Erciyes Üniversitesi Veteriner Fakültesi Dergisi

Research Article
*10.32707/ercivet.1867213*

***Imprint:***
Volume: 23(2)
Year: 2026
Page: 155-167

Alfatih Mohammed Ahmed ABOZAID[a]
Vehbi GÜNEŞ[b*]

[a] Master's Student, Erciyes University, fatihmohammed1995@gmail.com
[b] Prof., Erciyes University, vgunes@erciyes.edu.tr

[*] Corresponding Author

*Received: 1/19/2026*
*Accepted: 7/17/2026*

***Citation:***
Abozaid A.M.A., Güneş V. Serum clusterin as a sensitive biomarker for kidney disease in cats: A comparative evaluation in acute kidney injury and chronic kidney disease. Erciyes Univ J Vet Fac. 2026;23(2), 155-167. https://doi.org/*10.32707/ercivet.1867213*

Screened by iThenticate for Authors & Researchers

Except where otherwise noted, content in this article is licensed under a Creative Commons 4.0 International license. Icons by Font Awesome.

# Serum Clusterin as a Sensitive Biomarker for Kidney Disease in Cats: A Comparative Evaluation in Acute Kidney Injury and Chronic Kidney Disease

**Abstract**

Current biomarkers for feline kidney disease, including creatinine and blood urea nitrogen (BUN), have limited sensitivity for early injury and do not reliably distinguish acute kidney injury (AKI) from chronic kidney disease (CKD). This study aimed to evaluate serum and urinary clusterin (CLU) levels in felines presenting urinary system disorders, with a focus on acute kidney injury (AKI) and chronic kidney disease (CKD), to determine its potential as a sensitive biomarker of renal pathology. In the study group, blood samples were collected from a total of 38 cats. For the primary analysis, cats were classified according to their predominant renal status into two mutually exclusive groups: chronic kidney disease (CKD, n=19), acute kidney injury (AKI, n=19) from various breeds brought to Erciyes University Training and Research Hospital. Control group samples were also taken from 10 healthy cats brought to the same center for general health control. Clusterin quantification was performed using a competitive enzyme-linked immunosorbent assay (ELISA). Results indicated that mean serum clusterin concentrations were significantly elevated in diseased cats. The mean serum clusterin level was found to be 42.87 µg/mL (34.51 - 57.17) in all sick cats and 36.42 µg/mL (29.08 - 48.39) in healthy cats. Cats with chronic renal failure had statistically significantly higher mean clusterin levels (84.79±61.87 µg/mL) than cats with acute kidney failure (38.80±15.18 µg/mL) ($P<0.001$). Correlation analyses revealed strong positive associations between serum clusterin and conventional renal injury markers, including blood urea nitrogen (BUN, $r=0.756$), creatinine ($r=0.829$), and phosphorus ($r=0.744$; all $P<0.001$). Serum clusterin concentrations differed significantly between cats with renal disease and healthy controls and were further assessed by ROC analysis for discrimination between CKD and AKI. At an optimal cut-off value of 3.11, sensitivity was 77.8%, and specificity was 25%, indicating limited discriminatory performance. Despite statistical differences between groups, substantial overlap and low specificity resulted in poor classification accuracy. Overall, serum clusterin shows an association with renal disease status; however, its ability to distinguish CKD from AKI is limited under the current conditions, and it should not be considered a stand-alone diagnostic marker.

**Keywords:** Acute kidney injury, chronic kidney disease, clusterin, competitive enzyme-linked immunosorbent assay

# Kedilerde Böbrek Hastalıkları İçin Duyarlı Bir Biyobelirteç Olarak Serum Clusterin: Akut Böbrek Hasarı ve Kronik Böbrek Hastalığında Karşılaştırmalı Bir Değerlendirme

**Öz**

Kedilerde böbrek hastalığı için kullanılan mevcut biyobelirteçler, kreatinin ve kan üre azotu (BUN) dahil olmak üzere, erken dönem hasarı saptamada sınırlı duyarlılığa sahiptir ve akut böbrek hasarı (ABH) ile kronik böbrek hastalığını (KBH) güvenilir şekilde ayırt edemezler. Bu çalışma, üriner sistem hastalığı olan kedilerde serum ve idrar clusterin (CLU) düzeylerini değerlendirmeyi ve özellikle akut böbrek hasarı (ABH) ile kronik böbrek hastalığı (KBH) kapsamında renal patolojilerin duyarlı bir biyobelirteci olma potansiyelini araştırmayı amaçlamaktadır. Hasta grubunu, Erciyes Üniversitesi Eğitim ve Araştırma Hastanesi'ne getirilen farklı ırk ve yaşlardaki; toplam 38 hasta kedi, birincil analiz kapsamında kediler, baskın renal durumlarına göre iki birbirini dışlayan gruba ayrılmıştır: kronik böbrek hastalığı (KBH, n=19) ve akut böbrek hasarı (ABH, n=19). Kontrol grubuna ise aynı merkezde rutin sağlık kontrolü amacıyla getirilen 10 sağlıklı kedi dâhil edildi. Clusterin düzeylerinin kantitatif analizi, kompetitif ELISA yöntemi kullanılarak gerçekleştirildi. Elde edilen bulgular, hasta gruplarındaki kedilerde ortalama serum clusterin düzeylerinin sağlıklı kedilere kıyasla anlamlı derecede yüksek olduğunu göstermektedir. Tüm hasta kedilerde ortalama serum clusterin düzeyi 42.87 µg/mL (34.51-57.17) olarak belirlenirken, sağlıklı kedilerde bu değer 36.42 µg/mL (29.08-48.39) olarak saptanmıştır. Kronik böbrek yetmezliği olan kedilerde serum ortalama clusterin düzeylerinin (84.79±61.87 µg/mL), akut böbrek yetmezliği olan kedilere (38.80±15.18 µg/mL) göre istatistiksel olarak anlamlı derecede daha yüksek olduğu belirlenmiştir (P<0.001). Korelasyon analizleri, serum clusterin düzeyleri ile BUN (r=0.756), kreatinin (r=0.829), ve fosfor (r=0.744) gibi böbrek hastalığı belirteçleri arasında güçlü ve pozitif yönlü ilişkiler olduğunu ortaya koymuştur (P<0.001). Diğer gruplar arasında ise önemli farklılıklar saptanmamıştır. Sonuç olarak bu araştırmanın sonuçları, Serum clusterin düzeyleri, böbrek hastalığı olan kediler ile sağlıklı kontrol grubu arasında anlamlı olarak farklı bulunmuş ve CKD ile ABH arasındaki ayırt edici performansı değerlendirmek amacıyla ROC analizi ile incelenmiştir. 3.11'lik optimal cut-off değerinde duyarlılık %77.8, özgüllük ise %25 olarak hesaplanmış olup, bu durum sınırlı ayırt edici performansa işaret etmektedir. Gruplar arasında istatistiksel olarak anlamlı farklılıklar bulunmasına rağmen, belirgin örtüşme ve düşük özgüllük, sınıflandırma doğruluğunun yetersiz olduğunu göstermiştir. Genel olarak, serum clusterin böbrek hastalığı varlığı ile ilişkili görünmekle birlikte, mevcut çalışma koşullarında CKD ile ABH'ın ayırt etme kapasitesi sınırlıdır ve tek başına tanısal bir biyobelirteç olarak değerlendirilmemelidir.

**Anahtar kelimeler:** Akut böbrek hasarı, clusterin, kronik böbrek hastalığı, kompetitif enzim bağlı immünosorbent analiz



## Introduction

Urinary system diseases are highly prevalent in cats, with chronic kidney disease (CKD) and acute kidney injury (AKI) representing two of the most clinically significant conditions. CKD is a progressive and irreversible disorder characterized by sustained loss of renal function over at least three months and is a leading cause of morbidity and mortality in aging feline populations. In contrast, AKI is an acute and potentially reversible condition, developing over hours to days, and is associated with a sudden decline in glomerular filtration rate (GFR), often resulting in azotemia, uremia, and alterations in urine output (Monaghan et al., 2012). Differentiating AKI from CKD remains a critical but challenging aspect of clinical decision-making.

Early detection of renal dysfunction is essential to improve therapeutic outcomes. However, conventional biomarkers, including serum creatinine and blood urea nitrogen (BUN), are limited by low sensitivity in early-stage disease and their dependence on functional rather than structural renal changes (Yerramilli et al., 2016). Moreover, these markers do not reliably distinguish between acute and chronic renal pathology. Consequently, there is a need for biomarkers that reflect underlying cellular injury and provide earlier and more specific diagnostic information.

Clusterin is a multifunctional glycoprotein involved in cellular stress responses, apoptosis regulation, and tissue remodeling. It is upregulated in response to renal tubular injury and oxidative stress, supporting its potential role as a biomarker of kidney damage (García-Martínez et al., 2012). While clusterin is not organ-specific and is expressed in multiple tissues (Rosenberg and Silkensen, 1995), this limitation may be partially mitigated by the context of renal disease, where kidney injury can significantly increase both local production and systemic release. In particular, urinary clusterin is

thought to reflect direct tubular damage, whereas serum clusterin may represent a combination of renal release and systemic response to injury. Therefore, evaluating both serum and urinary concentrations may provide complementary information regarding the presence and extent of renal pathology.

Previous studies in dogs have demonstrated the diagnostic utility of urinary clusterin in renal disease. Increased urinary clusterin levels have been reported in dogs with leishmaniasis-associated nephropathy, and the urinary clusterin-to-creatinine ratio has been proposed as an early indicator of CKD (García-Martínez et al., 2012). Additionally, urinary clusterin has been associated with tubulointerstitial injury and progression to end-stage renal disease (Wu et al., 2018). Despite these findings, data on clusterin in feline renal disease remain limited, and no studies have comprehensively evaluated both serum and urinary clusterin in the context of differentiating AKI and CKD in cats.

We hypothesized that clusterin concentrations would be significantly increased in cats with renal disease compared to healthy controls, with distinct patterns between AKI and CKD reflecting differences in pathophysiology. Specifically, we postulated that urinary clusterin would more closely reflect acute tubular injury, whereas serum clusterin may provide additional information on systemic and chronic processes.

Therefore, the present study aimed to evaluate serum and urinary clusterin as diagnostic biomarkers of renal disease in cats and to determine their ability to differentiate AKI from CKD, thereby addressing a current gap in feline nephrology and improving the clinical utility of emerging biomarkers.

## Material and Method

### *Study Design*

Prospective case-control study

### *Ethics Statement and Informed Consent*

The research was conducted at the Erciyes University Faculty of Veterinary Medicine, Department of Internal Medicine. Acute kidney injury (AKI) and chronic kidney disease (CKD) were diagnosed, following the owners' willingness to participate in the study for the aim of treatments at the Erciyes University teaching and Research Hospital. Blood and urine samples were collected from patients and healthy cats that came for health check-ups. Erciyes University Animal Experiments Local Ethics Committee (ERU HADYEK) approved the study for animal experimentations (committee decision number: 21/199).

### *Animals and Sampling*

All animals were prospectively enrolled and evaluated at the Erciyes University, Faculty of Veterinary Medicine, Teaching and Research Hospital. A standardized diagnostic approach was applied, including complete physical examination (body temperature, heart rate, respiratory rate), hematology, serum biochemistry, and urinalysis, where available. Cats with neurological, respiratory, skin, and other diseases were excluded from the study.

Blood and urine samples were collected at the time of initial presentation (Day 0), before initiation of treatment whenever possible, to ensure that biomarker measurements reflected baseline disease status.

Cats were diagnosed with AKI (n=19) based on acute onset (≤7 days) of clinical signs, presence of azotemia (serum creatinine >2.5 mg/dL; blood urea nitrogen >35 mg/dL), and inappropriate urine concentrating ability (urine specific gravity <1.035), in accordance with IRIS AKI criteria. Additional supportive findings included oliguria/anuria or a documented increase in serum creatinine despite adequate fluid therapy and correction of hydration status. Kidney size was typically normal to enlarged on ultrasonography.


CC: BY-NC-ND

CKD (n=19) was defined according to IRIS guidelines as persistent renal dysfunction for ≥3 months, based on historical, clinical, and/or repeated laboratory findings. Diagnostic criteria included sustained azotemia with inappropriately low urine specific gravity (<1.035), along with supportive findings such as small, irregular kidneys on ultrasonography, hyperphosphatemia, and non-regenerative anemia.

Cats with concurrent systemic diseases (neurological, respiratory, dermatological, or other systemic conditions) were excluded. Information regarding hydration status and prior treatment was recorded, and sampling was performed before therapeutic intervention whenever feasible.

Clinically healthy cats (n=10) presented for routine check-ups were included as controls. These animals underwent thorough physical examination and laboratory testing (hematology, biochemistry, and urinalysis) to exclude subclinical disease. The control group was selected to approximate the study population in terms of general breed distribution; however, a perfect age matching between groups was not achieved due to the limited availability of healthy cats meeting the inclusion criteria, and this was considered a potential limitation. All control animals were confirmed to be free of systemic or urinary tract disease at the time of sampling. No power analysis or sample size determination method was used in this study. However, previous similar studies were taken into consideration.

***Hematology, Biochemistry and Urinary Analyses***

Blood samples were collected from the cephalic vein into tubes with an anticoagulant (BD, $K_3$EDTA, 3.8 mL) for haematology and into tubes without anticoagulants (Hemolab BD, SST, 6 mL) for biochemical analysis. Routine renal biochemical parameters (Creatinine, BUN, phosphorus) were assessed utilizing a fully automated biochemistry analyzer (Randox Monaco) situated in the Department of Internal Medicine, Faculty of Veterinary Medicine. Hematological studies were conducted utilizing a complete blood count apparatus (Exigo Eos Vet) situated in the same facility. Blood serum samples from both groups of cats were preserved at −20°C until analysis.

Urine samples were collected by either cystocentesis or catheterization for urinalysis (dipstick test and urine sediment examination). Dipstick strips (Hasvet VUC) were used for urinalysis, and preparation of urine sediment was performed to identify cells, casts, crystals, and/or microorganisms. Urine samples were centrifuged (Hettich, Zentrifugen) for 5 minutes at 3000 rpm to obtain sediments. The supernatant was collected and mixed by turning the bottle upside down. Five mL of urine was transferred to a centrifuge tube with a conical tip using a disposable plastic pipette. Each urine supernatant was split into two Eppendorf tubes and refrigerated at -80°C until analysis. A drop of the remaining sediment was placed on a microscope slide using a pipette. A coverslip was placed over the sample. The covered slide was placed on the microscope and examined using the low power (x10) lens followed by the high power (x40) lens in order to determine cells, casts, crystals, and/or microorganisms. The findings were graded as grade zero means no cells, grade one means 1-5 cells, and grade two means more than six cells in a high-power field. Pyuria (>six white blood cells/high power field), haematuria (>six red blood cells/HPF), and bacteriuria were also noted as reported by Lamchiagdhase et al. (2005).

***Urinary System Ultrasonography***

Ultrasonographic examination of the kidneys and urinary tract was performed in all study cats as part of the diagnostic work-up and case classification process. Examinations were conducted using a Mindray DC-N3 ultrasound system equipped with a 5.0–7.5 MHz convex transducer.

Ultrasonographic findings were systematically evaluated and recorded and were used as supportive criteria in disease classification, particularly for differentiation between acute and chronic renal pathology.

Renal morphology was assessed based on kidney size, cortical echogenicity, cortico-medullary differentiation, and pelvic changes. Kidneys were considered consistent with AKI when normal to enlarged renal size was accompanied by preserved or mildly altered cortical echogenicity without marked architectural distortion. In contrast, kidneys were classified as consistent with CKD when


CC: BY-NC-ND

reduced renal size, irregular contour, increased cortical echogenicity, loss of cortico-medullary distinction, and/or mineralization were present.

Thus, ultrasonography results were not used in isolation but were integrated with clinical findings and laboratory data to support final group allocation and to improve diagnostic accuracy in distinguishing AKI and CKD.

### *ELISA Analysis*

ELISA analysis a commercial Dog ELISA Clusterin Kit t was used for analyses (MyBiosource, MBS083314). Sensitivity: The sensitivity of this kit is 1.0 ng/mL. Detection Range: The detection range of this kit is 6.25 ng/mL-200 ng/mL. Standard Concentration Gradients (S6 to S1): 200, 100, 50, 25, 12.5, 6.25 ng/m. Since no company produced a clusterin ELISA kit for cats, the clusterin ELISA kit for dogs was used instead. Because clusterin shares a high degree, approximately 98.9% of homology of, the amino acid sequences of both cat (Cat Clusterin aminoacid sequences:>sp|A0M8S7 CAV1_FELCA OS=Felis catus OX=9685 GN=CAV1 PE=3SV=1) and dog (Dog Clusterin aminoacid sequences >sp|P33724|CAV1_CANLF OS=Canis lupus familiaris OX=9615 GN=CAV1 PE=1 SV=1) as shown in the UNIPROT database (Figure 1). ELISA was carried out and evaluated as instructed by the manufacturer. The optic densities were obtained at 450 nm by using a Biotek ELx800 ELISA reader. The standard curve and clusterin concentration in the urine and serum samples were determined using a 4-parameter logistic curve-fitting program.

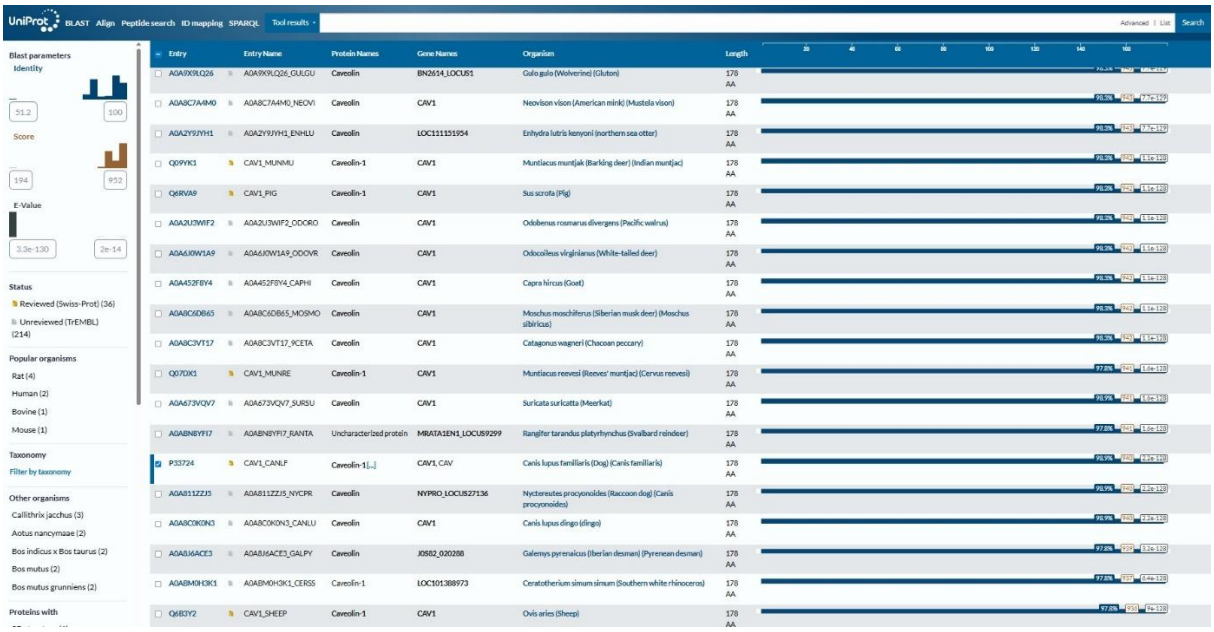



**Figure 1:** BLAST analyses were performed using the amino acid sequences of feline and canine clusterin retrieved from the UniProt database. The gray arrow indicates the canine clusterin database accession number (P33724) identified in the feline clusterin BLAST analysis.

### *Statistical Analysis*

The IBM-SPSS for Windows Release 25.0 program was used to perform statistical analyses (SPSS Inc, Chicago, IL, USA). Using the histogram, Q-Q graphs, and Shapiro-Wilk test, it was determined whether the data obtained from the study were suitable for normal distribution or not. Qualitative data were expressed as % (n). Normally distributed data are expressed as the Mean ± Standard Deviation (SD), while non-normally distributed data are expressed as the Median ($25^{th}$ and $75^{th}$ Percentiles). Normally distributed data were analyzed using the t-test on independent samples. The Mann–Whitney U test was applied to examine non-normally distributed data. A p-value of less than 0.05 was considered statistically significant. Correlations between variables were evaluated using either the

Pearson or Spearman correlation coefficient, depending on the distribution characteristics of the data. In addition, receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic performance of serum clusterin levels. The p-value of <0.05 was considered statistically significant.

## Results

### *Hematological and Biochemical Findings*

The sick cats' mean lymphocyte levels were significantly lower than those of healthy cats. The mean of BUN, Creatinine, and Phosphorus values of the patient cats were found to be significantly higher than those of healthy cats (P<0.05) (Table 1).

**Table 1.** Comparison of biochemical parameters between groups (mean±standard deviation)

| | **(Healthy Group) (n=10)** | **(Patient Group) (n=38)** | **P values** |
|---|---|---|---|
| **BUN (mg/mL)** | 15.18±6.58 (10.50-19.00) | 79.58±71.72 (34.50-107.70) | <0.001 |
| **Creatinine (mg/mL)** | 0.80±0.21 (0.58- 1.00) | 3.68±4.47 (1.20-4.05) | <0.001 |
| **Phosphorus (mg/mL)** | 5.04±1.68 (3.65- 6.50) | 7.24±3.56 (5.22- 8.19) | <0.05 |

*Data are presented as mean ± standard deviation (SD), with minimum–maximum values shown in parentheses. P value <0.05 was considered statistically significant, while P< 0.001 indicates a highly significant difference. BUN: Blood Urea Nitrogen SD: Standard Deviation mg/mL: Milligram per milliliter p: Probability value*

### *Urinary Analyses Findings*

The patient's mean specific gravity, blood, pH, protein, and WBC values were significantly higher than the reference values reported for cats. There were no significant differences between the study and control groups in other variables. The distribution of urine sediment examination parameters among patient cats. Kidney epithelial cells were absent in grade 0 (0%), while grade 1 and grade 2 accounted for 43.5% and 56.5% of cases, respectively. Crystalluria was detected in 47.8% of patient cats, with struvite crystals being the most prevalent (21.8%), followed by amorphous phosphate (8.7%), amorphous urate (8.7%), calcium oxalate (4.3%), and calcium carbonate (4.3%). Bacterial presence was not observed in grade 0 (0%), whereas grade 1 and grade 2 were identified in 74% and 26% of cases, respectively. Red blood cells were evenly distributed between grade 0 and grade 1 (34.8% each), with grade 2 representing 30.4% of cases. In contrast, white blood cells were predominantly observed at higher severity levels, with 65.2% classified as grade 2, followed by grade 1 (30.5%) and grade 0 (4.3%).

### *Renal and Urinary Bladder USG Findings*

The patient cats' average Vesica Urineria Wall Thickness (VUMT) values were greater than the reference values. On the other hand, the patient cats' right kidney cortical thickness (RKCT), right kidney medulla thickness (RKMT), left kidney cortical thickness (LKCT), and left kidney medulla thickness (LKMT) values were lower than the reference values.


CC: BY-NC-ND

### *ELISA Findings*

In serum samples, the levels of average clusterin were given in Table 2. According to these findings, cats with chronic renal failure had significantly higher mean/median clusterin levels than cats with acute kidney failure (P<0.001). The mean serum clusterin level in sick cats, 42.87 µg/mL (34.51±57.17) was significantly higher than in healthy cats, 36.42 µg/mL (29.08±48.39) (Figure 2). Cats with CKD had significantly higher serum clusterin levels (84.79±61.87 µg/mL) compared to those with AKI (38.80±15.18 µg/mL, P<0.001) (Figure 3). Serum clusterin levels showed a strong positive correlation with BUN (r=0.756, P<0.001), creatinine (r=0.829, P<0.001), and phosphorus (r=0.744, P<0.001), indicating its potential as a biomarker for renal dysfunction. In comparison between lower urinary tract infections and acute or chronic kidney disease, no significant differences or values were observed among seven cats diagnosed with lower urinary tract disease.

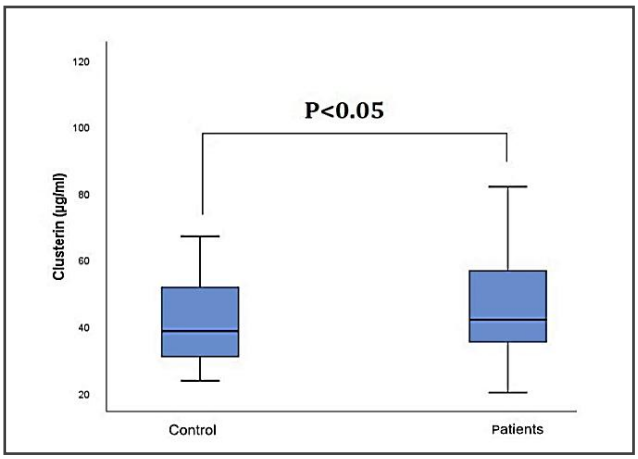



**Figure 2.** Appearance of the clusterin levels in patients and control cats

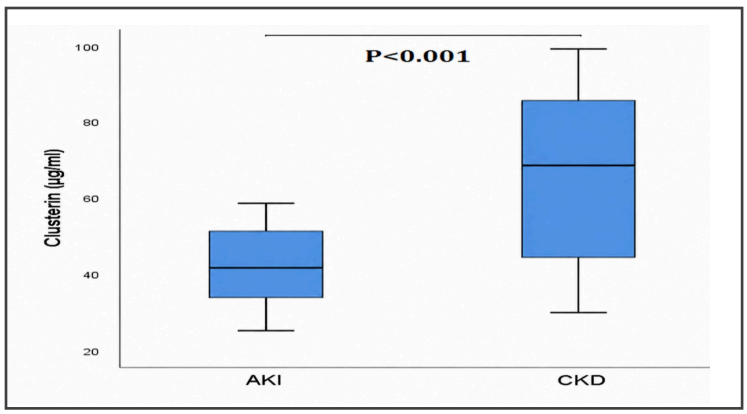



**Figure 3.** Appearance of the clusterin levels in cats with AKI and CKD.

Serum clusterin concentrations were significantly higher in cats with CKD compared to those with AKI (84.79±61.87 µg/mL vs. 38.80±15.18 µg/mL, P<0.001), indicating a strong association between elevated clusterin levels and chronic renal pathology (Table 2).


CC: BY-NC-ND

**Table 2.** Comparison of Clusterin levels measured in serum of cats with acute and chronic kidney failure (mean ± standard deviation).

| | **AKI Group (n=19)** | **CKD Group (n=19)** | **P Value** |
|---|---|---|---|
| **Serum Clusterin (µg/mL)** | 38.80±15.18 | 84.79±61.87 | <0.001 |

*Statistical analysis was performed to compare serum clusterin levels between the two groups. Values are expressed as mean ± standard deviation (SD). P value <0.05 was considered statistically significant and (P<0.001) indicates a highly significant difference between groups. AKI: Acute Kidney Injury. CKD: Chronic Kidney Disease*

Serum clusterin concentrations were significantly higher in the patient group compared with the healthy control group (42.87 ± SD vs. 36.42 ± SD, P< 0.001) (Table 3).

**Table 3.** Comparison of Clusterin levels measured in blood serum of healthy, patient groups (mean±standard deviation).

| | **(Healthy Group) (n=10)** | **(Patient Group) (n=38)** | **P Value** |
|---|---|---|---|
| **Clusterin (µg/mL)** | 36.42 (29.08-48.39) | 42.87 (34.51-57.17) | <0.001 |

*Values data were expressed as median (25$^{th}$ and 75$^{th}$ percentiles). P value <0.05 was considered statistically significant, and P<0.001 denotes a highly significant difference.*

Serum clusterin levels showed a strong positive correlation with all evaluated kidney markers. The strongest association was observed with serum creatinine (r = 0.829, P<0.001), followed by BUN (r = 0.756, P<0.001) and phosphorus (r = 0.744, P<0.001) (Table 4).

**Table 4.** Correlation between clusterin and kidney markers.

| **Variable** | **Correlation (r)** | **P-Value** |
|---|---|---|
| BUN | 0.756 | <0.001 |
| Creatinine | 0.829 | <0.001 |
| Phosphorus | 0.744 | <0.001 |

*Correlation analysis was performed using an appropriate correlation test (e.g., Pearson or Spearman, depending on data distribution). A P value <0.05 was considered statistically significant, while P<0.001 indicates a highly significant correlation. BUN: Blood Urea Nitrogen r: Correlation coefficient p: Probability value (statistical significance).*

When the cut-off point for serum Clusterin between CKD and AKI was taken as 3.11, the sensitivity, specificity, and area under the ROC curve (AUC) were calculated as 77.8% and 25%, respectively (Figure 4).


CC: BY-NC-ND

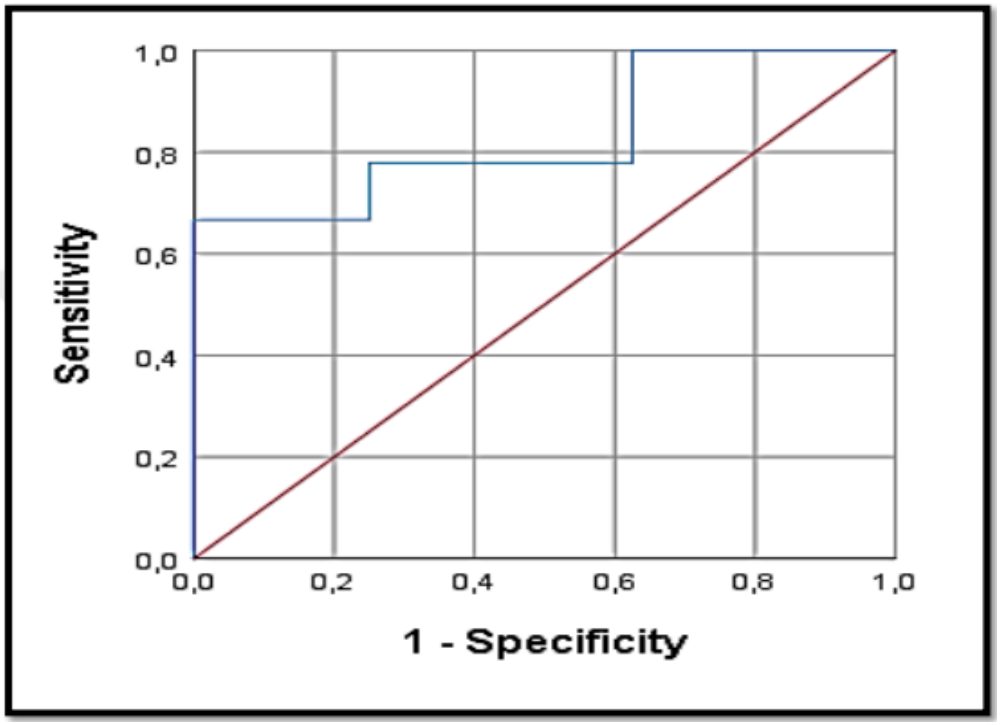



**Figure 4.** ROC analysis of clusterin in the serum of patient cats.

**Discussion and Conclusion**

Serum clusterin concentrations were significantly higher in cats with chronic kidney disease (CKD) (84.79 ± 61.87 µg/mL) compared with those diagnosed with acute kidney injury (AKI) (38.80 ± 15.18 µg/mL). This pattern suggests that serum clusterin is more strongly associated with sustained and progressive renal injury rather than acute insult, potentially reflecting ongoing tubular stress, maladaptive repair mechanisms, and chronic inflammatory remodeling rather than transient injury alone (Guo et al., 2016). The observed positive associations between serum clusterin and conventional renal biomarkers (creatinine, BUN, and phosphorus) further support its relationship with overall disease burden rather than isolated glomerular filtration changes, indicating that clusterin may function as a marker of cumulative renal damage and systemic response to renal dysfunction.

Importantly, the higher serum clusterin levels in CKD compared to AKI may also reflect differences in disease chronicity and compensatory protein expression, where prolonged renal injury leads to sustained upregulation of stress-response proteins. However, the overlap in standard deviations suggests substantial biological variability, which limits its use as a standalone discriminative marker and indicates that clusterin is more likely to be useful as part of a multimarker diagnostic panel rather than an independent diagnostic test.

Taken together, these findings suggest that serum clusterin may have greater diagnostic and pathophysiological relevance than urinary clusterin in feline renal disease under current analytical conditions. However, its moderate overlap between disease groups and correlation with non-specific inflammatory and metabolic parameters indicate that clusterin should be interpreted as a non-specific renal stress biomarker rather than a disease-specific diagnostic marker. Future studies should focus on longitudinal sampling and integration with established biomarkers to clarify its role in distinguishing AKI from CKD and in monitoring disease progression.


CC: BY-NC-ND

In the present study, median serum clusterin concentrations were significantly higher in the patient group compared with healthy controls ($P<0.05$), indicating an association between clusterin and the presence of renal disease. This finding is consistent with previous veterinary studies reporting altered clusterin levels in association with renal injury. For example, García-Martínez et al. (2012) demonstrated increased urinary clusterin in dogs with renal involvement, while other experimental studies have similarly reported changes in clusterin excretion following toxic or ischemic renal injury (Hidaka et al., 2002; Ishii et al., 2007).

Although the present study did not investigate underlying molecular pathways, clusterin is known to be a stress-responsive protein that is upregulated in conditions associated with cellular injury. Therefore, its increased serum concentration in diseased cats may reflect a general systemic response to renal tissue damage rather than a disease-specific mechanism. This interpretation is supported by its reported involvement in cellular stress responses in previous experimental and clinical models (Rosenberg and Silkensen, 1995).

It should be emphasized that mechanistic pathways such as oxidative stress, inflammatory signaling, and fibrosis-related processes have been described in other species and experimental settings but were not evaluated in the current study. Therefore, their relevance in this dataset remains speculative and cannot be directly inferred from the present results.

Overall, the observed increase in serum clusterin supports its potential role as a biomarker associated with renal disease presence in cats, but further studies are required to clarify its biological source, regulatory mechanisms, and clinical specificity in feline kidney disorders.

Urine clusterin is a recently found biomarker that correlates with and best predicts ESKD. Incomplete knowledge exists regarding the role of urine clusterin in the development of acute and chronic renal diseases. Increased clusterin gene expression in obstructed rabbit kidneys was linked to a reduction in renal concentrating ability and GFR values (Schlegel et al., 1992). Dieterle et al. (2010), compared urine clusterin with serum blood urea nitrogen (BUN) and creatinine and found a higher diagnostic performance for detecting proximal tubular injury.

To our knowledge, this study is the first report on serum clusterin levels in cats with AKI and CKD. Although the number of cats with AKI was low, cats with CKD had a statistically greater median concentration of serum clusterin than AKI cats ($P=0.021$). Clusterin was reported to be involved in a number of distinct mechanisms in response to kidney damage. According to the literature, clusterin expression is linked to the TGFβ signaling pathway. The progression of fibrosis is accelerated in chronic renal failure. The key fibrosis factor, transforming growth factor beta (TGF-β) plays a significant function. Through activation of the AP-1 transcription protein and protein kinase C, TGF-β1 increases clusterin expression in fibrosis, resulting in clusterin overexpression (Khan and Pandey, 2014).

Increased oxidative stress results in apoptosis, fibrosis, and inflammation. ET-1 releases vascular damage and cellular senescence in renal cells, as similarly observed in our study; this can result in an increase in clusterin synthesis (Gao et al, 2022; Ju et al., 2026). Multiple attacks to the kidney can lead to tubular injury as proposed by the "fibrosis hypothesis," which then triggers inflammation and additional damage to the tubulointerstitium, eventually leading to chronic kidney disease. Hodgkins and Schnaper (2012) reported that clusterin association with CKD stage 3 or the development of albuminuria may lend credence to the theory that tubular damage becomes more apparent at this stage.

In AKI, increased oxidative stress can lead to a variety of adverse outcomes, including renal cell death, fibrosis, and inflammation. Consequently, this may lead to enhanced clusterin synthesis.


CC: BY-NC-ND

Podocyte expression of clusterin was confirmed by its co-localization with the podocyte marker WT1 and its upregulation in the glomerulus of both diabetic nephropathy (DN) patients and streptozotocin-induced diabetic mice. Glomerular clusterin expression is elevated in DN, and this may serve to protect podocytes from the apoptosis induced by oxidative stress (Ju et al., 2026). Accordingly, we might presume that podocytes are more vulnerable to apoptosis brought on by oxidative stress in conditions where kidney damage has occurred, such as in CKD and AKI, and that this leads to an increase in the synthesis and expression of clusterin.

In the present study, clusterin and BUN exhibited a positive, strong, and statistically significant correlation ($P<0.001$, $r=0.756$). Furthermore. Clusterin and creatinine showed a positive, very strong, and statistically significant correlation ($P<0.001$, $r=0.829$). Furthermore, clusterin and phosphorus demonstrated positive. strong and statistically significant correlation ($P<0.001$, $r=0.744$). García-Martínez et al. (2012), demonstrated a 0.86 Spearman correlation between the UCL/Cr ratio and the UPC ratio suggesting a strong connection between them. Clusterin levels in the urine were discovered to be correlated with total protein ($r=0.28$, $P=0.018$) and total protein/creatinine ($r=0.26$, $P=0.02$) levels (Solichova et al., 2007). Clusterin amount in urine was not correlated with glomerular filtration rate, age, urine GMT/creatinine 1-microglobulin, urine albumin, or urine albumin/creatinine ratio. Combined with elevated serum clusterin, these results position clusterin as both a functional and structural biomarker for monitoring disease progression (Yan et al., 2020).

This study has several important methodological limitations that should be considered when interpreting the findings. First, the relatively small sample size limits statistical power and increases the risk of type II error, particularly in subgroup comparisons. Second, the study design was cross-sectional with a single sampling time point (Day 0), which precludes assessment of temporal changes in clusterin concentrations or evaluation of disease progression. Third, histopathological confirmation of renal disease was not available, and classification relied on clinical, laboratory, and ultrasonographic criteria. Although IRIS-based staging criteria were applied, this introduces a degree of diagnostic uncertainty, particularly in differentiating early CKD from AKI with incomplete recovery.

A further limitation is the heterogeneity of the study population. Although these cases were analyzed separately, residual confounding cannot be excluded, and this may have influenced biomarker concentrations. In addition, the absence of SDMA measurement limited the more refined staging of renal dysfunction and reduced the ability to correlate clusterin with modern functional biomarkers.

This study demonstrated that serum clusterin concentrations were significantly higher in cats with renal disease compared with healthy controls, suggesting an association with feline renal dysfunction.

Taken together, these findings indicate that serum clusterin may reflect the presence of renal disease in cats, whereas the diagnostic value of urinary clusterin remains uncertain under the current study conditions. However, due to the limited sample size, cross-sectional design, and lack of histopathological confirmation, these results should be interpreted cautiously. Further studies with larger cohorts, standardized disease staging, longitudinal follow-up, and comprehensive biomarker panels are required to clarify the clinical relevance and biological behavior of clusterin in feline renal disease.

❋ ❋ ❋

**Peer-review:** External, Independent.


CC: BY-NC-ND

**Acknowledgements:**
This study is derived from a master's thesis entitled determination of serum and urinary clusterin levels in cats with renal failure. This study was presented at the "9th International Selçuk Scientific Research Congress. This study was carried out in the Erciyes University Veterinary Teaching and Research Hospital as part of Erciyes University Scientific Research Projects Unit with project number TYL-2021-11508. I would like to thank the Erciyes University Scientific Research Projects Unit (BAP) and the Presidency for Turks Abroad and Related Communities: Türkiye Scholarship Program (YTB).

**Declarations:**

***1. Statement of Originality:***
This study is derived from a master's thesis entitled

***2. Author Contributions:***
***Concept:*** VG; ***Conceptualization:*** VG; ***Literature Search:*** AMAA; ***Data Collection:*** AMAA; ***Data Processing:*** AMAA; ***Analysis:*** AMAA; ***Writing – original draft:*** AMAA; ***Writing – review & editing:*** AMAA,VG.

***3. Ethics approval:***
The study was approved by Erciyes University Animal Experiments Local Ethics Committee (ERU HADYEK) for animal experimentations (committee decision number: 21/199).

***4. Funding/Support:***
This study was derived from the project supported by the Scientific Research Projects Unit of Erciyes University (TYL-2021-11508).

***5. Competing Interests:***
The authors declare no competing interests.

***6. GenAI Usage Statement:***
No GenAI tools were used at any stage of the study.

***7. Sustainable Development Goals:***




## REFERENCES

Dieterle F, Perentes E, Cordier A, Roth DR, Verdes P, Grenet O, Pantano S, Moulin P, Wahl D, Mahl A, End P, Staedtler F, Legay F, Carl K, Laurie D, Chibout SD, Vonderscher J, Maurer G. Urinary clusterin, cystatin C, β2-microglobulin and total protein as markers to detect drug-induced kidney injury. Nat Biotechnol 2010; 28(5): 463-9.

Gao P, Zou X, Sun X, Zhang C. Cellular senescence in metabolic-associated kidney disease: An update. Cells 2022; 11(21): 3443.

García-Martínez JD, Tvarijonaviciute A, Cerón JJ, Caldin M, Martínez-Subiela S. Urinary clusterin as a renal marker in dogs. J Vet Diagn Invest 2012; 24(2): 301-6.

Guo J, Guan Q, Liu X, Wang H, Gleave ME, Nguan CY, Du C. Relationship of clusterin with renal inflammation and fibrosis after the recovery phase of ischemia-reperfusion injury. BMC Nephrol 2016; 17(1): 133.

Hidaka S, Kranzlin B, Gretz N, Witzgall R. Urinary clusterin levels in the rat correlate with the severity of tubular damage and may help to differentiate between glomerular and tubular injuries. Cell Tissue Res 2002; 310(3): 289-96.

Hodgkins KS, Schnaper HW. Tubulointerstitial injury and the progression of chronic kidney disease. Pediatr Nephrol 2012; 27(6): 901-9.

Ishii A, Sakai Y, Nakamura A. Molecular pathological evaluation of clusterin in a rat model of unilateral ureteral obstruction as a possible biomarker in nephrotoxicity. Toxicol Pathol 2007; 35(3): 376-82.

Ju W, Nair V, Vart P, Smeijer JD, Hudkins KL, Moedt E, Larkina M, Perco P, Burdet F, Shedden K, Hwang M, Lee E, O'Connor C, Hartman J, Subramanian L, Bitzer M, Ibberson M, Duffin KL, Gomez MF, Alpers CE, Kretzler M, Heerspink HJL. Urinary clusterin as a biomarker of human kidney disease progression and response to the endothelin receptor antagonist atrasentan: An exploratory analysis from the SONAR trial. Nat Commun 2026; 17:2482.

Khan Z, Pandey M. Role of kidney biomarkers of chronic kidney disease: An update. Saudi J Biol Sci 2014; 21(4):294-9.

Lamchiagdhase P, Preechaborisutkul K, Lomsomboon P, Srisuchart P, Tantiniti P, Khan-u-Ra N, Preechaborisutkul B. Urine sediment examination: a comparison between the manual method and the iQ200 automated urine microscopy analyzer. Clin Chim Acta 2005; 358(1-2):167-74.

Monaghan K, Nolan B, Labato M. Feline acute kidney injury: 1. Pathophysiology, etiology and etiology-specific management considerations. J Feline Med Surg 2012;14(11): 775-84.

Rosenberg ME, Silkensen J. Clusterin: physiologic and pathophysiologic considerations. Int J Biochem Cell Biol 1995; 27(7): 633-45.

Schlegel PN, Matthews GJ, Cichon Z, Aulitzky WK, Cheng CY, Chen CL, Saso L, Goldstein M, Jänne OA, Bardin CW. Clusterin production in the obstructed rabbit kidney: correlations with loss of renal function. J Am Soc Nephrol 1992; 3(5):1163-71.

Solichova P, Karpisek M, Ochmanova R, Hanulova Z, Humenanska V, Stejskal D, Bartek, J. Urinary clusterin concentrations – A possible marker of nephropathy? Pilot study. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2007;151(2): 233–36.

Wu CY, Yang HY, Chien HP, Tseng MH, Huang JL. Urinary clusterin-a novel urinary biomarker associated with pediatric lupus renal histopathologic features and renal survival. Pediatr Nephrol 2018;33(7):1189-98.

Yan GY, Chen KY, Wang HC, Ma TY, Chen KS. Relationship between ultrasonographically determined renal dimensions and International Renal Interest Society stages in cats with chronic kidney disease. J Vet Intern Med 2020; 34(4):1464-75.

Yerramilli M, Farace G, Quinn J, Yerramilli M. Kidney disease and the nexus of chronic kidney disease and acute kidney injury: the role of novel biomarkers as early and accurate diagnostics. Vet Clin North Am Small Anim Pract 2016; 46(6): 961-93.




CC: BY-NC-ND