

Correlations Between the Advanced Stages of Chronic Kidney Disease and Non-Regenerative Anemia in Felines

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RESEARCH ARTICLE

Abstract

Anemia in felines with chronic kidney disease (CKD) has been associated with a decreased quality of life and a faster rate of pathology progression, having a complicated and more complex pathogenesis. The main cause of the non-regenerative anemia in these patients is the kidneys' inability to produce erythropoietin (EPO), a side effect being the destruction of the red blood cells and the decreased rate of the new red blood cells production. This study aims to highlight the correlation between the signs of IIIrd and IVth stage chronic kidney disease (characterized by: metabolic acidosis, azotemia, proteinuria, dehydration, malnutrition, hyperphosphatemia, hypertension) and normocytic, normochromic, non-regenerative anemia occurrence. In this study, ten feline patients of various breeds (European, Persian and British Shorthair) aged between 7 and 14 years old were included. 40% of the patients from the study were diagnosed with IIIrd stage of CKD, while 60% with IVth stage. The blood samples were analysed using ProCyte Dx Haematology Analyser – for hematology and Catalyst One Veterinary Blood Chemistry Analyser – for blood biochemistry. All four felines (n=4) with IIIrd stage of CKD have been diagnosed with mild non-regenerative anemia, while the other six patients (n=6) with IVth stage presented severe non-regenerative anemia.

Keywords: Chronic kidney disease; felines; non-regenerative anemia.

INTRODUCTION

The main purpose of the current research is to highlight the correlation between the progression of chronic kidney disease (CKD) of felines and non-regenerative anemia. (Winzelberg, 2019; Ross et al., 1982). In the advanced stages of this geriatric feline disease, non-regenerative anemia is refractory, mild to moderate with normal or increased leukocyte and platelet counts, indicating a failure of erythropoiesis. According to the recent research and also to the prevalence of cases from veterinary clinics, chronic kidney disease is mostly associated with a reduced or ineffective erythropoiesis, the bone marrow being unable to keep up with the demand of new RBCs. (Nivy and Segev, 2019; Uva et al., 2023). The kidney's peritubular interstitial cells in the inner renal cortex and outer medulla are the main source of erythropoietin (Chen et al., 2020). The chronic kidney disease, an irreversible process characterized by persistent structural changes in the kidneys and loss function is divided into four stages, of interest for this study being the IIIrd stage (moderate renal azotemia) and the IVth stage (systemic clinic signs are obvious and the risk of uremic crises are increased) (Brown, 2008). It's often associated with various causes like chronic interstitial nephritis, polycystic kidney disease, or infections (Grauer, 2005). The patients diagnosed with these two stages of CKD present mild or severe non-regenerative anemia depending on the reticulocytes (Chalhoub et al., 2011; Yerramilli et al., 2016).

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In CKD, several factors contribute to the development of non-regenerative anemia: erythropoietin deficiency, uremic toxins (as the kidneys fail, uremic toxins accumulate, which may have a direct inhibitory effect on erythropoiesis), iron deficiency (felines with CKD often experience gastrointestinal bleeding or reduced iron absorption due to uremia, as a critical component in hemoglobin synthesis and its deficiency can exacerbate anemia), inflammatory cytokines (CKD is often associated with chronic inflammation and inflammatory cytokines, such as tumor necrosis factor - TNF and interleukin-1 - IL-1, can suppress erythropoiesis by affecting bone marrow function), secondary hyperparathyroidism, nutritional deficiencies (felines with CKD frequently suffer from malnutrition due to reduced appetite and vomiting and nutritional deficiencies, especially in vitamin B12 and folate, impair red blood cell production) (Marino et al.,2014).

MATERIALS AND METHODS

This study was a retrospective cross-sectional analysis aimed at investigating the correlation between the advanced stages of chronic kidney disease and non-regenerative anemia in felines. It's focused on felines diagnosed with CKD and categorized into different stages according to the International Renal Interest Society (IRIS) guidelines.

This research was performed during one year (from July 2023 to August 2024) at the University Emergency Hospital Prof. univ. Dr. Alin Bîrțoiu in Bucharest on a total of 14 felines older than 7 years old of various breeds (European mostly, Persian and British Shorthair), both males and females, with different weights (2,3 – 4,5kg) and variable reproductive status, which were diagnosed with chronic kidney disease.

Each patient was clinical and paraclinical examined, by general and special methods, such as biochemical investigations (urea, creatinine, phosphorus) and hematological blood tests (red blood cells count, hematocrit, hemoglobin, reticulocytes count and percentage).

The staging of chronic kidney disease was made using creatinine values (according to International Renal Interest Society) related to urea and phosphorus values. The regenerative nature of anemia was assessed according to the number and percentage of reticulocytes. For blood biochemistry was used Catalyst One Veterinary Blood Chemistry Analyser and for hematology blood tests, ProCyte Dx Haematology Analyser. The results obtained from the paraclinical examinations and the physiological interval values were specified in each individual case.

The inclusion criteria for study population were: the feline patients diagnosed with CKD based on clinical signs, increased serum creatinine (≥ 2.0 mg/dL) and persistent abnormal urine specific gravity ($USG \leq 1.035$), felines aged 7 years or older, as CKD prevalence increases with age, the felines presented with non-regenerative anemia (hematocrit $< 25\%$, and reticulocyte count and RBCs count and RBCs indices – MCV, MCHC below reference range).

RESULTS AND DISCUSSIONS

During the study period, the biochemical and hematological examination results of 14 felines of varying ages are analysed: one patient aged 7 years old, two aged 8 years old, three aged 9 years old, two aged 10 years old, three aged 12 years old, two felines aged 13 years old and one aged 14 years old. The one patient aged 7 years old, two aged 8 years old, three aged 9 years old and two aged 10 years old (which were diagnosed half a year ago and followed various treatments) presented values of creatinine ranging between 2.9 and 4.9 mg/dL, therefore, they belong to IIIrd stage of chronic kidney disease. Others important parameters to sustain this staging are the values of urea between 53–76 mg/dL and the values of phosphorus, between 5.2–6.5 mg/dL. For the hematological results: hematocrit values were between: 22–27% and the reticulocyte count were between: 26–34x 10⁹/L. The values for the patients with IIIrd stage of chronic kidney disease are presented in Table 1.

Table 1. The values of the renal parameters and hematological results for the patients diagnosed with IIIrd stage of chronic kidney disease

Number of patient	Patient's age	Creatinine (mg/dL)	Urea (mg/dL)	Phosphorus (mg/dL)	Hematocrit (%)	Reticulocyte Count (x10 ⁹ /L)
1	7 years old	2.9	53	5.2	27	34
2	8 years old	3.5	60	5.9	25	30
3	8 years old	4	70	6.3	23	28
4	9 years old	4.1	72	5.9	24	27
5	9 years old	4.3	74	6.1	24	27
6	9 years old	4.4	75	6.3	23	26
7	10 years old	4.9	76	6.5	22	26
8	10 years old	4.9	76	6.5	22	26
Mean		4.02 ± 0.5	69.75 ± 1.1	5.96 ± 0.9	24 ± 0.8	28.25 ± 1.2

In IVth stage of chronic kidney disease are included the three patients aged 12 years old, two aged 13 years old and one aged 14 years old. They presented values of creatinine 5.1-7.5 mg/dL. The values of urea were 78-110mg/dL and phosphorus values were 6.6-8.5/dL. A disturbance in phosphate metabolism can occur early in CKD and becomes more pronounced as the disease progresses. In this study, a significant positive correlation was found between serum phosphate levels and both serum urea and creatinine levels. This correlation suggests that as kidney function declines, indicated by elevated urea and creatinine, phosphate levels rise proportionally. These findings imply that phosphate concentration increases in parallel with the worsening of renal function, making phosphate a potential independent predictor of CKD progression.

For the hematological results: hematocrit values were between: 17–22% and the reticulocyte count were between: 18-24x10⁹/L. The values for the patients with IVth stage of chronic kidney disease are presented in Table 2.

Table 2. The values of the renal parameters and hematological results for the patients diagnosed with IVth stage of chronic kidney disease

Number of patient	Patient's age	Creatinine (mg/dL)	Urea (mg/dL)	Phosphorus (mg/dL)	Hematocrit (%)	Reticulocyte Count (x10 ⁹ /L)
1	12 years old	5.1	78	6.6	22	24
2	12 years old	5.5	82	7	21	22
3	12 years old	5.9	89	7.3	20	21
4	13 years old	6.8	95	7.8	18	19
5	13 years old	7.2	106	8.2	17	19
6	14 years old	7.5	110	8.5	17	18
Mean		6.33 ± 1.2	93.33 ± 1.5	7.56 ± 1.1	19.16 ± 0.8	20.5 ± 0.7

In stages IIIrd and IVth of CKD, the clinical signs associated with more advanced kidney dysfunction and anemia became increasingly severe. The following table (Table 3) shows the most common clinical signs and the number of patients, respectively the percentage in which they were recorded.

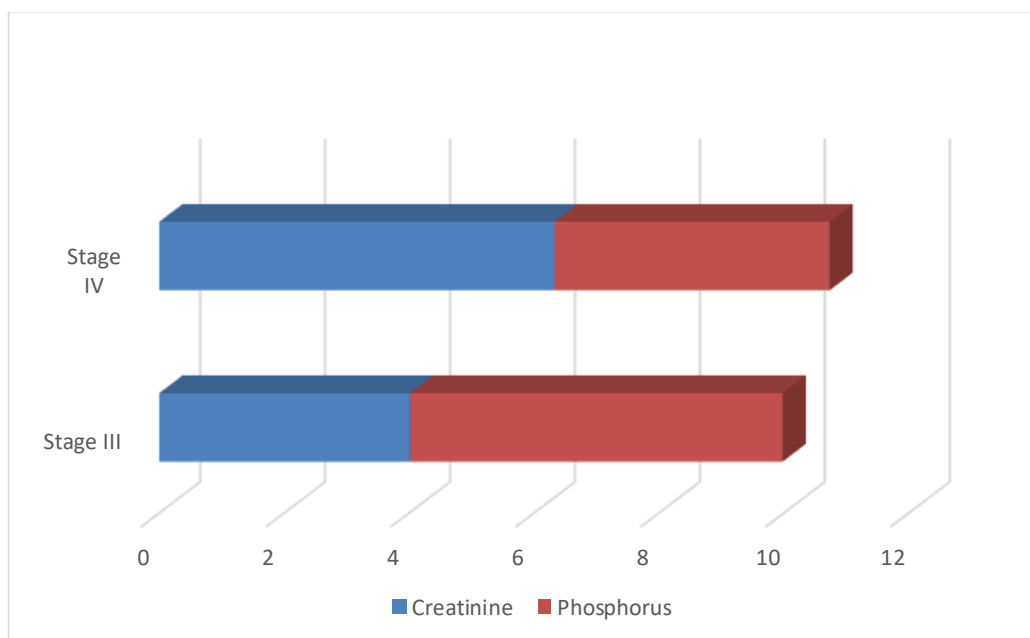


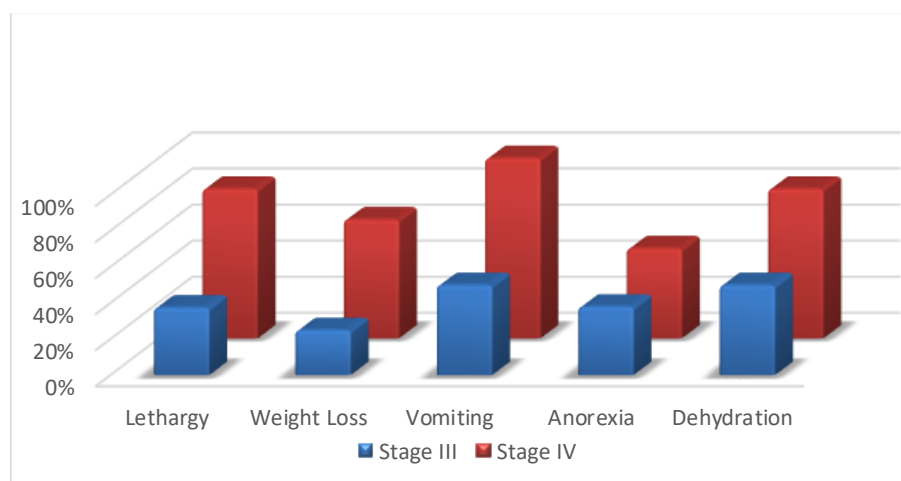
Figure 1. The mean values of creatinine and phosphorus for IIIrd and IVth stages of CKD.

In Figure 1 are presented comparatively the mean values of creatinine and phosphorus for IIIrd and IVth stages of chronic kidney disease, two of the critical markers used for indicating the progression of this disease.

Table 3. The clinical signs recorded in patients in stage IIIrd and IVth of chronic kidney disease

Clinical sign	Stage III rd	Stage IV th
Lethargy/Weakness	n=3 (38%)	n=5 (83%)
Weight loss	n=2 (25%)	n=4 (66%)
Polyuria/Polydipsia	n=2 (25%)	n=3 (50%)
Vomiting	n=4 (50%)	n=6 (100%)
Anorexia	n= 3 (38%)	n= 3 (50%)
Dehydration	n=2 (25%)	n=5 (83%)
Poor coat condition	n=2 (25%)	n=6 (100%)
Oral ulcers	n=1 (13%)	n=1 (25%)

For the IIIrd stage of CKD, most patients presented lethargy/weakness, vomiting and anorexia and for the IVth stage, the patients presented especially lethargy, weight loss, vomiting, dehydration and poor coat condition. In CKD Stage IIIrd, the anemia starts to become clinically significant, but the body may still compensate. In IVth stage, severe anemia (hematocrit<22%) reduces oxygen delivery to tissues and uremic toxins directly impair cellular metabolism, leading to extreme fatigue. As CKD progresses, felines lose more weight due to decrease of a muscle mass and poor nutrient absorption. In IVth stage, the weight loss is more profound because anorexia becomes a major issue. The frequency of vomiting increases from intermittent episodes in IIIrd stage to almost daily episodes in IVth stage. Vomiting is related to the accumulation of uremic toxins, which affect the stomach lining. In IIIrd stage mild dehydration may be managed with fluid supplementation, but in stage IVth, dehydration becomes severe and requires more aggressive fluid therapy. The poor coat condition is largely due to the chronic dehydration and malnutrition seen in advanced CKD. As kidney function declines, electrolyte imbalances further impair the health of the skin and hair.

**Figure 2.** The most common clinical signs for both advanced stages of chronic kidney disease.

CONCLUSIONS

This study explored the correlations between the advanced stages of chronic kidney disease and non-regenerative anemia in felines, focusing on CKD IIIrd and IVth stages. The analysis of biochemical, hematological data and clinical signs revealed significant relationships between the progression of renal dysfunction and the development of non-regenerative anemia. Elevated serum creatinine levels were a consistent marker of CKD progression. In IIIrd stage, creatinine levels ranged from 2.9–4.9 mg/dL, while in IVth stage, they exceeded 5 mg/dL. The rise in creatinine was strongly correlated with the severity of clinical signs, particularly lethargy and weakness. Urea levels were elevated in IIIrd and IVth stages, with values between 53–76 mg/dL in IIIrd stage and 78–110 mg/dL in IVth stage. Urea accumulation was closely linked to the presence of gastrointestinal symptoms such as vomiting and anorexia, as uremic toxins caused systemic effects, particularly on the GI tract. Hyperphosphatemia was evident in both CKD IIIrd and IVth stages with phosphorus levels between 5.2–6.5 mg/dL in IIIrd stage and rising above 6.6 mg/dL in IVth stage. In IIIrd stage of CKD, hematocrit levels were moderately reduced (22–27%), while in IVth stage, hematocrit dropped below 22%, indicating a severe non-regenerative anemia. This anemia is strongly correlated with clinical signs such as lethargy, weight loss and decreased quality of life. The reticulocyte counts were consistently low in both stages, confirming the non-regenerative nature of the anemia. Reticulocyte levels ranged from 26–34 x 10⁹/L in IIIrd stage and dropped further to 18–24 x 10⁹/L in IVth stage. This reduction of the reticulocytes count is linked to decreased erythropoietin production due to renal mass functional loss. In conclusion, this study confirms

the significant correlation between advanced stages of CKD and the development of non-regenerative anemia in felines. As CKD progresses to IIIrd and IVth stages, anemia becomes more severe, contributing to a range of debilitating clinical signs and reducing survival rates. Effective management strategies focusing on controlling anemia, hyperphosphatemia and uremic toxins are critical in improving the quality of life in cats with advanced CKD.

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Conflicts of Interest

The authors declare that they don't have any conflict of interest.

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