Prognostic factors in dogs with common causes of proteinuria

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Prognosefaktoren bei Hunden mit den häufigsten Ursachen der Proteinurie

Vergleichende Untersuchungen über den prognostischen Wert eines erhöhten Protein-Kreatinin-Verhältnisses (UPC) im Urin bei Hunden mit verschiedenen Grunderkrankungen sind kaum bekannt. Daher wurden Hunde, bei denen zwischen 2014 und 2015 mindestens einmal ein UPC 2,0 oder höher gemessen wurde, retrospektiv analysiert. Die Hunde wurden in Gruppen der häufigsten Grunderkrankungen eingeteilt, wie primäre Glomerulopathie, Morbus Cushing, Leishmaniose und in verschiedene Erkrankungen. Mögliche prognostische Faktoren wie UPC zum Zeitpunkt der Diagnose, Kreatinin, spezifisches Gewicht des Urins, Albumin und Hämatokrit wurden bewertet.

Neunundachtzig Hunde mit schwerer Proteinurie wurden in die Studie aufgenommen. Die mediane Überlebenszeit betrug 42 Tage. UPC und Überlebenszeit unterschieden sich nicht signifikant zwischen den Gruppen. Bei den Hunden mit primärer Glomerulopathie waren die für den Tod identifizierten signifikanten Risikofaktoren ein erhöhtes UPC ($p = 0{,}03$), ein erhöhtes Kreatinin ($p < 0{,}01$), ein niedriger Hämatokrit ($p = 0{,}04$) und ein niedriges spezifisches Gewicht des Urins ($p = 0{,}03$). Bei Hunden mit Morbus Cushing war nur das spezifische Gewicht des Urins ein signifikanter Risikofaktor für den Tod ($p < 0{,}05$). Bei Hunden mit Leishmaniose waren erhöhte UPC und Kreatinin signifikant mit der Sterblichkeit assoziiert ($p < 0{,}01$; $p < 0{,}01$).

Ein erhöhtes UPC ist ein Todes – Risikofaktor bei Hunden mit primärer Glomerulopathie und Leishmaniose, aber nicht bei Hunden mit Morbus Cushing. Dies kann durch eine unterschiedliche Pathogenese erklärt werden, die zu einer Proteinurie führt.

Schlüsselwörter: Azotämie, Hund, Morbus Cushing, glomeruläre Erkrankung, Leishmaniose, UPC

Summary

Little is known about the prognostic value of increased urine protein to creatinine ratios (UPC) comparing different underlying diseases in dogs. Therefore, between 2014 and 2015, dogs with a UPC of 2,0 or higher measured were retrospectively analysed at least once. They were divided into groups of the most common underlying diseases, namely primary glomerulopathy, Cushing's disease, leishmaniasis and in a group of different diseases. Possible prognostic factors, like UPC at time of diagnosis, creatinine, urine specific gravity, albumin and haematocrit, were assessed.

Eighty-nine dogs with severe proteinuria were included in the study. Median time of survival was 42 days. UPC and time of survival did not differ significantly between the groups. Among the dogs with primary glomerulopathy, identified significant risk factors for death included increased UPC ($p=0{,}03$), increased creatinine ($p<0{,}01$), low haematocrit ($p=0{,}04$) and low urine specific gravity ($p=0{,}03$). In dogs with Cushing's disease, only urine specific gravity was a significant risk factor for death ($p<0{,}05$). In dogs with leishmaniasis, increased UPC and creatinine were significant associated with mortality ($p<0{,}01$; $p<0{,}01$).

Increased UPC is a risk factor for death in dogs with primary glomerulopathy and leishmaniasis, but not in dogs with Cushing's disease. This can be explained by different pathogenesis leading to proteinuria.

Keywords: azotaemia, canine, Cushing's disease, glomerular disease, leishmaniasis, UPC

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Introduction

Proteinuria can arise from numerous causes, which are divided into prerenal, renal and postrenal causes.[17] Prerenal proteinuria occurs due to dysproteinaemia, renal proteinuria is caused by altered renal handling of normal plasma proteins, e.g. kidney disease and postrenal proteinuria is arising from proteins entering the urine after the urine reached the renal pelvis (e.g. inflammation of the lower urinary tract). Severe renal proteinuria in dogs is a hallmark of glomerular diseases and associated with progression of kidney diseases.[9] The increased amount of filtered proteins cause further damage in renal tissue in various ways.[3,23] The toxicity of some proteins for tubular cells is described as a progressive loss of tubular cell integrity, further increasing the proteinuria and leading to a vicious circle.

The most common method used to quantify proteinuria in dogs is the measurement of the urine protein to creatinine ratio (UPC), which is an estimate of the 24-hour urinary excretion of proteins.[8] UPC alone cannot be used to distinguish between different diseases,[17,39] however, severe proteinuria in dogs with UPC ≥2 is indicative for glomerular disease.[17]

An important aspect of patients with renal proteinuria is the presence of nephrotic syndrome, because it negatively influences the course of kidney disease.[15] In the study of Klostermann et al. (2011),[15] the median survival time was significantly shorter in dogs with nephrotic syndrome (12 days) compared to dogs without nephrotic syndrome (104 days).

Proteinuria is associated with impaired kidney function and a negative prognostic factor for the progression of kidney disease in dogs.[12,18,40] Jacob *et al.*[12] found that dogs with a UPC >1 had a three-fold higher risk of developing uremic crisis and death compared to dogs with a lower UPC.

One example of a disease with functional proteinuria in dogs is Cushing's disease. Hypertension, hemodynamic alterations caused by glucocorticoids leading to increased renal plasma flow and GFR are possible mechanism contributing to proteinuria.[35] In humans with Cushing's disease and proteinuria, glomerulosclerosis and membranoproliferative glomerulonephritis are described, although a cause-effect relationship between Cushing's disease and these renal lesions remain uncertain.[10] Up to 46 % of dogs with untreated ACTH-dependent hyperadrenocorticism have proteinuria, which may persist despite successful treatment of hypercortisolism.[11,25] Thus, dogs may be at risk for development of chronic kidney disease.

Infectious diseases can lead to kidney damage. For example, canine leishmaniasis associated nephropathy is mainly characterized by glomerular damage and is attributed to intraglomerular deposition of circulating immune complexes inducing inflammatory changes and leading to glomerulonephritis and tubulointerstitial nephritis.[11,21] Since the most common cause of death in dogs with leishmaniasis is kidney failure and proteinuria is used in the staging system for canine leishmaniasis,[37] further investigation in proteinuric dogs with leishmaniasis is of clinical interest.

However, little is known about the specific impact of increased UPC on the survival of dogs, further investigations are warranted. Different underlying diseases causing functional or pathologic variations in how the kidneys handle proteins might have different impact on prognosis and should be investigated to assist clinicians in determining prognosis and establish a diagnostic plan.

Therefore, the aim of this study was to assess dogs with severe proteinuria for their survival time, underlying diseases and possible prognostic factors like UPC at time of diagnosis, urine specific gravity, creatinine, albumin and haematocrit.

Materials and Methods

Study design

Cases were selected through a search in the laboratory results from the veterinary medical laboratory of the University of Zurich. The only inclusion criteria for dogs in this study was a single UPC of 2,0 or more measured during the years 2014 and 2015. If several UPCs were measured in one dog, we went back in the history to the first increase in UPC to 0,5 or higher. This point in time was then set as time of diagnosis. If only one UPC was measured in a dog, the time of this measurement was taken as the time of diagnosis. All further possible prognostic factors were then taken from time of diagnosis. Signalment and specific parameters from urinary test results and bloodwork were obtained from the patient's medical record (UPC, urine specific gravity, creatinine, albumin and haematocrit) at the time of diagnosis. Azotaemia was defined as a creatinine above the reference range of the laboratory of the University of Zurich of 50–119 mmol/l.

Urine sediment assessment, urine culture, blood pressure measurement and diagnostic imaging was performed in several, but not all cases. Diagnostic imaging findings were not included in this study. Kidney biopsies were not performed in any of these cases, autopsy was performed in five cases. If the patient died, time of death was recorded. Discharged patients were followed until

their last visit at the veterinary clinic.

To calculate the relative risk of disease for different breeds in Switzerland, AMICUS, the national database for the registration of dogs in Switzerland, offered the total numbers of dogs of the most popular breeds during the years 2014 and 2015.

Sample analysis

UPC, urine specific gravity, creatinine, albumin and haematocrit were determined in the medical laboratory of the University of Zurich with current standard procedures (Chemistry: Cobas Integra 800 Analyzer (Roche diagnostics, Rotkreuz), urine specific gravity: refractometer (Atago, Dietikon), haematocrit: blood filled glass capillaries after centrifugation at 15'000 g for 3 minutes).

Tests for several infectious diseases were performed in some dogs in the medical laboratory and Institute of Parasitology of the University of Zurich (*Anaplasma phagocytophila/platys* (antibody detection or PCR), *Angiostrongylus vasorum* (antigen detection), *Babesia canis* (antibody detection IFAT), *Borrelia burgdorferi* (C6 antibody detection ELISA), *Dirofilaria immitis* (antigen detection ELISA), *Ehrlichia canis* (antibody detection IFAT), *Leishmania infantum* (antibody detection ELISA), *Leptospira spp.* (microagglutination testing or PCR)).

Diagnosis

According to the diagnosis, all dogs included in the study were divided into 4 groups: primary glomerulopathy, Cushing's disease, leishmaniasis and other diseases based on the following criteria:

If no cause of proteinuria was found in the tests performed, a suspicion of primary glomerular disease was raised. According to the inclusion criteria, that only patients with severely increased UPCs of 2,0 or higher were assessed, glomerular pathogenesis was suspected, giving the group its name.

In dogs with Cushing's disease presented with typical symptoms, blood work abnormalities and variations seen in abdominal ultrasound compatible with Cushing's disease, a positive low-dose dexamethasone suppression test, and clinical improvement on medical treatment with trilostane, as described previously.[1,27]

Definitive diagnosis of leishmaniasis was based on clinical signs and laboratory findings. Leishmaniasis (n=11) was diagnosed with positive antibody titre measured at the clinic (7) or earlier at the private veterinarian (2), PCR testing (1) or visualisation of leishmania in a fine needle aspiration (1) of patient's tissue.[5] Dogs with concurrent other infectious diseases, diagnosis was made according to the medical record based on typical clinical signs for leishmaniasis, e.g. skin changes, uveitis, enlarged lymph nodes and rapid improvement under treatment against leishmaniasis.

The group with other diseases included all dogs with illnesses resulting in increased UPCs other than the three specified above, for example infectious causes, malignancies, or systemic inflammatory diseases.

Statistical analysis

Statistical analysis was performed with Microsoft Excel (2015) and the statistical program ICM SPSS Statistics Version 23,0, Cox-regression was performed to identify risk factors influencing survival time. P-values $<0,05$ were defined as statistically significant, and descriptive statistics were obtained. Survival time was calculated from the first instance of a UPC of or exceeding 0,5 until death or loss to follow up.

Results

Animals

A total of 186 dogs undergoing urine analysis had a UPC $\geq 0,5$ during the years 2014 and 2015. Of these dogs, 99 had a severely increased UPC (i.e., $\geq 2,0$) at least once during their visit to the clinic. Ten of these dogs were, however, excluded because of unavailable medical records. Finally, 89 dogs (37 males, 52 females) fulfilled the inclusion criteria. Of these dogs, 35 had a urine culture performed, in 80 cases urine sediment was assessed, 33 had a blood pressure measured.

Fifteen dogs tested negative for *Anaplasma phagocytophila*, one tested negative for *Anaplasma platys*. Nineteen dogs were negative and one was positive for *Angiostrongylus vasorum*. Twenty-seven dogs were negative for *Babesia canis*, four were positive. Four dogs were negative for *Borrelia burgdorferi*, three were positive. Thirty-three dogs tested negative for *D.immitis*. For *Ehrlichia canis*, 33 dogs were negative and two positive. Twenty-eight tested negative for *Leishmania infantum*, 11 were positive. Sixteen dogs tested negative for Leptospirosis, one was positive.

Death was recorded for 38 dogs during the study time. The median time of survival was 42 days (range: 0 to 1866 days). There was no statistically significant difference in survival time ($p=0,641$) between the different groups. Dogs with leishmaniasis were significantly younger than dogs in the other three groups ($p<0,01$). For all dogs, increased UPC at time of diagnosis was a risk factor for death ($p<0,01$). The higher the UPC was, the higher the risk of dying. There was no significant difference in UPCs between different diagnostic groups.

Table 1 presents an overview of the descriptive statistics of the different groups.

Risk factors

Identified risk factors of death included increased UPC, higher creatinine, lower haematocrit and lower urine specific gravity. An increased UPC is a significant risk factor in dogs with glomerulopathy and leishmaniasis, but not in dogs with Cushing's disease. Low albumin correlated with a shorter survival time, but results were not statistically significant (p=0,11 for all dogs, p=0,08 for dogs with leishmaniasis). In dogs with Cushing's disease, low urine specific gravity was the only risk factor for death identified. Further risk factors in each group are compared in table 2.

Glomerular diseases

Among the dogs with primary glomerular diseases, several breeds were overrepresented, including 6 mixed breed dogs, 5 Jack Russel Terriers and Yorkshire Terriers, 4 Golden Retrievers and Bernese Mountain dogs and two Flat Coated Retrievers. Calculated with the prevalence of different breeds in Switzerland during study time, 4 breeds had an increased relative risk to develop glomerular diseases compared to mixed breed dogs, as shown in table 3.

Leishmaniasis

Three dogs with leishmaniasis were concurrently positive for *Babesia canis*, one was positive for *Dirofilaria immitis* and one was positive for *Ehrlichia canis*. Leishmaniasis included six mixed breed dogs, two Galgo Espanols, and one dog per breed of Dogue de Bordeaux, German Pointer and Labrador Retriever. Increased UPC and creatinine values were significantly associated with increased risk of dying.

Different diagnosis

The dogs in the group with different diagnosis suffered from neoplasia (e.g., mammary gland neoplasia, testicular neoplasia, sarcoma, mass in the spleen or the lungs, multicentric B-cell lymphoma, and mast cell neoplasia), uroliths, myasthenia gravis, aspiration pneumonia, chronic bronchitis, pulmonary hypertension, thrombosis, infection with *Ehrlichia canis*, *Leptospira* and infection with *Angiostrongylus vasorum*. Dog breeds in this

Table 1: Dogs involved in a study on prognostic factors in dogs with common causes of proteinuria (n=89). The table shows the numbers of dogs in the different group of diagnosis, age at time of diagnosis, urine protein to creatinine ratio (UPC) and survival times of deceased dogs.

Diagnosis	Number of dogs	Median age at time of diagnosis in years	Median UPC (range)	Median time of survival in days of deceased dogs and their range in days (n=38 dogs)
Glomerulopathy	46	9,02	6,00 (1,4–21,2)	15 (0–1405)
Cushing's syndrome	16	10,28	4,40 (2,1–14,1)	1,7 (6–402)
Leishmaniosis	11	5,22	4,7 (2,1–19,8)	62 (4–311)
Different diagnosis	16	10,04	3,10 (1,9–9,5)	68 (9–1866)

Table 2: Possible prognostic risk factors for death in the different groups of dogs with common causes of proteinuria and level of significance (significant values in bold).

Diagnosis	Increased UPC (≥0.5)	Azotaemia (creatinine >119 mmol/l)	Hypoalbuminemia (albumin <29 g/l)	Anaemia (haematocrit <44 %)	Low urine specific gravity
Glomerulopathy	**p=0,03**	**p<0,01**	p=0,11	**p=0,04**	**p=0,03**
Cushing's syndrome	p=0,15	p=0,18	p=0,91	p=0,91	**p<0,05**
Leishmaniosis	**p<0,01**	**p<0,01**	p=0,08	p=0,61	p=0,43
Different diseases	p=0,92	p=0,43	p=0,93	p=0,25	p=0,96

Table 3: Dog breeds with increased relative risk for glomerular diseases in Switzerland based our study on prognostic factors in dogs with common causes of proteinuria (n = 89)

Overrepresented breeds in the group of dogs with glomerulopathy	Number of affected dogs in this group	relative risk to develop glomerulopathy compared to occurrence of the breed in Switzerland according to AMICUS
Bernese Mountain dogs	4	8,4
Jack Russel Terriers	5	6,4
Golden Retrievers	4	5,6
Yorkshire Terriers	5	5,6

group included two Golden Retrievers, while every other breed was only represented once. No statistically significant risk factors were identified.

Discussion

Across all dogs, an increased UPC at time of diagnosis was a significant risk factor for death and the risk increased further with higher values, which confirms the results of other studies.[12,17,40] UPC did not differ significantly among different diagnoses, therefore, it is not possible to draw conclusions about the underlying disease from the UPC value, as was shown in previous studies.[39]

More than half of all dogs were diagnosed with primary glomerular kidney disease based on proteinuria and the lack of an identified underlying disease. Although the median survival time was short (15 days), the range was broad. This finding supports other studies that have reported a range from months up to two years, depending on the stage of the disease.[29] The time of survival is comparable to the results reported by Klosterman et al. (2011).[15] We did not evaluate for nephrotic syndrome, but in view of the similar results, some patients in our study were possibly suffering from nephrotic syndrome. A major factor determining the prognosis of dogs with glomerulopathy is the underlying disease.[39] In a study several years earlier, the median survival time for dogs with glomerulonephritis was 28 days,[2] whereas survival time was only 5 days for dogs with amyloidosis.[33] However, for further evaluation, a more detailed work up and renal biopsy in certain cases is necessary, which, due to its retrospective nature, could not be performed in our study.

The high creatinine level identified as a risk factor for death in dogs with glomerular diseases is in accordance to previous studies where being azotemic was identified as a risk factor in kidney diseases.[6] It has previously been shown that the single measurement of increased creatinine, as in our study, already predicts reduced survival time.[24]

A further significant negative prognostic factor in dogs with glomerular diseases is a low haematocrit, which can be explained by advanced kidney damage causing erythropoietin deficiency or gastrointestinal blood loss.[30]

Low urine specific gravity was a significant risk factor for death in dogs with glomerulopathy. As shown in previous studies, urine specific gravity is not a sensitive diagnostic tool for kidney disease, as the ability to concentrate urine is lost late in disease progression.[6] Therefore, if a dehydrated animal has an inappropriately low urine specific gravity, the presence of advanced disease is expected and measurement of UPC might be indicated.

Hypoalbuminemia was not a statistically significant risk factor for death. This is discrepant with human studies, where it was identified as a risk factor for acute kidney insufficiency and for chronic kidney damage.[34] Possible explanations for it not reaching significance in our dogs with glomerular diseases include the measurement of dehydrated animals with falsely increased albumin and altered metabolism of albumin compared to dogs without primary glomerular kidney disease.

Compared with the overall prevalence of various dog breeds in Switzerland, Bernese Mountain dogs, Jack Russell terriers, Golden Retrievers and Yorkshire terriers were overrepresented in our study population, raising the suspicion of breed-specific predispositions for kidney disease. Bernese mountain dogs have a high incidence of kidney disease at younger ages compared with other breeds and are known for a familial membranoproliferative glomerulonephritis.[26] Therefore, evaluation for kidney disease in a Bernese Mountain dog is recommended even early in life.

Until this study, an increased risk for kidney disease in Jack Russell terriers was not known and they were even listed as a breed with lower incidence of glomerulopathies in one publication.[1,24,26] The reason for this discrepancy with our data remains obscure, possible bias of owners who are more concerned and therefore more likely to see a vet is possible. Further studies to evaluate the risk in this breed are necessary.

Juvenile kidney dysplasia is described in Golden Retrievers, but these dogs are usually less than three years old at initial presentation, which is below the age of our dogs, making this pathogenesis unlikely.[4,14] However, in Sweden, an increased prevalence of chronic kidney disease in Golden Retrievers has been described.[26]

Yorkshire terriers belong to the breeds with the highest incidence of chronic kidney disease.[26] In another study, this breed was not identified as a risk factor.[24] However, additional screening for kidney diseases in Yorkshire terriers might be worthwhile.

One-fifth of the dogs in this study were diagnosed with Cushing's disease. Proteinuria can be induced with steroid treatment in dogs and is reversible after discontinuation of treatment as was shown in one study.[32] A study assessing long-term follow-up of renal function in dogs with hyperadrenocorticism could not find evidence for impaired kidney function.[22] This is in accordance with a previous study of 85 dogs with pituitary-depen-

dent hypercortisolism, where a high UPCs was not identified as a risk factor for death.[7] Therefore, transient functional renal proteinuria is suspected, being reversible under treatment, which might explain why a high UPC among these dogs was not identified as a negative prognostic factor. The mean UPC in this study was higher than in previous studies, and possibly biased because only cases with UPCs of 2 or above were included. Thus, Cushing's disease needs to be considered as a differential diagnosis even in severely proteinuric dogs, although, it is uncertain why some dogs treated for Cushing's disease remain proteinuric. In medically treated dogs, suggested pathophysiology include that serum cortisol levels may exceed physiological concentrations temporarily as the primary cause is not removed.[36] However, in surgically treated dogs, reoccurrence of proteinuria may indicate recurrence of the disease or concurrent disease and warrants clinician's attention. It is important to note that a high UPC at the time of diagnosis does not imply a worse prognosis for Cushing's disease in dogs but controlling increased UPCs in dogs with hypercortisolism is recommended, as is considering further diagnostics if persistent.

Low urine specific gravity was a risk factor for death in dogs with hyperadrenocorticism. This can be explained by more severe diseases resulting in signs of central diabetes insipidus, or urinary tract infection, which patients of those conditions are prone to.[27]

In dogs with leishmaniasis, a high UPC was identified as a risk factor for death, which is in accordance with previous studies,[37] where prognosis was poor to guarded with a UPC >1. The influence of high UPC on survival time in contrast to Cushing's disease can be explained by the pathologic renal proteinuria, which leads to at least partially irreversible kidney damage. Because reduction of UPC under treatment is described,[21] treatment as early as possible is essential to try to prevent further kidney damage and chronic kidney disease.

Consistent with our findings, azotaemia has previously been identified as a negative prognostic factor.[31]

Hypoalbuminemia was not identified as a risk factor for death in our data in dogs with leishmaniasis, which was surprising, because it is often present in dogs with leishmaniasis and tends to increase under treatment as UPC decreases.[28] Therefore, low albumin might be more useful as a monitoring tool than a prognostic factor in leishmaniasis. However, a compensatory reduction of albumin due to hyperglobulinemia and therefore complicating it as a prognostic factor is possible.[31]

Co-infection with other infectious diseases is possible in dogs with leishmaniasis, because the vectors for other infections are found in the same geographic region and cross-reactivity in serology appears less likely.[16] Testing for other infectious diseases such as babesiosis, dirofilariasis, ehrlichiosis and hepatozoonosis, appears warranted in proteinuric dogs with leishmaniosis, however, was not performed in the present study.

Infectious agents found in dogs with different diseases included *Ehrlichia canis*, *Leptospira australis* and *Angiostrongylus vasorum*. There is only one case report of a dog infected with *Ehrlichia canis* and concurrent amyloidosis and kidney failure. Possible explanation for the proteinuria includes glomerulonephritis, fever and kidney damage caused by renal bleeding secondary to the thrombocytopenia.

If a diagnosis of an infectious disease is made in a proteinuric dog, measurement of UPC and following of it under treatment is recommended as a monitoring tool and to differentiate prerenal proteinuria caused by fever or inflammation from renal proteinuria due to glomerulonephritis.[19]

Several proteinuric dogs with different diseases were diagnosed with neoplasia. In human medicine, malignant neoplasia is associated with glomerular kidney disease and nephrotic syndrome, as well as potential kidney failure and paraneoplastic glomerulopathies.[13,38] However, the exact pathological mechanism and the incidence of paraneoplastic glomerulopathy in veterinary medicine remains unknown but seems to be an important differential diagnosis.

This study has several limitations. A major limitation is that the diagnostic work up was not standardized. In some cases, UPC was only measured once. Not all dogs underwent full diagnostic work-up including diagnostic imaging, urine culture, blood work and testing of all possible infectious diseases necessary to make a definitive diagnosis of primary glomerulopathy. Therefore, it is possible that diseases were missed and secondary glomerular diseases wrongly classified as primary glomerular diseases.

However, even if all differential diagnosis by blood and urinary tests are excluded, kidney biopsies might be necessary to precisely define primary glomerular disease, which was not performed in any of the dogs in this study. Nevertheless, the aim of the study was to analyse common clinical cases with severe proteinuria assessed by the methods possible for each case.

According to the nature of retrospective studies, measurements were not always documented in detail. For example, it was not always noted, when urine specific gravity was measured, although, it seemed to be at the time of initial evaluation.

Furthermore, therapeutic interventions, diet, general health status and dehydration status were not evaluated. Dogs were defined as azotemic solely based on one creatinine measurement and other kidney values were not considered, independent of body weight and size. Hydration status was not included. Therefore, missed diagnoses in badly muscled dogs or overinterpreted values in dehydrated dogs are possible and mean survival time needs to be interpreted carefully.

Time of diagnosis can further bias time of survival because survival time is always dependent on when and how diagnosis is made.

There might also potentially be an underlying bias because only UPCs from the laboratory were used. Dogs presenting over the weekend, when only urine dipstick testing is available, or if severe proteinuria was present but no UPC was measured, were not evaluated. Furthermore, disease awareness to measure UPC may be dependent on the clinician.

Because the groups were small, it is possible that significance was not reached in certain parameters.

Conclusion

A high UPC is a negative prognostic factor in dogs with glomerular diseases and leishmaniasis, but not in dogs with Cushing's disease, which is an important difference concerning prognosis in these diseases. This might be explained by different pathogenesis leading to irreversible renal damage in glomerulopathies and leishmaniasis compared to functional transient renal proteinuria in Cushing's disease.

Additional negative prognostic factors were identified like azotaemia in dogs with glomerular diseases and leishmaniasis, as well as low haematocrit and low urine specific gravity in dogs with glomerular diseases. Further studies are necessary to investigate prognostic factors in larger groups of proteinuric dogs with a standardized work-up.

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Facteurs de pronostic chez les chiens présentant des causes courantes de protéinurie

On sait peu de choses sur la valeur pronostique de l'augmentation du rapport protéines/créatinine urinaires (UPC) en fonction des différentes maladies sous-jacentes chez le chien. Par conséquent, entre 2014 et 2015, les chiens ayant une UPC de 2,0 ou plus ont été étudiés rétrospectivement au moins une fois. Ils ont été divisés en groupes des maladies sous-jacentes les plus courantes, à savoir la glomérulopathie primaire, la maladie de Cushing, la leishmaniose et dans un groupe de maladies diverses. Les facteurs pronostiques possibles, comme l'UPC au moment du diagnostic, la créatinine, le poids spécifique de l'urine, l'albumine et l'hématocrite, ont été évalués.

Quatre-vingt-neuf chiens présentant une protéinurie sévère ont été inclus dans l'étude. La durée médiane de survie était de 42 jours. L'UPC et le temps de survie ne différaient pas significativement entre les groupes. Parmi les chiens atteints de glomérulopathie primaire, les facteurs de risque de décès significatifs identifiés comprenaient une UPC élevée ($p=0,03$), une créatinine élevée ($p<0,01$), un hématocrite bas ($p=0,04$) et un poids

Fattori prognostici nei cani con cause di proteinuria più comuni

Gli studi comparativi sul valore prognostico dell'aumento del rapporto proteine-creatinina urinaria (UPC) nei cani con diverse patologie di base sono rari. Pertanto, tra il 2014 e il 2015, sono stati esaminati retrospettivamente cani con diagnosi di UPC almeno una volta pari o superiore a 2,0. I cani sono stati suddivisi in gruppi di malattie di base più comuni, come glomerulopatia primaria, malattia di Cushing, leishmaniosi e malattie diverse. Sono stati valutati i potenziali fattori prognostici, come l'UPC alla diagnosi, la creatinina, il peso specifico delle urine, l'albumina e l'ematocrito.

Ottantanove cani affetti da proteinuria grave sono stati inclusi nello studio. Il tempo di sopravvivenza mediano è stato di 42 giorni. L'UPC e il tempo di sopravvivenza non differivano significativamente tra i gruppi. Nei cani con glomerulopatia primaria, i fattori di rischio significativi identificati per la morte sono stati l'aumento dell'UPC ($p=0,03$), l'aumento della creatinina ($p<0,01$), il basso ematocrito ($p=0,04$) e il basso peso specifico delle urine ($p=0,03$). Nei cani con malattia di Cushing, solo il peso specifico delle urine era un fattore di rischio significativo per la morte ($p<0,05$). Nei cani affetti da

spécifique urinaire bas (p=0,03). Chez les chiens atteints de la maladie de Cushing, seul le poids spécifique de l'urine était un facteur de risque de décès significatif (p<0,05). Chez les chiens atteints de leishmaniose, l'augmentation de l'UPC et de la créatinine était significativement associée à la mortalité (p<0,01; p<0,01).

L'augmentation de l'UPC est un facteur de risque de mortalité chez les chiens atteints de glomérulopathie primaire et de leishmaniose, mais pas chez les chiens atteints de la maladie de Cushing. Cela peut s'expliquer par une pathogénie différente entraînant la protéinurie.

Mots clés: azotémie, chien, maladie de Cushing, maladie glomérulaire, leishmaniose, UPC.

leishmaniosi, UPC e creatinina elevati erano significativamente associati alla mortalità (p < 0,01; p < 0,01).

L'aumento dell'UPC è un fattore di rischio di decesso nei cani affetti da glomerulopatia primaria e leishmaniosi, ma non nei cani con la malattia di Cushing. Ciò può essere spiegato da una diversa patogenesi che porta alla proteinuria.

Parole chiave: azotemia, cane, malattia di Cushing, malattia glomerulare, leishmaniosi, UPC

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