent with prior reports that link renal dysfunction to impaired erythropoietin production and chronic inflammation. As kidney function declines, the ability to produce erythropoietin, the hormone that stimulates red blood cell production diminishes, leading to reduced erythroid precursor cells in the bone marrow and worsening anemia [8]. In the study by Lippi et al. (2021), anemia was reported in approximately 60% of dogs, with the highest prevalence observed in the more advanced CKD IRIS stages. The frequency of anemia increased particularly in dogs with CKD IRIS stages 3 and 4, in which the frequency exceeded 70% [15]. In dogs with CKD, anemia prevalence rises from 47% in IRIS stage 2, to 71% in stage 3, and 82% in stage 4. Severity also increases, with moderate to severe anemia more common to be found in later stages. Morphological abnormalities in red blood cells, such as anisocytosis and poikilocytosis, become more frequent as CKD progresses, indicating worsening bone marrow function [15,16]. Although the chi-square test supported an association between CKD stage and anemia, the uneven distribution of cases across categories limited statistical robustness.

Gunawan et al. (2023) reported a dog with IRIS stage 4 CKD that exhibited severe non-regenerative anemia in conjunction with a markedly elevated SDMA concentration (64 μg/dL; reference range: 0–14 μg/dL) [17]. This suggests that dogs with severe anemia due to advanced kidney disease can have significantly increased SDMA concentrations. SDMA levels were higher in dogs with severe anemia compared with non-anemic dogs, suggesting that progressive renal impairment is associated with anemia severity. Aging itself is associated with mild decreases in hematocrit and serum iron, likely due to iron-restricted erythropoiesis and low-grade inflammation, but these changes are less pronounced than those seen with significant renal dysfunction [18]. Therefore, this relationship was not consistent across all anemia categories, likely due to the small sample size in severe groups.

Ordinal logistic regression failed to demonstrate SDMA as an independent predictor of anemia severity after adjusting for creatinine and age. In contrast, creatinine was strongly associated with CKD stage, reaffirming its established role as a renal biomarker. These findings suggest that while SDMA reflects renal dysfunction, it may not directly drive the pathogenesis of anemia.

ROC curve analysis demonstrated that SDMA had a moderate discriminatory capacity for identifying clinically relevant anemia, with an optimal cutoff of 18.5 μg/dL. At this threshold, specificity was relatively high (81.2%), but sensitivity was modest (56.8%). This performance profile suggests that SDMA may be more useful as a “rule-in” test for anemia associated with renal dysfunction, as elevated values strongly support the presence of disease, whereas normal or near-normal values do not reliably exclude it.

The superior performance of SDMA compared to creatinine (AUC 0.666 vs. 0.592, respectively) is consistent with its known ability to detect renal impairment earlier and more reliably than creatinine, which is strongly influenced by factors such as muscle mass, hydration status, and extrarenal conditions [19,20]. The moderate, but not excellent, discriminative capacity observed in this study indicates that SDMA alone should not be considered a definitive diagnostic tool for anemia in CKD but rather a complementary biomarker to be interpreted alongside hematological indices (HCT, reticulocyte count), renal staging, and iron status.

Importantly, the relatively high specificity observed for SDMA suggests that its greatest clinical utility may lie in identifying subsets of dogs where anemia is more likely to be of renal origin. This may help differentiate CKD-related anemia from anemia due to other etiologies such as nutritional deficiencies, chronic inflammation, or bone marrow disorders. On the other hand, the limited sensitivity underscores the need for caution, as relying solely on SDMA could result in underdiagnosis of clinically relevant anemia, particularly in earlier CKD stages or when multiple factors contribute to anemia development.

Taken together, these results highlight the potential utility of SDMA in the clinical evaluation of dogs with CKD. While SDMA may not serve as a strong independent predictor of anemia severity, it demonstrates moderate diagnostic accuracy and outperforms creatinine in identifying clinically meaningful anemia. Larger, balanced cohorts are needed to validate the cutoff identified in this study and to clarify the role of SDMA in the complex interplay between renal dysfunction and anemia in canine patients.

5. Conclusions

In conclusion, both the prevalence and the morphological abnormalities of anemia in dogs increase progressively with advancing IRIS stages. Although SDMA concentrations were elevated in dogs with more advanced CKD and severe anemia, multivariable analysis did not establish SDMA as an independent predictor of anemia severity after accounting for creatinine and age. Nevertheless, ROC curve analysis indicated that SDMA has a moderate discriminatory ability for detecting clinically relevant anemia, with relatively high specificity but limited sensitivity. These findings suggest that SDMA may serve as a useful adjunctive biomarker in the clinical evaluation of dogs with CKD, particularly as a supportive "rule-in" test to identify anemia of renal origin, but should not replace conventional hematological and biochemical assessments. Further studies with larger and more balanced populations are warranted to validate the diagnostic thresholds and better define the clinical role of SDMA in the early recognition and management of CKD-associated anemia in dogs.

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Institutional Review Board Statement: The study was conducted according to the guidelines for the care and use of animals, and approved by the Institutional Animal Care and Use Committee (IACUC) of INI Veterinary Service (Protocol No. IACUC-INIVET-2025-001). Informed consent was obtained from the dog owners prior to inclusion of their animals in the study.

Data Availability Statement: The data supporting this study are derived from hospital/clinical records and contain sensitive information. Therefore, they are not publicly available but may be provided by the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Borin-Crivellenti, S.; Crivellenti, L.Z.; Gilor, C.; Gilor, S.; Silva, D.G.; Maia, S.R.; Costa, P.B.; Alvarenga, A.W.; Fernandes, A.L.; Santana, A.E. Anemia in canine chronic kidney disease is multifactorial and associated with decreased erythroid precursor cells, gastrointestinal bleeding, and systemic inflammation. *Am J Vet Res* **2023**, *84*, 1–6. DOI: 10.2460/ajvr.23.05.0097.
2. Cernaro, V.; Coppolino, G.; Visconti, L.; Rivoli, L.; Lacquaniti, A.; Santoro, D.; Buemi, A.; Loddo, S.; Buemi, M. Erythropoiesis and chronic kidney disease–related anemia: From physiology to new therapeutic advancements. *Med Res Rev* **2019**, *39*, 427–460. DOI: 10.1002/med.21527.
3. Clase, C.M.; Carrero, J.J.; Ellison, D.H.; Grams, M.E.; Hemmelgarn, B.R.; Jardine, M.J.; Kovesdy, C.P.; Kline, G.A.; Lindner, G.; Obrador, G.T.; Palmer, B.F. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a KDIGO Controversies Conference. *Kidney Int* **2020**, *97*, 42–61. DOI: 10.1016/j.kint.2019.09.018.
4. Gunawan, M.; Amelia, F.; Resyana, N.N.; Zulfaichsanniyati, R.C.; Zaenab, S.; Widyaputri, T. IRIS-stage 4 CKD in a dog: diagnostic approaches and staging of chronic kidney disease: a case study. *J Exp Biol Agric Sci* **2023**, *11*, 216–225. DOI: 10.18006/2023.11(1).216.225.
5. Hamza, E.; Metzinger, L.; Metzinger-Le Meuth, V. Uremic toxins affect erythropoiesis during the course of chronic kidney disease: a review. *Cells* **2020**, *9*, 2039. DOI: 10.3390/cells9092039.
6. Hanna, R.M.; Streja, E.; Kalantar-Zadeh, K. Burden of anemia in chronic kidney disease: beyond erythropoietin. *Adv Ther* **2021**, *38*, 52–75. DOI: 10.1007/s12325-020-01524-6.
7. Imenez Silva, P.H.; Mohebbi, N. Kidney metabolism and acid–base control: back to the basics. *Pflugers Arch* **2022**, *474*, 919–934. DOI: 10.1007/s00424-022-02696-6.
8. International Renal Interest Society (IRIS). IRIS Staging of CKD (modified 2023). *IRIS Kidney* **2023**. Available online: https://www.iris-kidney.com (accessed on August 25, 2025).
9. Kashani, K.; Rosner, M.H.; Ostermann, M. Creatinine: from physiology to clinical application. *Eur J Intern Med* **2020**, *72*, 9–14. DOI: 10.1016/j.ejim.2019.10.025.

10. Khairat, A.S.; Harun, H.; Viotra, D. Symmetric Dimethylarginine as a Biomarker for Chronic Kidney Disease. *Bioscientia Med* **2023**, *7*, 3602–3608. DOI: 10.37275/bsm.v7i9.866.
11. Lippi, I.; Perondi, F.; Ghiselli, G.; Santini, S.; Habermaass, V.; Marchetti, V. Anemia in dogs with acute kidney injury. *Vet Sci* **2024**, *11*, 212. DOI: 10.3390/vetsci11050212.
12. Nabity, M.B.; Lees, G.E.; Boggess, M.M.; Yerramilli, M.; Obare, E.; Yerramilli, M.; Rakitin, A.; Aguiar, J.; Relford, R. Symmetric dimethylarginine assay validation, stability, and evaluation as a marker for the early detection of chronic kidney disease in dogs. *J Vet Intern Med* **2015**, *29*, 1036–1044. DOI: 10.1111/jvim.12835.
13. Portolés, J.; Martín, L.; Broseta, J.J.; Cases, A. Anemia in chronic kidney disease: from pathophysiology and current treatments, to future agents. *Front Med* **2021**, *8*, 642296. DOI: 10.3389/fmed.2021.642296.
14. Radakovich, L.B.; Pannone, S.C.; Truelove, M.P.; Olver, C.S.; Santangelo, K.S. Hematology and biochemistry of aging —evidence of “anemia of the elderly” in old dogs. *Vet Clin Pathol* **2017**, *46*, 34–45. DOI: 10.1111/vcp.12459.
15. Relford, R.; Robertson, J.; Clements, C. Symmetric dimethylarginine: improving the diagnosis and staging of chronic kidney disease in small animals. *Vet Clin N Am Small Anim Pract* **2016**, *46*, 941–960. DOI: 10.1016/j.cvsm.2016.06.010.
16. Rysz, J.; Gluba-Brzózka, A.; Franczyk, B.; Jabłonowski, Z.; Ciałkowska-Rysz, A. Novel biomarkers in the diagnosis of chronic kidney disease and the prediction of its outcome. *Int J Mol Sci* **2017**, *18*, 1702. DOI: 10.3390/ijms18081702.
17. Siwinska, N.; Zak, A.; Slowikowska, M.; Niedzwiedz, A.; Paslawska, U. Serum symmetric dimethylarginine concentration in healthy horses and horses with acute kidney injury. *BMC Vet. Res* **2020**, *16*, 396. DOI: 10.1186/s12917-020-02621-y.
18. Szlosek, D.; Robertson, J.; Quimby, J.; Mack, R.; Ogeer, J.; Clements, C.; McCrann, D.J.; Coyne, M.J. A retrospective evaluation of the relationship between symmetric dimethylarginine, creatinine and body weight in hyperthyroid cats. *PLoS ONE* **2020**, *15*, e0227964. DOI: 10.1371/journal.pone.0227964.
19. Taderegew, M.M.; Wondie, A.; Terefe, T.F.; Tarekegn, T.T.; GebreEyesus, F.A.; Mengist, S.T.; Amlak, B.T.; Emeria, M.S.; Timerga, A.; Zegeye, B. Anemia and its predictors among chronic kidney disease patients in Sub-Saharan African countries: a systematic review and meta-analysis. *PLoS ONE* **2023**, *18*, e0280817. DOI: 10.1371/journal.pone.0280817.
20. Wasung, M.E.; Chawla, L.S.; Madero, M. Biomarkers of renal function, which and when? *Clin Chim Acta* **2015**, *438*, 350–357. DOI: 10.1016/j.cca.2014.08.039.